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ADENOMA OF THE THYROID WITH HYPERTHYROIDISM (THYROTOXIC ADENOMA). HISTORY OF THE RECOGNITION OF THIS DISEASE AS A CLINICAL ENTITY. A STUDY OF THE SYMPTOMATOLOGY WITH BASAL METABOLIC RATES.*

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Recent advances in the practical application of indirect calorimetry have rendered it possible for the physician to measure accurately and fairly readily under standard conditions one of the most fundamental phenomena of life, namely, the rate at which the life process of combustion is proceeding within the body. Calorimetry, like the taking of the temperature, is a measurement of certain heat phenomena. Just as the thermometer has furnished the means of distinguishing accurately and readily two great classes of diseases, the febrile and the afebrile, indirect calorimetry similarly allows precise differentiation of three large groups of diseases: (1) diseases characterized by a normal rate of metabolism; (2) diseases characterized by an increased rate of metabolism, and (3) diseases characterized by a decreased rate of metabolism. Furthermore, just as there are various diseases with abnormal temperatures, there are several diseases that have per se abnormal basal metabolic rates. So far the most clearly

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defined groups of cases with abnormal basal metabolic rates are those due to disturbances in the functional activity of the thyroid gland. In this paper I shall discuss the condition of hyperthyroidism due to adenoma of the thyroid gland which is entirely distinct from the hyperthyroidism of exophthalmic goiter.

The confusion in recognition and classification of diseases with hyperthyroidism, usually considered under the group name of exophthalmic goiter, (Parry's, Graves', or Basedow's disease), is due to the fact that there are at least two separate and distinct clinical entities, as yet generally unrecognized, classified under this one term: the one, true exophthalmic goiter and the other, adenoma of the thyroid with hyperthyroidism. For this reason, the pathologist has been unable to find a consistent histologic picture in all the cases diagnosed exophthalmic goiter by the clinician.

HISTORY OF THE RECOGNITION OF ADENOMA OF THE THYROID WITH HYPERTHYROIDISM AS A CLINICAL ENTITY

Möbius in 1887 suggested that Basedow's disease is due to an abnormally increased activity of the thyroid gland. Greenfield (1893) was the first to demonstrate a specific pathologic alteration in the thyroid gland as the cause of exophthalmic goiter; he showed that in exophthalmic goiter there is a characteristic increase in the parenchyma with simultaneous enlargement of the individual cells from a cuboidal to a columnar shape and a decrease in the size of the acini and a reduction in the colloid content. His studies were limited to six typical cases of exophthalmic goiter. Other observers found that frequently hypertrophy was present in insignificant amounts only or was entirely absent in some of the cases clinically diagnosed exophthalmic goiter. MacCallum (1905) and Kocher (1912) considered, however, that very small areas of hypertrophy, sometimes only a few cells in scattered acini, fulfill the requirements for the pathologic confirmation of the clinical diagnosis of exophthalmic goiter. The absence of hypertrophy in cases clinically diagnosed exophthalmic goiter was explained by the fact that the case was either atypical or of short duration. Lewis (1906) stated, however, that the secondary exophthalmic goiter of some years' standing does not differ histologically from the simple colloid or parenchymatous goiter unassociated with Basedow's syn-

drome. Wilson, in his report of 1908, recorded an apparent disagreement between the pathologic findings and the clinical diagnosis as then made in 20 per cent of the cases.

Clinically it was early recognized that under the generic name of Basedow's disease were atypical cases which were subdivided by various authors into more or less ill defined, inconsistent groups and designated as primary and secondary (Gauthier and Buschan), *formes frustes,* or *incomplete* (Marie), goiter heart (Kraus, Gitterman and Stern), sympathicotonic and vagotonic (Eppinger and Hess), Basedowoid (Stern), Basedowized (Kocher). Of these the syndrome described by Gitterman most closely resembles that designated here as adenoma of the thyroid with hyperthyroidism. Although Gitterman recognized the characteristic age of occurrence in these cases and the association of a goiter of long duration, he considered the syndrome essentially from the viewpoint of cardiac therapy.

Plummer has come to the conclusion from an intensive study of the clinical findings in the large number of cases of different types of goiter examined at the Mayo Clinic, that there are two separate and distinct clinical types of hyperthyroidism, each associated with a distinctive pathologic change in the thyroid gland; that in one type the hyperthyroidism associated with the clinical syndrome of true exophthalmic goiter is always accompanied by hypertrophy and hyperplasia of the thyroid gland; and that in the other type the hyperthyroidism, pathologically not associated with this typical hypertrophy and hyperplasia but with the occurrence of adenoma in the gland, is due to the adenoma and that the resulting clinical syndrome is distinguishable from that occurring in true exophthalmic goiter. These conclusions were reported by Plummer in 1911 before the American Medical Association, but they first appeared in literature in his discussion of Marine's paper in 1912, as follows:

"Dr. Marine has done excellent work on the thyroid. My observations, however, do not confirm his conclusions that the anatomic changes in the thyroid in cases of exophthalmic goitre are neither constant nor specific. We have known for several years that hyperplasia of the thyroid is present in most cases with a well developed clinical complex of Graves' disease; that marked hyperplasia is seldom noted in the thyroid except in patients having Graves' disease, and that exophthalmos is but rarely associated with any type of goitre except the hyperplastic. In each year of our series, in fact, in all reported series, there have been sufficient exceptions to the above rules to cause doubt in definitely associating the toxic symptoms, exophthalmos and hyperplasia of the thyroid. In going over my statistics for the last

five consecutive years I find that exceptions to the above rules have gradually diminished. This has come about from a clearer conception of the clinical pictures that may accompany hyperplasia and "simple goitre" (adenoma and diffuse colloid).

"The statistics of operation at the Mayo Clinic seem to warrant these conclusions: (1) that hyperplasia of the thyroid never exists without a production of thyroid secretion in excess of the demands of the individual; (2) that exophthalmic goitre is a clinical entity associated with a definite pathologic process in the thyroid; (3) that, if hyperplasia of the thyroid is of a sufficient degree or extends over a long enough period, exophthalmos is almost sure to develop; (4) that no matter how intense the intoxication from an adenomatous or colloid goitre not associated with hyperplasia, exophthalmos will not develop. Patients having simple goitre noticed the goitre at the average of 22.8 years, the evidence of intoxication at 36.6 years and came to operation at 39.6 years. That a patient 23 years of age having an adenoma has a definite fixed chance of developing thyrotoxicosis during her thirty-seventh year and that the symptoms may so closely resemble the clinical complex of Graves' disease that the two cannot be distinguished is one of the strongest arguments in favor of the latter disease being directly due to a disturbance of the function of the thyroid."

In 1913 Wilson showed that in cases of exophthalmic goiter as defined and diagnosed by Plummer the thyroid always shows histologically typical parenchymatous hypertrophy and hyperplasia. Wilson, as well as other observers, has been unable, as yet, to find any consistent pathologic differentiation of adenomas that produce symptoms of hyperthyroidism and those that do not produce symptoms of hyperthyroidism.

Goetsch in 1916 emphasized the importance of the relative number of mitochondria in thyroid adenoma and stated the belief that they were more numerous in those adenomas causing symptoms of hyperthyroidism and that thereby a means was afforded of distinguishing pathologically between adenomas that produce hyperthyroidism and those that do not produce hyperthyroidism; this differential feature apparently is not confirmed by the data reported in his later papers. Goetsch (1916) is also of the opinion that there is a very different form of intoxication in thyroid adenoma from that found in true Basedow's disease and is in this respect in agreement with the position maintained and repeatedly emphasized by Plummer since 1911.

In addition to the two distinct clinical entities of adenoma of the thyroid with hyperthyroidism and exophthalmic goiter Plummer recognizes a small intermediate group. At operation the thyroid in these cases is found, on pathologic examination, to have beside the adenoma more or less typical areas of hypertrophy and hyperplasia of the parenchyma, varying between very

small intra-adenomatous or extra-adenomatous areas to a small adenoma embedded in a typical hypertrophic parenchymatous thyroid. A discussion of this group is reserved for a subsequent paper.

In the differential diagnosis of adenoma with hyperthyroidism and exophthalmic goiter it is obviously necessary to exclude definitely cases presenting the syndrome of neurasthenia, usually of the cardiac type, with many of the earmarks of hyperthyroidism, but in which no hyperthyroidism nor over-activity of the thyroid is actually present. The co-existence of an enlarged thyroid, often not distinguishable from those producing hyperthyroidism, renders the exclusion of many neurotic cases most difficult, and in certain instances impossible unless the basal metabolic rate is known. Many of these patients with normal basal metabolic rates give a definite reaction to the epinephrin sensitiveness test, as pointed out by Goetsch and by Woodbury. In our opinion a normal basal metabolic rate eliminates hyperthyroidism.

The determining points in the differentiation of exophthalmic goiter and adenoma with hyperthyroidism were presented by Plummer in 1913. These principle points were:

1. The difference in the average ages of the patients when the goiter was first noticed. Enlargement of the thyroid was noted from five to ten years earlier in life by the patients with non-hyperplastic goiter than by the patients with hyperplastic (exophthalmic) goiter.

2. The time elapsing between the appearance of the goiter and the onset of the hyperthyroid symptoms. In exophthalmic goiter the symptoms of hyperthyroidism followed the onset of the goiter within nine-tenths of a year, while fourteen and one-half years elapsed before the thyrotoxic symptoms appeared in the group of non-hyperplastic adenomas with hyperthyroidism.

3. The relative frequency of exophthalmos in exophthalmic goiter contrasted with its almost complete absence in non-hyperplastic adenomas with hyperthyroidism. Exophthalmos occurred in 87 per cent of the cases of true exophthalmic goiter with symptoms lasting more than two years. It was less frequently present in the early stages of exophthalmic goiter, averaging 50 per cent in cases of less than three months' duration. In contrast, exophthalmos, even of questionable degree, was only rarely noted in cases of non-hyperplastic adenomas with hyperthyroidism. It

did not occur in any of the twenty-five cases of most intense intoxication in which operation was done in 1912.

An immense mass of evidence of the differences in the average blood pressures of the two syndromes has been collected by Plummer. A brief resumé of this work published in 1915 demonstrated a definite tendency to hypertension in adenoma with hyperthyroidism which is not found in exophthalmic goiter. Finally, the differences between the clinical picture of exophthalmic goiter and non-hyperplastic adenoma with hyperthyroidism led Plummer (1916) to point out in a condensed but valuable article, the probability of a different etiology in the two diseases. The isolation of the active principle of the thyroid, thyroxin, in pure crystalline form by Kendall (Dec. 25, 1914) and the subsequent studies of its physiologic activities have been of the utmost importance to a true concept of exophthalmic goiter and of hyperthyroidism and hypothyroidism, but a discussion of this phase of the problem is beyond the scope of the present article.

Since 1914 Plummer has used as a working basis the following hypothesis: "The active agent of the thyroid gland is a catalyst that accelerates the rate of formation of a quantum of potential energy in the cells of the organism." In 1916 Plummer stated that "the thyroid plays an important part in metabolism and that the evidence of high metabolism dominates the clinical syndrome of hyperthyroidism; and further, that the rate of metabolism is dependent on the thyroid hormone and that this function is not specific for certain tissues but is common to all the cells of the organism." Shortly after Plummer's paper was read, an exhaustive review of the variations in the metabolic rate in goiter was published by DuBois (1916) with a comparative study of the methods of direct and indirect calorimetry in these disorders. DuBois showed: (1) that the measurement of the heat production gives the best index of the severity of the disease and of the effect of treatment; (2) that the specific dynamic action of protein and glucose is within normal limits; (3) that the methods of direct and indirect calorimetry agree within the limits of technical errors, and in consequence (4) that the law of the conservation of energy holds good in exophthalmic goiter. Simultaneously, Boothby demonstrated in Cushing's clinic at the Peter Bent Brigham Hospital that the basal metabolic rate determined by the comparatively simple gasometer method of

indirect calorimetry is of great value in the diagnosis and treatment of thyroid disorders. The result of Plummer's recognition of the clinical value of metabolic rate studies was the establishment at the Mayo Clinic of the Metabolism Laboratory by Boothby and Sandiford in March, 1917. In this paper I shall present a preliminary analysis of the symptomatology and basal metabolic rate studies in hyperthyroidism due to adenoma of the thyroid based on Plummer's conception of the disease.

SYMPTOMATOLOGY AND BASAL METABOLIC RATES

Definition.—Adenoma of the thyroid with hyperthyroidism is characterised by an increased basal metabolic rate excited by an excess of the normal thyroid hormone in the tissues. About middle age the adenomatous tissue after a considerable quiescent period gradually begins to furnish an excessive amount of the apparently normal thyroid hormone (thyroxin) and this produces the increased metabolic rate and intoxication clinically evidenced by nervousness, tremor, tachycardia, loss in strength and weight, and a tendency to hypertension, and in the later stages myocardial disintegration. The underlying cause or stimulus that activates the thyroid to adenomatous growth and oversecretion is not known.

Pathology.—A simple descriptive key for the classification of the surgical pathology of the thyroid which involved no assumptions as to the clinical interpretation was evolved by MacCarty in 1912; the present study is based on the reports from the laboratories of the Section of Surgical Pathology. The pathologic condition of the thyroid in the cases classified as adenoma with hyperthyroidism was diagnosed either single (or multiple) granular, necrotic, cystic (degenerated), fibrous, calcareous, hemorrhagic, or hyaline degenerated or degenerating fetal or colloid adenoma in a normal or colloid thyroid. To avoid confusion in this study, no cases are included in which the pathologist reported even the smallest amount of hypertrophic parenchymatous tissue either intra-adenomatous or extra-adenomatous.

Symptoms.—Seventy-seven per cent of the patients suffering from hyperthyroidism of thyroid adenoma on coming to the Clinic are more than 40 (the average age is 48) and give a history of having had a more or less hard nodular goiter for many years (the average is nineteen years). For a long period the adenoma causes no symptoms, except that locally there may be a slight

feeling of fullness and possibly a tendency to a globus hystericus. For two or three years previous to examination a gradual change in general health takes place; the patient becomes more nervous and excitable and in the early stages he may have even a feeling of unusual "well-being" and of over-enthusiasm for work which is coupled, however, with the inability to maintain for long either mental or physical effort. The patient speaks of a good appetite and thinks he should be gaining in weight, but does not do so; somewhat later he finds that in spite of his hearty eating he is losing weight and his endurance is markedly decreased. His skin becomes warm and moist with a tendency to perspire freely. He feels that his heart is beating faster and harder, his attention probably having been directed to it first on going up stairs; later he notices palpitation even when he is at rest. The blood pressure often shows hypertension. Rarely can a patient give a definite date of onset of these symptoms since they come on gradually and insidiously; in consequence they are elicited only by careful direct questioning. Usually about one year before the patient comes to the Clinic his symptoms become distinctly accentuated, and frequently the goiter enlarges. Later, a distinct increase in nervousness and mental instability, a moderate tremor, a marked loss in weight in spite of an increased appetite, and a loss of strength, and an increase in dyspnea on exertion necessitate a material modification in the patient's mode of life. The heart beats fast and hard although it may not equal the violence of the beats in exophthalmic goiter. In the older and more severe cases there is evidence of cardiac insufficiency with more or less edema of the legs and ankles, frequently accompanied by myocardial disintegration evidenced by irregular rhythm due either to premature contractions or auricullar fibrillation. Gastro-intestinal crises, exophathalmos, thrills and bruits of so frequent occurrence in exophthalmic goiter are characteristically absent.

This history, on anlysis, is found to be characteristic of the systemic effects that might be expected from an increased metabolic rate, for in such a condition as much work is thrown on the heart to maintain the volume of blood required by the patient at his moments of rest as is needed by the normal person at a slow walk. During his waking hours all the additional blood requirement of muscular effort must be superimposed on this

high basal level. It is no wonder that in the early stages there is cardiac hypertrophy that progresses to cardiac overstrain with dilatation and degeneration in the later stages, and that in spite of the ingestion of large amounts of food loss in weight and strength is progressive. Due to the gradual and insidious character of the onset of the hyperthyroidism, which causes the increased metabolic rate the heart first hyperthophies and only in the later stages gives evidence of cardiac decompensation and disintegration. Then, like the broken compensation of the athlete's heart, the cardiac failure may quite suddenly dominate the picture, and for the relief of these symptoms the patient consults the physician. Not infrequently the casual relationship of the goiter may even then pass unrecognized and the patient be treated for ordinary cardiac decompensation.

As the duration of hyperthyroidism is prolonged and the metabolic rate gradually increases the factor of increased functional demand, as pointed out by Willius, is supplemented by actual myocardial changes resulting from the presence of an excess of the thyroid secretion (thyroxin). The rapidity of myocardial disintegration from this point depends on several factors: (1) the intensity and rapidity of progression of the hyperthyroidism; (2) the age of the patient (the heart of a young patient better tolerates the hyperthyroidism); (3) the presence of preexisting heart disease; (4) the physical stresses and strains to which the patient is subjected, and (5) the presence of preexisting hypertension. A large number of seriously damaged hearts is found in cases of adenoma with hyperthyroidism because of the insidious onset of the hyperthyroidism and its occurrence in patients of middle age. The scope of this paper, however, does not permit a more detailed consideration of the cardiac phase.

Age of patients.—The average age of these 281 patients at the time of examination was 47.6 years.

Patients under 20	4	(1.4 per cent)
Patients between 20 and 29	20	(7.1 per cent)
Patients between 30 and 39	41	(14.5 per cent)
Patients between 40 and 49	82	(29.1 per cent)
Patients between 50 and 59	92	(32.6 per cent)
Patients between 60 and 69	42	(14.9 per cent)

The average age of the 167 patients with adenomas without hyperthyroidism in whom the adenomas were of sufficient size to justify operation or for whom the operation was advised as a preventive against future hyperthyroidism was slightly younger, 43.8 years. This age, however, does not represent the average age of all patients with adenomas without hyperthyroidism who came to the Clinic, because for small adenomas without symptoms which occur in young persons operation is rarely advised. Exophthalmic goiter brings the patient to the Clinic, as a rule, ten years earlier in life than does the hyperthyroidism due to thyroid adenoma; in the four groups of cases of exophthalmic goiter (thirty-six, fifty-five, fifty-two, and fifty-two cases) in which the metabolic studies were made the average age of the patient at the time of the examination was 35.0, 36.7, 38.0 and 33.0 years, respectively.

Duration of goiter.—The time elapsing between the appearance of the goiter in adenoma with hyperthyroidism and the arrival of the patient at the Clinic was 17.9 and 19.7 years in the two groups. In a series of 167 cases of adenomas without hyperthyroidism that came to operation the duration of the goiter was slightly less, 16.9 years. In marked contrast to this is the duration in the four groups of exophthalmic goiter in which the patients had known of the existence of a goiter for only 2.8, 3.0, 3.5 and 3.2 years on the average, respectively. When from the averages of these groups the patients who had had goiter for more than five years are excluded the the average duration is 1.6, 1.0, 1.1 and 1.4 years, respectively. These patients may be rightly excluded because they had had either former exacerbations of exophthalmic goiter or a previously existing adenoma.

Duration of symptoms.—The duration of symptoms of hyperthyroidism before the patient comes to the Clinic is distinctly longer in cases of adenoma with hyperthyroidism than in cases of exophthalmic goiter. In the two groups of the former the length of time was 2.0 and 2.2 years, while in the latter the duration in the four groups was 1.6, 1.4, 1.7 and 1.3 years, respectively; however, if from these groups of exophthalmic goiter those cases are excluded in which the duration of the goiter was five years or more the average duration of symptoms is 1.3, 1.0, 1.3

and 1.0 years, respectively. The significant point is that the adenomas do not produce hyperthyroidism on the average for 15.9 and 17.5 years after their appearance while in exophthalmic goiter the symptoms of hyperthyroidism usually occur either coincidently with the appearance of the goiter or within a few weeks or months thereafter. Furthermore, the onset of symptoms in adenoma with hyperthyroidism is gradual and indefinite, while in exophthalmic goiter the patient not infrequently can even name the day of onset.

Blood pressure.—A complete analysis of the blood pressure readings will not be attempted in this paper; only a few salient points will be mentioned. The systolic blood pressure averages distinctly higher in adenoma with hyperthyroidism than either in the adenomas without hyperthyroidism or in exophthalmic goiter. The diastolic blood pressure is distinctly higher both in adenoma with hyperthyroidism and in adenoma without hyperthyroidism than it is in exophthalmic goiter. These statements hold good both for "floor" blood pressures, taken in the office at the time of the general examination while the patient is sitting, and for blood pressures taken when the patient is lying down, although the characteristic differences are emphasized in the blood pressures taken during the excitement of the physical examination. Many factors must be considered in a study of the significance of blood-pressure readings, the chief of which are the size of the peripheral cross-section and the amount of blood being driven through the periphery in a unit of time. It is evident that as a result of the increased metabolic rate both in adenoma with hyperthyroidism and in exophthalmic goiter the blood flow increases materially to meet the requirement of greater oxygen utilization while the patient is at rest. In the case of exophthalmic goiter there is an average high systolic blood pressure but a rather low average diastolic, giving a high pulse pressure; this combination coupled with an increased blood flow, indicates a relatively open periphery. On the other hand, the higher systolic and higher diastolic with increased blood flow in adenoma with hyperthyroidism indicate the association of definite hypertension. Likewise, in adenoma without hyperthyroidism the high diastolic with an increased systolic, but to a comparatively less degree, together with a normal blood flow also indicates an associated hypertension. Furthermore, there

TABLE 1.

Average Metabolic Rate and Blood Pressure in Adenoma and

	Adenoma						Exophthalmic			
	Without Hyperthyroidism			With Hyperthyroidism			Two ligations, 2 Months'			
Number of cases averaged in each group	167	18		201	75		36			
Age, years	43.8			47.7	47.4		35.0			
Duration of Goiter, years	16.9			17.9	19.7		2.8	(1.6)*		
Age at Onset of Goiter, years	26.9			29.8	27.7		32.2	(33.4)		
Duration of Symptoms, years				2.0	2.2		1.6	(1.3)		
Age at Onset of Symptoms, years				45.7	45.2		33.4	(33.7)		
Systolic B. P.	143			156	160		147			
Diastolic B. P.	85			86	86		73			
Pulse Pressure (On the Floor	58			70	74		74			
Pulse Rate	91			102	113		126			
Haemoglobin	75			73	74		70			
B. M. R.	+2	−4	−8	+28	+35	+7	+66	+50	+42	+19
Systolic B. P.	127	118	118	113	116	134	140	133	132	126
Diastolic B. P.	77	76	72	80	81	79	77	72	73	75
Pulse Pressure (At Time of Test	50	42	46	63	65	55	63	61	59	51
Pulse Rate.	78	74	72	97	102	80	122	115	108	93
Weight							51.7	48.1	55.8	
	Before Treatment	Before Treatment	Two Weeks After Thyroidectomy	Before Treatment	Before Treatment	Two Weeks After Thyroidectomy	Before Treatment	Ten Days After Second Ligation	After 2 Months' Rest	Two Weeks After Thyroidectomy

*The cases in this group of more than five years' brackets because the duration of the goitre is confused

is a greater difference between the average floor systolic blood pressure and the average resting systolic blood pressure both in adenoma with hyperthyroidism and in adenomas without hyperthyroidism (13 mm., 14 mm., and 16mm.) than in exophthalmic goiter (7 mm., 8 mm., 8 mm., and 9 mm.), indicating the tendency to hypertensive contraction of the vascular tree. These facts led Plummer, in 1915, to state that adenoma of the thyroid both with and without symptoms of hyperthyroidism is frequently associated with vascular hypertension, causing a relatively contracted periphery, while in exophthalmic goiter, although the systolic pressures are high, there is no hypertension of the arterial tree but rather a relatively open periphery.

Basal metabolic rate.—A study of the basal metabolic rate brings out several very interesting facts, especially from the practical standpoint. Two distinct groups of adenomas of the thyroid have the same pathology, but one group is characterized

TABLE 1.

Exophthalmic Goiter Before and After Treatment

GOITER

Rest and Thyroidectomy			One Ligation and Thyroidectomy					Thyroidectomy	
Before Treatment......	After Second Ligation and 2 Months' Rest..	Two Weeks After Thyroidectomy.........	Before Treatment......	After 1 Ligation and 2 Weeks After Thyroidectomy............	Before Treatment.....	Ten Days After 1 Ligation............	Two Weeks After Thyroidectomy......	Before Treatment....	Two Weeks After Thyroidectomy..........
	55		52				22	52	
36 7			38		...	...	...	33	
3 0	(1.0)		3.5	(1.1)	...	...	...	3.2	(1.4)
33.7	(35.7)		34 5	(36.9)	...	...	...	29.8	(31.6)
1 4	(1.0)		1.7	(1.3)	...	...	...	1.3	(1.0)
35 3	(35.7)		36.3	(36.7)	...	...	...	31.7	(32.0)
148			148		...	...	...	142	
75			76		...	...	...	78	
73			72		...	...	...	64	
124			121		...	...	...	121	
71			74		...	...	...	74	
+66	+42	+16	+52	+15	+57	+41	+16	+36	+8
140	134	129	140	124	138	124	120	133	122
74	71	76	73	75	72	64	73	72	73
66	63	53	67	49	66	60	47	61	49
122	109	90	113	90	116	109	92	109	88
49.2	53.9		...	...	...	...	...	...	...

duration are omitted from the averages given in the
by a pre-existing adenoma.

by hyperthyroidism with an increased basal metabolic rate and the other group presents no definite evidence of hyperthyroidism and the basal metabolic rate is within normal limits. The clinical histories of these two groups show a gradation from the adenoma with hyperthyroidism into the adenoma without hyperthyroidism both in the number and intensity of the symptoms that point to hyperthyroidism and in the lower basal metabolic rate. However, there is a change in the general character of the history and a distinct difference in the impression made by the patient on the examiner in the group of patients with adenomas and a basal metabolic rate above + 10 per cent and those with rates below + 10 per cent. Although in an individual case a reading of + 9 per cent or + 11 per cent or even between + 8 per cent and + 12 per cent does not absolutely determine the presence or absence of hyperthyroidism, if on a check reading the basal rate persistently remains above + 10 per cent fewer

clinical errors will be made if such readings are accepted as positive of mild or beginning hyperthyroidism and those with rates below + 10 per cent as not indicating hyperthyroidism. Patients having simply neurasthenia, even those whose symptoms most closely simulate hyperthyroidism, do not have persistently elevated basal metabolic rates. On the other hand, occasionally a normal metabolic rate is found in a case of quiescent hyperthyroidism either from exophthalmic goiter or adenoma that may be misleading unless attention is paid to the history of the disease carefully elicited from the patient. Such findings instead of decreasing the value of the metabolic rate really increase its practical value just as a normal or nearly normal temperature does in remittent or intermittent febrile diseases. On the other hand the number of these cases is very small and does not include the large group of neurasthenics who give a positive epinephrin reaction, but who have normal basal metabolic rates. We have found no evidence that this group of neurasthenics with normal basal metabolic rates, although they have some of the symptoms resembling those of mild hyperthyroidism, is dependent on variations in the physiologic activity of the thyroid gland, as suggested by Goetsch.

Technical errors of material magnitude in a properly conducted laboratory for routine work occur in less than 1 per cent of the cases. A moderate elevation of the metabolic rate sometimes occurs from the fear of the patient in submitting to the test. This is of practical significance, however, only in the borderline cases and therefore a check rate on a subsequent day should be obtained in patients whose first rates are between + 10 per cent and + 20 per cent before a final conclusion is reached. An elevated temperature curve due to a cold, sore throat, incipient tuberculosis or other cause raises the basal metabolic rate; the temperature curve at the time of the test must be known, therefore, because the febrile diseases as a group give an increased metabolic rate.

In adenoma with hyperthyroidism the curative effect of partial thyroidectomy (frequently simple enucleation of the adenomatous mass) is very strikingly shown by the drop in the basal metabolic rate within two weeks after thyroidectomy: the average metabolic rate fell from + 35 per cent to + 7 per cent or well within normal limits. In 67 per cent of the cases tabulated it

returned to normal within two weeks after operation; in 80 per cent it dropped to below + 15 per cent, in 92 per cent to below + 20 per cent, and in all the cases to below + 30 per cent. Plummer has frequently pointed out that thyroidectomy almost immediately cures the patient who has hyperthyroidism from adenoma and that recurrence does not follow unless a new adenoma or parenchymatous hypertrophy develops in the remaining gland. This is in contrast with the results obtained from thyroidectomy in exophthalmic goiter. Even in the mild cases of exophthalmic goiter with an average basal metabolic rate of + 36 per cent before operation which dropped to + 8 per cent after thyroidectomy only 45 per cent are within normal limits at the end of two weeks, although 76 per cent are below + 15 per cent. In a more severe type of exophthalmic goiter in which it was necessary to precede the thyroidectomy by a single ligation the average metabolic rate fell from + 52 per cent to + 15 per cent after operation; only 38 per cent of these were within normal limits and only 52 per cent below + 15 per cent. The improvement from a single ligation is shown in the average of twenty-two cases in which the average metabolic rate before treatment was + 57 per cent, and after the single ligation + 41 per cent; after thyroidectomy the average metabolic rate dropped to + 16 per cent. The first of two groups of the most severe type of exophthalmic goiter in which two ligations were performed and, after from two to four months rest at home, thyroidectomy was done showed an average metabolic rate obtained before treatment of + 66 per cent; after the second ligation and just before the patient went home the average metabolic rate was + 50 per cent; on return after prolonged rest at home the average metabolic rate was + 42 per cent, and after thyroidectomy it dropped to + 19 per cent. In the second group, similar to the first except that no metabolic rate was obtained directly after the second ligation and before the patient went home, the average metabolic rate before treatment was + 66 per cent; after the two ligations and approximately three months' rest at home the average metabolic rate was + 42 per cent and finally, after thyroidectomy, the average metabolic rate was + 16 per cent. The basal metabolic rate in only 36 per cent of the patients with exophthalmic goiter who had two ligations, rest at home, and thyroidectomy

returned to within normal limits two weeks after thyroidectomy; in 21 per cent it was still above + 30 per cent.

The metabolic rates in exophthalmic goiter will not be discussed in this paper, except to point out that after thyroidectomy: (1) the degree of hyperthyroidism is materially decreased; (2) the improvement, especially in the more severe cases is not so rapid or complete as in adenoma with hyperthyroidism; and (3) hyperthyroidism may still persist in certain cases and necessitate a second, and, rarely a third thyroidectomy.

SUMMARY

1. According to Plummer's classification there are two separate and distinct types of hyperthyroidism, each due to a different pathologic change in the thyroid gland: in the one type, the hyperthyroidism associated with the clinical syndrome of true exophthalmic goiter is always accompanied by diffuse hypertrophy and hyperplasia of the thyroid gland, in the other type the hyperthyroidism, not associated with this typical diffuse hypertrophy and hyperplasia, but with the occurrence of adenoma in the gland, is due to the adenoma, and the resulting clinical syndrome is distinguishable from that occurring in true exophthalmic goiter.

2. The syndrome associated with the hyperthyroidism from adenoma of the thyroid is considered by Plummer to be a distinct clinical entity and may be defined as a disease associated with adenoma, characterized by an increased basal metabolic rate excited by an excess of the normal thyroid hormone in the tissues. About middle age the adenomatous tissue gradually begins to furnish an excessive amount of the apparently normal thyroid hormone (thyroxin) and this produces the increased metabolic rate and intoxication clinically evidenced by nervousness, tremor, tachycardia, loss in strength and weight, and a tendency to hypertension, and in the later stages myocardial disintegration. The underlying cause or stimulus that activates the thyroid to adenomatous growth and over-secretion is not known.

3. Detailed metabolic rate and blood pressure studies are reported in seventy-five cases of adenoma with hyperthyroidism in which the average basal metabolic rate before treatment was + 35 per cent and after operation + 7 per cent. Similar studies of 201 cases before treatment are also given in which the average

basal metabolic rate was + 28 per cent. In contrast the average basal metabolic rate in 167 cases of adenoma without clinical evidence of hyperthyroidism was + 2 per cent; in eighteen of these cases the average basal metabolic rate before operation was — 4 per cent and it remained practically unchanged, — 8 per cent, as a result of thyroidectomy.

4. Three groups of exophthalmic goiter cases of varying degrees of severity were studied. In thirty-six patients with the severest type of the disease the average metabolic rate before treatment was + 66 per cent; these patients were subjected to rest in bed and two ligations at an interval of a week or more and within ten days after the second ligation the basal metabolic rate

TABLE 2.

Improvement Following Operative Treatment

B. M. R.	Adenoma with Hyperthyroidism after Thyroidectomy		Exophthalmic Goiter					
			After Thyroidectomy		After 1 Ligation and Thyroidectomy		After 2 Ligations, Home and Thyroidectomy	
	Percent below	Percent above	Percent below	Percent above	Percent below	Percent above	Percent below	Percent above
+10	67	33	45	55	38	62	36	64
+15	80	20	76	24	52	48	48	52
+20	92	8	91	9	67	33	59	41
+30	100	0	96	4	87	13	79	21
+40			100	0	94	6	87	13
+50					98	2	97	3
+60					100	0	100	0

was + 50 per cent. After three months' rest at home these patients returned to the Clinic and were found to have an average basal metabolic rate of + 42 per cent, with corresponding clinical improvement; within two weeks after thyroidectomy the rate had dropped to + 19 per cent. In a second group, fifty-two moderately severe cases, the patients were subjected to a single ligation and thyroidectomy one to two weeks later. The basal metabolic rate before treatment was + 52 per cent. after thyroidectomy + 15 per cent. In twenty-two the basal metabolic rate before treatment was + 57 per cent and ten days after the preliminary ligation was + 41 per cent; within two weeks after thyroidectomy the basal metabolic rate in this group had fallen to + 16 per cent. In fifty-two patients with mild exophthalmic goiter on

whom a primary thyroidectomy was performed the average basal metabolic rate before treatment was + 36 per cent and two weeks after operation + 8 per cent.

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A CASE OF DYSTROPHIA ADIPOSOGENITALIS

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Two considerations have impelled us to report the following case of dystrophia adiposogenitalis. One of the outstanding characteristics of the condition in question is a more or less pronounced psychotic trend. The subjects are frequently introverted and have a more or less pronounced inferiority complex. Timme has recently emphasized this fact. There are in the literature, however, relatively few cases reported with regard to psychopathological features. A second consideration is the desirability of more data on the therapeusis of the condition.

The patient, E. O'F., male, age 16, was first seen in the dispensary, January 28th, 1920. At that time plans were made to keep him under observation while undergoing treatment for his endocrine disorder. As a matter of fact, he proved to be a recalcitrant patient and it was only with difficulty that sufficient co-operation was obtained to permit carrying out a diagnostic and therapeutic study. For this reason the data reported are deficient in certain particulars,—and especially as regards basal metabolism and blood sugar determinations.

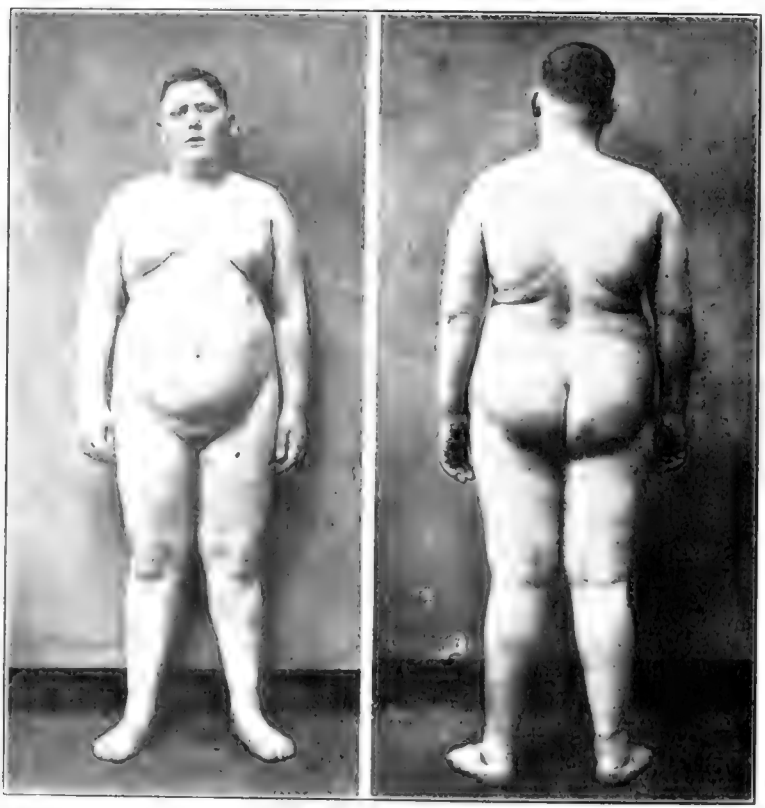
Family History: One grandfather was inebriate. The mother, now 50 years of age, is short, stout and has gradually gained in weight for the past 15 years. She stated that all her family have the same tendency toward obesity. Otherwise, the family history afforded no pertinent data. There is no evidence in the family strain of gigantism, dwarfism, goitre, or diabetes.

Personal History: The patient was born in Baltimore, March 12th, 1904. The mother "felt poorly" during her entire pregnancy; she had frequent attacks of dizziness and often refused food. She suffered much discomfort from what seemed like a lump in her neck. The patient was a full-term child, and except for his being undersized, his early development was normal. Breast feeding was continued until his third year and weaning was accomplished with some difficulty. The patient slept with his mother up to the time he came to the clinic. Since the age of 10, the patient has become exceedingly obese, this having become especially noticeable in the past three years. During this latter period he has grown in height 3½ inches. He had enuresis until the age of 4, but rarely since. He never has had night terrors. He has had the usual childhood diseases, including measles and chickenpox.

The patient did fairly satisfactory work in school from the 6th to the 15th years, reaching only, however, the high 5th grade.

He has always enjoyed good general health. There has been no complaint of headache or dizziness; no visual complaints; no difficulty of any of the special senses. During the past 5 years the patient has complained of dyspnoea on exertion, which has advanced in proportion to his obesity. There have been no gastro intestinal complaints except occasional nausea and vomiting and an inclination to constipation. The appetite is excessive.

The patient states that he usually urinates from 5 to 7 times a day, and there is some hesitancy. Nocturia has been absent.



Photographs of patient, E. O'F., showing genital infantilism, distribution of fat, lumbar lordosis and genu valgum.

Present Illness: The patient resents teasing, is inclined to be infantile, cries on the slightest provocation, and is inclined at times to be over affectionate. He has frequent spells of irritability. His employer states that he appears bright and alert in the morning, but is dull, obtuse, and complains of feeling tired "all over" in the afternoon. At home, it is noticed that the patient is over-affectionate, especially in regard to his mother. He is very obstinate and sullen at times. He

takes little interest in his work and gets along poorly with his associates on account of his sensitive and quarrelsome nature. The patient is ashamed of sleeping with his mother and is afraid that someone outside may discover it and make fun of him.

Recently he has shown an increasing tendency to be quarrelsome, irritable and stubborn. He shows little initiative in his work, is rarely punctual, and is inclined to lie to his employer.

He has a fair range of activities; goes swimming with other boys and plays baseball, although he feels handicapped and sensitive on account of his obesity and lack of genital development, about which he constantly worries.

Recently, his mother has been very much concerned regarding the increasing frequency of his crying spells, his marked infantilism and his complaints of weakness and tired feelings, especially marked in the evenings.

Mental Status: The patient is markedly infantile in his general demeanor. He is apprehensive, especially when any special tests are made, and cries when the finger is pricked. He talks in a well-modulated, high-pitched voice, and impresses one as being stupid. Point scale estimate of mental age by Dr. Scott reveals that of 10½ years: the intelligence coefficient is .77.

Physical and Endocrine Status: The patient is 5 feet 1½ inches in height and weighs 162 pounds. He presents a striking appearance with special reference to distribution of fat and rudimentary condition of the genitals. The deposits of fat are especially marked in the mammae, which are large and pendulous. He has a marked protruding and over-hanging abdomen, a large pad of fat just above the symphisis pubis and across the buttocks. The thighs are large, graceful and tapering. The pelvis is broad, suggesting the feminine type. He exhibits genu valgum and there is a slight degree of lumbar lordosis.

Measurements in the various planes of the body are as follows:

In the planes of the nipple		96 cm.
Planes of umbilicus		106 cm.
Planes of trochanters		102 cm.
At the internal malleolus, right and left		23 cm.
10 cm. above internal malleolus	right	26.2 cm.
	left	26.0 cm.
20 cm. " " "	right	35.0 cm.
	left	35.5 cm.
30 cm. " " "	right	38.0 cm.
	left	39.0 cm.
40 cm. " " "	right	47.5 cm.
	left	47.7 cm.
50 cm. " " "	right	54.0 cm.
	left	54.0 cm.
60 cm. " " "	right	60.0 cm.
	left	59.0 cm.
At the styloid process of ulna	right	17.5 cm.
	left	17.2 cm.
10 cm. above process of ulna	right	24.0 cm.
	left	23.5 cm.
20 cm. " " " "	right	25.5 cm.
	left	25.0 cm.
30 cm. " " " "	right	28.5 cm.
	left	28.0 cm.
40 cm. " " " "	right	34.5 cm.
	left	34.0 cm.
Sub-mental plane		51.5 cm.
Occipital mental plane		50.0 cm.

The skull is somewhat of the acromegalic type. There is a slight tendency towards prominence of the malar bone, and the lower half of the face is more prominent than the upper. There is a slight palatine ridge. The jaw is broad, with slight spacing of the teeth. The dates of dentition were not obtained, but the mother states that she thinks

there has been retardation of second dentition. The teeth are of normal color, shape and consistency.

There is a slight disproportion between size of the extremities and trunk. The torso-leg measurements are 46.80 cm. and the spread of arms, 56 cm. The hands and feet are small. The patient wears a no. 5½ shoe. The distance from the styloid of the ulna to the tip of the second finger is 18½ cm. A moderate degree of flat foot is present. The joints cannot be hyperextended.

Marked under-development of the genital organs is evident, corresponding to those of a boy 10 years younger. The penis is rudimentary and the scrotum is small and buried in fat. Both testicles are undescended. No evidence of puberal changes is found. There is no history of autoerotism or of any homo- or hetero-sexual trends. There is a marked deficiency of hair. This is especially marked in the axillae and pubic regions. On close examination, three short hairs are seen in the left axilla and four in the right. There is slight eyebrow deficiency. The hair of the head is fine and dry and has a slight tendency to curl. There is a marked ridging of all the nails. There is also a tendency to brittleness, and they crack readily. They are of slow growth. Several white spots are noticed, especially on the thumbs and the first and second fingers.

No abnormal areas of pigmentation were made out in the skin. It is thick and dry and shows no atrophy, naevi, or eruptions. There is a marked tendency toward "goose-flesh," especially marked on the arms and legs. There is a slight mottling of the face. On light stroking with the soft part of the finger tip, a red line is obtained with a broad, white border.

In the mucous membranes there are no abnormal pigmentations and no atrophy. The tongue is thick, with a normal number of papillae.

The patient shows a rapid muscle fatigability, especially during the skipping and hopping tests. When seen for the first time in the dispensary, after one hundred hops he complained of feeling exhausted and immediately rested on a couch. General weakness of all the muscle groups is present, but there is fair carriage.

The tonsils are small and atrophic. The axillary and inguinal lymphatic glands are not palpable. There is no thyroid enlargement detectable by palpation.

The systolic blood pressure is 140, the diastolic, 80. The pulse, at rest, is 68, standing, 80. The vessel walls show no sclerosis. The relative cardiac dullness measures 2½ x 10½ cm. There is no retromanubrial dullness. The heart sounds are of good quality and intensity, the second pulmonic being more marked than the aortic.

Blood examination shows:

R. B. C.—4,126,000.
Hemoglobin—75%
W. B. C.—8,960.

Differential Count:

P. M. N.,	64. %
P. M. E.,	1. %
Lymphs.,	26. %
L. M.	5. %
Trans.	3. %
P. M. B.,	.5%

The red cells are of normal size, shape and color. No parasites are found.

The urine is normal in constituents and shows normal range of specific gravity.

The radiographic examination shows an apparently normal sella turcica. In the bony structures there is delayed ossification for the age. The lungs are clear and no evidence of any mediastinal abnormality is detected. The teeth show nothing abnormal.

The perimeter chart shows normal visual fields for white, blue and green.

Treatment and Progress: Since the patient was unable to come into the hospital, arrangements were made with his employer to have him return to the dispensary at occasional intervals. The patient consented to return to the clinic for observation on Sundays. A resumé of his progress follows.

Beginning February 11th, 1920, he began to receive desiccated pituitary (whole gland, Armour preparation)—two grains, four times a day.

February 18th, 1920, the patient's mother reports that she has noticed that he shows less tendency toward weeping, is less irritable and stubborn, appears more active and alert, does not resent teasing as much as previously and sleeps better. He complains less of shortness of breath. He complains of frequency of urination, stating that he often urinates twelve and thirteen times a day; he also complains of frequent nocturia, three to five times a night.

February 20th, 1920, the patient states spontaneously that he is feeling better and stronger, has more vigor and does not notice the shortness of breath that he had previously. He ascends three flights of stairs and shows no abnormal degree of dyspnoea. He continues to complain of frequency of urination, but states that he has no nocturia.

February 25th, 1920, the mother states that the patient is more industrious, shows more initiative in work, is punctual, is sleeping better, is less irritable and has not had a crying spell for the past two weeks. Pituitary medication is increased to 12 grains a day.

March 3rd, 1920, the patient returns for observation and for blood and urine examination. While venous blood was being drawn he had a short fainting attack and crying spell. The next day he complained of dizziness while at work and was sent home by his employer. However, he was able to return the next day without any complaint. On March 4th, his mother states he had the first enuresis that was noticed since childhood.

March 10th, 1920, the patient's mother reports he has more self-confidence, shows more interest, is more buoyant at work and has no somatic complaints. He shows an increase in range of activities and is beginning to make plans with other boys in regard to preparations for a ball team. He appears less emotional, less infantile and associates more with boys of his own age. (Previously he has been in the habit of domineering the boys of his neighborhood five or ten years younger than himself.)

March 16th, 1920. The patient is becoming much dissatisfied because he is not losing any weight. In the hope of stimulating his catabolic processes, desiccated thyroid gland, 2 grains daily, is prescribed, the pituitary being reduced to 8 grains.

March 23rd, 1920. The pulse is 88 and blood pressure 140/85. The weight is 160 pounds and the temperature, 98.6°. There are no somatic complaints and no objective evidence of any tendency toward hyperthyroidism. The urine examination is negative.

March 27th, 1920. In the hope of stimulating genital development desiccated suprarenal gland, 4 grains a day is added to his other treatment. The patient's mother continues to note general improvement in his condition. She states that the boy is now walking home in half the time in which he did previously. He is getting along better

with his associates, and the people in the neighborhood notice a marked change in him, but the patient remains discontented since he has not been losing any weight.

March 28, 1920. The patient returns for observation. He shows his first loss in weight since treatment began, this amounting to two pounds. The pulse is 98; the blood pressure, 135/78. Measurement of the different planes of the body reveals a decrease of 4 cm. in the planes of the umbilicus, indicating a change in body configuration. The urine examination is negative. The differential blood count shows: P. M. N., 60.5%; P. M. B., 0.%; P. M. E., 1.%; Lymphs., 29.%; L. M., 5.5%; Trans, 4.%.

The patient exhibits a slight, fine tremor of the hand, but no other objective symptoms of hyperthyroidism. The von Graefe and all other eye signs are negative; there are no complaints of nervousness or palpitation; no vasomotor symptoms. The patient states that he urinates usually from five to seven times a day, but that he has lost all his former tendency to polyuria. His bowels move from two to four times a day. The patient thinks that he is getting along much better in his work, and he does not have any weak spells in the afternoon, as previously. He spontaneously mentions that all his friends and associates are very much surprised at the change in him. He mentions with some degree of ostentation that he can now walk home in thirteen minutes, when it previously took him twenty-five. He has no spells of shortness of breath. He is taking exercise regularly, playing baseball with more vim than ever before.

Subsequent to March the patient became increasingly less cooperative. During April, May and June, he received suprarenal, 12 grains, thyroid, 2 grains, and pituitary, 8 grains, daily. During this period his weight dropped from 162 to 152 pounds.

In June a slight growth of hair was apparent in the axillae and in the pubic region. No evidence of hyperthyroidism could be detected. He continued dissatisfied because there was no noticeable change in the size of the genitalia, although frequent erections were reported. Despite the medication, his basal metabolism at this time was found to be 4 per cent below normal. In view of the initial blood pressure finding of 140, careful observations were made at intervals to forestall any deleterious effects from the thyroid medication. An electrocardiographic examination at this time disclosed no abnormalities. There was no significant change in pulse rate or blood pressure. There appeared to be some further redistribution of fat, the diameter at the plane of the umbilicus decreasing 1.5 cm. more. At the same time the diameter at the plane of the nipples was augmented 2.5 cm.

During July, treatment was discontinued. During August, it was resumed in the same dosage as before. The patient, however, refused to return to the hospital for any further study. When seen at his home he stated that marked changes in his genital organs had occurred. He seemed apprehensive and complained that the medicine was "too strong."

On August 27th, 1920, he was seen for the last time. He refused to continue with any further treatment and was discharged. He was stubborn and self-assertive in demeanor, in striking contrast with his infantile behavior when first seen. He was working regularly, driving a two-horse team and earning twelve dollars a week. A striking change in the genital sphere was evident. Both testicles had descended. By palpation the diameter of each was estimated as 1.5 cm. The penis had increased somewhat in size, and the crines pubis and axillary hirci, although still scanty, were obviously augmented. The patient had developed a marked reticence as regards sex matters. He felt

alarmed at the genital changes. He continued to deny any autoerotic episodes and there was no evidence of heterosexual activity. There were no significant changes in blood pressure, pulse, or body measurements. The weight had again reached 160 pounds.

SUMMARY

A boy of 16 presented a case of dystrophia adiposogenitalis with psychic infantilism and marked fatigability. During the course of six months he was treated with desiccated pituitary, thyroid and suprarenal gland substance. At the end of the period there was a striking change in the psychic attributes from infantile to self-assertive stubbornness. He had become able to carry out a full day's work and to engage in vigorous athletics. At the same time the testicles had descended and erections were frequent. There was some growth of axillary and pubic hair.

DISCUSSION

To what extent should the psychic changes in the patient be ascribed to "desensitization" and suggestion, and to what extent to the medication? The data do not permit any very satisfactory conclusion. At the beginning of the treatment the prognosis, assuming that suggestive therapeutics alone were to be employed, could not have been at all favorable. Yet striking improvement, from a psycho-pathological point of view, did occur. The patient was transformed from a querulous, childish weakling to a robust lad, psychically fairly well adapted to his environment, and able to do a creditable day's work. He developed a keen interest in baseball and swimming and showed qualities of leadership.

The therapeutic plan carried out was not at all satisfactory as a scientific study. Each of the gland substances should, of course, from this point of view, have been administered independently and over periods of at least a year. In view of the uncooperative attitude of the patient, however, it seemed desirable to make the treatment as effective as possible, at once. The pituitary was administered on the supposition that the chief etiologic factor in the case was hypopituitarism. Favorable results from this alone seemed to appear promptly. The psychic attributes began to alter and the muscular fatigability to decrease. The thyroid was added in the hope that it would add to the patient's enthusiasm by augmenting a supposedly sluggish metabolism, and especially by leading to a decrease in weight. The fact that there was an initial systolic blood pressure of 140,

however, seemed to preclude any very vigorous pushing of the thyroid medication. As a matter of fact, the trend of the available literature seems to indicate that the addition of thyroid to pituitary material, on empirical grounds, is advisable in cases of the type discussed.

Whether the addition of suprarenal substance contributed to the therapeutic results, cannot be determined. That tumors of the adrenal cortex may cause an accentuation of the masculine characteristics is well known. Glynn has reviewed the literature on this point, up to 1912, in some detail. Apparently the therapeutic efficacy of the desiccated gland substance as a sexual stimulant has been but little investigated. Animal experimentation on the point has also received little attention. In 1916, one of us in collaboration with Augusta D. Hoskins reported the results of a preliminary study of the effects of suprarenal feeding in the white rat. The data, while not conclusive, numerically, seemed to indicate testicular hypertrophy as a result of the feeding. There is under way, at the Phipps Clinic, at the present time, a continuation of the study.

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DETERMINATION OF RELATIVE ACTIVITY OF THE THYROID LOBES.*

(With 3 figures in text)

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Muscular activity can be measured and recorded by means of a modern string galvanometer. The electrocardiograph gives a record of the cardiac mechanism by registering the changes in electric potential which occur with each phase of the cardiac cycle. Bayliss and Bradford in 1885 reported an investigation of the electrical changes attending glandular activity. Cannon and Cattell and later Gesell, have recorded the secretory action of the salivary and thyroid glands by placing one electrode of a galvanometer upon the gland and the other on neighboring tissues. They have offered evidence that the electrical changes are dependent upon variations in the activity of the glandular tissue itself. It is reasonable to suppose that the glandular activity of superficial glands, such as the thyroid, can be recorded by means of electrodes placed upon the skin directly over the glands.

In the electrocardiograph we have an instrument well adapted for such observations. The tension of the fibre can be adjusted to meet requirements and the resistance and standardizing currents can be utilized to regulate the deflection of the string. The camera makes possible a graphic record of the electric changes. In the following observations no attempt was made to measure the thyroid activity of one individual as compared with another but rather to estimate the activity of one lobe of the thyroid as compared with that of the opposite side. The procedure consists in attaching one electrode to the left leg or placing it on the back in the interscapular region, and placing the other electrodes on the right and left lobes of the thyroid, the second lead of the electrocardiograph being used for the right lobe and the third lead for the left lobe. Small German silver electrodes, $\frac{3}{4}$ inch square, were substituted for the ordinary electrodes used in obtaining a cardiographic record. The tension of the string was adjusted so that the deflections would fall within the photographic field. A record with an electrode placed on the manubrium was first made

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in order to determine the deflection produced by the skin and body tissues, excluding so far as possible the influence of the thyroid gland. When a lobe of the thyroid was connected, with adjustments unchanged, the negative deflection increased. By changing "leads" without readjusting, the negativity of each lobe was compared with the manubrium and with that of the opposite side. The negative deflection was recorded photographically. The following observations have been made.

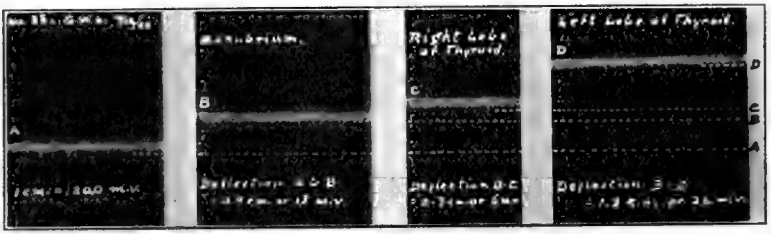

Fig. 1. (Reduced ½) Adolescent hypertrophy of thyroid with no evidence of thyrotoxicosis. Right lobe larger than left.
A-B=deflection produced by skin and other tissues.
B-C=additional deflection caused by right lobe of thyroid.
B-D=additional deflection caused by left lobe of thyroid.
The activity of the left lobe is greater than that of the right.

Case 1. (88) G. W. L. 4/12/20. Male, age 20. Adolescent hypertrophy of the thyroid gland with no evidences of thyrotoxicosis. The right lobe was larger than the left.

The tension of the string was adjusted to give a deflection of 1 cm. for each 20 millivolts. The lead from left leg to the manubrium gave a deflection of 0.9 cm. The lead from left leg to the right thyroid gave a deflection of 1.2 cm., 0.3 cm. more than from the manubrium. The lead from the left leg to the left thyroid gave a deflection of 2.2 cm., 1.3 cm. more than from the manu-

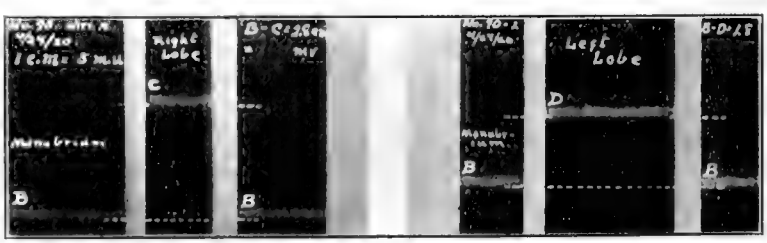

Fig. 2. (Reduced ½) Simple bilateral hypertrophy with normal basal metabolism. Right lobe larger than left.
B-C=deflection caused by including right lobe.
B-D= deflection caused by including left lobe.
The activity of the right lobe is greater than that of the left.

brium. If this difference indicates the relative negativity of the two lobes we may state the condition in the following equation:—

Activity of right lobe: *activity of left lobe* :: *0.3 cm., 1.3 cm.*, and the right lobe, the larger of the two, is the less active.

Case 2. (90) Mrs. N. 4/24/20. Age 32. Moderate bilateral hypertrophy with no symptoms of hyperthyroidism and with a normal basal metabolism. The right lobe is slightly larger than the left.

One electrode was placed in the interscapular space, the two small electrodes upon the two thyroid lobes. The tension of the string was adjusted so that a deflection of one centimeter was equivalent to 5 millivolts. The difference between the deflection in leads from the manubrium and from the right thyroid was 3 cm. The difference between the deflection in leads from the manubrium and from the left thyroid was 1.8 cm. *Activity of right thyroid*: *activity of left thyroid* :: *3.0 cm.* : *1.8 cm.*, and the right thyroid, the larger of the two lobes, is presumable more active than the left.

Fig. 3. (Reduced ½) Mild hyperthyroidism. Both lobes slightly enlarged.
B-C=deflection caused by including right lobe.
B-D=deflection caused by including left lobe.
The activity of the two lobes is equal.

Case 3. (31) 4/27/20. Mrs. E., Age 22. Slight bilateral hypertrophy of the thyroid with symptoms of a mild hyperthyroidism. The lobes are equal in size.

The tension of the string was so adjusted that 1 cm. deflection equaled approximately 5 millivolts. The difference between the deflection in leads taken from the manubrium and from the right thyroid was 1.7 cm. The difference between the deflection in leads taken from the manibrium and from the left thyroid was 1.8 cm. A second observation on this patient gave a deflection of 1.3 for the right lobe and 1.5 for the left lobe. The activity of the two lobes is presumably equal.

The three cases recorded, the first showing relatively greater activity in the left lobe, the second showing more in the right and the third showing equal activity, indicate that the application of this method may be of practical value. Our observations are too limited to do more than suggest a method by which the activity of the right and left lobes of the thyroid may be compared and graphically recorded.

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THE HYPOPHYSIS CEREBRI OF THE WOODCHUCK (MARMOTA MONAX) WITH SPECIAL REFERENCE TO HIBERNATION AND INANITION

(With 5 figures in text)

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INTRODUCTION

In the thirty-four years which have elapsed since Marie created clinical interest in the hypophysis cerebri by associating disease of this organ with acromegaly, and especially during the last twenty-five years, or since Oliver and Schäfer (1895) announced that extracts of this ductless gland have a distinct power to increase general blood pressure, a vast amount of anatomical, physiological and clinical information has accumulated. Naturally this has been accompanied by various theories regarding the physiological role of this structure. One of these theories is that ordinary physiological sleep and the longer periods of dormancy seen in hibernating mammals are associated with activities of the

hypophysis. An examination of the principal observations upon which this idea rests may serve to place the subject in its proper setting.

In reviewing the literature on the theories of hibernation the writer ('16) called attention to the large number of authors who considered hibernation among the higher forms, at least, as merely an extreme form of ordinary daily sleep as seen in man and mammals. Hibernation, therefore, naturally suggested itself as being a favorable condition for investigating the factors involved in the production of sleep. Attention was also called to the views of Salmon ('05, '10) who argued that by virtue of some vasomotor or toxic power on the nervous system, the hypophysis is a center for the production of normal sleep . He discusses his theories again in 1916.

From the two preceding assumptions—(1) ordinary sleep and hibernation are merely degrees of the same phenomenon and (2) the hypophysis is a chief center in the production of sleep—Gemelli ('06) was led to a histological examination of the hypophysis of twenty-two adult European marmots (Marmota marmota). Some of these were sacrificed while hibernating and others during the active state in the spring and summer. He found no changes in pars nervosa (processus infundibuli) nor in pars intermedia (juxta-neuralis); but in pars anterior (distalis) a great reduction in the chromophilic cells during dormancy was observed—suggesting a stage of lessened activity. He, therefore, concluded that Salmon's view could not be correct because such a view involved a stage of hypersecretion on the part of the hypophysis during winter sleep. He further noted many mitotic figures in the spring after waking up. This would indicate that the time of greatest activity on the part of this organ was not during dormancy but after the animal becomes active.

The hypophyses of seven American marmots (Marmota monax), which like the European species have several months of profound dormancy (Howell '15), were examined microscopically by Cushing and Goetsch ('13, '15). Here particularly the hypophysis of hibernating animals was compared with that of the active animal of early spring. They interpret their findings as confirming in general the statements of Gemelli on the decrease in size of the whole organ and the loss of specific staining re-

action of the cells of pars anterior during winter-sleep. In their summary they state: "The gland not only diminishes in size, but the cells of the pars anterior in some animals at least completely lose their characteristic staining reaction to acid and basic dyes. At the end of the dormant period the gland swells, and as the cells enlarge they again acquire their differential affinity for acid, basic, and neutral stains and at the same time karyokinetic figures may appear" ('15 p. 46). They suggest that hibernation may be ascribed to a period of physiological inactivity possibly of the entire ductless gland series, but certainly more especially of the hypophysis. They cite clinical and experimental cases showing a distinct tendency to somnolence, storage of fat, subnormal temperature, slow pulse and respiration, lowered blood pressure and retardation of sexual development in hypopituitarism. One must agree that these symptoms suggest a tendency towards the conditions prevailing during winter-sleep of animals and that the tendency to associate certain forms of morbid somnolence with functional disturbances of the hypophysis (Dana '16) is well founded.

A far more extensive study of the ductless glands in relation to the onset of hibernation was carried out by Mann ('16) on the thirteen-lined ground squirrel (Citellus tridecemlineatus). From this study there was no suggestion of a distinct relation of the ductless glands to the production of lethargy. With reference to the hypophysis he found in some cases during dormancy a loss of the differential staining qualities of the granular cells of the pars anterior, some decrease in the size of the cells and an irregularity in their grouping. But these changes were inconstant and in several hibernating animals the hypophyses could not be distinguished from those of active ones.

The above summary shows that the results of Gemelli and of Cushing and Goetsch on the marmot as interpreted by them tend to show that there exists a stage of hypofunction on the part of the hypophysis during hibernation. The combined studies upon which this conclusion rests involve a total of twenty-nine animals. It appears, however, that the comparison was made largely between the dormant state and the active state following hibernation. It is clear, as pointed out by Mann ('16, p. 176) that the critical period is that just preceding hibernation. It is the conditions of this period that should be compared with those prevail-

ing during subsequent dormancy. This point is of special importance in animals that are sexually active only during the spring immediately after waking up, because of the probable close interrelation of the gonads and the hypophysis, a relationship which is generally accepted.

That there is some influence of the sex glands on the hypophysis rests largely upon the effects following castration and spaying. Observations on these effects (for review of the literature see especially Livingston '16, Addison '17a) are, however, conflicting. It appears that in the case of the albino rat Hatai ('13b) found it was only the male hypophysis that was markedly affected (enlarged) by gonadectomy. Addison ('17a) showed that this enlargement was accompanied by hypertrophy of the basophilic cells of pars anterior. Others have recorded enlargement of some of the other types of cells in a number of other animals. In the rabbit, Livingston ('16), who submits by far the most accurate data on this species, found no constant effect on the weight of the hypophysis by spaying and castration; while a more recent study on the rabbit by Hayami ('19) corroborates the findings of some of the earlier workers on this species by reporting hypertrophy of the hypophysis as a result of castration and of vasectomy followed by Röntgen rays treatment, the causal factor being the interstitial cells of the testis. Bell ('19, p. 195) also finds evidence of increased secretory activity in the anterior lobe and in pars intermedia after oöphorectomy in the cat, especially in regard to the eosinophilic cells.

The relationship of the gonads and hypophysis, as far as the influence of the latter on the former is concerned, is better established and is evident from the sexual disturbances accompanying disease of the hypophysis found recorded extensively in clinical literature. Extracts of the hypophysis, especially of pars anterior, are reported to stimulate the growth of the sexual glands (Goetsch and Cushing '13, Goetsch '16) although Hoskins ('16) and others (for a review of the literature see Hoskins' paper) fail to corroborate this. Such extracts are also apparently beneficial in some cases of sexual impotence (Stelwagen '16). Other generative structures are also influenced by the extract. This is particularly true of a stimulating effect on the mammary gland (Ott and Scott, Schäfer and Mackenzie, Herring, Gavin, Ham-

mond, Simpson and Hill, Gaines, Houssay and co-workers—literature well reviewed by Hill '16, Houssay '18).

While Cushing and Goetsch did not have the sexual glands from all their animals, they make the assumption that a very marked activation occurs in the reproductive organs when the animals emerge from the dormant state, "and it is tempting to attribute this to the influence of the functionally reactivated pars anterior" ('15, p. 41). In two previous publications the writer ('17, '18) has fully corroborated this surmise by describing the marked enlargement of the testes and ovaries which occurs during the spring awakening in the American marmot. These studies showed a suddenly increased activity both in spermatogenesis and oogenesis and a distinct hypertrophy of the interstitial cells at that time.

So it is obvious that a difference between the hypophysis of the hibernating period and that of the unusually active period immediately following, which is the rutting season, gives no valid evidence regarding the modification of the hypophysis during the dormant state. What occurs during this spring awakening is unusual activity following a long state of rest in most of the physiological processes but especially in those involved in the sexual cycle. It follows, then, that there is needed in the case of the marmot a careful comparison of conditions just preceding hibernation with those of lethargy in order to determine if there are significant structural changes detectable in the dormant animal. This apparently has not been made.

Finally all the data so far submitted are only roughly quantitative. The time has come, as has recently been emphasized by Hammar ('20), when it is necessary to extend anatomical data, particularly on the glands of internal secretion, upon a more accurate quantitative basis, in order to facilitate the making of reliable deductions from pathological and experimental material. Since there are at least three more or less distinct components (Tilney, '13, recognizes at least four) in this organ, each probably of different functional significance (most strikingly brought out recently by Allen '20), these several structures must be investigated. It is conceivable that one part might respond by hypertrophy and yet not be detected by the weight of the whole organ because of compensatory changes in another part, etc.

In view of these conditions and the failure of Mann ('16) to corroborate on another species the reported observations on the marmot, it seemed desirable to extend the inquiry by using more accurate quantitative procedure. There might, of course, be some differences in the way various species respond. It was also expected that histological findings in the hypophysis during the very active period immediately after waking up might give facts of importance regarding the response of the various cellular elements to this condition of hyperactivity, and thus add to our knowledge of the significance of the various types of cells described especially in pars anterior.

It is interesting to note that Saito ('19) has reported that in the horse the weight of the hypophysis varies with the month of the year.

MATERIAL AND METHODS

The material upon which this report is based consists of the hypophyses of thirty-two adult woodchucks from the vicinity of Ithaca, New York. Fifteen of these animals are among those studied for Nissl changes in nerve cells during hibernation (Rasmussen and Myers '16) and are known as Series I in my records. These fifteen and two additional animals (No. 1 and No. 2, Series II) taken together constitute a series of nine males and eight females. One male hypophysis was so damaged in the process of preparation that it was only of cytological value. Of the remaining sixteen perfect organs four (two from males and two from females) were taken before hibernation; four (two from males and two from females), during dormancy; five (three from males and two from females), after waking up but before being fed; three (one from a male and two from females), in the spring while active and after having been fed one, two and three weeks. The smallest male of the non-fed active group that was killed after hibernation, was not used in volumetric calculations, thus leaving in the three principal groups an equal number of each sex and thereby reducing the error due to sex-differences if such differences should exist.

All these animals were killed instantly by transfixing the heart quickly through the chest wall, in most cases without the use of any anaesthetic. Most of the blood was immediately washed out with physiological saline solution at body temperature by perfusion through the aorta. The saline was followed by a sat-

urated aqueous solution of bichloride of mercury to which had been added 10 per cent of formalin. The whole body was thus fixed very quickly while still warm or still cold depending upon whether the animal was active or was lethargic.

Following the removal of the brain, the hypophysis was carefully dissected out and further fixed for 48 hours in a saturated aqueous solution of bichloride of mercury. After washing in running water for 36 hours, the tissue was dehydrated as usual and imbedded in paraffin. The time intervals in the reagents were the same for all specimens so that the shrinkage ought to be very nearly the same in all cases. This point is of importance because the method of fixing *in situ* made it impossible to get the weight of the fresh gland as a check upon volumetric changes produced by the histological technique.

The above material was used for determining the volume of the whole organ and its different parts, the volume of cells and of nuclei, and for a differential count of the basophilic and acidophilic cells of pars anterior. Each hypophysis was cut into serial section 5 μ thick and mounted upon six slides. The plane of section was horizontal, i. e., through the greatest diameter, so as to decrease the number of sections and to present to the best advantage the three principal regions traversed. The first slide was stained with Delafield's hematoxylin and eosin; the second, with methylene blue and eosin; the third, with the aniline blue-orange G-phosphomolybdic acid mixture used in the well known Mallory's aniline blue connective tissue stain; the fourth, with acid fuchsin followed by the aniline blue and orange G mixture as regularly done in Mallory's connective tissue stain; the fifth, with Delafield's hematoxylin and acid fuchsin; and the sixth, with one of the preceding methods depending upon which stain needed checking.

Another series of hypophyses was available from the fifteen animals utilized in the study of the mitochondrial content of nerve cells during hibernation (Rasmussen '19) in the report of which the data concerning the animals are given. They are registered as Series IV and No. 51 and No. 56 of Series III. This material was fixed also *in situ* by injecting Regaud's fixer (one part of commercial formalin neutralized with magnesium carbonate and four parts of a 3% aqueous solution of potassium bichromate) after the blood had been washed out with oxygen-

ated Locke's fluid. The organ was dissected out and further fixed for five days in Regaud's mixture, changing the solution every day, and followed by 3% aqueous solution of potassium bichromate for nine days, changing the solution every day. This preserves the mitochondria well (Cowdry '16). The tissue was imbedded in paraffin with the same precautions exercised with the other material regarding equal duration by all samples in the various reagents including the paraffin bath. Serial sections were cut 5 μ thick until about halfway through the block. The block of tissue and the knife of the microtome were then further cooled by means of a piece of ice held against them. A known number of sections (from 20 to 30) only 2 μ thick were then cut. The rest of the block was cut 5 μ. This gave an uninterrupted series and at the same time enough very thin sections for more detailed study. The 5 μ sections were mounted on about six slides with the point indicated where the thinner sections belonged. Some were stained in hematoxylin and eosin and the remainder for mitochondria in Altmann's anilin fuchsin (20% acid fuchsin in anilin water) and a 1% aqueous solution methyl green (Cowdry '16). Knowing the number of 2 μ sections taken out of the series it was possible to use them for determining the volume of the whole gland and of its various parts since, as will be explained later, it is necessary to use only every tenth section. The 2 μ sections were mounted upon separate slides (three or four sections to a slide) and stained as above for mitochondria after various degrees of dechromation.

The fifteen hypophyses fixed by this second method represent five animals (three males and two females) in each of the first three stages represented by the material first described.

A difference in the fixation necessarily meant that the volumetric data had to be worked out separately for each lot of material. It was found, however, that the figures from each lot were between practically the same limits, dehydration and imbedding having apparently caused sufficient shrinkage to obliterate any differences that might have existed immediately after fixation. For a differential count of the cells of pars anterior only the first described material (formalin-corrosive sublimate fixation) could be used; for mitochondria, only the second (neutral formalin-potassium dichromate fixation). For the rest of the work both lots could be used, the volumetric data being thus

based upon thirty whole hypophyses—nine from animals killed before hibernation, between Sept. 4 and Dec. 3, rectal temperature 35°C—38°C; nine from animals sacrificed while dormant, between Feb. 3 and Mar. 18, rectal temperature 7°C to 16°C; nine from animals killed after waking up, between Mar. 16 and April 18, rectal temperature 34°C—37°C; three from animals having been awake several weeks without food and then having been fed one, two and three weeks, killed between April 5 and April 18, rectal temperature 36°C—38°C.

The method of determining the volume of the gland and its various parts as well as the size of cells and nuclei was the paper method of Hammar as used by Jackson ('17). The mathematical basis of this procedure is more fully explained in a later publication (Jackson '19). Suffice it to say that for determining the volume of the whole gland and of the various lobes every tenth section of the series was projected upon standardized paper by means of an Edinger projection apparatus at a magnification of 77 diameters and the various parts outlined, then cut out and weighed. Knowing the weight of one sq. cm. of paper, the surface area of each outlined area is obtained. This was reduced to actual area by dividing by the magnification (77^2) and then multiplied by the thickness (50 μ) represented by each of the selected sections to give the actual volume. There was left on the organ only an extremely thin fibrous capsule and since the lumen of the residual cavity (intraglandular cleft) and large cyst not containing colloid, or hyaline substance, were discarded when cut out, the weights represent essentially parenchyma and vascular stroma.

In determining the volume of cells and nuclei all the nuclei and vascular stroma in focus at the same time were traced within an area easily outlined by means of a camera lucida and at a magnification of 2100 diameters (Zeiss 2 mm. apochromatic objective, compensating ocular 8). The vascular stroma was cut out and discarded. The remaining paper, represented the essential parenchyma, was weighed. The nuclei were counted, cut out and discarded, and the paper (now representing cytoplasm only) again weighed. The difference between the two weights gives the nuclear area. From these figures and the known weight of a unit area of the paper, the magnification and the number of nuclei (which also represents the number of cells), the average volume

of the entire cell and of its nucleus were calculated. In the case of pars anterior this was carried out on four different regions on a section passing through the organ near its greatest diameter. These regions were selected from about the same positions in each case. These are indicated by the four crosses in figure 1. There is sufficient variation in the cells in different parts of the lobe and a fair degree of regularity in the positions where these differences are located to make this procedure necessary. Each of the four areas contained from 61 to 154 nuclei and the four together involved in the neighborhood of 300 nuclei. In pars intermedia only two fields were taken—one from about the middle of each lateral half as viewed in sections passing through the greatest diameter of the whole gland. The cells bordering the residual cavity as well as those next to pars nervosa were not included in the area outlined because these are invariably smaller (fig. 4) than those forming the main bulk of this lobe. In each field in pars intermedia 35 to 85 nuclei were outlined and the two fields together yielded in the neighborhood of 100 nuclei.

The method of cutting out the nuclear areas is of some consequence on account of the tedious task which it involves in an extensive research. Jackson used a sharp scalpel and placed the paper on a wax plate such as is used for reconstruction in the making of anatomical models. The wax plate renders cutting easy but small particles of the wax composition may adhere and if unnoticed produce an appreciable error. The main objection, however, is that it is fatiguing to the hand. While it is no quicker, it is much easier and just as accurate to cut out even the smallest nuclei by means of a fine manicuring scissors with increasing curvature toward the point. One can cut for hours without inconvenience. When a nucleus has been cut out a slit is made from the resulting hole over to the nearest nucleus, etc. When the paper becomes too frail one blade can be inserted into the outlined nucleus and the area excised without communicating with any other hole.

In making the differential count of cells in pars anterior only the granular or so-called chromophilic (acidophilic and basophilic) were enumerated—these being in the minority and the cells usually associated with active secretion. In each animal an entire section near the greatest diameter of the organ was explored systematically by means of a mechanical stage from side

to side, stopping for a count as soon as all parts of the previous area had passed out of the field of vision. A section explored in this manner yielded from 206 to 284 fields, with a total count of 8,759 to 13,086 acidophiles and 263 to 3,572 basophiles. To detect any distinct variation in the proportion of the three types of cells it was deemed sufficient to determine the average number of cells of the two types per field, since it had previously been found that there was no marked variation in the size of the cells taken as a whole, from which it follows that the average number of total cells in a unit area (say an entire microscopic field where the magnification, lenses, etc., are kept constant) would be the same in the different stages.

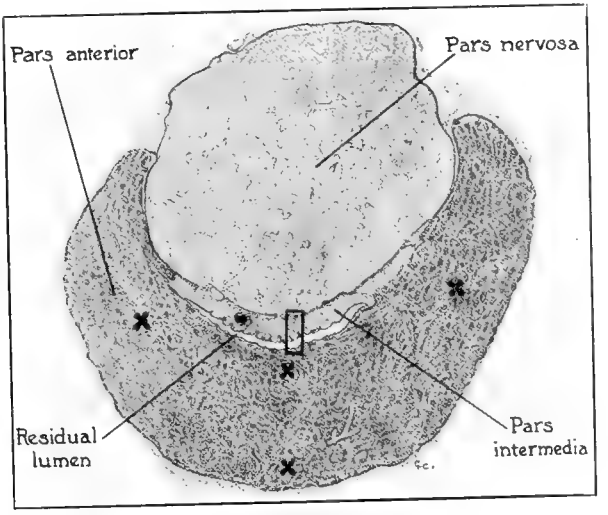

Fig. 1. Horizontal section through the hypophysis of the woodchuck at about the greatest diameter showing the general arrangement of parts. Formalin-corrosive sublimate fixation; methylene blue-eosin stain. X 20.

DESCRIPTION OF THE HYPOPHYSIS OF THE WOODCHUCK

a. General features

The main bulk of the hypophysis of the woodchuck (as already briefly described by Cushing and Goetsch '15) is a flattened disc from 3 to 4.5 mm. in diameter and from 1 to 2 mm. in thickness near the center and thinner towards all edges (dimensions obtained from the fixed material). It lies horizontally in a very shallow sella turcica. The glandular portion forms a distinct crescentic mass half encircling the nervous por-

tion, as shown in figure 1. The infundibular stalk is short and delicate and breaks readily close to the distal enlarged portion. Only in a few cases was much of the infundibulum and adjacent portion of the tuber cinereum retained. From these it appears that all the regions recognized by Tilney ('11, '13) are present. The infundibular stalk is solid through its greatest extent so that it belongs in Vincent's ('12) third class represented in man, monkey, ox, pig, rabbit, etc. It is accompanied by a thin layer of glandular tissue, two to four cells in thickness, continuous below with the main bulk of pars intermedia. The cytoplasm of the cells of this thin layer is much less abundant, the nuclei are slightly smaller and more nearly spherical and stain more deeply than in the cells which form the greater part of pars intermedia. The cells are arranged in anastomosing strands in a stroma almost as vascular as that of pars anterior. The extent to which they surround the infundibular stalk cannot be determined from the material at hand.

The thin layer of cells just described becomes thicker as it spreads out on the under surface of the eminentia saccularis of the tuber cinereum. Thus there is what Tilney terms a pars tuberalis in the juxta-neural glandular tissue. The extent of the pars tuberalis cannot be described here because not enough of the hypothalamus was retained in any case.

The part of the gland primarily investigated was only the enlarged disc-shaped portion consisting of processus infundibuli, which will be designated by the more familiar term pars nervosa; that part of the glandular pars infundibularis that is associated with processus infundibuli, which will be spoken of as pars intermedia; and pars distalis, or the main body of glandular tissue, which will go by the better known name of pars anterior. If additional structures were present they were excluded from the tracings. The point where the pars nervosa rather suddenly narrows down to become the infundibular stalk, a point which is also the upper limit of pars anterior, was taken as the upper boundary line and, therefore, only that portion of the gland below this level is included in the volumetric data. The naked infundibular stalk was always present above this line but pars intermedia usually broke at this point or slightly above except in a few cases where the line of separation was through the floor of the third ventricle. The structures included constitute, however,

the better known parts and by far the main bulk of the organ.

b. Pars nervosa

Pars nervosa is solid and pear-shaped, with the infundibular stalk representing the stem. In cross section it is nearly round (fig. 1). A very thin fibrous capsule covers the entire surface. There are no histological features that are either unique or of importance, but they conform to the general description given for other mammals. Fibers constitute the main bulk. It is well supplied with blood vessels. Small masses of homogeneous colloid-like material, somewhat larger than the cells present, are scattered about in all parts of the lobe. They lie free in interstitial spaces.

c. Pars anterior

Pars anterior is crescentic in shape and closes in around the lateral borders of pars intermedia so as to come in contact with

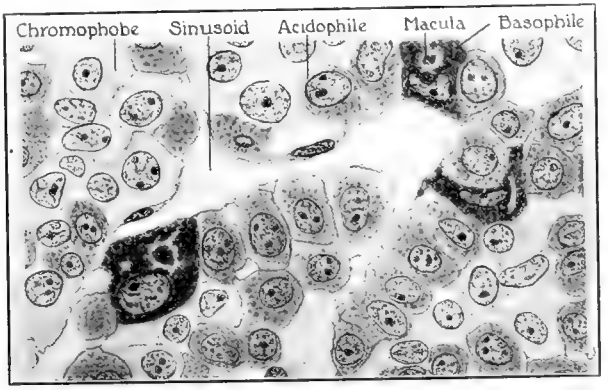

Fig. 2. Small area of pars anterior showing types and arrangement of cells. Formalin-corrosive sublimate fixation; Mallory's acid fuchsin-aniline blue-orange G connective tissue stain. X 1000.

pars nervosa (fig. 1). It is also invested with a delicate fibrous capsule. The cell arrangement is of the most common type, namely, irregular anastomosing cords separated by a rich system of sinusoidal capillaries (figs. 1 and 2). Nothing simulating acini was seen strictly within pars anterior.

The cells appear to be of three distinct types, usually termed chromophobes but also termed chief cells and reserve cells (lightly staining and devoid of many coarse granules), and acidophilic and basophilic chromophiles (staining intensely due to the presence in the cytoplasm of coarse granules which are either dis-

tinctly acidophilic or distinctly basophilic). As shown in figure 2 where the three types are shown in three tones of shading, there is a striking absence of intermediate forms. These three types of cells were found to stand out most clearly tinctorially with Mallory's acid fuchsin—aniline blue—orange G connective tissue stain after formalin-corrosive sublimate fixation. For a study of basophiles, as was also the experience of Addison ('17), omitting the acid fuchsin gives the clearest preparation with maximum contrast. The basophilic cells take the aniline blue and, therefore, stand out in great contrast against the yellow acidophiles and almost colorless chromophobes. However, the acidophiles are best seen when stained with acid fuchsin. As shown by Cooper ('19) it is the same cells that stain intensely yellow with orange G and intensely red with acid fuchsin.

The chromophobes are somewhat more numerous than the chromophiles. They form the body of the cords and, while often seen next to the capillaries, do not show much tendency to border on the blood channels. They vary much in size, a few being

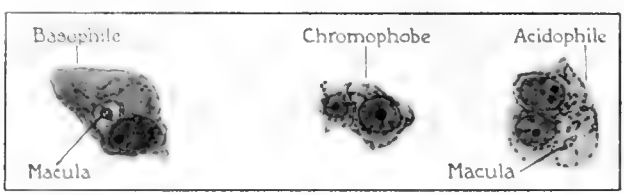

Fig. 3. Cells from pars anterior showing the mitochrondrial content. Neutral formalin-potassium dichromate fixation; acid fuchsin-methyl green stain. X 1000.

among the larger cells encountered while most of the smallest cells are of this type. As has often been noted, the boundaries of the individual cell are difficult to make out with most stains. The mitochondria (fig. 3) are mostly granules ½ μ or less in diameter. Short rods are often seen and occasionally a rod as long as 2½ μ as well as comma-shaped mitochondria are observed. If the cytoplasm is scanty, the mitochondria may be reduced to a single perinuclear layer. The nucleus is of the usual type, either round or somewhat elongated, rather smooth in outline and containing from one to three nuclei and a fairly coarse chromatin network.

The acidophiles are somewhat less numerous than the chromophobes. They are, on the whole, slightly larger and show a

decided tendency to occupy the periphery of the cell cords so that they are mostly found directly in contact with the endothelium of the vascular channels (fig. 2). This arrangement has been repeatedly noted in other animals by various investigators. Uniform, round granules fill much of the cytoplasm, especially next to the nucleus. The margin being usually less densely packed with these acidophilic bodies, the limits of the individual cell are fairly distinct. In some of the larger cells there is a lighter colored area resembling a large vacuole in the interior of which is a body possessing the same staining properties and granules as the denser cytoplasm. Addison (17a, b) has discussed this structure under the heading "Golgi apparatus" and upon the basis of his work on the albino rat after castration considers it to be a definite cell organ. Gemelli ('07 and earlier publication listed in this reference) has also described large vacuoles and a Golgi reticulum in the chromophilic cells. In the woodchuck material here described this structure has been designated "macula"—the term tentatively applied by Addison ('17a). This structure is seen in the acidophiles best in the material fixed in neutral formalin-potassium dichromate and stained with acid fuchsin—methyl green, but even then only in a small percentage of the cells; although it is very likely present in a great many more, if not in all, but in a smaller and less conspicuous form. It is probable that with the technique used here it shows up only in the cells where the light zone has been greatly exaggerated by the action of the reagents. One of the largest and most conspicuous maculae observed in the acidophiles is sketched in figure 3.

Mitochondria are present in large numbers (fig. 3). They differ in no way from those already described. It is difficult to be sure of the relative number of mitochondria by the method here used because the large acidophilic granules also take the fuchsin stain and if dechromation is carried to the extent that these larger granules do not stain red, one cannot always be sure of having brought out all the mitochondria present. However, their small size and deep red color make their identity fairly certain even when the cytoplasm is still somewhat red.

The nucleus is slightly eccentric but in structure differs in no particular from that of the chromophobes.

The basophilic cells are least numerous, there being only about one of these to every ten acidophiles. Under usual conditions there is, however, a great variation between individual animals. In one case there may be as few as one basophile to about thirty acidophiles and in another animal as many as one basophile to three acidophiles (table 4). In nearly all cases they are more numerous towards the periphery of the lobe but not at the extreme edge. This peripheral distribution has been seen in other animals (Tilney '11), but denied by Jackson ('17) as a characteristic feature in the albino rat. They occur singly, as a rule, but where numerous may be in clumps so that the majority of the cells in a high power field of the microscope are basophiles. They show some tendency to occupy the regions next to the sinusoidal blood vessels. In outline they are more irregular and as shown in figure 2 may occupy irregular spaces between other cells. The largest cells met with are usually of this type, although there are many medium sized basophilic cells.

The cytoplasm is literally filled with coarse basophilic granules except for a conspicuous light ring or irregular space about a distinct macula, as described in the acidophiles. Practically every cell must contain such a structure, judging from the number of cells in which it is actually present in the section. Naturally a great many cells are so cut that the portion in a particular section does include the macula. This structure varies greatly in size, and to some extent directly with the size of the cell. In the largest cells it may be as large as the nucleus. In the smallest cells it may be smaller than the nucleolus. It is situated most often near the center of the cell. The light area about the macula and the macula itself may be greatly flattened as if by external pressure. While the surrounding vacuole-like region is usually fairly regular in outline, it may be very irregular and branched, as seen in the largest cell in figure 2. In very large cells an additional light area, variable in size, resembling a vacuole, is occasionally seen. The macula shows the same structures and staining reactions as does the dense cytoplasm outside of the light area.

The mitochondria are of the same form as those in the other cells but show a greater tendency to be arranged in rows. They appear less distinct on account of the denser cytoplasm. Probably for this reason they seem somewhat less numerous in proportion

to the amount of of cytoplasm than in the other two types of cells.

The nucleus is almost always very eccentric and is very frequently irregular in outline, with a tendency for the concave side to be next to the macula. Its structure does not seem to differ from that of the other nuclei.

As shown in figure 4, the cells of pars anterior which form the anterior wall of the residual lumen are distinctly smaller, more irregular in outline and stain more densely. In some sections these smaller cells form a two layered wall separated from the rest of pars anterior throughout the entire length of the cavity by a plexus of capillaries. These smaller cells are mostly chromophobic in general reaction.

d. Pars intermedia

Pars intermedia, as is clear from figure 1, constitutes a very small part of the hypophysis. Table 1 shows that it may form less than one per cent of the entire organ and is always less than four per cent. It consists of a lamina fairly uniform in thickness usually with a smooth posterior surface, which is closely applied to the thin capsule of pars nervosa. In four out of thirty cases, however, lobules of cells from pars intermedia invaded the neural lobe for a considerable distance. The residual lumen may follow along with this ingrowth. This encroachment of pars intermedia upon pars nervosa has been noted now and then by others. Herring ('08) in his description of the mammalian hypophysis states that this is most frequently met with in the region of the neck of the gland and that islets of epithelial cells may be found throughout pars nervosa. Cushing and Goetsch ('10) state that it is not uncommon in so-called normal human hypophyses, while Erdheim ('03) and Lucien ('09) found it more prevalent in advancing years.

Pars intermedia rarely comes to the external surface of the organ except at the most dependent point and of course along the hypophyseal stalk above pars anterior. Over half of its anterior border is separated from pars anterior by the residual lumen. There is a tendency for the intermediate lobe to surround the margins of this cavity and to form a little of its anterior wall. It extends some distance peripherally between pars anterior and pars nervosa beyond the hypophyseal cavity.

As is almost universally the case among animals, this part of the hypophysis is poorly provided with blood vessels. Almost no capillaries are seen in its interior. The posterior border is well supplied with vessels but they do not extend very far in the anterior.

The general histological features are shown in figure 4. It will be noted that four types of cells are present. The main bulk of the lobe is formed of cells which upon measurement (table 3) are seen to have about twice the volume of the cells of pars anterior. The abundant cytoplasm of these cells is devoid of many large granules and therefore, while rather basophilic in reaction, appears distinctly lighter than pars anterior and hence its limits can be readily ascertained by almost any stain. These cells are irregular in shape due to mutual compression. The central cytoplasm is denser and contains more mitochondria

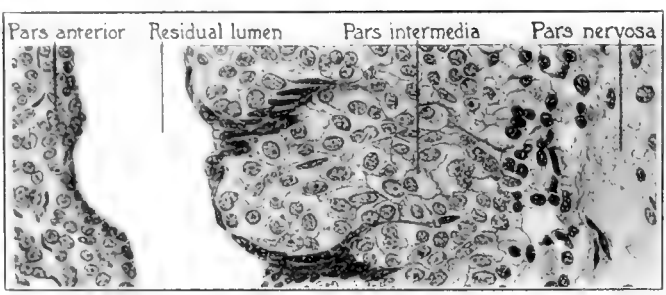

Fig. 4. Narrow strip through pars intermedia and a small part of adjacent pars anterior and pars nervosa. An enlarged view of the rectangular area outlined in figure 1. Formalin-corrosive sublimate fixation; methylene blue-eosin stain. X 400.

than the peripheral cytoplasm (fig. 5 B), which has the general appearance of being composed of more fluid areas separated by denser strands radiating from the central cytoplasm. According to Lewis and Maurer ('20) the lighter areas between the denser strands are filled with secretory antecedents.

The nucleus is usually eccentric in position, rather vesicular in appearance and round or more or less elongated in shape.

Along the posterior margin a variable number of cells occur which are much smaller and contain much denser cytoplasm and a heavier staining nucleus. They are responsible for the darker shading along the posterior boundary of pars intermedia in figure 1. In figure 4 their hyperchromatic nuclei are best seen

while figure 5 C is a sketch of three of these cells under higher power. The scanty cytoplasm is rich in mitochondria. The stratum which these cells form is not usually as wide as in the case illustrated in figure 4. It is as a rule more irregular in thickness, not being seen at all in places and in other limited areas being one-third as wide as the entire thickness of pars intermedia.

The anterior margin, which forms the posterior wall of the hypophyseal cavity, is lined by cells which may be either greatly flattened or high columnar as shown in figures 4 and 5 A. The columnar cells form groups which extend a variable distance into the substance proper—a great exaggeration of the tendency

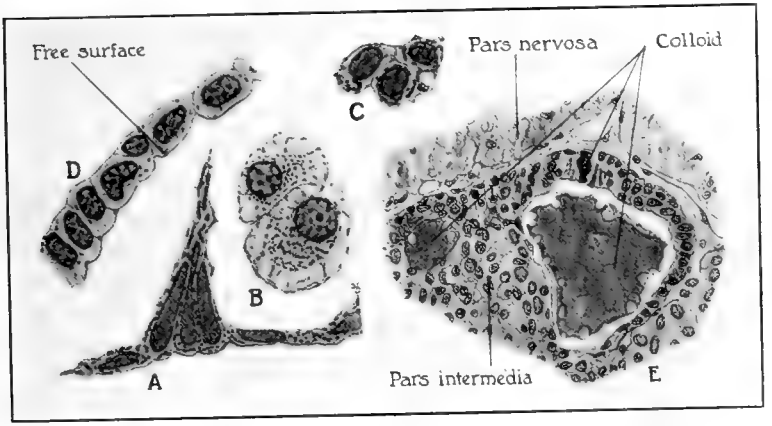

Fig. 5. Details from pars intermedia. The four small groups of cells show the mitochrondria of the different types of cells: A, typical cells lining the residual lumen and a trabeculum of long columnar cells which extend into pars intermedia; B, two typical cells forming the main bulk of pars intermedia; C, three small cells found next to pars nervosa; D, cells from the wall of a colloid-containing vesicle. Neutral formalin-potassium dichromate fixation; acid fuchsin-methyl green stain. X 1000. E, small area from pars intermedia and adjacent pars nervosa showing relation of colloid masses to surrounding tissue. Hematoxatin and eosin. X 265.

shown by Cooper ('19, fig. 4 B) in the California ground-squirrel. Protoplasmic trabeculae appear to project far beyond the deepest nuclei but gradually diminish in size till beyond recognition. Long spindle-shaped cells, sometimes reaching through the entire thickness of pars intermedia, have been observed in several other species (Herring '08). At the surface where the columnar cells become continuous with the flattened cells, transitional forms are found. Each trabeculum is marked by a depres-

sion so that the anterior margin of pars intermedia is scalloped when seen in section (fig. 1).

The cytoplasm, though very scanty in the columnar cells especially, is well provided with mitochondria (fig. 5 A). The nuclei of the columnar cells are long and spindle-shaped and very hyperchromatic.

Another type of cell is found associated with the larger masses of colloid, which appears more or less abundantly. Occasionally a colloid mass is seen which is larger in diameter than the thickness of the entire juxtaneural lobe. Such accumulations as are shown in figure 5 E are more common. The larger masses contain a series of vacuoles around the margin (fig. 5 E). These are most likely the effects of some of the reagents. While the smaller colloid bodies are surrounded by the usual type of cell as if they had accumulated in intercellular spaces, the larger ones are surrounded at least partly by what appears to be a special epithelium. This epithelial wall is usually a single layer of cells but in places may consist of a double layer. An incomplete wall is seen in the largest vesicle in figure 5 E. The cells vary in shape from squamous to columnar. They are much smaller than the majority of the cells in pars intermedia. The cytoplasm is more homogeneous in appearance and, as pointed out by Lewis and Maurer ('20) in the pig, is very poor in mitochondria (fig. 5 D). The nucleus has a dense reticulum containing many large blocks of chromatin. Small masses of colloid may be found either in the cells or between them (fig. 5 E). These colloid cysts are not to be confused with the detached portions of the residual lumen mentioned by Vanderburgh ('17) in the guinea pig.

e. Residual lumen

A distinct residual lumen (hypophyseal cavity) is always present. It frequently contains colloid. While in general its outline is regular, it may be broken up at the margins by a fusion of its walls. As a result of this, small detached acini-like structures with high columnar cells and almost invariably containing colloid may be found between pars intermedia and pars anterior beyond the lateral borders of the main cavity. It is possible that some of the acini occasionally described in pars anterior as having columnar cells and a lumen containing colloid are similarly detached portions of the hypophyseal cavity. In the woodchuck the columnar cells forming the wall of the detached cavities are

identical with those found in groups or trabeculae along the posterior wall of the main cavity; but, unlike the guinea pig's hypophysis (Vanderburgh '17), there are no cilia. When some of these outlying acini are followed in serial sections, they are found to communicate with the main lumen. Others have been completely cut off. As already mentioned, in rare instances the cavity may extend into pars nervosa along with the invading masses of pars intermedia cells. The residual lumen does not extend up along the infundibular stalk. No cilia were ever seen with certainty projecting into the cavity. It is surprisingly free from cellular debris.

f. During hibernation

In comparing the hypophysis as above described, which may be taken as the condition existing in the autumn before hibernation, with those taken from dormant animals, the difference, if any, was so slight that nothing short of careful volumetric analysis could be relied upon. Any unusual feature found during winter sleep could usually also be found in non-hibernating ones. There seemed to be nothing that was characteristic of the hypophysis during dormancy. The hyperchromatic and pyenotic character of the nuclei, described as being typical of the hibernating state, was found only here and there and was just as evident before lethargy. Methylene blue was purposely introduced to give a sharper nuclear stain but neither this nor hematoxylin, to say nothing about the other stains, brought out any difference. Nor was there any apparent difference in the average size of the cells. Limited regions were found in pars anterior of all the animals where the cells were smaller than usual. These areas are so irregular that no general examination warranted any statement as to the relative number of cells involved. The cells of pars anterior in the neighborhood of pars intermedia and the residual lumen invariably are smaller than the average. On the other hand, cells on the outer margin are slightly larger. This was true of all the animals and not merely in those hibernating, as one would infer from Cushing and Goetsch ('15). Judging from the area and number of sections the whole organ did not seem particularly smaller during hibernation, as has been reported, when the body weight was taken into consideration.

g. Post-hibernating period

There was, however, an unmistakable difference in several particulars between the hypophyses taken in the spring, after resumption of activity, and those taken from dormant animals and from animals killed before the onset of winter-sleep. These variations, together with the general similarity between lethargic and pre-lethargic animals, can best be demonstrated by a consideration of the results obtained by the volumetric study carried out. It might be stated here, however, that no evidence of cell division was seen in any case, notwithstanding the fact that such has been seen by Gemelli and by Cushing and Goetsch during the post-hibernating period and that the material here used was fixed instantaneously *in situ* immediately after death. Washing out the blood before perfusing with the fixer is a possible though not very probable explanation of this negative result.

TABLE 1.

Volumetric data on the whole hypophysis and its three principal parts before, during and after hibernation in the woodchuck.

Animal				Whole Hypophysis		Percentage of Whole Hypophysis Formed by		
Number Involved	Number of Each Sex	Rectal Temperature C.	Av. = Average Mi. = Minimum Ma. = Maximum	Volume cc.	Percentage of Maximum Gross Body Weight	Pars Anterior (Distalis)	Pars Intermedia (Juxta-neuralis)	Pars Nervosa (Processus Infundib.)
BEFORE HIBERNATION								
9	4 Female 5 Male	35 to 38	Av.	0.00633	0.000235	47.2	2.41	50.4
			Mi.	0.00545	0.000161	40.6	0.97	45.5
			Ma.	0.00750	0.000280	50.7	3.84	56.3
DURING HIBERNATION								
9	4 Female 5 Male	7 to 16	Av.	0.00641	0.000235	44.9	2.51	52.6
			Mi.	0.00542	0.000198	34.6	1.05	45.9
			Ma.	0.00741	0.000291	50.6	3.71	63.2
AFTER HIBERNATION NOT FED								
9	4 Female 5 Male	34 to 37	Av.	0.00865	0.000322	43.7	2.76	53.5
			Mi.	0.00488	0.000222	38.4	1.60	47.0
			Ma.	0.01099	0.000380	49.7	3.56	59.3
AWAKE SEVERAL WEEKS FED ONE, TWO OR THREE WEEKS								
3	2 Female 1 Male	36 to 38	Av.	0.00722	0.000312	45.6	2.51	51.9
			Mi.	0.00500	0.000267	37.5	1.80	44.5
			Ma.	0.01027	0.000353	53.7	3.21	59.2

VOLUME OF THE PRINCIPAL PARTS OF THE HYPOPHYSIS

a. Before Hibernation

The results of the volumetric analysis of the parts of the hypophysis of thirty animals with related data are tabulated in table 1. The volume of the whole hypophysis is merely the sum of the three principal parts which are listed in the last three columns. The average of the nine hypophyses obtained before hibernation was 0.00633 cc. Rather than making an extensive table with individual volumes, the condensed tabulations include only the smallest and the largest organ encountered in addition to the average, in order to indicate the range of individual variation. These limits happen to be very narrow in this group (0.00545 to 0.00750). It must be remembered that these volumes refer to the fixed material and therefore represents only about half of the real volume (Jackson '17). Since the hypophyses of the larger animals are, as a general rule, larger than those of the smaller animals, it is necessary to take into account the size of the animal. This has been done by placing in the next column the percentage of the body which is represented by the organ, assuming that its specific gravity is 1. This averages 0.000235 per cent, but there is an enormous individual variation (0.000161 to 0.000280). Although such marked variations have been noted in other animals (Hatai '13a, Jackson '17, and others) as well as in man, one source of error here is the necessity of taking the gross (and not the net) body weight. From over a hundred woodchucks in which the writer has determined the gastrointestinal contents it may be said that the gross body weight includes anywhere from 1 to 10 per cent of such contents . But this seemed unavoidable because the essential point to determine was to what extent the hypophysis was modified by hibernation and by the restoration of activity, etc., but during this time the body weight is decreasing from lack of food and water till at the time of awakening 25 to 30 per cent has been lost.

The body weight was obtained in the fall before hibernation by weighing the living animal on a spring scale. Those that were kept in captivity for some time were weighed several times before dormancy set in. Each animal was ear-marked with a punch so as to be identified. Although many of the animals were kept under conditions which were almost identical with the normal

habitat (Rasmussen '15), some lost and others gained weight while being fed in the fall before hibernation. Therefore, the maximum body weight obtained while active was used in making the calculations listed in tables 1 and 2. Nearly all the animals weighed between 2000 and 3000 grams.

From the last three columns in table 1 it is seen that the glandular portion (pars anterior and pars intermedia) constitute about half of the organ and pars nervosa the other half. Pars anterior varies from 40.6 to 50.7 per cent, average 47.2 per cent. Pars intermedia represents only 2.41 per cent on the average, but varies enormously (0.97 to 3.84 per cent). As will be shown in table 2, this variation is largely due to a sex difference. The females have a much smaller pars intermedia, but since the number of animals of a particular sex is the same in each of the three principal groups, this does not invalidate seriously a comparison of averages based on both sexes in these groups.

When compared with the only other data which have been found on the proportion of the whole organ formed by the principal components (Jackson '17, on the rat, Björkman '15, on the rabbit), it is found that pars anterior of the woodchuck constitutes about half and pars intermedia only about one-third the proportion that the corresponding parts represent in the hypophysis of the albino rat. On the other hand pars nervosa is more than six times the proportion found in the rat. In the rat, pars intermedia is as large as pars nervosa and each constitutes about 7½ per cent of the whole organ. In the rabbit, the proportions are much like those in the rat in that pars anterior constitutes by far the greatest bulk (66-73 per cent); while pars nervosa represents from 14 to 19 per cent, and pars intermedia 10 to 15 per cent. Numerous comparative data on the size of the hypophysis are given by Livon '09, but these refer only to the organ as a whole.

b. During hibernation

The figures obtained from the nine dormant animals are in every particular essentially like those from animals killed before hibernation. All are well within probable errors when individual variations and the limited number of animals are taken into consideration. If the percentage which the organ formed of the body weight had been calculated from the weight of the animal when killed, the hypophysis would have appeared to be about 25

per cent larger than is characteristic of the pre-hibernating stage, hence the necessity of knowing the original weight before emaciation sets in. It is reasonably certain, therefore, that the hypophysis does not diminish in size during hibernation in the woodchucks here investigated.

c. After hibernation

In comparison with the two preceding groups this third group, which consists of animals that had been awake from several days to several weeks with no food available, shows an increase of fully one-third in the size of the hypophysis. The whole gland varies from 0.000222 to .000380 per cent of the maximum gross body weight, average 0.000322. This agrees with the findings of Gemelli and of Cushing and Goetsch. There is not enough variation from the above two groups in the relative proportion of the lobes to indicate any particular difference in the rate of hypertrophy of the three parts. If anything, pars nervosa has increased slightly more than pars anterior—just the reverse of what one would expect from the supposed decrease in the latter pictured by previous investigators.

The reason for this general hypertrophy has already been suggested earlier in this article where reference was made to increased activity especially in the sex gland during the rutting period and the interrelation of the hypophysis and gonads. The great variation in pars intermedia is again largely due to a sex difference.

Attention should be drawn to the difference in the effects of inanition in this hibernating species of rodent even when active and in the albino rat, a non-hibernating rodent. Jackson ('17) found in the adult that inanition produced generally a relative decrease in pars anterior with evidence of atrophy and degeneration. In all probability animals that regularly hibernate have a degree of resistance to inanition and other conditions such as is not generally found. The storage of an enormous amount of fat and the great reduction in oxidation readily suggest that inanition effects during dormancy would be largely obviated; but it is rather strange that upon waking up and becoming active after one-fourth or more of the body weight has been lost, there are no inanition effects even after three or four weeks deprivation of food and water with rapid loss of body weight.

The last group of three animals, fed one, two or three weeks respectively after having been awake several weeks without food, do not differ essentially from those that had not been fed. It is evident that the hypertrophy of the hypophysis during the rutting season goes on independently of the food factor.

d. Sex differences

The volumetric data on the lobes brought out the fact that there is a fairly constant sex difference. To show this more clearly, all the females were grouped together and an equal number of males so that there were as many males as females from each of the four groups or stages. The results are tabulated in table 2. It appears from this that the male gland is about 13

TABLE 2.

Sex differences in the hypophysis of the woodchuck based on 13 males (average body weight—2638 grams) and 13 females (average body weight—2480 grams). Males 6.4 per cent heavier than the females.

	Whole Gland		Pars Interior		Pars Intermedia		Pars Nervosa	
Sex	Volume cc.	Per cent of Body Weight	Volume cc.	Per cent of Body Weight	Volume cc.	Per cent of Body Weight	Volume cc.	Per cent of Body Weight
Male	.00731	.000278	.00348	.000132	.00022	.0000083	.00365	.000138
Female	.00614	.000248	.00296	.000120	.00014	.0000056	.00303	.000122
	Larger in Male than in Female by 19.5 per cent		Larger in Male than in Female by 16.9 per cent		Larger in Male than in Female by 56.8 per cent		Larger in Male than in Female by 20.4 per cent	

per cent heavier than the female when the 6.4 per cent difference in body weight is taken into account. Similarly each lobe is larger in the male. Pars nervosa follows closely the whole organ but pars anterior is only about 10 per cent larger in the male. It is pars intermedia, however, that is markedly different in the two sexes, being 50 per cent larger in the male than in the female of the same body weight. Of the 13 females only one had a gland near the upper limits and of the males only one had a gland near the lower limit.

In albino rats above 50 grams in weight the females have a larger hypophysis than the males (Hatai '13a). Jackson ('17) finds that this is chiefly, if not entirely, due to a larger pars anterior. His figures on pars intermedia, however, indicate, if anything, that it is slightly larger in the male. Wittek ('13)

found that in cattle the hypophysis is also relatively larger in the female. In the human species (Caselli '00, Lucien '11) the female hypophysis is apparently slightly larger, especially as percentage of body weight and the same seems to be true of the rabbit (Björkman '15).

Pregnancy, which may cause enlargement of the hypophysis (Comte '98, Erdheim and Stumme '09 and others), is no complicating factor in the animals used for this study since the woodchuck does not breed in captivity. All the reproductive organs of these animals were carefully examined and fixed for other studies and no cases of pregnancy were found.

TABLE 3.

Volumetric data on the parenchyma cells of pars anterior and pars intermedia of the hypophysis of the woodchuck before, during and after hibernation. All figures in micra. Same animals in the various groups as in Table 1.

Av.—Average Mi.—Minimum Ma.—Maximum	PARS ANTERIOR				PARS INTERMEDIA			
	WHOLE CELL		NUCLEUS		WHOLE CELL		NUCLEUS	
	Volume	Diameter	Volume	Diameter	Volume	Diameter	Volume	Diameter
BEFORE HIBERNATION								
Av.	854.2	11.8	84 9	5 45	1790 8	15.1	108.5	5.92
Mi.	781.9	11.4	76.0	5.25	1524.5	14 0	103 3	5.82
Ma.	922.8	12.5	88 2	5 52	2047.6	16.0	119.0	6.10
DURING HIBERNATION								
Av.	860.3	11.8	90.7	5.57	1889 9	15 3	108 8	5.92
Mi.	814.5	11.6	83.5	5.42	1349.3	13.0	105 5	5 86
Ma.	1098.1	12.8	100.8	5.77	2563.7	17.4	131.1	6.30
AFTER HIBERNATION—NOT FED								
Av.	847.5	11.7	92.1	5.60	2392.5	16 6	118 8	6 10
Mi.	671.3	10.8	81.2	5.37	1952.5	15 0	106 4	5 88
Ma.	1005.2	12.4	105.1	5.86	2865.0	18 0	132 6	6.33
AWAKE SEVERAL WEEKS—FED ONE, TWO OR THREE WEEKS								
Av.	881.1	11.9	96.0	5.68	1668.4	14.7	111 7	5.97
Mi.	814.5	11.6	94.4	5.65	1504.4	14.2	102.5	5.81
Ma.	915.0	12.0	97.4	5.71	1790 8	15.0	121.1	6.14

SIZE OF CELLS AND NUCLEI IN PARS BUCCALIS

a. Pars anterior

The result of the volumetric study of cells and nuclei of thirty animals are collected in table 3. With reference to pars

anterior before hibernation it is seen that the average cell diameter is 11.8 μ and the average volume is 854.2 cu. μ. The nuclei average 5.45 μ in diameter and 84.9 cu. μ in volume. During hibernation these figures are not decreased, being the same for the cell and slightly larger for the nucleus. Similarly after hibernation and before feeding there is but little change in the size of the whole cell (a decrease, if anything, but too slight to be of any significance), but the nucleus apparently slowly increases. There are so few animals in the last group that the effect of feeding is not established.

The atrophic changes during hibernation described by Gemelli and by Cushing and Goetsch are not supported by these measurements, nor do the cells as a whole seem to get larger after becoming active in the spring.

The inanition effects described by Jackson ('17) in the rat (reduced and vacuolated cytoplasm, hyperchromatism and pycnosis of the nucleus) are not in evidence in the emaciated woodchuck.

b. Pars intermedia

The cells in pars intermedia (excluding the smaller cells, with hyperchromatic nuclei and located in the posterior portion and also excluding the cells lining the residual lumen) are about twice the size of the cells of pars anterior. The nuclei are also

TABLE 4.

Relative number of acidophilic and basophilic cells in pars anterior of the woodchuck hypophysis based on counting from 206 to 284 fields in each of four animals (2 males and 2 females) in each of the three groups. Figures refer to the number of cells per field.

The headings below refer to the averages obtained from individual animals.	Before Hibernation		During Hibernation		After Hibernation	
	Acido.	Baso.	Acido.	Baso.	Acido.	Baso.
Average of all four animals	36.3	4.5	40.6	4.7	46.9	14.7
Minimum	33.8	1.1	38.5	4.0	40.3	12.6
Maximum	39.2	12.7	44.6	4.9	54.4	16.7

larger being nearly 6 μ in diameter as compared with 5.5 μ, the diameter of pars anterior cells. Here again there is no difference between the pre-hibernating period and that of dormancy. The third, or post-hibernating group, shows a perceptible increase in the size of both cells and nuclei. This, however, is not supported by the three fed animals in the last group.

RELATIVE NUMBER OF ACIDOPHILES AND BASOPHILES IN PARS ANTERIOR

a. Before hibernation

To check the assertion that during hibernation there is a loss of the differential staining power of the cells in pars anterior, the average number of acidophiles and basophiles present in a microscopic field was determined in two males and two females from each of the three principal groups. These data, as filed in table 4 show that before hibernation there were 36.3 acidophiles and 4.5 basophiles per field. The basophiles varied between such wide limits (1.1 and 12.7) that the average is not worth much. The mean value was, of course, lower than the average.

b. During hibernation

The figures obtained during hibernation do not vary much from those already given. The range of variation was much more limited in the case of the basophiles, while the acidophiles are slightly more numerous. Dormancy, therefore, produces no striking modification in the number of chromophilic cells which appear as a rule at least as numerous during hibernation as before. One case was found to contain three times as many basophiles before as was ever found during lethargy but the rest had distinctly fewer. The intensity of the differential stain was as great as was generally the case in the preceding group.

c. After hibernation

After waking up a marked increase in the number of basophiles is indicated (14.7 as compared with 4.7 during and 4.5 before hibernation). There appears to be only a slight increase in acidophiles. Since the anterior lobe is a third larger at this time (table 1), the total numerical increase is unquestionable—amounting to about four times in the case of the basophiles. This increase in chromophile cells fully accounts for the enlargement of the pars anterior. The basophiles also stain more strongly with the basic dyes so that they stand out more prominently. The macula is therefore more evident in thin sections and the whole Golgi apparatus—if such it is—is generally larger than at any other time. The increased differential staining properties of the basophiles is fully in accord with all previous observations. It cannot be said that the acidophiles stain more intensely.

Here again the decrease in the specific staining reaction noted by Jackson ('17) in the rat during inanition is not dupli-

cated in starving woodchucks with a loss in body weight from 30 to 40 per cent, in round numbers (Rasmussen and Rasmussen '17, p. 141).

d. Significance of the different types of cells in pars anterior

The many writers that have commented on the significance of the different types of cells in pars anterior (for literature Biedl '16, Schäfer '16, Cooper '19) may be classified into two main groups. Probably a majority (St. Remy, Benda, Caus and Van der Stricht, Herring, Stendell, Pirone, Launois, Thaon and Joris, Sandri, Noronha, Vanderburgh, Cooper and others) favor the view that they are merely different functional stages of the same general type of cell. The basophilic are generally regarded as containing the ripe secretion and the other types as being in earlier stages of the secretory process. The other group (Lothringer, Rogowitsch, Stieda, Flesch, Gemelli, Scoffidi, Thom, Guerrine, Erdheim, Kon, Kraus, Schäfer, Addison, etc.) believe they represent at least two different functional types, there being a strong tendency to favor the derivation of the chromophiles from the chromophobes, but to consider the acidophiles and basophiles as functionally different; but ideas vary greatly.

The almost total lack of intermediate forms, particularly between the acidophiles and basophiles, as judged after staining with a differential stain such as Mallory's acid fuchsin—aniline blue—orange G, does not favor the view that the three kinds of cells are different functional stages of the same cell. In the very active rutting period when the hypophysis enlarges, one would from the first theory expect to see many transitional forms.

The lack of any modification of the general cell picture during profound dormancy in the woodchuck leaves us with no positive suggestion from this source as to the functional significance of any of the constituents of the hypophysis; but the marked response to increased activity shown by the basophilic cells, indicates that this type is more intimately related to processes which are readily influenced by the changed conditions incident to hyperactivity. The susceptibility of the basophiles is also shown by the increase in size, number and vacuolization which they undergo in the albino rat after castration (Addison '17a). Although the acidophiles also are affected by ovariotomy in the human female, Rössle ('14) noted as well a decrease and even

lack of basophiles. Possibly in time the greatly modified basophiles pictured by Addison in the rat would become so necrotic as to be absorbed, thus bringing the above two observations into substantial agreement. According to Lucien ('11) there is a marked increase in the basophilic cells in the aged and Raeder ('20) reports that in the feeble-minded, where the hypophysis is involved more often than any other ductless gland, the most frequent change is a deficiency of the basophilic cells.

Until the appearance of the different cells during specific stages of their activity is more fully known it is hazardous to attempt any elaborate interpretation of the findings here reported.

SUMMARY

1. The hypophysis cerebri of the woodchuck has all the structures generally recognized. The processus infundibuli and the distal portion of the infundibulum are solid. There is a well preserved residual lumen. The whole organ (after fixation and embedding) forms normally 0.000235 per cent of the gross body weight.

2. Pars anterior (distalis) forms a crescentic lobe which constitutes 46 per cent of the entire organ before and during hibernation. It has the usual rich blood supply. Three types of cells are recognized in this lobe: chromophobes, acidophiles and basophiles. The lack of intermediate forms (tinctorially) militates against the theory that these three types are only different functional stages of the same cell.

3. Pars intermedia (juxta-neuralis) represents only 2.46 per cent of the whole gland (average of pre-hibernating and hibernating stages). The great bulk of this structure is composed of the usual large cells. An irregular stratum of smaller cells forms the posterior boundary. The cells next to the residual lumen are greatly modified into squamous and into long spindle-shaped columnar cells. Colloid is frequently abundant—the larger masses being partly or entirely surrounded by a wall of special cells.

4. A sex difference is apparently revealed by the volumetric analysis of the lobes. The male gland averages 13 per cent larger than the female. This difference is equally shared by pars nervosa and pars buccalis (glandularis), but of the two components of the latter pars intermedia is 50 per cent larger while

pars anterior is only 10 per cent larger in the male. However, only 26 animals (13 males and 13 females) are considered.

5. Hibernation produces no change in the weight or histological structure of the hypophysis when compared with the pre-hibernating gland, which is the standard of greatest reliance. The atrophic appearance of pars anterior (suggesting a stage of hypofunction) as previously reported is not confirmed.

6. Immediately after waking up in the spring, during the rutting season, hypertrophy takes place in the hypophysis amounting to 33 per cent in animals kept in captivity. This is distributed proportionately among the three principal parts of the gland. The chief cells and their nuclei in pars intermedia apparently increase slightly in size. While the average volume of the cells in pars anterior shows no variation, the nuclei show a little enlargement. The conspicuous change accompanying the heightened activity is a tripling of the relative number of basophiles and a distinct increase in their staining reaction.

7. It is believed that a failure to compare the hypophysis of the hibernating stage with that of the stage just before the onset of dormancy and the tendency to interpret the post-hibernating conditions as the normal state, are responsible for the idea that winter-sleep in the marmot produces atrophic changes. The return to the pre-hibernating condition evidently occurs late in the summer after the active stage of the sexual cycle has terminated, as is the case with the interstitial cells of the testis and ovary. The limited number of animals involved and the great range of individual variation are also probable sources of error which are to some extent applicable to this study as well.

8. There is a striking difference in the reaction of the woodchuck and of the albino rat (a non-hibernating species) to inanition. While inanition in the rat produces atrophic changes in the hypophysis (Jackson), starvation even in the spring during several weeks of activity and after three months deprivation of food during dormancy, is attended with no such characteristics but rather with hypertrophy of the whole organ and hyperplasia of some of its elements.

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THE CONTROLLING FACTORS IN AMPHIBIAN METAMORPHOSIS: A REVIEW

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(Contributions from the Zoölogical Laboratory of the Museum of Comparative Zoölogy at Harvard College, No. 327, and from the Bermuda Biological Station for Research, No. 124.)

I. In the study of the factors which control the developmental processes in animals, the most fruitful results undoubtedly have been achieved in the investigations upon the metamorphosis of amphibians. The profound changes which are attendant upon the process of metamorphosis occur with great abruptness and are obviously the expression of correspondingly abrupt alterations in the physiological processes within the organisms. The researches on the endocrine organs have demonstrated that these sudden changes are caused by the secretory activity of the ductless glands; in other words, that the hormones of the endocrine glands control, to a very large extent, the changes which come about during metamorphosis.

The literature dealing with the relation of the ductless glands to metamorphosis is extremely varied, and the results have not hitherto been coördinated in a single paper. In addition, many of the conclusions which have been reported conflict with one another. The writer aims, therefore, to present the subject in the space of a few pages, and, as far as possible, to coördinate the material which has appeared in the literature. The historical development of the work on the ductless glands will not be included since it is widely known and may be found by consulting any text-book of physiology.

Among the ductless glands which function in promoting the developmental processes in amphibians, the most important is the thyroid. This fact was first disclosed when tadpoles were fed upon the desiccated gland.

II. *Thyroid feeding:* Gudernatsch, assuming that during the metamorphosis of amphibians the metabolic rate was abnormally high, concluded that if a substance could be found which would increase the metabolism of the larvae, the speed of metamorphosis would be greatly accelerated. Pragmatically to prove such a contention he undertook a series of feeding experiments in which he attempted to raise the metabolic rate of some young

tadpoles. The work which previously had been done on the endocrine organs had firmly established the fact that certain of the internal secretions effect a high metabolic rate in mammals. This prompted Gudernatsch to employ the extract of several of the ductless glands in his feeding experiments. The results were striking; hardly, however, to be interpreted as the result of a mere increase in the metabolic rate, but rather to an acceleration of the developmental processes themselves. Growth was arrested immediately the extract was administered; particularly was this true in the case of the thyroid, but the developmental processes proceeded so rapidly that within less than a month a mature frog had resulted, which appeared to be normal in every respect save that it was ridiculously small. Thus, though the metabolism may have been greatly stimulated, it did not cause a more rapid growth (that is an increase in size), but was directed to the hastening of development. The initial assumption of Gudernatsch ('12 and '14) that a stimulant of larval metabolism should cause a precocious metamorphosis was thereby justified; the hindering of growth was simply a result which had not been foreseen. The work was immediately confirmed by numerous observers both in this country and in England. Hoskins ('16) of Minnesota showed, not only that metamorphosis was accelerated, but that the thyroid feeding caused also a comparative enlargement of many of the internal organs. Herring ('17) proved that a similar phenomenon occurred when white rats were fed upon thyroid. In short, Gudenatsch's discovery raised a host of interesting problems, the solutions of which are at the present time just beginning to be reached.

The first questions which naturally arose were: Does the thyroid gland in these larval forms bring about metamorphosis? If so, how? What forces does it set into motion? Is it assisted in its work by the other ductless glands? What relation does the thyroid bear to the nervous system? The thyroid gland was known to contain iodin. What, then, is the relation of iodin to the thyroid and to metamorphosis? These are only a few of the more important questions which were immediately raised after the discovery had been made known.

III. *Thyroidectomy:* The first question—does the thyroid gland cause metamorphosis—might reasonably be answered if it could be shown that thyroidectomy prevented metamorphosis.

The operation involved in removing the anlage of the thyroid gland from young larvae is uncommonly difficult. It was accomplished simultaneously, however, by two investigators who worked independently. To quote Hoskins and Hoskins ('19):

> "The first operations were performed by one of us in April, 1916, and in the spring of 1917 and 1918 the experiments were repeated. We learned in November, 1916, that Doctor Allen [See Allen, '18] of the University of Kansas, had performed similar experiments with R. pipiens at about the time when our first were made."

The results of the two experiments accord with each other entirely. They both show that metamorphosis cannot take place in the absence of thyroid gland. The intestine retains its larval characteristics and the development of the brain is almost completely stopped. As to sexual maturity, both authors agree that the development of the gonads is in no way affected by thyroidectomy (Allen '17b). In other words, the hormone which provokes the frog partially to metamorphose has no influence upon sexual growth. Hoskins and Hoskins ('19) note further that the lungs seem also to continue their normal development. The liver, thymus,[1] spleen and kidney are arrested in their growth and continue to retain their larval form. In addition to these features, the larvae grow rapidly and attain sizes which sometimes are absurdly large. In the Hoskins' experiments, one grew to a length of 72 mm. while control specimens averaged between 40 and 45 mm. Thyroidless larvae have been kept over a period of more than two years without completion of metamorphosis.

The earliest apparent differences between thyroidectomized and control larvae are in the skeletal elements. It would seem, inasmuch as the legs fail to develop normally, that the calcium metabolism must be interfered with by the thyroid removal. Terry ('18) describes the general processes of calcification and ossification as progressing much more slowly in the operated tadpoles.[2] Buds of legs appear, it is true, but their failure further to develop is caused by the failure on the part of the skeletal part to push into the buds. Nevertheless, it seems to me highly questionable that the thyroid directly controls calcium metabolism. The pituitary has been demonstrated (p. 86 below) to

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[1] That the thymus should fail to undergo atrophy as a result of thyroid removal does not indicate a close connection between the two glands, but simply that the thymus along with many other organs fails to lose its larval form. This fact Rogers ('18) fails to observe.

[2] Hofmeister ('94) also noted that thyroidectomy was followed by an abnormal growth of bones.

have a direct connection with the growth of bones, and it appears more probable that the changes which occur in the pituitary after thyroidectomy themselves in turn affect ossification. In this light, the thyroid would control calcification only in so far as it had control over the hypophysis. It has also been suggested that the hypertrophy of the hypophysis following thyroid extirpation may be responsible for the acceleration in growth rate of the thyroidless tadpoles (Hoskins and Hoskins, p. 18).

In view of the fact that the lungs continue their normal development, it was of interest to see whether the thyroidless larvae would live out of water. On being put in a moist chamber they continued to live for two days, but owing to the fact that food could not be obtained as under normal circumstances, death threatened from inanition. The Hoskins ('19) tried also to force metamorphosis by putting the larvae in a moist chamber on a bed of wet Spirogyra, where they were kept for two days. Though there was a slight diminution in the tail volume and length, no positive results were obtained.

At this point an observation of Allen's ('18, p. 508) is of interest. He found that, though metamorphosis be arrested by thyroidectomy for as long as four months, yet if the tadpoles are fed upon desiccated thyroid the process of metamorphosis is resumed, and normal frogs result. This is of singular interest since it shows that the thyroid hormone is capable of promoting metamorphosis in the absence of the gland itself, that the active principle which produces the changes occurring in metamorphosis is a definite chemical substance, and not one which requires the living cell to synthesize it at the moment it is needed. It would seem to indicate further that the thyroid gland functions rather to store certain chemical substances taken in as food than to manufacture them.

Undoubtedly the most remarkable result of the investigations on thyroidectomy is the effect—or, better, the lack of it—which the operation has upon the *germ* cells. Apparently they continue their development totally unaffected. It has been shown by Swingle ('18b) that inanition may hinder greatly the development of germ cells. The same investigator ('18a) declares that feeding with thyroid extract, though greatly accelerating development, in no way hastens the growth of the gonads. Also Allen ('18) and other observers have emphasized the fact that thy-

roidectomy does not delay in the slightest the development of the testes and ovaries. In other words, substances which hasten the proliferation of the soma cells do not materially affect the germ cells. It is interesting to speculate concerning the bearing which these facts may have upon Weismann's hypothesis concerning the independence of germ and soma. Certainly a very marked degree of independence is here manifested beteen the two types of tissue. Whether a complete independence exists, is very difficult to determine with accuracy. Spermatozoa actually were seen in both Allen's and the Hoskins' larvae. The growth of oöcytes was, on the other hand, definitely slower, the largest which were obtained being about 300 micra in diameter. There seemed to be no definite correlation between the development of the oöcytes and the bodily growth and in none of the experiments were sufficiently mature eggs formed to make larval reproduction possible.[3] If larval reproduction can be effected under laboratory conditions, the outcome will be of singular interest to the student of Weismannism.

Superficially, the results recorded above may seem to conflict with the conclusions reached by Hofmeister, Jeandelize and Eiselsberg, who state that thyroid removal in the higher animals has a detrimental effect upon the gonads. It must be recalled that their experiments were performed, for the most part, upon adult animals. In such cases, the effect seems rather to disturb the physiological equilibrium than to prevent the growth of the gonads. In this connection, a view expressed by Max Kollmann ('19) is of interest. He believes that the thyroid gland favors the permanence of certain secondary sexual characters, but that it does not bring about their growth. In other words, having once reached sexual maturity, the thyroid is needed to maintain the physiological balance. That this is the case also seems evident from a recent work of Giacobini ('19), who has shown that sterility in women is frequently caused by a deficiency of the thyroid.[4]

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[3]Duméril ('67) has reported larval reproduction in amblystoma tigrinum found near Lakes Xochimilco and Chalco (eight miles from Mexico City)—a region which is practically free from any traces of iodin (Gadow, '08). De Filippi ('61) also found Triton larvae with mature sex organs in the Formazza valley, near Andermatten.

[4]He states also that thyroid injections relieve incipient symptoms of sterility.

Unfortunately, no attempts have been made as yet to force thyroidectomized larvae which have metamorphosed on a thyroid diet, to reproduce.

The theories of Uhlenhuth regarding the effect of thyroidectomy will be discussed below.

IV. *Iodin and the thyroid:* The relation which the halogen atom, iodin, bears to the thyroid, and more especially to the phenomena of amphibian development, has long been disputed and is at the present time still an unsettled question. As early as 1820 iodin was used in treating diseases of the thyroid, but it was not until 1895 that Baumann actually demonstrated the existence of this substance in the follicles of the gland, and proved that it was compounded with a protein. As to the powers of the thyroid secretion there are those who maintain that its activity is determined by its iodin content, and another group who believe that the amount of iodin which the thyroid contains is entirely a secondary factor, and that its power to stimulate metabolic processes depends upon the protein molecule with which the iodin is associated.

The chief cause of the disagreement lies in the interpretation of the results obtained from amphibian experimentation. Let us examine first the evidence of those who hold that iodin is the active element.

Marine and Williams ('08) observed that when thyroglobulin rich in iodin was fed to dogs they lost more weight than when the preparation contained a smaller percentage of iodin. Hunt ('07) and Hunt and Seidell ('08) also concluded that the activity of the thyroid depended upon its iodin content. By testing the various substances obtained by alkaline hydrolysis on metamorphosing tadpoles, Marine and Rogoff ('16) reached the same conclusion. In the same year, Oswald expressed a view which entirely accords those just noted. G. E. Smith ('17) also has shown that birth mortality in pigs in regions where the "hairless pig malady" occurs is greatly lessened if the sow is fed upon iodin during gestation.

The most important results, however, are those of Swingle ('19a and b). He found, in the first place, that if tadpoles are fed upon a mixture of one part iodin and one hundred parts flour, their metamorphosis is greatly accelerated, identically as it is by feeding with thyroid extract. KI has a similar effect but

it acts much more slowly, while iodoform is excessively toxic. With the mixture of iodin and flour, Swingle found that growth was stopped almost immediately, but that complete metamorphosis had resulted in less than a month. The writer repeated this portion of Swingle's work while at Bermuda Biological Station (1919) and attained results which were practically identical with those of Swingle. The iodin feeding was conducted on Bufo agua larvae which averaged about 10 mm. in length. Seven days after the first administration, hind limb buds were very clearly in evidence. The fore-limb buds appeared four days later. At the end of twelve days the hind limbs were 3 to 4 mm. in length and atrophy of the tail had set in.[5]

Swingle carried the work still further and found that thyroidectomized larvae would immediately metamorphose if put upon a thyroid diet. This result is undoubtedly far-reaching in its importance. The two most interesting deductions, to use Swingle's own words ('19a, p. 413), are as follows:

> "If animals without the vestige of a thyroid gland are stimulated to complete metamorphosis in an abnormally short time by iodin, it would appear that iodin functions within the organism as a hormone itself, and that the gland functions chiefly for storage purposes. The evidence from the thyroidectomized larvae indicates that the animal body is capable of utilizing iodin directly without the intermediation of the gland."

As an evidence for the theory that the thyroid functions to store iodin for future use, Swingle offers the fact that the glands of iodin-fed larvae are considerably larger than those of the controls, and a histological examination revealed the fact that the colloidal content of the follicles was greatly increased.

The unavoidable conclusion is that, as far as amphibian metamorphosis is concerned, iodin is certainly the activating substance which effects the changes. It would be a stretch of language, however, to say that iodin causes metamorphosis; more accurately, it should be stated that metamorphosis cannot go to completion in the absence of iodin. The processes of development are set in motion by the fertilization of the egg, and the end and aim of the developmental process is the production of a mature frog. The larval stage is reached and all of the potentials

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[5]Mr. Leland C. Wyman of the Harvard laboratories is now making a thorough histological examination of the thyroids from the tadpoles used in these experiments.

of an adult frog lie within the cells of the animal, but to complete its development, a call is made upon the environment for iodin. It should be emphasized that the larva has to reach a very definite stage in life history before it can utilize iodin. If administered before a length of approximately 10 mm. is reached, it serves only to kill. The point that must be made clear is that iodin does not cause metamorphosis but simply acts like a lubricant in assisting the developmental potentials residing within the larva.

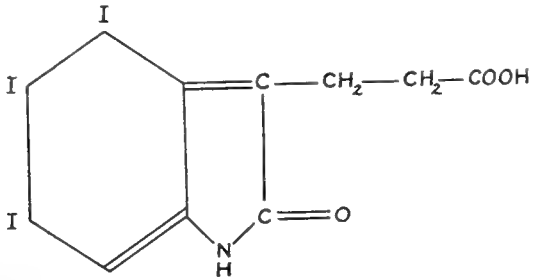
Let us now consider the experiments of those who deny the correlation between iodin and thyroid activity.

Working in the amphibian field, the only two authors whose researches seem to cast doubt upon the functional activity of iodin are Graham ('16) and Abelin ('17). By feeding fractionated parts of the thyroid extract they have gained evidence that some fractions which are really low in iodin content are exceptionally active in promoting metamorphosis. The evidence which they present, while interesting, is by no means conclusive, and particularly must it be accepted with caution after the positive results which Swingle has set before us. There is, however, a series of chemical investigations which demand the most careful consideration.

E. C. Kendall ('18, '19a and b) of the Mayo Clinic at Rochester, Minnesota, after eight years' work, in which he used some two tons of thyroid glands, finally succeeded in isolating and analyzing the active principle of the thyroid gland, and has called it "thyroxin."

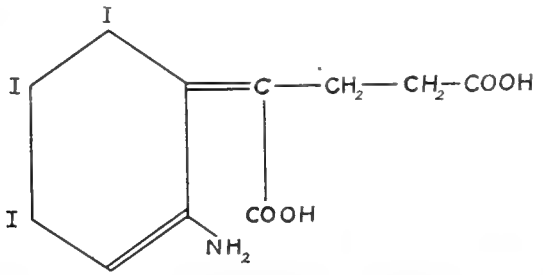
Attacking the problem, as he has, from the chemist's viewpoint, and experimenting liberally upon human subjects, he has reached the conclusion that the iodin content, for man at least, does not give to the active principle of the thyroid its powers to stimulate metabolism. The formulae which Kendall believes to represent the structure of the active principle are two in number: one an active form and the other an inactive substance which exists when the hormone is being held in reserve. The active constituent has as its structural base an indole group possessing three substituted iodin atoms on the benzene ring, and an oxygen

and a propionic acid radical attached to the imino group. Structurally it is represented as follows:



and bears the technical designation of 4, 5, 6 triiodo 4, 5, 6 trihydro 2 oxyinodolepropionic acid; the shortened form being thyroxin.

In an alkaline solution, the NH and CO groups of the imino ring undergo hydrolysis, which results in the opening of the ring and the formation of NH_2 and COOH. This change converts the functioning thyroxin into its inactive form, shown in the next formula:



Both the extract and the synthesized thyroxin act in the same way when put into an alkaline medium; when the solution is made acid, however, the ring closes and the substance again becomes active. It is Dr. Kendall's belief that in the body the conversion from the inactive to the active thyroxin is effected by the action of the amino acids. It has also been suggested that CO_2 may also aid in bringing about this change.

On account of the peculiar action of the imino group in the presence of acids and bases, Dr. Kendall has been led to the belief that the imino side-chain—not the iodin atoms—are responsible for the physiological activity of the substance. He has also furnished experimental evidence to uphold this contention.

One third of one mgm. of thyroxin will increase the metabolic rate of an individual weighing 150 pounds one per cent. The open-ring formula, which contains just as many iodin atoms, increases only in very slight measure the metabolic rate. Hence it seemed reasonable to conclude that it is the closure of the ring which causes its activity.

Those who are skeptical of Kendall's stand have made the suggestion that thyroxin ought still to act if the iodins were replaced by bromine atoms. Swingle ('19c), while not disproving this suggestion, immediately fed some tadpoles upon bromine and found that it in no way stimulated metamorphosis,[6] but was, on the contrary, highly toxic.

Kendall thereupon performed some tadpole-feeding experiments himself and found that both the open-ringed and the closed-ringed thyroxin stimulated metamorphosis in exactly the same way. From these results he arrived at the following conclusions:

> "Thyroxin, therefore, appears to have two separate and distinct functions: The effect upon the metabolic rate which is brought about by the CO-NH groups within the molecule; and the physiological changes involved in the metamorphosis of the tadpole brought about by the iodin contained is not specific to thyroxin, but can be obtained by a large number of other iodin compounds and by elemental iodin itself, and appears to be inherent within the iodin atom. But the unique effect of thyroxin on the metabolic rate is due to the specific chemical structure of the molecule and this is not shared with any other substance so far known" ('19b, pp. 136-137).

The view thus expressed seems to be reasonable, and, if accepted, it effects a successful explanation of the divergent views which have heretofore existed concerning the importance of iodin.

Before concluding the consideration of the thyroid and metamorphosis a word must be said regarding the theories which Uhlenhuth ('19d) has recently advanced. According to this investigator there are two substances which incite metamorphosis; one, the iodin, which causes morphological changes such as the atrophy of the tail and the loss of the gills; the other an "excretor substance," a protein, which is produced by growth and which excites the thyroid gland to functional activity. The time of production of this hypothetical excretor substance determines when a larva shall metamorphose. He adds further that the thyroid secretion which is made active by this excretor sub-

[6] It is interesting to note, however, that prolonged inhalation of bromine fumes produces profound changes in the thyroid (Pellegrin, '17).

stance is responsible for growth. It might be noted here that inasmuch as tadpoles which are fed upon iodin do not grow, one could say that it was due to an absence of the "excretor substance." Such hypotheses as these are really of great interest, but until they are backed by experimental proof, they are of little scientific value.

In a later paper, Uhlenhuth ('19e) groups the changes which occur during metamorphosis under four main headings and then attempts to show that the changes in any group can be made to go on independently of the others. He uses the sex organs to illustrate his point. As was shown above, their development can go on independently of the other phenomena of Anuran development. That the other changes—gill reduction, leg growth and the enlargement of the tongue—can go on independently of one another lacks experimental proof.

V. *The other endocrine glands.* From the consideration of the thyroid it is evident that this gland controls the development of a large number of the internal organs; however, it exerts practically no influence over the growth of bones and has little control over the development of the germ cells. Let us, therefore, examine the other endocrine glands and find to what extent they control these processes.

The desiccated substance of the pineal organ has been shown by recent workers to be a powerful metabolic stimulant. McCord and Allen ('17) find that in a dilution of 1 to 100,000 it produces a complete retraction of melanophores of amblystoma larvae. But of much greater importance is the inhibitory effect which the pineal organ appears to have upon the growth of the germ cells. Foà ('12) reports upon an interesting work in which he removed the pineal from roosters, and found that the operation was followed by a marked hyperthrophy of the testes as well as of the crest. The work of Foà has been paralleled recently by some experiments on guinea-pigs. Horrax ('16) studying some eighty cases of successful pinealectomy in guinea pigs and rats, finds the operation had no effect upon body weight, but that it accelerated greatly the development of the testis. This was confirmed both by the early date at which breeding commenced and by histological examination. The results in the female were not conclusive. The work of Horrax needs confirmation. If it can be shown conclusively that the pineal gland exerts a definite

inhibitory influence upon sexual development, it is placed beyond a doubt among the endocrine organs. Whether these observations are applicable in explaining phenomenon of sexual development in amphibians, has never been determined, but it would indeed be of great interest to find whether the maturation of the germ cells would be accelerated in the event of pinealectomy.

As for the parathyroid glands, there is every indication that they are isolated both functionally and anatomically from the other endocrine glands, and probably perform no function in the promotion of metamorphosis. Kamo ('17) reports that the removal of the thyroid produces no effect on the parathyroids; Allen ('19b), however, believes that a slight hypertrophy results. The most interesting function of the parathyroids, however, lies in their power to prevent tetanus.

It has been observed by several, during the last few years, that thymus extract causes violent convulsions when fed to certain amblystoma larvae. The effect was first noted by Lenhart ('15). This peculiar action of the thymus has led to an uncommonly interesting piece of theoretical work by Uhlenhuth. In the first place, he interprets the violent convulsions following thymus feeding as tetanus. He observed further and it is upon this observation that the validity of his whole theory rests that the two species of amblystoma which became tetanous when fed upon thymus are species which do not possess the parathyroids until a later stage. He states also that the larvae which have their parathyroids developed do not become tetanous when fed upon thymus (see Uhlenhuth, '18). On a basis of these observations, Uhlenhuth ('19c) concludes that the thymus secretes a tetany-producing substances which is normally neutralized by the parathyroids.

The hypothesis of physiological antagonism which Uhlenhuth has thus set before us is most unusual and requires, therefore, our careful consideration. In the first place, the theory requires corroboration. At present there seem to be open at least three main channels by which further evidence for or against his theory can be secured.

(1) Probably the most vulnerable spot lies in his statement that amblystoma *opacum* and *maculatum* do not possesses parathyroids in the early stages. If it can be shown conclusively that this statement is true, the theory will be put upon a very substantial foundation. (2) Noël Paton and his co-workers ('17) have shown that the salts of guanidine and methyl-guanidine produce all the symptoms of tetany and that the salts of guanidine increase in parathyroidectomized animals. In the light of Uhlenhuth's theory the thymus would probably effect the increase in the salts of guanidine. Hence, if it could be demonstrated that the thymus secretes guanidine, the theory would be well substantiated. (3) A further method for demonstrating the efficacy of Uhlenhuth's theory lies in finding whether an injection of desiccated parathyroids ameliorates in any way the symptoms of tetany (parathyreopriva). Honeyman ('19) working under the direction of Noël Paton, has already attempted to disprove the contention of Uhlenhuth. He removed both the thymus and the parathyroid glands simultaneously from a guinea pig and tetanus ensued in exactly the same manner as it does when the parathyroids are removed. The contrary evidence which he gives is by no means conclusive. The chief objection is that the work was done upon a very much higher animal, and one from which, as a matter of fact, according to Park, the thymus can not be completely removed. It was done, besides, upon a matured animal, while Uhlenhuth's experiments were performed on species which were in their larval stage.

The thymus gland, aside from having little influence upon metamorphosis in amphibians, is probably not an endocrine organ. The investigations of Dustin ('13), Hoskins ('18), and Badertscher ('20) have shown that its most important function is probably in hematopoiesis. The results of thymus feeding

are contradictory. Swingle ('17) reports that it has no effect upon the rate of metamorphosis, and Hoskins ('16) states that it has no constant effect; Gudernatsch ('17), on the other hand, has had positive results in his thymus feeding experiments. Recently, Allen ('20a) has reported evidence that the extirpation of the thymus produces no effect upon the rate of metamorphosis. Uhlenhuth ('19b) has come forward with a theory which aims to account for discrepancies in the results. Put in form of a syllogism the theory would be stated as follows: 1. The thyroid gland causes metamorphosis. 2. In normal food there are certain substances which incite the thyroid gland to secretory activity. 3. In that the thymus as food does not possess substances which incite the thyroid, thymus feeding has an inhibitory effect upon metamorphosis. In the light of his experimental evidence, the theory seems reasonably sound. He fed one set of tadpoles upon thymus, taking pains to prevent any other food substances from getting into the water, and found that the effect was definitely inhibitory. To another group he fed thymus, but permitted other food substances to be contained in the water. This group metamorphosed normally.

Excluding the thyroid, the anterior lobe of the pituitary undoubtedly is the most important of the ductless glands concerned in amphibian metamorphosis. The fact that the hypophysis is associated with acromegaly at once suggests that the gland may control the growth of bones, and the investigations of Erausquin ('17) show that such is the case. It is widely agreed, moreover, that hypophysectomy inhibits growth. The very striking work of Aschner ('12, p. 68) on dogs is an interesting example. From one of two brother puppies the pituitary was extirpated. After six months, the normal pup was very nearly three times the size of its brother. In the amphibian field we have more recently the results of Allen ('17a and '19b) and P. E. Smith ('16a, b and '18) which briefly are as follows: If young larvae have their pituitaries removed, there follows a general retardation of growth, incomplete metamorphosis, a complete retraction of the pigment cells (8 days after extirpation, Allen), failure of legs to develop, and lastly a very marked effect upon the thyroid. The results of feeding pituitary, on the other hand, are somewhat contradictory. Hoskins ('16) believes that it has little or no effect upon growing tadpoles. Smith ('18), however,

reports a marked increase in growth rate both of normal larvae and those from which the pituitaries have been removed. Kojima ('17) shows that feeding of the extract to normal larvae causes a marked hypertrophy of the pituitary gland itself.

It has been believed for some time that the gonads and the pituitary bear an intimate relationship one to the other. According to Noël Paton ('13, p. 186) castration causes marked changes in the anterior lobe of the hypophysis. Addison ('17) has recently made the interesting observation that castration in the Albino rat is followed by a marked increase in the number of basophilic cells in the hypophysis. He believes that the interstitial cells of the testis and the basophils in the anterior lobe are intimately connected and it is his opinion that the latter control the former. In 1916 Goetsch stated that the extract from the anterior lobe when fed to tadpoles greatly accelerates their sexual development. Finding that the extirpation of the anterior lobe causes no change in the testis of amphibians, Allen ('17a) objects strenuously to Goetsch's conclusions. On such a basis it seems to me that the objections are wholly unjustified.

The results of feeding the extract of the anterior lobe of the hypophysis to thyroidectomized larvae are also of great interest. Larson ('19) for instance, has fed the anterior lobe of the hypophysis to thyroidectomized rats, and finds that it has a "beneficial" effect upon their growth. Whether the tethelin (extract of the anterior lobe) takes the place of the thyroid hormone or whether it simply stimulates the metabolic rate was not decided. The experiments of Hoskins and Hoskins ('20) also show interesting results. They find that thyroidectomized Rana sylvatica larvae will almost completely metamorphose when fed upon tethelin. They conclude that the extract acts as a stimulant to the normal metabolic rate.

DISCUSSION

Granting the fundamental principle of the embryologist that "ontogeny tends to repeat phylogeny," a very suggestive deduction is at once forthcoming from the work which has just been discussed. The fact that amphibians in their life history change from water-breathing to land animals makes it evident that land amphibians are descended phylogenetically from the fish. If, therefore, iodin prompts an amphibian to undergo this change

from a water to a land animal what can be said of the factors which control the embryological development of higher animals during the corresponding ontogenetic stages, during the disappearance, for instance, of gill slits from the mammalian foetus? Since iodin causes the atrophy of the gills and other phenomena associated with metamorphosis, according to the principle just enunciated it should likewise effect corresponding changes in the ontogenetic development of higher animals. What evidence can be offered in support of such a deduction?

Dr. C. R. Stockard in his lectures at Wood's Hole during the summer of 1920 expressed his firm conviction that iodin is one of the most important factors which controls the embryological development of mammals. As the result of his experimental work has not as yet been published, one cannot pass judgment upon his conclusions. However, a series of experiments reported by Ukita ('19) tend strongly to support Stockard's stand. This writer has shown that if the thyroid of a pregnant rabbit is removed on the tenth day of gestation, the date of birth of the offspring is postponed from 60 to 70 days, and that the young when born are weak, and are possessed of thyroids which have undergone marked hypertrophy.

Such results as these give to the invesetigations of amphibian metamorphosis an intensely practical aspect, and indicate, in addition, that endocrinology as a science will be concerned in the future not alone with the physiology of mature indviduals, but also with embryological development.

SUMMARY

1. The metamorphosis of amphibians cannot take place in the absence of the thyroid hormone; feeding desiccated thyroid to growing tadpoles greatly accelerates their rate of metamorphosis. Thyroidectomy interferes with bone growth and causes the liver, intestine, thymus, brain, kidney, and spleen to retain their larval state. The gonads and lungs develop normally in the absence of the thyroid. A larva in which the metamorphosis has been arrested by the extirpation of the thyroid will metamorphose normally if fed upon thyroid extract. The thyroid lends permanence to the secondary sexual characteristic rather than causes their growth.

2. The metamorphosis of normal frog larvae is greatly hastened by feeding with organic iodin. Thyroidless tadpoles can be made to metamorphose by iodin feeding.

The structural formula for the active principle of the thyroid has been worked out, and the substance is called thyroxin.

3. The organic extract of the pineal gland accelerates metabolic processes. From the work of Foà and Horrax, it would seem that the pineal hormone inhibits the growth of the testis.

4. Uhlenhuth's theory that the parathyroids in amphibians neutralize a tetanus-producing secretion from the thymus needs further proof.

5. The thymus is primarily a lymphopoiëtic organ. Desiccated thymus does not affect metamorphosis save as it hinders it, when used in excess as food. There is no demonstrated influence which the thymus exerts over sexual development. The thymus is probably not an endocrine gland.

6. The cells of the pituitary are closely related functionally to the interstitial cells of the testis; the anterior lobe probably stimulates sexual development. It also accelerates growth, as feeding experiments with tadpoles show. Further, it assists in bone ossification.

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THE SYMPATHETIC NERVOUS SYSTEM IN DISEASE, by W. Langdon Brown. Published by the Joint Committee of Henry Frowde, Hodder and Stoughton, Ltd., 17 Warwick Square, London, E. C. 4. 10/6 net, 161 p.

This small book of 161 pages deals with a subject the importance of which is just beginning to dawn on the medical profession. The book is based on the Croonian Lectures delivered before the Royal College of Physicians of London in 1918. It seems especially fitting that this important subject should have been emphasized by being discussed before this able body of physicians.

The book is of great interest to students of endocrinology because it points out so clearly relationships which exist between the vegetative nervous system and the endocrine glands. The discussion, however, is confined almost entirely to the sympathetic division of the vegetative system.

The book consists of seven brief chapters in which the anatomy and physiology of the sympathetic nervous system; the sympathetic system in its relation to the endocrine glands, to the digestive and circulatory systems; vagatonia; and general response of the sympathetic systems are discussed. This book helps the clinician in interpreting in terms of physiology many of the symptoms which are commonly met in the every day practice of medicine.

The relationship of the sympathetic nervous system to the endocrine glands is well shown in the following quotation: "Designed as an intensive preparation for action or defense, the sympathetic response may be so dissociated, perverted, or prolonged as to produce through the thyroid gland Graves' disease with its danger to life, through the pituitary body, diabetes insipidus with its attendant discomforts, through the pancreas and other endocrine glands, excessive mobilization of the blood-sugar, which is the first stage of the metabolic disorder that culminates in diabetes; it may disorganize digestion by exciting spasm and atony in stomach and bowels, and inhibiting the secretion of digestive juices; it may keep blood pressure at a level which is inappropriate for the task of the heart and the arteries. These effects are not necessarily distinct—thus, intestinal stasis from sympathetic inhibition causes poisons of putrefactive origin to be absorbed, which in their turn lead to vasoconstriction, and hence an unduly raised blood-pressure."

The relation of the sympathetic stimulation and glycosuria as he sums it up is of especial interest. The author states that underaction of the pancreas and over action of the adrenals, thyroid and pituitary can all lead to glycosuria and that the loss of sugar balance can be produced through the sympathetics in the following way:

"(1) Sympathetic stimulation increases blood-sugar as a defensive measure. (2) Sympathetic stimulation causes increased secretion of adrenals, thyroid, and pituitary. (3) Vagus stimulation excites secretion of the pancreas, and on the generalization of the opposing actions of the parasympathetic and sympathetic it would appear probable that sympathetic stimulation inhibits the secretion of the pancreas; the antagonism between its internal and external secretions does not mean an antagonistic nervous supply; it means a diversion of nervous energy from one channel to another. (4) The general effect of sympathetic stimulation is katabolic, and mobilization of blood-sugar is a preparation for katabolic action. (5) Therefore the sympathetic both by increasing the secretion of glands which diminish carbohydrate tolerance and by inhibiting the gland which increases carbohydrate tolerance, would raise the blood-sugar above the leak-point, and glycosuria would result."

Such data emphasize strongly the interdependence of the vegetative nervous system and the endocrine glands, and show that endocrinology and visceral neurology cannot profitably be treated independently.—F. M. P.

NEUVAS ORIENTACIONES SOBRE LA DIABETES INSIPIDA. By Gregario Marañón, Madrid, 1920.

Starting from the theory of Schäfer, in which a diuretic action is attributed to hypophyseal extracts, the author oriented his own investigations on the supposition that diabetes insipidus is due to an excess of the hypophyseal hormone, that is to say, to a hyperfunctioning of the hypophysis. The results of his studies have given rise to the contrary idea, since he has succeeded in demonstrating that in a large number of cases there are encountered symptoms which point to a hypofunctional disturbance of the hypophysis. This conception is confirmed at autopsy by the finding of lesions which are the effective cause of this essential polyuria. The opinion is strengthened by the specific corrective influence of injections of hypophyseal extracts on the disorder and the action of these preparations in the normal organism.

Marañón concludes that diabetes insipidus is a disease produced by an insufficiency or lack of an internal secretion of the pars intermedia or pars posterior of the hypophysis cerebri, a secretion which normally regulates and moderates diuresis by acting on the renal cells through mediation of a neuro-endocrine complex, or indeed by causing vaso-dilatation of the arteries of the kidney simultaneously with a general modification of the circulatory apparatus.

In concise and suggestive terms, with much erudition Marañón presents the etiology, symptomatology, course, prognosis and

treatment of diabetes insipidus, making of this monograph a work full of interest.—I. O.

THE MORPHOLOGY AND EVOLUTIONAL SIGNIFICANCE OF THE PINEAL BODY. PART I. By Frederick Tilney and Luther F. Warren, Philadelphia, 1919, The Wistar Institute of Anatomy and Biology. The American Anatomical Memoirs.

This monograph represents part I of an extensive study of the pineal body which the authors have undertaken to put out in three parts. Parts two and three are promised to include the physiology, pathology and clinical aspects of the epiphysis.

The authors first take up a general review of the literature concerned with the pineal body from the historical standpoint. This is followed by a very exhaustive review of the comparative morphology, embryology, anatomy and histology of the pineal going from the cyclostomes to the mammals. Following this review there is a discussion of the significance of the pineal region based upon phylogenetic consideration as well as upon histological study.

The summary and conclusions are as follows:

I. The pineal region is preponderatingly glandiferous in its derivatives. The morphogenetic impulse imparted by such a gland-forming area could not fail to have a profound influence upon one of its constituents, the epiphysis.

II. a. The pineal body cannot be a vestige from the evidence based upon its gross morphology, for the following reasons: 1. The phyletic constancy of the epiphysis in the vertebrate phylum; 2. Its variations and morphologic specializations; 3. Its relatively greater phyletic constancy with reference to other structures in the pineal region; 4. The gross evidence of its progressive specialization in ophidians, birds, and mammals; 5. The increase in the epiphyso-cerebral index, from the earliest stages to the latest periods of life in man; 6. The resistance to the encroachment of a prominent neomorph in the mammalian brain, that is, the corpus callosum, which has produced such marked alterations in the other constituents of the diencephalic roof-plate.

b. The pineal gland cannot be considered a vestige in the light of the histological evidence, since the tendency toward specialization is definitely in the interest of glandular formation in ophidians, chelonians, birds, and mammals. Ontogenetically, in two forms at least, in Felis domestica and man, the development of the pineal body follows the general lines of glandular differentiation. The pineal body is, therefore, a glandular structure and as such, is necessary in some way to metabolism.

III. The histology of the organ gives clear evidence that the epiphyseal complex of vertebrates possesses a pluripotentiality the fundamental inherent tendency of which is in the interest of glandular differentiation, but in a few instances, as in cyclostomes, amphibia, and in primitive reptiles, the pineal organ may become further differentiated in the interest of a highly specialized sensory mechanism which has, or has had, visual function. As a gland, it may in some cases, contribute its secretion to the cerebrospinal fluid, but in the higher vertebrates, as in ophidians, chelonians, birds, and mammals, it is an endocrinic organ, contributing the products of its secretion to the blood stream.

IV. a. There is no direct relation between the parietal eye and the pineal body, but each is of itself an adaptive modification answering the demands for, or representing, an inherent impulse toward the development of a parietal eye, on the one hand, or a glandular organ, on the other.

b. The pineal body as it appears in mammals cannot be regarded as the vestigial or metamorphosed, degenerated or atrophic residuum of the parietal eye in vertebrates.

V. The phylogenetic significance of the parietal eye in vertebrates as the homologue of the median eye in invertebrates should be accepted with much reservation. Until such time as the homology between the vertebrate pineal region and some corresponding area of the invertebrate brain is much more firmly established than at present ,the parietal eye as an index in the evolution of the vertebrates from the invertebrates has but little value.—G. H.

Abstract Department

Two cases of ACHONDROPLASIA (Dos casos de acondroplasia). Cavengt (S.), Arch. Espan pedediat. (Madrid), 1919, 3, 706-710.

A clinical history of two cases of evident achondroplasia in a girl of 13 years and a boy of 16 years. Radiography showed a normal sella turcica. Pluriglandular opotherapy was without result.—G. M.

ADRENAL HYPOPHYSEAL medication in asthmatic crises and the pathogenic considerations suggested (La médication adrénalino-hypophysaire de la crise d'asthme et les considérations pathogéniques quélle suggère). Bensaude & Hallion. Bull. gen. Therap. (Paris), 1920, **171**, 434-438.

The authors have made a study of the mechanism of the asthmatic spasm by recording the variations of respiratory expansion of the lung as influenced by intravenous injections of adrenalin and pituitary extracts. Adrenalin alone relaxes the bronchioles which explains the therapeutic efficiency of this drug in asthma. In very large doses the drug diminishes the respiratory expansion, however. This phenomenon is not attributable to a broncho-constriction but to an excessive congestion produced in the lung and consequent pulmonary edema. It it probable that all doses of adrenalin actually relax the bronchial musculature. On the other hand the hypophyseal extract is broncho-constricting in large doses,—doses much larger than would be used clinically. In small doses no appreciable bronchial spasm is produced: no restraint on the respiratory oscillations is observable; in fact they may be amplified. This latter effect of the pituitary extract is interpreted as the response of the lung to the lowering of the blood pressure induced in the pulmonary vessels. The decongestion of the lungs facilitates their expansion, which is diminished by the circulatory engorgement. The concurrence of these two effects, the relaxation of the bronchial musculature by adrenalin and the diminution of the pulmonary blood pressure by pituitary extract, is a justifiable explanation of the beneficial effects observed in their use in asthmatic spasms.—F. S. H.

The flow of ADRENAL blood in the dog (Sur le débit du sang surrénal chez le chien). Boncompte (J. T.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1205-1206.

Measurements of the suprarenal blood flow have been made on animals the blood of which has been rendered incoaguable by peptone or hirudin. At the suggestion of Gley the author repeated the experiments on dogs simply anesthetized with chloral, and without anticoaglulant. The dogs weighed from 9.3 to 15 Kgs. A carefully sterilized canula was inserted into the left suprarenal vein.

The average of a number of determinations gave from 3 to 3.9 cc. per minute. Measurement of the blood flow during and immediately after stimulation of the peripheral and of the splanchnic of the same side (40 seconds' duration) in five expermients gave 1.9 cc.; 6.1 cc.; 5.4 cc.; 0.4 cc.; 4.3 cc. per minute. These results are so inconstant that more experiments must be made to eliminate the variable factors.—T. C. B.

ADRENAL hyperglycemia (Contribucion experimental al estudio de la hiperglucemia adrenalinica). del Campo (Clavero), Eco. med.-quir., 1920, —, — (Jan., Apr.).

The author's investigations confirmed those of earlier observers, to the effect that destroying the hepatic plexus in rabbits did not prevent adrenin hyperglycemia.—G. M.

ADRENAL hemorrhage in children (Apoplexie surrénale chez les enfants). Comby (J.), Arch. med. d' enf. (Paris), 1918, **21**, 651-656.

Five case reports are here presented of adrenal hemorrhage in children which is considered as either the direct or contributing cause of their death. The opinion is expressed that no treatment is availaing in true adrenal apoplexia.—F. S. H.

The musculature of the central veins of the ADRENALS in man. (La musculature des veines centrales surrénales de l'homme.) Dubreuil (C.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1096-1098.

A description of the smooth muscle fibers of the suprarenal veins in man.—T. C. B.

(ADRENALS) Antibody production after partial adrenalectomy in guinea-pigs. Guenther (A. E.), Nebraska State M. J. (Norfolk), 1918, **3**, 15-19.

A general review with no new data.—F. S. H.

ADRENAL insufficiency and gastric ulcers (Insuficiencia suprarrenal y ulcera gastrica). Hernando (T.), An. de la Acad. med-quir. de Madrid, 1919, **6**, 378-400.

Many interesting clinical cases are described of gastric ulcers in Addisonians. A pathogenic relation is established between the two fundamental conditions by virtue of: (1) the lymphatic condition which accompanies the adrenal insufficiency, according to the investigations of Neusser and Wiesel, Marañón and others, and the frequency with which a large number of gastric ulcers are met with (Hernando, Arrese, De-Buen); (2) Disorders of adrenal insufficiency usually are vagotonic in nature and vagotonia predisposes to hypersecretion and that to ulcers (Eppinger); (3) In adrenal insufficiency there usually occurs, according to the studies of the author, free hydrochloric acid, an important condition in the pathology of ulcer; (4) In adrenal insufficiency infections are frequent, while Rosenow attaches great importance to infection in the pathology of ulcers. Admitting adrenal insufficiency as the predisposing pathological agent in ulcers, it is easy to explain several phenomena, such as the causative influence of fatigue and emotions, since fatigue uses up the circulating adrenalin, and emotion, which Cannon showed to be a factor augmenting the production of adrenalin, could very well result in using up of the same.—G. M.

Tuberculosis of the ADRENAL capsules in a man of twenty-six years. Death by cachexia (Tuberculose des capsules surrénales chez un homme de vingt-six ans. .Mort par cachexiè). Moutard-Martin (R.), Bull. et mem. Soc. med. d hôp. d. Par. 1917, N. S. **41**, 1161-1162.

A case report presenting no novel data. The weights of the adrenals at autopsy were 20 and 40 grams, respectively.
—F. H. S.

(ADRENAL) A case of Addison's disease. Oliensis (A. E.) & Mendelson (J. A.), N. York M. J., 1917, **105**, 156-157.

A more or less typical case of Addison's disease with marked asthenia and cutaneous pigmentation is described. Desiccated adrenal was given by mouth and adrenin was given intravenously but the case had advanced to such a stage that these measures were not fairly tested. The patient died one day after treatment was begun. At autopsy the adrenals were found to be tubercular.—I. M.

(ADRENAL THYROID) Addison's disease and exophthalmic goiter (Maladie d' Addison et goitre exopthalmique). Raymond (Félix), Bull. et mem. Soc. méd. d. hôp. d. Par. 1917, 41, 1131-1138.

Report of a case of Addison's disease in a soldier of 26 years followed in 6 months by the onset of Basedow's disease. The author is of the opinion that a relation exists between the adrenal and thyroid function and gives a paragraph report of the favorable results he has obtained in treating Addison's disease by adrenal-thyroid opotherapy. The system of medication followed is to administer 0.5 gram adrenal powder and 0.1 gram thyroid powder twice a day for 6 consecutive days. The desiccated thyroid is then discontinued for 10 days while the adrenal preparation is still given, and on the 20th day a 10 days' treatment with the combined glandular products is again given. Beneficial results were obtained in 3 cases out of 22 treated.

—F. S. H.

(ADRENAL) Recent researches on the functions of the adrenal capsules (Quelques recherches récentes sur les fonctions des capsules surrénales). Roger (H.), Presse méd. (Par.), 1917, 25, 665-668.

After reviewing briefly the important contributions already made to our knowledge concerning the function of the adrenals, the writer reports in this paper several interesting experiments carried out in his own laboratory. In the first of these an attempt was made to determine the pathological physiology underlying the clinically observed elevation of blood pressure in cerebral embolism or in apoplexy. Experimental cerebral embolism in rabbits was found to result in a marked increase in arterial pressure in decapsulated as well as in normal animals. However, in the normal animal the high level is maintained for a considerable length of time, while in the case of the one with adrenals previously removed the sharp rise was found to be followed almost immediately by a fall to normal or below. The author considers that this observation demonstrates an important role of the adrenals.

In a second experiment the relation of the adrenal secretion to vagus activity was studied. Stimulation of the peripheral stump of the cut vagus in the normal rabbit causes a slight lowering of blood pressure with a slowing of the heart rate to about 15 beats per minute, but the previous rate is promptly resumed upon removal of the stimulus. When the adrenals had previously been extirpated, such stimulation produced a greater depression of arterial tension and the slowing of heart rate was far more extreme (average interval of 29 seconds instead of

normal of 4 seconds between beats). In the decapsulated animal return to normal rate upon removal of the stimulating current was found to be greatly delayed. When the experiment on the decapsulated animal was repeated but with continuous injection of adrenalin, it was found that the results were almost identical with those on the normal animal. The author concludes from these observations that normally a tendency to inordinate action on the part of the vagus causes the adrenals to give off more of their secretion into the circulation, which in turn tends to balance the vagus overactivity.

The author further reports the discovery of a new substance in the adrenals, the action of which is antagonistic to that of adrenin. It is a black pigment precipitated by alcohol from the hot water extract of the whole gland. When redissolved in water made slightly alkaline with sodium carbonate and injected intravenously, it causes only a slight lowering of the blood pressure, but when such injection into a normal animal is followed by electrical stimulation of the vagus peripheral stump, the result is almost identical with that obtained in the case of the decapsulated animal. This substance is non-dializable and is alcohol insoluble, while the reddish brown pigment containing adrenalin is readily dializable and alcohol soluble.

The fact that injection of large doses of adrenalin causes an acute pulmonary edema suggests to the writer the possibility that over-activity of the adrenals in some terminal conditions may be the cause of this phenomenon. It was found that the edema fluid produced experimentally by injection of successive doses of adrenalin causes a definite rise in blood pressure when injected intravenously into other animals, whereas, edema fluid from the respiratory tract resulting from enormous injections of isotonic salt solution and isoviscous gum arabic solution has no such effect.—I. M.

ADRENALS, The relation of the spinal cord to the spontaneous liberation of epinephrin from the ——. Stewart (G. N.) & Rogoff (J. M.), J. Exper. M. (N. Y.), 1917, **26**, 613-656.

The purpose of the experiments reported in this paper was to determine the situation of the central nervous mechanism which sustains the spontaneous liberation of epinephrin from the adrenals. The method employed was that of severing the cervical and dorsal spinal cord of cats at various levels, testing adrenal blood before and again after section (from a cava pocket) for epinephrin. The denervated eye reaction of Meltzer, and rabbit intestine and uterus segments were used for detecting the epinephrin. It was found that section of the cord in the

level of the lowest cervical vertebra does not interfere with the liberation of the secretion which is in every respect the same as that obtained with the intact nervous system. After section of the cord in the mid-dorsal region the spontaneous liberation of epinephrin from the adrenals is abolished within the limits of detectability by the methods employed. The portion of the cord concerned in the liberation of epinephrin does not appear to extend much below the third thoracic segment.—I. M.

(ADRENAL) Contribution to the histo-pathological study of the suprarenal capsules and tetanic intoxication (Contribucion al estudio histopathologico de las capsulas suprarrenales de la intoxicion tetanica). Sabucedo (G.), Siglo méd. (Madrid), 1920, **67**, 230-236.

The author injected Indian rabbits with minimum lethal doses of tetanus toxin with the object of producing tetany of five or six days' duration. When the animal was about to die it was killed and the adrenals were promptly excised in order to avoid post-mortem alterations. In the cortical zone nothing of note was observed, but in the medulla necrotic lesions were found (chromatolysis, nuclear pycnosis) and diminution of the chromaffine substance, which indicated lack or scarcity of adrenalin. The importance of suprarenal exhaustion is demonstrated in death from tetany as observed by modern authors as is also the desirability of the employment of adrenalin as indicated by Marañón some time ago.—E. B.

Congenital lack of both ADRENALS and Addison's disease. Critical observations on the biochemistry of the adrenal system (Angeborenes Fehlen beider Nebennieren, und Morbus Addisoni mit kritischen Betrachtungen zur Biochemie des Adrenalsystems). Strauss (H.), Biochem. Ztschr. (Berlin), 1917, **79**, 51-67.

A description of a classical case of Addison's disease in which, at autopsy, no traces of the adrenal glands could be found. The case is interesting from the association of the lack of the adrenals and Addison's disease, and from the association of the Addison's disease with **status thymico-hypoplasticus** discovered at necropsy. The author discusses in some detail the necessity for more exact criteria in determining the extent of a deficiency of the adrenal system as a whole, but offers no particular solution for the problem.—F. S. H.

Massive hemorrhage of the ADRENAL in adult sixty-four years of age. Weidman (F. D.), Proc. Path. Soc. (Phila.), 1917, **37**, 3.

A description is given of a case in which a massive hemorrhage of the adrenal was found post-mortem in a man of 64. The veins showed extensive thrombosis and necrosis. The case is notable in that such hemorrhage, while common in the very young is seldom met with in the aged. The history notes did not refer to any symptoms that might be associated with this lesion.—I. M.

(ADRENIN) A survey of some elements of cardiac excitability. Burridge (W.), Quart J. Exper. Physiol. (Lond.), 1920, **12**, 355-366.

Among other factors, adrenin is considered in connection with cardiac excitability.—T. C. B.

(ADRENIN) Researches on the perfused heart: its mode of working. Burridge (W.), Quart. J. Exper. Physiol. (Lond.), 1920, **12**, 339-346.

Of endocrine interest in that the heart perfused with Ringer's solution is likened to a machine working without a lubricant. The normal lubricant is adrenin which facilitates certain actions of calcium. "Since blood contains adrenin, and Ringer's solution does not, the calcium tension of Ringer's solution must be higher than that of the blood to compensate for the absence of adrenin."—T. C. B.

Lethal dose of ADRENIN in man. (Beitrag zur Frage der für den Menschen tödlichen Suprarenindosis). Fischer (A. W.), Müchen. med. Wchnschr. 1920, **67**, 872-873.

Instead of novocain one cc. of a solution of adrenin 1:1000, was injected. Immediately after the injection the patient complained of severe pains in the neck and the head with tachycardia. The pupils first enlarged but later contracted. The pulse disappeared and death ensued. Post mortem examination showed status thymolymphaticus with poorly developed adrenal cortex. It is a question whether the status thymolymphaticus or the adrenin was the cause of the death.—J. K.

(ADRENIN) The influence of subcutaneous adrenin injections on the blood picture of normal and sick children (Der Einflusz subkutaner Adrenalininjektionen auf das Blutbild gesundes und kranker Kindes). Grimm (G.), Jahrb. f. Kinderh. (Berlin), 1919, **89**, 442-460.

Grimm studied the blood picture one-half and two hours after the subcutaneous injection of 0.5-1.0 mg. of adrenalin. He

found that the typical biphasic reaction occurred in sucklings as well as in older children and adults. This reaction comprises a rapid increase in the lymphocytes in the first half hour and its replacement within two hours by the picture of a polymorphonuclear leucocytosis. This reaction was not affected by intercurrent infections or extreme involvement of the lymph glands. It was also obtained after splenectomy. However, a weak reaction with absence of the lymphocytic phase was obtained in children of a "lymphatic constitution."—C. H. G.

The effect of ADRENALIN on muscular fatigue in Leptodactylus acellatus (L. Gir) and in Bufo marinus. Guglielmetti (J.), Quart. J. Exper. Physiol. (Lond.), 1919, **12**, 139-151.

Data published elsewhere. See Endocrin., **3**, 183.

ADRENIN injections intralaryngeally in the treatment of chronic bronchitis and bronchial asthma (Las inyecciones intralaringeas de adrenalina en el tratamiento de la bronquitis cronica y del asma bronquial). Gutierrez, Gamero & Acosta. An. de la Acad. med.-quir. de Madrid, 1919, **6**, 434-437.

The authors treated 20 cases of these disorders by intratracheal injections of 10 drops of adrenalin (1:1000) with great success. Daily injections for 2 or 3 days usually produced a cure.—G. M.

(ADRENIN) Studies on recovery from narcotics through injections into the heart (Über Wiederbelebungsversuche durch Herzinjecktion bei Narkosezufällen). Heydloff (E.). Monatsschr. f. Geb. u. Gyn. (Berlin), 1920, **51**, 318-330.

Summary of the literature and report of a case of collapse under morphin with cessation of heart-beat, recovery from which was induced by the injection of 2 cc. 1 per cent adrenalin solution directly into the heart through the 4th left intercostal space after massage had proved a failure.—F. S. H.

ADRENALIN administration by way of the alimentary tract. (De l'administration de l'adrénaline par la voie digestive). Lesné. Bull. et. mem. Soc. méd. d. hôp. d. Par. 1920, N. S. **44**, 800-801.

The intra-rectal injection of adrenalin in doses of 2 milligrams for children from 5 to 10 years old, and 3 or 4 milligrams for adults does not have a constant effect on the arterial pressure; it varies with the individual. At times there is a slow rise of the maximum tension and an augmentation of the oscillo-

metric index without modification of the diastolic tension. At other times a hypotension is observed. The maximum action is obtained in 15 to 20 minutes and all modifications disappear in an hour or an hour and a half.

But one should not judge the action of adrenaline solely on these paradoxical results, since it is regarded as certain that, given in large and fractionated doses, either by mouth or by rectum, this drug has a manifest influence on either chronic or acute adrenal insufficiency. The choice of the mode of introduction of adrenalin into the digestive tube is not without importance since its toxicity disappears when it is ingested, while when injected into the rectum it is toxic in the same doses as given subcutaneously. Although adrenalin is not altered by pepsin or pancreatin in vitro, the liver acts as a detoxicating barrier to the ingested drug, which barrier does not intervene to as effective an extent when intra-rectal administration is used. In view of these facts the rectal route is to be preferred whenever possible, for with small doses more rapid and efficacious results are obtained.—F. S. H.

ADRENALIN, The effects upon the blood pressure of the injection of—in dementia praecox. Lowrey (L. G.), Boston M. & S. J., 1920, **183**, 209-210.

The author, contrary to previous reports, did not observe a maintained blood pressure following the injection of adrenalin in cases of pubertas precox. In 54 of 60 of such cases there was an increase in the blood pressure following adrenalin. In 18 other psychopathic cases there was a depression in four.
—H. W.

Emotional reaction to ADRENIN (La reaccion emotiva á la adrenalina). Marañón (G.), Med. Ibera (Madrid), 1920, **145**, 353-357.

When small amounts of adrenin are injected into a subject, if the sympathetic system is sensitive, general and local phenomena are produced. The local reactions described by Goetsch are a zone of blanching around the point of injection, surrounded by a reddish zone and accompanied by erection of the hairs (goose-flesh). The general reactions which we described some ten years ago (Observations of the action of adrenin in man: Boletin de la soc. de biol. Madrid, June, 1911), are the well known changes in arterial pressure and carbohydrate metabolism and, in addition, motor phenomena (localized tremor of the hands extending to the arms and at times to the entire body); vaso-motor and secretory phenomena (pallor and reddening of the face, sweating, at times lachrymal secretion and

mild diuresis), and finally various subjective sensations (mild shivering, precardial oppression, feeling of respiratory oppression). All these phenomena are the same as those characterizing the emotions in general and are in accord with Cannon's hypothesis that a sudden secretion of adrenin into the circulation operates in the cause of the vegetative reaction to emotion. A sensitive subject, for example one with latent **hyperthyroidism,** when treated with adrenin, gives the syndrome of terror without having been terrified. At times this circumstance is recognized by the subject himself who declares of his own volition "It seems as if I was afraid but I am calm." This artificial reproduction of the emotion syndrome without emotion is very important and definitely refutes the classic hypothesis of Lange and James that emotion is the conscious perception of the vegetative phenomena of the emotional act. Nevertheless, at times the injection of the adrenin sensitizes the endocrine vegetative apparatus of emotion to such a degree that, in a centripetal manner, inversely to the normal, there is also produced a psychic emotion and the subject, after coolly perceiving the vegetative phenomena of emotion for some time, becomes psychically emotional. All the emotions produced by these injections are accomplished with great facility. For example, one of the female clinical patients spoke of her absent children, of the dangers they ran without her care, of the possibility that on her return this would be confirmed with sorrow, but all without emotion. Ten minutes after the injection of half a milligram of adrenin the same woman gave evidence of the physical signs of emotion induced by the drug, but entirely without psychic emotion; mention of her children, however, was sufficient immediately to arouse bitter weeping. This experience has been repeated in countless other cases with a distinct intensity according to the pathological and temperamental circumstances of the individual.

It appears as if adrenin can reproduce all the emotional syndromes except the psychic factor. This factor alone is lacking to emotional expression, and when we complete it with an emotional memory, which previously was insufficient to produce an emotional reaction because of the lack of sensitization by the somatic element, the emotion is produced in all its integrity.

This emotive action of adrenin occurs with extraordinary facility in **hyperthyroid** subjects, as Goetsch and others have demonstrated by the local reaction. It occurs also in other patients who clinically are not hyperthyroid, but in whom the vegetative system is excitable and unstable (emotional neuroses, neurasthenia, hysteria, epilepsy, menopause, etc.). Nevertheless it must be recognized that the majority of these cases have symptoms of latent hyperthyroidism. In reality this reac-

tion denotes the sensitiveness of the endocrine-vegetative system to emotion, a sensitivity which is found in all cases of excitability of the vegetative nervous system primarily and consecutively associated with endocrine disturbances, above all, those of hyperthyroidism and hyperadrenalism.—G. M.

ADRENIN content of the suprarenals in different diseases and a microchemical reaction for adrenin [Ueber den Adrenalingehalt der Nebennieren bei verschiedenen Krankheiten und mikrochemische Reaktionen von Adrenalin (Chromoreaktion Ogatsche Silbermethode)]. Ohno (S.), Verhandl. d. jap. path. Gesellsch. (Tokio), 1916, **6**, 15.

Ohno finds Ogata's silver method as satisfactory as the chrome reaction for determining the adrenin content of suprarenal substance. He investigated the adrenin content of the glands in the case of various diseases. The average amount of adrenin in the left suprarenal of man was 2.82 mg. Among all the diseases studied, the patients having beriberi had the greatest quantity of adrenin. In 5 cases this averaged 9.45 mg. The least amount was found in bronchial asthma. The quantity was fairly high in "contracted kidney," in 4 cases averaging 4.16 mg. The average in hemophilia (number of cases not stated) was 9.16 mg.—R. G. H.

The effect of ADRENIN upon the blood and splenic function (Die Adrenalinwirkung auf den Blut des Menschen, und ihre Beziehung zur Milzfunktion). Schenk (Paul), Med. Klin. (Berlin), 1920, **797**, 279; 309-312.

The injection of adrenalin in individuals showing a normal blood count and normal spleen, produces after 30 minutes a large increase of white blood cells, especially the lymphocytes, 14 to 24 per cent. A half hour later a polynuclear increase takes place. It takes six hours for the blood to return to normal. Injections of adrenalin into malarial patients causes an increased lymphocyte count together with an eosinophilia. The polynuclears are decreased. In tubercular states, injection of adrenalin is followed by an increase of red blood cells, haemoglobin and white cells, i. e., polynuclears, lymphocytes, large mononuclears and eosinophiles.—J. H. L.

The BLOOD SUGAR in narcosis and diseases of the nervous system. (Blutzucker Untersuchungen bei Narkosen und Nervenkrankheiten. Chantraine (H.), Zentralbl. f. inn. Med. (Leipzig), 1920, **41**, 521-529.

During ether narcosis the blood sugar is increased. This increase may range from 30 to 50 per cent. During narcosis with ethyl chloride the blood sugar remains unaltered. When the author experimentally produced concussion of the brain in rabbits by striking the heads with a hammer, no influence on the blood sugar could be detected. In patients with nervous diseases the quantity of blood sugar was the same as in normal persons.—J. K.

Tumor of the CAROTID BODY, excision with ligature of carotid arteries. Schley (W. S.), Am. Surg. (Phila.), 1917, **66**, 252-254.

A case of tumor of the carotid body with excision of the same along with the common, internal and external carotid arteries is described. The tumor was of twenty years' duration but had recently taken on an increased rate of growth. Its pathological nature and the symptoms, if any, produced by it are not described. Review of 75 cases of carotid tumor reported up to 1916 shows that of 54 cases operated upon 42 recovered from operation. Of these 42, 10 more cases died later from recurrences, local or metastatic, making 22 deaths in the operated cases.—I. M.

The early diagnosis of DIABETES. Addis (T.), J. Am. M. Ass. (Chicago), 1917, **69**, 109-111.

The chief emphasis of the article is laid on a functional test which is described. The patient, suspected of having early diabetes, is given 0, 25, 50, and 100 grams of glucose on four successive days. A positive reaction indicative of true diabetes mellitus is a sharply rising curve of sugar excretion. The urine is collected at the end of 2 and of 4 hours after each ingestion and sent to the laboratory for examination. The test is performed immediately after arising in the morning. The amount of water given with the sugar is uniformly one pint (500 cc.).
—R. G. H.

DIABETES, some personal equations and pathogenic coefficients in—. Anklesaira (B. N.), Indian M. Gaz. (Calcutta), 1917, **3**, 439-443.

The article is a picturesque amplification of the Bengalese adage, "No one is a gentleman who is not a diabetic at forty." Diabetes, according to the author, is a condition due to a long series of insults to the organism, and particularly to the alimentary canal. In his experience diabetes is always preceded by chronic constipation. The result of repeated violations of

hygiene is a slow intoxication which finally manifests itself as diabetes. The proper treatment is to reverse the etiological processes by diet, exercise, and general hygiene.—R. G. H.

DIABETES mellitus complicated with lipemia and xanthoma. Bates (L. B.), Proc. M. Ass. Isthmian Canal Zone (Mt. Hope), 1917, **9**, 49-52.

A case report. The patient, a white Jamaican woman of 34, came for treatment because of many fine, tender, discrete papules in the skin. Syphilis was suspected. When blood was drawn for a Wassermann reaction it was discovered that the serum was a creamy fluid. Routine examination of the urine showed sugar 5.8 per cent. An analysis of the blood showed ether extractives 6.34 per cent, of which 53.68 per cent was fat and 46.32 per cent cholestrin and other lipoids. The blood sugar was 0.10 per cent. The author adds that xanthoma is a rare condition, found chiefly in male subjects; of 36 cases reported 5 only were in females. The subjects are commonly of the florid, obese type, and nearly all have ranged between 25 and 50 years in age.—R. G. H.

Exanthema in juvenile DIABETES. (Exanthem bei kindlichen Diabetes). Bihlmeyer (G.), München. med. Wchnschr. 1920, **67**, 720-721.

A child of six with serious diabetes showed a blueish exanthema. Death in coma resulted. Postmortem examination disclosed a diminished number of small islands of Langerhans but no other changes.—J. K.

El factor renal en la glucosuria y en la DIABETES. Bonilla (E.), Siglo méd. (Madrid), 1919, **66**, 883-885.

This is a study of the interventional conjunction of the renal factor in glucosuria. Reference is made to various cases of renal diabetes, characterized by the small amount of sugar eliminated, by the lack of influence of the dietary regime and by the absence of hyperglycemia. Treatment by "nefrina" is considered the most rational.—G. M.

(DIABETES) Observations upon the various types of diabetics under the present methods of treatment. Brigham (F. G.), Boston M. & S. J., 1920, **183**, 165-170.

Nothing new.—H. W.

DIABETES; the initial fast and tolerance testing. Brown (E. J.), Illinois M. J. (Chicago), 1917, **32**, 12-17.

Exposition of and practical comments on the Allen treatment. A general article, not amenable to abstracting.
—R. G. H.

Three cases of DIABETES. (Drei Diabetesfälle). Gerhardt, Münchn. med. Wchnschr. 1920, **67**, 888.

Demonstration of three patients who, though always showing glucosuria were markedly improved by a low protien diet.
—J. K.

Treatment of DIABETES complicated by pulmonary tuberculosis. Janney (N. W.), & Newell (R. R.), J. Am. M. Ass. (Chicago), 1920, **75**, 153-158.

These authors quote statistics regarding the frequency of tuberculosis among diabetics. They describe the clinical aspects of the association of diabetes and tuberculosis. The progress in treatment of these cases is considered at length. They summarize their findings as follows: the data presented indicate that the untreated diabetic is more likely to develop pulmonary tuberculosis than when maintained sugar-free by modern dietetic methods. In a series of sixteen diabetic cases complicated by pulmonary tuberculosis showing activity, twelve patients definitely improved during a course of institutional treatment; the diabetic symptoms improved in a majority of cases. The principles of the treatment recommended are the judicious employment of sufficient undernutrition combined with rest to maintain the patient sugar-free and control the tuberculosis. Fasting is unnecessary to obtain good results. Ill-advised fasting may lead to fatal outcome. Rest is at least as important as in the treatment of uncomplicated pulmonary tuberculosis.
—F. C. P.

The relation between DIABETES MELLITUS and clinical syphilis. Rosenbloom (J.), J. Am. M. Ass. (Chicago), 1917, **68**, 1232-1234.

A brief review of the literature dealing with the etiological relation of syphilis to diabetes and a report of sixty-two cases of diabetes mellitus studied from this angle. R. found positive evidence of syphilis in 10.3 per cent of these cases, but since none of those who received antisyphilitic treatment showed an increase in tolerance for carbohydrates, it is concluded that there is no etiological relationship between them and that the two diseases exist independently.—I. M.

DIABETES in children. Joslin (E. P.) & Gray (H.), Med. Rec. (N. Y.), 1917, **92**, 40.

This communication deals with diabetes in children as regards etiology, improvement in prognosis and treatment, based upon analysis of 123 cases under 15 years of age. In a high percentage of cases obesity, lack of exercise and infections were considered of prime importance as regards etiology. With the better treatment the prognosis is not so hopeless as it was formerly considered to be. Of 53 cases that had been under Joslin's supervision 31 were dead and 15 were still living in one series, while of the other 7 cases 2 were dead and 5 living, making an average duration of over 5 years.—I. M.

The blood lipoids in DIABETES. Joslin (E. P.), Bloor (W. R.) & Gray (H.), J. Am. M. Ass. (Chicago), 1917, **69**, 375-378.

The authors made a complete analysis of the blood lipoids in 131 samples of blood from 87 diabetic patients by Bloor's fat method and compared them with 23 analyses of blood from normal individuals. The three lipoid fractions (total fatty acids, lecithin and cholestrol) were determined separately in each case, not only in the whole blood but in the plasma and in the corpuscles as well. It was found that all grades of diabetes are distinguished by a marked increase in lipoids of the blood and the increase is progressive with the seriousness of the disease. The average normal blood lipoid level is 0.59 per cent. In mild diabetes the average is about 0.83 per cent, in cases of moderate severity 0.91 per cent, and in severe cases about 1.41 per cent. The highest value found was 16.3 per cent, which was found in a very severe case. Although the total of fatty acids is trebled, the cholesterol is only doubled and the lecithin is increased but one-third. The increase in cholesterol is particularly significant in that it seems to be pathognomonic of prolonged diabetic hyper-lipemia. The variation in the lipoids takes place chiefly in the plasma, the corpuscles of diabetics showing little or no increase in lecithin and cholesterol over the normal. No difference was found in diabetics with and those without nephritis. Cases with acidosis showed a higher level of total lipoids than those without acidosis and cases with moderate acidosis showed a much higher lipoid level than others with severe acidosis. There seems to be a normal blood-lipoid threshold similar to that for sugar. This is about 0.67 per cent. The lipoids decrease with fasting and increase on a diet of fat or carbohydrate. It was found also that the blood lipoids do not rise and fall with changes in blood sugar. The blood lipoid level is a much more accurate test of the severity of diabetes than is the sugar content. High lipoids indicate a grave prognosis.—I. M.

Reaction to pyrogenetic substances as a constitutional index with especial reference to DIABETES mellitus (Ueber pyrogenetisches Reactionsvermögen als konstitutionelles Merkzeichen, unter besonderer Berücksichtigung des Diabetes mellitus). Schmidt (R.), Ztschr. f. klin. Med. (Berlin), 1918, 85, 303-318.

The experiments reported were undertaken to study the constitutional reaction of different individuals, especially diabetics, to pyrogenetic agents. Various protein preparations, such as milk, deuteroalbumose and tuberculin were injected subcutaneously, the temperature being taken before and for some time after the injection. It was found that different individuals differ widely in their reactions to the same pyrogenetic agent, some showing a prompt and constant response while others react but slightly or not at all. From the latter the author assumes the existence of what he calls an "afebrile diathesis," which is manifested most commonly in individuals who show other stigmata of metabolic degeneration.

Diabetics examined were found to respond but slightly or not at all. While there is no direct parallel between the body temperature and degree of hyperglycemia, the inability of the body to metabolize carbohydrates efficiently seems to be closely associated with this "afebrile diathesis."—I. M.

(DIABETES) The blood sugar during a voyage from Holland to India. (Over het bloedsuikergehalte tijdens de reis Holland-Indie). Schut (H.), Geneesk. Tijdschr. v. Ned. Indie (Batavia), 1920, 60, 424-429.

In the tropics the amount of blood sugar is about 30 per cent higher than in Holland. When people with this large quantity of sugar go on the mountains or make a voyage, the blood sugar becomes normal. The so-called "low fever" frequently observed in India may be considered as an effort of the body to oxidize the surplus of sugar. The author examined the blood of people making a voyage from Holland to India. As long as they are on sea the amount of sugar is not increased, even when they are in the tropical seas. It was possible to examine three mild cases of diabetes in all of which the glycosuria disappeared during the voyage.—J. K.

The association between DIABETES MELLITUS and tuberculosis Solis-Cohen (S.), Med. Rec. (N. Y.), 1917, 92, 40.

This is a brief expression of opinion on the relationship of these two diseases. While there are no reliable statistics and no other data pointing to a definite relation between them, the

author points out that the family histories of cases show certain facts which indicate some fundamental association. This is vaguely referred to by the terms constitutional, congenital or hereditary in these conditions. Diabetes is likely to eventuate in tuberculosis.—I. M.

DIABETES and eucalyptus (L'eucalyptus et le diabéte). Trabut. Bull. gén. therap. (Paris), 1920, **171**, 429-430.

Good results are reported in the treatment of diabetes, but no specific citations made, from the use of a decoction of 10 to 15 grams of eucalyptus leaves (species: E. globulus; E. diversicolor; E. rostrata) per liter of water boiled down to small volume. The amount administered is not given.—F. S. H.

(DIABETES) The relation of the acid-base equilibrium of the body to carbohydrate metabolism and its application in human diabetes. Underhill (F. P.), J. Am. M. Ass. (Chicago), 1917, **68**, 497-500.

The literature dealing with the effects of various agents on the blood sugar and glycosuria is briefly discussed. From the experimental work done along this line it is clear that a condition of acidosis facilitates the elimination of carbohydrates from the body, whereas in alkalosis there is a tendency to conserve carbohydrates. The author applies this idea to the treatment of cases of human diabetes, pointing out that the conventional diabetic diet consists mainly of acid producing foods, such as meats, fats and cereals, which aggravate the condition of acidosis. A severe case of diabetes was treated over a period of two years with definite benefit to the patient. Milder cases likewise respond favorably. Alkali was given as sodium bicarbonate in carbonated water in quantities just sufficient to keep the reaction of the urine near the point of neutrality to litmus. It was divided in seven equal doses and given at intervals throughout the daylight hours.—I. M.

A study of the significance of heredity and infection in DIABETES MELLITUS. Williams, (J. R.), Am. J. M. Sc. (Phila.), 1917, **154**, 396-406.

The author considers in some detail the relation between the various so-called degenerative diseases, diabetes mellitus, arteriosclerosis, cancer and nephritis. He points out that they appear to be in a sense products of civilization in that they are almost unknown among nomadic peoples living in a primitive state. He cites statistics to show that these four conditions have increased tremendously in frequency within the past few

decades. With the view of determining the relation of arteriosclerosis, obesity and cancer to diabetes and to throw more light on the hereditary element in diabetes, he obtained full data regarding all relatives of 100 cases of diabetes mellitus and of 100 non-diabetics suffering from gastro-intestinal or other common disturbances. The evidence strongly indicates the possibility of infection as an important factor in precipitating the metabolic collapse recognized as diabetes. The writer concludes that the liability to diabetes and arteriosclerosis is transmissible from parent to child and emphasizes the importance of safeguarding individuals with family history of such conditions from all infections.—I. M.

(DIABETES MELLITUS) The effect of undernutrition on muscular force; a study of the influence of low diets, or the Allen method of treatment on the physical vigor of diabetics. Williams (J. R.), Arch. Int. Med. (Chicago), 1917, **20**, 399-408.

An interesting study is reported in which the muscular vigor of a number of diabetics was tested by means of the Collins dynamometer while receiving different diets, to show the effect of the Allen method of treatment on the muscular strength. The common clinical observations that diabetics as a rule are distinctly weaker physically than normal individuals was confirmed. There was shown to be a direct relationship between food tolerance and muscular vigor. The continued use of a low diet for many months, even though it falls short of the energy requirements of the body, provided it is within the physiological limitations of the body to metabolize it, will cause an appreciable gain in muscular tone, although the amount of physical effort that such a person may be able to put forth may be considerably below the normal. This is in accord with the clinical experience that nutrition within the tolerance of the patient gives the greatest comfort, strength and sense of well being. The investigation shows also that while diabetics living on a diet below normal physiologic requirements possess a diminished muscular power, feeding them beyond metabolism limitations causes not only a further reduction in their tolerance for food but also an even greater loss of strength.

The general conclusion is drawn that diabetics gain in physical vigor as they become and remain sugar free, while over-feeding causes a definite and often a serious loss of strength.—I. M.

A fatal case of DIABETES MELLITUS associated with large-cell hyperplasia Williams (J. R.) & Dresbach (M.), Am. J. M. Sc. (Phila.), 1917, **153**, 65-78.

A fatal case of diabetes mellitus is described in which the pancreas was found to be practically normal while the lymph nodes, liver and particularly the spleen showed the presence of large-cell hyperplasia. This is the fourth case of the kind on record. Examinations of the formalin fixed sections by means of specially stained frozen sections and by means of the polariscope revealed the presence of extensive deposits of lipoids. The hyperplasia in these cases is said to resemble the cell changes in Gaucher's disease of the spleen in some ways but the large cells found in the latter condition do not contain the deposits of lipoid material. Furthermore, Gaucher's disease is a familiar disease while the condition discussed in this paper is not. A brief discussion of the newer ideas of fat metabolism is also given.—I. M.

The treatment of DIABETES MELLITUS. Williamson (R. T.), Lancet (Lond.), 1917, **1**, 650-652.

The author describes five different graded diets which he employs in uncomplicated cases of diabetes mellitus. If in a given case the glycosuria does not disappear within a few days on one of these diets, another is selected and given a trial. If none of them improve the condition within a week's time, he institutes fasting days, on which the patient is allowed only tea or coffee, beef tea, or whisky-and-soda. When the diets fail to check the glycosuria after a satisfactory trial, he resorts to the use of drugs such as sodium salicylate, aspirin or quinine salicylate. He claims to have clearly demonstrated the ability of these drugs to diminish the glycosuria in mild and moderately severe cases. Potassium bromide is also given in cases suffering from insomnia or marked neurasthenia. The ordinary rigid diabetic diet is said by this writer to be unsuited to cases with persistent acidosis and should be supplemented with a small amount of carbohydrate, while meat is to be restricted. —I. M.

Observations upon DUCTLESS GLAND therapy. Lawrence (C. H.), Boston M. & S. J., 1920, **183**, 160-165.

The author believes that though the symptoms of early stages of endocrine disorders are often polyglandular in character, there exists a "characteristic and recognizable syndrome for a primary derangement of each individual gland." The recognition of the syndrome is essential for the intelligent administration of glandular therapy. This belief is apparently based upon the following case report. A nurse 37 years old, since the age of 13 had suffered attacks of "hay-fever" with asthma for the last 3 years. Cutaneous tests were negative to

pollens but positive to meat, milk, several kinds of fish, many vegetables, chocolate and coffee. Removal of these from the diet eliminated the asthma, but she could not maintain weight. She was troubled a great deal with extreme sleepiness irrespective of the amount of rest secured. At 16 years of age the patient rapidly grew tall, but was never weak or nervous. These and other factors led the author to suspect pituitary dysfunctioning. She was given whole pituitary and advised to eat anything desired. As long as pituitary substance was taken anaphylactic symptoms did not occur although the diet was general. Omission of the therapy was always followed within 48 hours by a return of the anaphylactic symptoms.—H. W.

The pharmacology and therapeutics of the DUCTLESS GLAND preparations. Sajous (C. E. de M.), Penn. M. J. (Athens), 1917, **21**, 178-184.

The writer discusses in some detail the normal functions and the disorders of the **adrenal, thyroid** and **pituitary** glands and the therapeutic uses of the preparations derived from them. It is his opinion that the adrenal secretion, while passing through the lung capillaries, takes up oxygen and becomes a constituent of hemoglobin. To this new constituent, termed by him adrenoxidase, is attributed catalytic properties, by virtue of which it sustains oxidation within the tissues of the entire body when carried to them by the blood stream. This respiratory function is the fundamental principle of the therapeutic application. When, therefore, the secretory activity of the adrenals is more or less inhibited toward the end in infectious diseases, the use of adrenalin is indicated and is often a great life-saving measure. Its striking effects in relieving attacks of bronchial asthma are claimed to be due to this property and to its power to evoke a defensive reaction through which the poisons causing the bronchial spasm are broken down.

As opposed to the secretory theory of pituitary function, the author maintains that its function is to protect the body against certain intoxications by enhancing the activity of the other ductless glands, notably the adrenals and thyroid. The organ is viewed as a chief co-ordinating nervous center or ganglion of the sympathetic system. The anterior lobe is looked upon as a contractile body much as is the spleen. According to the theory, it periodically projects a serum-like fluid, containing the contents of red and white cells, over a layer of sensory cells resembling those of the nasal olfactory area. When this fluid contains certain poisons, the sensory cells react and excite the ductless glands to inordinate activity

through sympathetic nerve paths. As evidence for this theory he recalls cases of acromegaly in which hyperthyroidism is a prominent accompaniment of the erethic stage, whereas in the asthenic stage signs of myxœdema and Addison's disease appear. The therapeutic effect of pituitary substance is attributed to its content of adrenal principles which combined with nuclear bodies gives it a long list of uses.

The function of the thyroid is said by the author to be closely related to the phenomenon of immunity and through the over stimulation of this defensive mechanism by infectious thyrotoxicoses are initiated. Thyroidectomy should, therefore, be done less frequently in these conditions and removing of foci of infection resorted to more frequently.—I. M.

ENDOCRINE disturbances of syphilitic origin (Alteraciones endocrinas que tienen un origen sifilitico). Albadalejo (L.), Estudios med. (Murcia), 1920, pp. 3-17.

Syphilis frequently produces lesions of the endocrine glands, at times directly (as conjunctival infiltration gumma) and at times indirectly as in one of the author's cases with syphilitic lesions of the sella turcica which involved the **hypophysis**. Just as the **adrenals** are very sensitive to tubercular infection, so are the **thyroid** and **hypophysis** sensitive to syphilis. In such cases opotherapy has only a relative efficacy depending on a complementary anti-syphilitic treatment. Four cases of syphilitic endocrine lesions are described with syndromes of **thyroid** insufficiency in two, and of hypophyseal insufficiency in two.—G. M.

(ENDOCRINE GLANDS) Tetany in children. Payne (W. W.), Guy's Hosp. Gaz. (Lond.), 1920, **34**, 106-108.

The relationship of the ductless glands (particularly the parathyroids) to calcium metabolism, is reviewed in this paper. —J. H. L.

ENDOCRINE ORGANS as factors in the treatment of skin diseases (Die sich aus den Einflusz der endokrinen Drüse ergebenden therapeutischen Gesichtspunkte bei Erkrankungen der Haut. Pulay (E.), Therap. Halbmonatsh. (Berlin), 1920, **34**, 302-305.

The sexual organs have a certain influence on the skin. Seborrhoea becomes more marked at puberty; infection with microsporon audouini in children is nearly incurable but in puberty it disappears without any treatment. A dermatitis symmetrica dysmenorrhoica has been described. All kinds of skin dis-

ease may be influenced by menstruation. The pigmentation during pregnancy is well known. Seborrhoea often disappears during pregnancy. In myoma of the uterus loss of hair has often been observed. Skleroderma beginning at the menopause has been described. All these facts point to the existence of relations between the skin and gonads. But we must not expect too much from treatment with ovary or corpus luteum in skin disease. There are only a few cases known in which a skin disease during pregnancy has been cured with corpus luteum.—J. K.

(ENDOCRINE ORGANS) La Emocion. Turro (R.), Siglo méd. (Madrid), 1919, **66**, 1074-1076.

A review and criticism of the different theories concerning emotion. In the first period of the development of this study, the psychological theories regarded the emotions as having an organic origin determined by psychic states. Turro justly states that these ideas do not permit of a clear view of this intricate subject. Later there appeared a modern phase that we may call physiological, which affirms the existence in emotion of an organic base which presents itself in all emotional manifestations that the organism is capable of producing experimentally without intervention of a psychic factor. These modifications are engendered by the endocrine organs so that it can be affirmed that emotion involves a passing endocrine crisis characterized by hyperthyroidism and hypersuprarenalism on the one hand, and hypopituitarism on the other. This crisis may become so intense as to assume a permanency which gives rise to emotional diseases. The critical stage of permanent emotionalism has been admirably described by Marañón. The psychic impressions tend to influence the endocrine system and give origin to its manifestations; hence, if we inject **adrenalin** in a subject affected with **hyperthyroidism**, there is brought about an emotional crisis that is purely "endocrine", the subject not exhibiting psychic emotion (Marañón). If the excitation is very great, the subject becomes autoemotional, the humoral current proceeding in the direction of the psychic centers. According to Achucarro, the nerves may be the point of union between the psychic and endocrine elements which intervene in all emotions. Turro seems to be in complete accord with this view and method of clearing up the problem of emotion.—E. B.

ENDOCRINE origin of some intestinal changes. (Algunas alteraciones intestinales de origen endocrino). Hernando (T.), An. de la Acad. med.-quir. (Madrid), 1919, **6**, 17-37.

The author presents an extensive study of the question together with a complete bibliography. He studied primarily the diarrheas of Graves' disease which he considers of vagotonic origin, since he was able to produce them by injection of pilocarpine and stop them by atropine. In some cases also he was able to influence the production of the hyperchlorhydria. He calls attention to the frequency of these diarrheas of **thyroid** origin, which are not always well diagnosed and are resistent to the usual treatment, yielding well, on the other hand to atropine and to adrenin enemas. He further studied the diarrheas of adrenal insufficiency, characteristic of Addison's disease and the frustrated forms of adrenal insufficiency. In the second part he discusses constipation in the endocrine states. In certain pathological conditions of the **hypophysis** constipation occurs, at times due to the lack of the hypophyseal hormone which stimulates intestinal contractility. Given the inhibitory effects which adrenin exerts on the intestinal motility, it is logical to suppose that there will be constipation in those pathological conditions in which an excess of adrenin is produced. The constipation of the arteriosclerotics, and above all of women during the menopause can be attributed to this factor, which agrees with the ideas of Culbertson and Marañón. Hernando finally takes up the constipation of **hypothyroid** disturbances. In some of these cases this symptom was almost the only one of athyroid disorder, and it rapidly improved under opotherapy. He accepts, as an explanation of the hypothyroid constipation, the hypothesis of Levi and Rothschild, according to which the lack of thyroid secretion produces an increase in the concentration of the calcium ion, to which is due the diminution of the neuromuscular excitability of the intestine, which in turn influences the lack of tone of the vagus.

—G. M.

ENDOCRINE therapy of ozena (**Endocrinoterapia del ozena**). de Olavarria (L.), Rev. Españ. de laring. otol. y rinol. (Madrid), 1919, **7**, 56-86.

The author studied 120 cases of ozena and found that 65 per cent of the subjects were affected with disturbances of menstruation of hypophyseal and dysthyroidal origin. In all such he used **ovarian, thyroid** and **hypophyseal** opotherapy, and if disturbances of growth were evident, thymus was included. The results obtained were very satisfactory, 37 of the 107 treated having been cured. According to his statistics ozena predominates in the female sex, appearing in the pubertal period and reappearing at the menopause, becoming attenuated during pregnancy and increased during menstruation. Frequently

obesity accompanies the disorder. All of these data speak in favor of an endocrine factor in ozena.—G. M.

Contribution to the etiology of ENDOCRINE syndromes (Contributo all 'etiopatogenesi delle sindromi endocrine). Pentagna (O.), Pediatria (Naples), 1920, **28**, 455-469.

The author analyses 115 cases of endocrine disturbance observed in the Naples clinic since 1914, among a total of twenty thousand children examined. In 46 per cent of the cases syphilis was found, either in the patient or in the parental anamnesis. Pentagna concludes, therefore, that syphilis may be an important etiological factor in determining endocrine dysfunction. The influence of lues is not interpreted as being a direct syphilitic manifestation but rather as due to the action of the syphilitic toxins during embryonal life, producing congenital alterations in the endocrine glands. Later in life this alteration manifests itself as a dysfunction.—G. V.

(ENDOCRINOLOGY) The psychology of INSANITY (La psicología de la locura). Delgado (Honorio F.), Crón. Méd. (Lima, Peru), 1919, **36**, 675; Abst., J. Am. M. Ass., **74**, 565.

Delgado remarks that experience has shown the important part played by moral factors in the development of mental derangement; in fact, he deems this the principal factor. Of course every psychic process has its molecular concomitant, but Delgado reiterates anew "the priority of the function—the conception which is rejuvenating medicine in all its branches now." "Modern endocrinology is also demonstrating the connection between the psychologic activity and the somatic activity, and the influence of one on the other."

Review of the past year's literature on ENDOCRINOLOGY. (Jaaroverzicht van de literatuur over de klieren met inwendige afscheiding). Stuurman (F. J.), Nederl. Maandschr. v. Geneesk. (Leiden), 1920, 1, 401-420.

A good review.—J. K.

(ENDOCRINOPATHIES) A peculiar variation of Bloch's syndrome (Una curiosa variante del sindrome de Bloch). Juarros (C.), Siglo méd. (Madrid), 1920, **67**, 417-418.

The author makes note of the frequency with which endocrine factors intervene in the psychoneuroses, holding it necessary to make a careful study of patients in order to avoid confusion with respect to diagnosis of hysteria and neuras-

thenia. He describes the symptomatology of Bloch's syndrome and refers to the case of a woman who presented this syndrome during a prolonged absence of her husband and who also manifested signs of **hyperthyroidism** which disappeared following employment of **ovarian** preparations and antithyroid serum.
—E. B.

(GENERAL) The relationship of the external appearance of the body to disease. Draper (G.), N. Y. State J. M. (N. Y.), 1920, **20**, 273-279.

An interesting article in which the author attempts to show that the endocrine organs are to a large degree responsible for the external appearance not only in health but also in disease. Physiology, anatomy, psychology and immunity are considered the "four panels" primarily representative of life; the proper correlation among these is influenced by and to a great extent determined because of the endocrine functioning. Diet, toxins and environment are factors which influence the harmonious balance between the "four panels" and the endocrine organs, any imbalance resulting in characteristic alterations of the bodily structure and its functions.—H. W.

GLANDULA INSULARIS. Luksch. Deutsche med. Wchnschr. (Berlin), 1920, **46**, 900; Wiener klin. Wchnschr., 1920, **33**, 743.

Luksch reports the autopsy findings in the case of a woman who died at 34. In the neck and in the axillae were found bits of tissue which, upon histological examination, were seen to consist of cells in the form of islets without surrounding capsule. Pende has previously described this structure under the name of "Glandula insularis." He assumes that it has an endocrine function. Pende found the gland both in children and in puppies. Kohn has taken issue with Pende and regards the structure as merely an early form of fatty tissue. Luksch does not hazard an opinion as between these two.—J. K.

GLYCOSURIA during pregnancy. Hitchcock (C. W.), J. Mich. M. Soc. (Detroit), 1920, **19**, 399-404.

Lactosuria is common during both pregnancy and the puerperium. This condition is entirely physiological and must be differentiated from the various types of glycosuria. From 30 to 50 per cent of pregnant women are less tolerant to glucose than non-pregnant women. Such cases do not show hyperglycemia and, therefore, are not diabetic. True diabetes, of course, may be present in pregnancy.—H. W.

(GONADS) A case of hermaphroditism verus bilateralis in a goat (Een geval van hermaphroditism verus bilateralis bij de geit). Kredit (G.), Tijdschr. v. Diergeneesk. (Utrecht), 1920, **47**, 134-139.

Testicular tissue was found in both ovaries of a goat. The organs did not show any sign of ovulation. —J. K.

Disturbance of the endocrine function of the GONADS Quimby (W. C.), N. Y. State J. M. (N. Y.), 1920, **20**, 279-281.

Case reports. I. Precocious puberty in a girl of seven years associated with a tumor of the ovary (hypergenitalism). Following a fall at the age of four years bleeding from the vagina occurred, which was not associated with pain; the breasts enlarged and pubic hairs appeared. Bleeding from the vagina occurred again at six and a half years and at seven. This last period was associated with pain, nausea and vomiting. The sella was normal; the Wassermann reaction was normal. A tumor of the right ovary was removed. No post-operative history is given.

II. Delayed puberty; associated with possible hypophyseal dysfunction (hypogenitalism). A girl of 16 years had never menstruated. She suffered from polydipsia and polyuria and fainting spells; she was never strong; growth was stunted; her height was 49 inches at 16 years. Secondary sex signs were moderately developed. No hypophyseal tumor was shown and the patient passed from under observation.—H. W.

(GONADS PLACENTA) Substances which actively regulate the growth of the genitals (Substanzen, die das Wachstum des Genitales wirksam anregen). Schröder, Monatsschr. f. Geb. u. Gyn. (Berlin), 1920, **51**, 433-434.

The question of infantilism is bound up with the lack of stimulation to growth of the genitals. The interstitial cells of the ovary are important. Schröder was able to get enormous development of the genital canal in growing animals by injection of a **placenta** preparation. In male animals the utriculus masculinus alone hypertrophied. The substance accordingly is not specific but acts on both sexes. A substance acting similarly was obtained from the liver, but none was found in the spleen. Schröder is of the opinion that the compound is a cholesterol. Whether or not it is a hormone he is not sure. Its action in cases of infantilism is yet to be studied.—F. S. H.

(GONADS) Hermaphroditism in man. Sheppard (H.), Anat. Rec. (Phila.), 1920, **19**, 55-65.

Published previously in abstract. See Endocrin., 1920, **4**, 460.

(HYPOPHYSIS) Hypophyseal changes in experimental diphtheria infection (Über die Hypophysenveränderung bei experimentellen Diphtherieinfection). Adachi (O.), & Tanaka (K.), Verhandl. d. jap. path. Gesellsch. (Tokio), 1916, **6**, 23-24.

The authors infected guinea-pigs and rabbits with Bacillus diphtheriae. The hypophysis of each was then subjected to histological examination. It was found that the pars intermedia reacted to the intoxication more than did the remainder of the hypophysis. The cell boundaries were indistinct and the nuclei pycnotic. In case of the more severe reactions only granular masses remained in place of the cells. Often necrotic masses were seen in the intermediate zone, which was otherwise relatively little changed. Near the juncture of the anterior lobe and pars intermedia a confluence of the cells was often observed. In the anterior lobe the granules of the eosinophile cells in many cases had disappeared. In some there were round-cell infiltration and necrotic areas. The posterior lobe was relatively little changed. The changes described were found in animals dying from the infection within three to fifteen days. In general, the guinea-pigs reacted more than did the rabbits.—R. G. H.

Experiments in the transplantation of the HYPOPHYSIS of adult Rana pipiens to tadpoles. Allen (B. M.), Science (N. Y.), 1920, n. s. **52**, 274-276.

Grafts of three kinds were used, viz., anterior lobe, intermediate lobe and combined intermediate and posterior lobes. The graft was thrust into a pocket under the skin above the right eye. Three hundred and eighty-four operations were performed. 1. "The anterior lobe transplanted to normal, to pituitaryless, and to thyroidless tadpoles in each case produces a marked acceleration of growth so that the tadpoles thus treated are conspicuously larger than those into which the other parts of the hypophysis have been transplanted. They are larger than normal controls and larger than controls into which muscle tissue has been transplanted in the same way and at the same time as the above operations." 2. "Normal tadpoles into which the intermediate lobe is engrafted become much more darkly colored than the controls, while those which have been made to turn white as a result of removal of the anlage of the hypophysis exclusive of the posterior lobe are

made to change back from white to black when the intermediate lobe is engrafted into them." 3. Tadpoles into which the combined intermediate and posterior lobes are transplanted show not only the color change mentioned above but they also suffer a marked contraction of the body walls. Within twelve hours they appear very emaciated. This characteristic gradually disappears, in the course of ten days. These tadpoles show apparent retardation of growth. When the intermediate and posterior lobes are dissected apart and transplanted separately it is seen that this phenomenon is due wholly to the posterior lobe. It is probably caused by the well-known property that this portion of the hypophysis possesses of bringing about muscular contraction. The following conclusions are justified: 1. The anterior lobe of the hypophysis stimulates growth and metamorphosis: 2. The intermediate lobe is very largely if not wholly concerned in regulating such color changes as are controlled by the hypophysis; 3. The posterior lobe causes marked contraction of the body walls and at least apparent retardation in growth.—F. A. H.

(HYPOPHYSIS) Early diagnosis of early pituitary tumor with ocular phenomena. Benedict (W. L.), Am. J. Ophthal. (Chicago), 1920, **3**, 571-584.

Pallor of the discs and changes in the visual fields should always excite suspicion of pressure processes, the etiology of which should be less hastily ascribed to tabes and other neuritic processes. Ocular phenomena develop early in cases of pituitary tumor. The decision as to operation should properly rest on changes in the visual field and appearances of the optic disc since the indications for operation disappear with the development of optic atrophy.—H. W.

HYPOPHYSEAL cachexia in a case of cancer of the HYPOPHYSIS (Uber hypophysäre Kachexie bei Hypophysenkarzinom). Budde, München. med. Wchnschr., 1920, **67**, 826-827.

A woman of 27 showed swollen glands in the neck; after removal and x-ray treatment the tumor began to grow again and now very rapidly. Histological examination showed the tumor to be a carcinoma. Three months after these symptoms began there were observed symptoms of increased brain pressure, loss of pubic and axillary hair, loss of pigment of the hair of the head, with pigmentation of the linea alba and amenorrhea. Autopsy disclosed cancer of the hypophysis, destroying the whole gland and metastases in the lungs. Tumors of the hypophysis rarely give rise to metastasis in other organs. It is

extremely rare that symptoms caused by the metastasis are observed preceding those from the hypophysis. Only one previous case of this type has been published.—J. K.

(HYPOPHYSIS) Pituitrin in obstetrical practice (Pituitrine in de verloskundige praktyk). Catz (B. F.), Nederl. Maandschr. v. Geneesk. (Leiden), 1920, **1**, 377-382.

Description of 8 obstetrical cases in which pituitrin was of great value.—J. K.

(HYPOPHYSIS) Pituitrin. Conley (A. A.), Journal-Lancet (Minneapolis), 1917, **37**, 505-507.

Conley reports very satisfactory results from the use of pituitrin for deflation of atonic intestines, emptying of atonic bladders, and as a uterine stimulant.—R. G. H.

(HYPOPHYSIS) Hypophyseal cachexia. Remarks on syphilis of the pituitary (Ueber hypophysäre Kachexie; ein kasuistische Beitrag zu Syphilis der Hypophysis. Feit (Herman), Med. Klin. (Berlin), 1920, **16**, 421-422.

Report of a luetic individual manifesting symptoms of hypopituitarism and cachexia. The face was yellow and beardless, the voice boyish in timbre and the genitals were undeveloped. A history of polyuria and polydipsia was given. The blood showed 50 per cent small lymphocytes, 5 per cent large lymphocytes, 43 per cent polynuclears and 2 per cent eosinophiles. No changes in the sella were seen. After two salvarsan injections his subjective symptoms improved, his strength came back, and the polyuria and polydipsia disappeared. A gain in weight is recorded. His increased lymphocyte count was not altered.—J. H. L.

(HYPOPHYSIS) Dystrophia adiposogenitalis. Foerster. Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1066.

Demonstration of a man of 37. Seventeen years ago he became fatter; 12 years ago the penis became smaller and the patient became impotent. He complains now of severe headaches, of ready fatigability and of a general feeling of being ill. The breasts are of the female type. The roentgenogram shows an enlargement of the sella turcica.—J. K.

The HYPOPHYSIS and its active principles. (Die Hypophyse und ihre wirksamen Bestandtheilen). Führer (H.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1066; Therap. Halbmonats. (Berlin), 1920, **34**, 437-442.

A general review on the physiology and pathology of the hypophysis. Most commercial preparations (pituitrin, coluitrin, pituglandol) are simply extracts from the cow's gland. Hypophysine (Hoechst), however, is a preparation containing the four alkaloids of the gland in absolute chemical purity. Extracts from human are as active as extracts from animal glands. [The validity of this claim is by no means generally conceded.—Ed.]—J. K.

(HYPOPHYSIS) Pathogenesis and metabolism in diabetes insipidus with special regard to the chemical analysis of the blood (Zur Frage der Pathogenese und der Stoffwechselvorgänge beim Diebetes insipidus mit besonderer Berucksichtigung der chemischen Untersuchungen des Blutes). Gorke (H.), Arch. f. Verdauungs-Krank. (Berlin), 1920, **26**, 365-398.

Description of four cases with complete examinations. The author comes to these conclusions. Diabetes insipidus is a disease accompanied by polyuria. The polyuria is chiefly caused by a loss of power of concentration of the kidneys for NaCl and other salts. Nitrogen is excreted in normal concentrations. In the blood serum there is a marked hyperchloraemia and an increased depression of the freezing point. When extra doses of NaCl are given the quantity of NaCl in the serum is increased and this increase forms a new stimulant to increase the diuresis. Retention of water in the body after administration of NaCl is possible, but is never very marked. The excretion of extra doses of NaCl is somewhat delayed but rarely takes more than one day. When the quantity of NaCl in the body is reduced the hyperchloraemia and the hyperosmosis become less marked, though a normal freezing point is never reached. The quantity of urine becomes less though always remaining much higher than normal. Fever has but little influence on diuresis. Quantities of urine as in normal persons are never observed. The influence lasts only during a short time. When the fever continues for a long time the diuresis reaches its original height again. When the quantities of fluids given are diminished, the body loses water and thus loses weight, but the quantity of excreted urine is but very little diminished and its concentration remains low. This proves once more the loss of power of concentration of the kidneys. When the quantity of fluid given is diminished, symptoms are observed (tachycardia, thirst, nausea, headache, vertigo), closely resembling uremia. However, these symptoms have no relation whatever to real uremia; they are due only to the loss of water from the tissues. The only way to increase the concentrating power of the kid-

neys is by subcutaneous or intravenous injections of extracts of hypophysis. These injections cause a diminished diuresis, and increased concentration of urine, the hyperchloraemia disappears, the freezing point of the serum becomes normal and the quantity of proteins in the serum is somewhat diminished. These injections do not always cause retention of water. When this happens it is caused by the diminished diuresis. When the diuresis is diminished by injection of extract of hypophysis the body may lose much water by the bowels, the skin and the salivary glands. The diminishing of the diuresis and the increase in concentration are proportional to the quantity of extract injected. Several injections given one soon after the other may cause complete anuria for 9 to 12 hours. When the injections are stopped all symptoms of diabetes insipidus reappear immediately. Three patients with diabetes insipidus showed a marked anhydrosis. In three cases the roentgenogram did not show any sign of hypophyseal disease but as these patients showed amenorrhea the idea is suggested that the hypophysis plays a part in the disease. Two of the patients showed dystrophia adiposogenitalis. This, too, speaks for a hypophyseal influence. Only one patient showed small modifications on the x-ray plate. [The author in his excellent article forgets that Aschner and others have observed atrophy of the generative organs after lesions of the midbrain without any lesion of the hypophysis. There are also many authors who deny any relation between the hypophysis and dystrophia adiposogenitalis.]
—J. K.

(HYPOPHYSIS) The etiology of cystoplastic osteitis (Zur Ätiologie der Ostitis cytoplastica). Hamann (Otto), Med. Klin. (Berlin), 1920, **16**, 63-64.

A case of cystoplastic osteitis, affecting the tibiae of both legs, which yielded to pituitary medication. Hamann concludes that osteitis osteoplastica, leontiasis ossea, and Paget's disease, are due to a hypopituitary condition. The hypopituitary cases all show a regressive condition upon bony growth, leading to cystic bone formation, as in the above mentioned case.—J. H. L.

(HYPOPHYSIS) Studies on proteinogenous amines. IX. Is histamine a normal constituent of the hypophysis cerebri? Hanke (M. T.) & Koessler (K. K.), J. Biol. Chem. (Balt.), 1920, **43**, 557-565.

In contradistinction to the published reports of Abel and Kubota of the finding of 18 mg. of histamine in 1 pound of

dried substance of whole pituitary gland, and their statement that "histamine is the plain-muscle stimulating and depressor constituent of the posterior lobe of the pituitary gland," the authors of this paper conclude, on apparently valid evidence, that the perfectly fresh hypophysis contains no histamine and express the opinion that Abel and Kubota's contention is untenable. They hazard the suggestion that the histamine found by Abel and Kubota in the dried pituitaries may have been the result of the action of putrefactive bacteria on histidine. Exact details are given of the methods of preparation of the various extracts of the fresh pituitary glands, methods which they claim are not sufficiently vigorous to prevent the recovery of histamine for either colorimetric or physiological testing if such be present. However, the methods were sufficiently vigorous to destroy the oxytocic principle, at least in the extracts obtained, for none of them caused contraction of the excised virgin guinea-pig uterus.—F. S. H.

Action of HYPOPHYSEAL extracts on diuresis in dogs and rabbits (Action des extraits hypophysaires sur la diurèse chez les chiens et les lapin). Houssay (B. A.), Galan (J. S.) & Negrette (J.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1248-1250.

The posterior lobe of the bovine hypophysis was used in a 20 per cent decoction in saline solution acidified to 0.25 per cent. The experiments were made in three ways: 1.—Action on the diuresis during 24 hours in animals, which fed themselves voluntarily; 2.—Action on animals the food and water of which were measured; 3.—Action on normal and provoked diuresis, collecting the urine at intervals of 1 to 2 hours before and after injection of hypophysis.

It was found in brief that extract of hypophysis provokes an oliguria of short duration in rabbits, with considerable anorexia. In rabbits on a fixed regime there is no effect in 24 hours, although there is an immediate oliguria. In dogs, the extract induces diuresis, which manifests itself during several hours, but does not influence the 24 hour quantity; this quantity may sometimes be diminished. The hypophysis inhibits the diuresis produced by the ingestion of water, probably by retarding its absorption.—T. C. B.

HYPOPHYSIS and scleroderma (Ipofisi e sclerodermia). Izar (Guido), Riforma med. (Napoli), 1920, **36**, 482-486.

A preliminary discussion is given of the multiplicity of factors assigned as causes for scleroderma from which Izar

comes to the conclusion that the theory of a causative endocrine disturbance is the most securely founded. Nevertheless, he cannot agree to a monoglandular conception of the disorder because of the strict interrelationship so often shown in glandular functioning. The case described refers to a girl 7 years old, with well defined scleroderma, giving a positive Cushing reaction and showing an enlarged sella turcica on radioscopic examination. Consequently opotherapy was initiated (pituitary extract and hypophysine). After the sixth injection further development of the sclerodermic lesion was stopped and in less than fifty days the patient was greatly improved. The treatment was continued and seven months after the first treatment the patient was cured.—G. V.

(HYPOPHYSIS) A study of the haemodynamic reaction of the cerebrospinal fluid and hypophyseal extracts. Jacobson (Conrad), Johns Hopkins Hosp. Bull. (Baltimore), 1920, 31, 185-196.

Briefly stated, the object of the investigation was a study of the physiological effects of intravenous injections of unconcentrated and concentrated spinal fluid, human, bovine and artificial, in contrast with similar injections of hypophyseal extracts, anterior lobe, posterior lobe, pars intermedia and whole gland, in the hope of reaching some definite conclusion regarding the presence or absence of the pituitary secretion in the cerebrospinal fluid.

It was observed that cerebrospinal fluid from human and bovine sources in concentration gives physiological reactions identical with those obtained from the injection of various tissue extracts, effects most probably due to the presence of histamine. There was no definite evidence of the presence of a pressor substance in the cerebrospinal fluid suggestive of any posterior lobe secretion. It seems therefore rather improbable that the pituitary gland, as claimed by Herring, discharges its secretion into the ventricles or into the cerebrospinal fluid. All pituitary gland extracts showed marked variability as far as the responses on intravenous injection are concerned. They all show a depressor effect common to tissue extracts in general. It was noted that: (a) Anterior lobe exhibits depressor effects mainly; (b) Posterior lobe a moderate depressor followed by a specific pressor effect; (c) Pars intermedia has a small depressor, followed by a pressor effect; (d) Whole gland showed a neutralization of the depressor and pressor effect; (e) The posterior lobe secretion, if it is a specific secretion, is most probably produced in the pars intermedia and finds its way into the pars nervosa. The author further observed that

the posterior lobe extract on intravenous injection appeared to have an anti-diuretic effect rather than a diuretic one and that glycosuria was produced by intravenous injection of posterior lobe extract in a number of cases. This glycogenic effect is more marked in the rabbit.—J. F.

(HYPOPHYSIS) Combination of hypophyseal adiposity with poliomyelitis (Kombination von hypophysärer Fettsucht mit Poliomyelitis). Kastan, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 898.

A case is reported, but without any details of special endocrine interest.—J. K.

Correlation between the vasodynamic action of PITUITRIN and that of the ADRENALS (Corrélation entre l'action vasodynamique de la pituitrin et celle des surrénales). Kepinow (L.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1134-1135.

The study of the vasodynamic properties of pituitrin led to the question whether this action was dependent on adrenalin circulating in the blood, or on a modification in the sense of an augmentation of the secretion from the adrenals. The answer seemed to lie in the study of the vascular action of pituitrin in the absence of adrenalin. The experiments were done on dogs, the adrenalin being eliminated either by tying the suprarenal vessels, or clipping them with forceps. When the action of the adrenals is thus eliminated, the injection of pituitrin fails to cause a rise in blood pressure, but if the suprarenal veins are released after such an injection, the blood pressure is augmented and presents all the characters of an injection of pituitrin under normal conditions. The indications are that there is a functional interdependence between the vasoconstrictor action of pituitrin and the action of adrenalin. [Hoskins and McPeek reported in 1913 that occlusion of the adrenal circulation in dogs causes no change in the pressor effect of pituitrin. The disparity should be further investigated.—Ed.]—T. C. B.

(HYPOPHYSIS) Pituitary tumor with general edema in two cases of nanism, one of the Paltauf type, the other of the pituitary type. Kraus (W. M.), J. Nerv. & Ment. Dis. (N. Y.), 1917, **45**, 193-213.

These two cases of dwarfism were described together because of certain signs in common. Both showed low basal metabolism, hypoplasia of sexual organs, edema, greatly increased carbohydrate tolerance, lack of body hair, deficent ossification

of epiphyses of large bones and smallness of stature. The skin was dry and wrinkled in both cases and the general appearance was cretinoid. In the first case the sella turcica was shown by x-ray to be greatly enlarged and there were definite eye signs and symptoms of hypophyseal tumor. This man, 48 years of age, was mentally infantile and presented a general appearance resembling in several respects that of an ape. The Paltauf case showed no enlargement of the sella turcica, but at autopsy the posterior lobe of the pituitary body was found to be practically replaced by colloid and the anterior lobe was not made out. The testes were very small and of the infantile type. Development had evidently ceased between the fifth and eighth years. For some months before death this patient showed marked somnolence like that described by Cushing in connection with hypophyseal disease and compared with the phenomenon of hibernation.—I. M.

A case of senile osteomalacia cured by HYPOPHYSIN (Ein mit Hypophysin geheilter Fall von seniler Osteomalazie). Lang (K.), Berl. klin. Wchnschr., 1920. **57**, 658-659.

The patient was a woman of 65 years; her height was 1.27 M. and her weight was 25 Kilos. The whole skeleton showed symptoms of osteomalacia; there was general atrophy of the muscles but no symptoms of tetany. The thyroid was swollen; there were diarrhea and a tremor manifested. The results obtained with phosphorus and cod liver oil and with antithyroidin tablets were meagre. **Adrenin** gave dangerous complications. Following injections of hypophysin (the dose is not given) the patient rapidly improved, though during this treatment the blood pressure became much higher.—J. K.

(HYPOPHYSIS Encephalitis lethargica and pituitrin (Encefalitis letargica y pituitrina). Luengo E. . Rev. de sanidad militar (Madrid), 1920, **66**, 331.

The author is of the opinion that the hypophysis takes a part in the phenomena of encephalitis lethargica and obtained good results by use of pituitrin in the disorder.—G. M.

(HYPOPHYSIS) Adiposo-genital dystrophy accompanied by epileptic attacks (Distrofia adiposo-genital frusta con ataques epilepticos). Malamud (T.), Prensa Med. Argentina (Buenos Aires), 1920, **7**, —— (June 30th).

Case report of an epileptic of 14 years with adiposity and menstrual difficulties. Improvement followed subcutaneous hypophyseal opotherapy.—B. A. H.

HYPOPHYSEAL and adjacent tumors (**Hypophysen—und Hypophysengegendtumoren**). Oberndorfer, München. med. Wchnschr., 1920, **67**, 946-948.

Description of some cases.

1. **Rudimentary acromegaly.** A man of 40 died from acute yellow atrophy of the liver. He had two enormous toes. Autopsy showed an enlarged posterior lobe of the hypophysis, the eosinophil cells invading the posterior lobe.

2. **Combination of acromegaly and dystrophia adiposogenitalis.** In this case the patient (a man of 21) died from otitis media. Postmortem showed no trace of hypophyseal tissue. The gland had been replaced by a tumor the size of a hen's egg which compressed the third ventricle.

3. **Dystrophia adiposogenitalis** in a woman of 39. A tumor of the hypophysis the size of a hen's egg was found at autopsy. The tumor had destroyed the sella turcica and had grown into the sphenoidal sinus. There still remained some small residua of the posterior lobe.

4. **Dystrophia adiposogenitalis** in a man of 55. Postmortem: Teratoid of the hypophysis. No hypophyseal tissue left.

5. **Dystrophia adiposogenitalis** in a woman of 63. Postmortem: Hypophysis normal but compressed by a cyst of the infundibulum.

6. **Dystrophia adiposogenitalis** in a woman of 21. Postmortem: Sarcoma of the infundibulum the size of a pigeon's egg.

7. A boy of nearly 6 years with many pigmented birthmarks, headache, paleness and vomiting but no adiposity; exitus. Postmortem: Glioma of the infundibulum.

8. In a patient who died without any typical symptoms, a cancer of the infundibulum compressing the hypophysis was found.—J. K.

Adiposo-genital syndrome with tumor of the **HYPOPHYSIS**; radio-therapy: regression of the symptoms (**Syndrome adiposo-genital chéz un malade porteur d'une tumeur de l'hypophyse: radiotherapie: regression des symptômes**). Reverchon, Worms & Rouquier, Bull. et. mem. Soc. med. d. hôp. d. Par. 1920, n. s., **44**, 1084-1085.

A report of physical regression due to pituitary involvement in a young soldier of 27 years. The disturbance probably was due to the effects of an internment caused by the explosion of a shell of high caliber. Radiographic examination having showed an enlarged sella turcica, x-ray applications were made at once for 6 months, with the result that the ocular symptoms

remained stationary, and the evidences of glandular insufficiency gradually passed away.—F. S. H.

Action of the HYPOPHYSIS on renal function (De l'action de l'hypophyse sur les fonctions renales). Romme (M.), Presse méd. (Par.), 1917, **25**, 533.

The author studied the action of various pituitary extracts on the renal function in different subjects. He found that the different gland preparations used gave varying results and considers that this fact accounts for the discrepancies previously reported. In all of his cases posterior lobe material produced a tendency to oliguria with an increase in the concentration of urinary chlorides. He concludes from this that **diabetes insipidus** is due to a reduced activity of the hypophysis. Extracts of the anterior lobe of the hypophysis had no effect on the urine excretion.—I. M.

(HYPOPHYSIS) The effect of pituitary injection on the blood pressure of febrile patients. Schmidt (H. B.), Arch. Int. Med. (Chicago), 1917, **19**, 1059-1061.

The object of the experiment described in this paper was to discern whether or not injections of pituitary extract in therapeutic doses cause a rise in blood pressure in man comparable to that observed in animals. Twenty-seven observations were made on fifteen febrile patients with different diseases. No definite and constant rise was produced in systolic blood pressure after intramuscular injections of the extract, but the diastolic pressure rose in all cases, as much as 15 mm. in some cases. The maximum height was observed after about 30 minutes. Extracts and desiccated gland substance given by mouth had no such effect, even in large doses. Subsequent injections showed the same effects as the primary injection in the same patient.—I. M.

(HYPOPHYSIS) Tumores de la hipofisis. Segura (E. V.), Rev. Asoc. méd. argent. (B. Aires), 1916, **25**, 184.

A brief note to the effect that in four cases the author has obtained remarkable results (visual improvement) by complete excision of the tumors.—R. G. H.

Present knowledge of INTERNAL SECRETIONS. (Gegenwärtige Stand der Lehre von den inneren Sekretion). Asher (L.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1028-1030; 1056-1057.

A general review without new data, which fails to give all our present knowledge on the subject. The author is quite sure that the adrenals produce adrenaline and that this has the same action as adrenaline when injected. In the same way dystrophia adiposogenitalis and diabetes insipidus are certainly related to the hypophysis, according to the author. Not a word is said about the highly important work of Leschke, Aschner, Camus, Roussy and others on the function of the midbrain in these diseases.—J. K.

INTERNAL SECRETIONS and tachycardia (Las taquicardias y las secreciones internas). Bonilla (E.), Siglo méd. (Madrid), 1920, **67**, 688-691.

The author studied the influence of the various internal secretions on cardiac rhythm considering that the greater part of the so-called essential tachycardias are due to latent conditions of **hyperthyroidism**. The emotional tachycardias, many examples of which were frequent during the European War, are produced, in persons predisposed, by the innate hyperthyroid activity of the emotional act. At times these emotional tachycardias are accompanied by hypertension (Aubertin) which can be explained on a basis of emotional **hyperadrenalism**.—G. M.

(INTERNAL SECRETIONS) Continued fever of sympathetic origin. (La fièvre continue d'origine sympathetique). Cawadias (A.), Ann. de Méd. (Paris), 1920, **7**, 450-455.

A case report is given, as well as a general discussion of those patients in whom there occurs a continuous fever of a mild type which fails to react favorably to any treatment and the diagnosis of which cannot be based on any specifically known cause. Frequently an unstable pulse, emotivity, fatigability and vasomotor troubles are also present. An intensive reaction to adrenaline with negative response to atropine indicates a sympathetic disturbance. No **thyroid** disorder is evident, but occasionally Sergent's white line is present, which may or may not indicate **adrenal** insufficiency as the direct cause of the disturbance. However, since the syndrome described is not due to intoxication, infection or to tuberculosis, it is considered idiopathic and probably has its origin in some disturbance of the internal secretions. The prognosis is favorable and the treatment consists in complete moral, physical and mental repose.—F. S. H.

The influence of INTERNAL SECRETIONS on blood pressure and the formation of bile. Downs (A. W.), Proc. Am. Physiol. Soc., Am. J. Physiol. (Balt.), 1920, **51**, 193-194.

Correction of citation, Endocrin., **4**, 470. The article referred to was afterwards published in full in Am. J. Physiol., 1920, **52**, 498-507. For data see abstract of this latter article.

(INTERNAL SECRETIONS) Studies on the anatomical changes which accompany certain growth disorders of the human body. Keith (A.), J. Anat. (Lond.), 1920, **54**, 101-115.

The name "diaphysial aclasis" is suggested for the disease commonly known to clinicians as multiple exostoses. Because of its relation to achondroplasia it is suspected that the disorder may be due to a disturbance of some of the endocrine glands—most likely of the **thyroid**.—W. J. A.

The INTERNAL SECRETIONS. Scott (T. B.), Practitioner (Lond.), 1917, **99**, 474-481.

The writer discusses the rapidly increasing knowledge of the internal secretions and their therapeutic and pathological significance. He deals with Graves' disease as a pluriglandular disturbance, elaborating on the interrelationship existing between the activity of the **thyroid** and the **adrenals** and between the former and the **parathyroids**. He recommends parathyroid extract in the treatment of acute Graves' disease on the assumption that it normally acts as a balance against overactivity of the thyroid. In cases of the disease with low vascular tension adrenin or suprarenal extract is employed on the ground that its pressor activity is in abeyance in the disease when the depressor action of the thyroid secretion is excessive. In cases in which nerve disturbance is noticeable he uses parathyroid and suprarenal preparations with the manometer as a guide. He expresses great faith in the use of parathyroid for the relief of paralysis agitans, citing examples of its having been employed repeatedly with beneficial results. **Pituitary** extract is claimed to have had undoubted virtue in Graves' disease in his hands. Cases are cited to show its value as a restorer of power in the feebleness of old age.—I. M.

(MAMMA) Epitelio-sarcome de la glande mammarie. Bergeret & Botelho, Gynec. et obst. rev. (Paris), 1920, **1**, 139-147.

Of no endocrine interest.—F. S. H.

(MAMMA) Prolonged mammary secretion. Curettage. Cure (Sécrétion mammaire prolongée. Curettage. Guérison). Hamant (M.), Bull. soc. obst. et gynec. (Paris), 1920, **9**, 164-168; see also Gynec. et obst. rev. (Paris), 1920, **1**, 395-396.

A young woman of 23 years gave birth to a child which she nursed for nearly a year. Although the child was weaned at this time the milk flow continued notwithstanding the application of the usual means to cause it to cease. This condition having continued for two years and more the woman sought medical assistance and the author being of the opinion that a relation exists between the function of lactation and the placenta, considered that the prolonged flow of milk might be due to the intra-uterine retention of some placental fragments from the conception of 2 years previously. He consequently advised a curettage. The advice was accepted and the flow of milk began to diminish 4 or 5 days after the operation and 2 weeks later had entirely stopped. Nevertheless, H. was unable to find any placental cells in the detritus of the curettage. Three months after the operation the patient was relieved of a tubal pregnancy evident on abdominal palpation. No milk flow occurred after this second surgical interference. As an explanation for the result obtained from the curettage H. considers the possibility of placental residues already alluded to as maintaining a constant uterine reflex irritation. He does not look favorably upon an explanation based on psychic factors because the flow of milk did not stop quickly enough. In the discussion M. M. Remy and Froelich dissent from Hamant's explanation.

—F. S. H.

Clinical pathology of the MIDBRAIN (Zur klinischen Pathologie des Zwischenhirns). Leschke (E.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 959-961; 996-997.

The author denies the existence of a relation between the hypophysis and diabetes insipidus on the ground that extirpation of the hypophysis in animals never gives rise to polyuria when the midbrain is not touched during the operation. Extirpation of the lobus posterior produces no symptoms at all; extirpation of the anterior lobe gives rise to hypophyseal cachexia. Likewise, when pathological processes destroy the hypophysis without affecting the midbrain polyuria is never observed, only cachexia, when the anterior lobe is involved. On the other hand, it is possible to produce polyuria by piqure behind the infundibulum in the tuber cinereum of the midbrain. There are many cases known (bullet wounds, brain tumors, gummata, tubercles of the infundibulum, tumors of the

pineal, hemorrhagic insults of the midbrain, and internal hydrocephalus) in which, without any lesion of the hypophysis, diabetes insipidus has occurred through changes in the midbrain. Not only is there a close relationship between the midbrain and diabetes insipidus, but also diabetes mellitus may be closely related to diseases of this part of the brain. The fact that extirpation or diseases of the whole or part of the hypophysis are never followed by glycosuria is an argument against the existence of hypophyseal diabetes. On the other hand, diseases of the midbrain may cause diabetes. Thus may be explained the diabetes that is seen in syphilitic meningitis. This may be expected, for there is a close relation between diabetes insipidus and diabetes mellitus. The author found that in diabetes mellitus with polyuria the kidneys had depressed concentration power. It is the same with diabetes insipidus. In two cases of diabetes mellitus the author found microscopic changes in the cells of the hypothalamus between the corpora mamillaria and the infundibulum. In a third case, however, no changes were found. The midbrain may be the seat of the cause of diabetes mellitus, but it certainly is not the only one.

Dystrophia adiposogenitalis has no dependence upon conditions in the hypophysis. Out of 41 cases the gland was found perfectly normal in 18; in the other cases the hypophyseal tissue was as often increased as diminished. On the other hand, in all cases of dystrophia there are changes in the midbrain. When in the course of experimentation the midbrain is wounded, the animals develop atrophy of the generative organs (Aschner). Adiposity, however, is not always observed. Dystrophia adiposogenitalis may be combined with other midbrain symptoms, as polyuria, subnormal temperature, etc. Other symptoms, due to pathological changes in the midbrain, are: disturbed heat regulation, disturbed pupil reactions, and changes in the sweat and vasomotor reactions.—J. K.

Oxycephaly and NANISM (Oxycephalie et nanism). Isola (A.), Butler (C.), & Mussio-Fournier (J. C.). Bull. et mem. Soc. méd. d. hôp. d. Par., 1920, **44**, 1122-1128.

Anthropometric and clinical study of a curious case of dwarfish, which is diagnosed as oxycephaly and not infantilism because the latter is eliminated by the occurrence of menstruation and the development of the secondary sexual characteristics. Nevertheless an endocrine disturbance of undetermined nature is considered as a possibility.—F. S. H.

Abortive forms of OSTEOMALACIA (Ueber Abortivformen der alimentären Osteomalazie). Koch, München. med. Wchnschr., 1920, **67**, 883.

Of no endocrine interest.—J. K.

Rickets and OSTEOMALACIA. (Rachitis und Osteomalazie). Lehnerdt, Ztschr. f. ärzt. Fortbildung (Jena), 1920, **17**, 433-437; 460-466; 489-498.

Of no endocrine interest.—J. K.

On the postnatal development of the OVARY (albino rat), with especial reference to the number of ova. Arai (H.), Am. J. Anat. (Phila.), 1920, **27**, 405-462.

A careful quantitative study of the number of ova and corpora lutea at all ages from birth to 947 days has been made in the albino rat. Not primarily of endocrine interest.

—W. J. A.

(OVARY) Precocious menstruation with hypergenitalism (Menstruatio praecox mit hypergenitalismus). Lebhardt, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 875.

A very brief case report of a girl in whom regular menstruation appeared at 11. At operation a malignant tumor of the ovary was found and removed. No other details are given.

—J. K.

(OVARY) Contribution to the knowledge of normal and pathological OVULATION and the related uterine processes (Beiträge zur Lehre von der normalen und krankhaften Ovulation und der mit ihr in Beziehung gebrachten Vorgänge am Uterus). Meyer (R.), Arch. f. Gynäk. (Berlin), 1920, **113**, 258-315.

An extensive discussion of ovulation presenting but meagre experimental data. The course of ovulation is defined as consisting of ripening of the ovum and the independent follicular luteinization, together with the functional preparation of the uterine mucosa. The death of the egg cell is said to follow that of the follicle or its previously delimited **corpus luteum.** The final step is the death of the mucosa (Schleimhauttod). According to this conception menstruation is the expression of the failure of the natural processes which result from fertilization and hence the "rule" is the pathological exception. M. considers that the survival of an ovum past menstruation

is impossible. The clearing up of the chemical processes in the functionally prepared and functioning uterine mucosa can only be accomplished when recognition is paid to the fact that the pregravid phenomena are to be sharply differentiated from menstruation considered as a functional death, since it should rather be looked on as a functional failure. One should not speak of a menstrual cycle and premenstrual uterine conditions, since the mucosa, because of the shrunken span of life of the unfertilized ovum, and because of a certain stage of development of the next egg of 3 to 4 weeks duration, will be renewed to a functional pre-gravid state. There is no menstrual cycle, but only a mensual ovulation cycle, the consequence of the failure of domestication. This cycle lasts from the death of one egg to that of another.—F. S. H.

(OVARY) Relation of hyperplasia of endometrium to so-called functional uterine bleeding. Novak (E.), J. Am. M. Ass. (Chicago), 1920, **75**, 292-297.

Since functional uterine bleeding, occurring at the menopause or near the time of puberty, is very frequently accompanied by an endometrial hyperplasia, and since currettage fails to bring a permanent cessation of the menorrhagia, Novak believes that the endometrial changes causing functional bleeding are mere local manifestation of the endocrine disturbance of the ovary. The remarkable cyclic changes of the uterine mucosa which are associated with normal menstruation are directly due to the internal secretory activity of the ovary; hence, if the ovarian secretions are disordered, he assumes that the endometrial response will be abnormal and, conversely, in functional uterine hemorrhage from the hyperplastic endometrium the ovarian secretions are presumably either primarily or secondarily at fault.—F. C. P.

Cancer of the OVARY involving the sigmoid flexure. Truesdale (Philemon E.), Ann. Surg. (Phila.), 1920, **72**, 218-223.

A case report.—J. F.

(OVARY) The ripe human graafian follicle together with some suggestions as to its mode of rupture. Thompson (A.), J. Anat. (Lond.), 1919, **54**, 1-40.

A detailed morphological study is given in which the author is inclined to minimize the influence of the accumulation of liquor folliculi in bringing about the rupture of the follicle, which he considers to be produced by the vascular and nervous disturbances of menstruation or coitus.—W. J. A.

(PANCREAS ADRENALS) A case of endogenous adiposity. (Ein Fall von endogener Fettsucht). Arnold, München. med. Wchnschr., 1920, **67**, 945.

Demonstration of a girl of 13 who had endogenous adiposity since she was two years old. The heart was large and there were manifested status thymolymphaticus and alimentary glucosuria. The weight was 180 pounds. The author is of the opinion that in this case "the adrenal system dominates the pancreas".—J. K.

Degenerative changes in the PANCREAS during gestation (Transformation dégénérative du pancréas pendant la grossesse). Aron (M.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1122-1125.

Chiefly of histological interest. Changes in the peripheral lobules of the pancreas of a pregnant bat are described and hypotheses as to the cause discussed.—T. C. B.

(PANCREAS) Hematic formation in the islands of Langerhans of the embryonic pancreas (Hématiformation dans l'ilôts de Langerhans du pancréas embryonnaire). Aron (M.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1119-1122.

Of histological interest.—T. C. B.

(PANCREAS) The behavior of the pancreas in diabetes in larger children; also studies on the normal structure of the gland at these ages (Das Verhalten der Pankreas beim Diabetes gröszerer Kinder, sowie Untersuchungen über den normalen Bau der Drüse in diesem Alter). Heiberg (K. A.), Arch. f. Kinderh. (Stuttgart), 1916, **65**, 388-391.

Heiberg counted the number of Islands of Langerhans in 50 cmm. of pancreatic tissue and determined the average number in a series of 15 normal children and of 8 diabetics of similar age, 7-18 years. Of the normal children 7 had 76-150 islands per 50 cmm. and 8 had over 150. Of the 8 diabetics only one had over 75 islands per 50 cmm. Heiberg emphasizes the need for the study of the pancreas and the islands, to be placed on a quantitative basis. (Set also Hammar, Endocrin., **4**, 37-46.) —C. H. G.

(PANCREAS) Fat digestion and diagnosis of pancreatic insufficiency (La digestion des graisses et le diagnostic de l'insuffisance pancréatique). Labbé (M.), & Labbé (H.), Ann. de Méd. (Paris), 1920, **7**, 424-435.

Not of endocrine interest.—F. S. H.

(PANCREAS) Two cases of pancreatitis (acute and chronic) [Deux cas de pancreatite (aigue et chronique)]. Phêlip (J. A.), Arch. d. Méd. d. Enf. (Paris), 1920, **23**, 357.

The author reports a case of acute pancreatitis in a child of seven and one of chronic pancreatitis in a child of ten. In the latter there was also an associated cystic dilatation of the gall bladder. Both cases are of surgical interest only.
—C. H. G.

PANCREAS and its diseases (Over pancreas en pancreasziekten). Vermast (P. F.), Tijdschr. v. Diergenessk. (Utrecht), 1920, **47**, 232-246.

A general review, of no endocrine interest.—J. K.

(PARATHYROIDS) Anatomical and pathological studies of the parathyroids of 64 insane patients (Étude anatomo-pathologique des parathyroïdes de 64 aliénés). Laignel-Lavastine & Duhem (P.), Ann. de méd. (Paris), 1920, **7**, 409-425.

Contrary to general opinion, the authors were unable to establish the consistent presence of 4 parathyroids in the human subjects studied. Out of the 64 persons examined but 11 had 4 of these glands; in 18 cases 3 were present; in 15 cases 2; in 17 but one was found, and in 3 no parathyroid tissue was demonstrable.

The cells of the gland acini have been designated as the principal cells and the so-called "secondary cells" have been renamed the eosinophil cells because of their particular affinity for eosin. Two types of glandular parenchyma are also described, the one consisting largely of acinar cells and called the acinal type, the other, because of its indefiniteness, is designated as the disperse or diffuse type. Differences in number, form and structure of the parathyroids are found to occur in different subjects and in those of same person.

In senile dementia and a third of the observed cases of general paresis, there was evident a transformation of a more or less large part of the glands to the eosinophile type, which was usually accompanied by a vascular congestion. Fat infiltration of various degrees of intensity was evident in 63 of the cases. A slight increase of connective tissue was frequently noted, although abundant sclerosis was markedly rare. Colloid was found in 26 subjects and occurred as intra-acinal drops more or less abundant.—F. S. H.

On the PARATHYREOID duct of Pepere and its relation to the postbranchial body. Robertson (M.), J. Anat. (Lond.), 1920, **54**, 166-169.

A cyst- or duct-like epithelial structure is described in relation to the thyroid, parathyroid and thymus glands of cats and dogs. In the thymus it is said to give rise to the corpuscles of Hassall by a process of budding.—W. J. A.

(PARATHYROIDS) The cause of Trousseau's symptom in tetany (Zur Kenntnis des Trousseauschen Phänomens bei der Tetanie). Schäffer (H.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1073-1075.

Of no immediate endocrine interest.—J. K.

(PARATHYROID) The phosphate and calcium content of serum in the condition of guanidine tetany. Watanabe (C. K.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1918, **15**, 143-145.

The aim of the experiments reported was to study the phosphate and calcium changes in the blood in guanidine tetany for comparison with those occurring in parathyroid tetany. Other workers had previously shown that the lack of parathyroid is accompanied by increased elimination of ammonia, decreased acid excretion and lowering of the hydrogen ion concentration like that following administration of guanidine hydrochloride. Parathyroidectomy causes a marked decrease in the elimination of phosphates in the urine with retention in the blood and also a decrease in the calcium of the tissues. Guanidine nitrogen is increased in parathyroid tetany. Therefore, it was hoped to determine whether the increase in guanidine is the only cause of this phenomenon or whether other factors are involved in the production of parathyroid tetany. Marriott and Howland's methods were employed. Rabbits were given sublethal doses of guanidine hydrochloride subcutaneously and blood samples were taken just before and again 10 to 48 hours after the injection. The phosphate content of the blood was markedly increased but the reduction of calcium was doubtful. No final conclusion as to the main question was reached.—I. M.

The Vineland experience with PINEAL gland extract. Wagner (H. P.), J. Am. M. Ass. (Chicago), 1917, **68**, 1340-1341.

The author briefly reviews the experiments carried out at Vineland in which twenty-seven mentally deficient children were fed a preparation of pineal gland over a considerable period of time to determine if this gland has some active principle, lack of which might be associated with the retarded mental development. While the results were mildly suggestive of a positive reaction, on the whole the findings were little dif-

ferent from those in the control group and the author concludes that the substance of the pineal gland is entirely inert. —I. M.

On the PINEAL region in human embryos. Warren (J.), Anat. Rec. (Phila.), 1917, **11**, 428-429.

Attention is called to three special features in the development of the pineal region in the human embryo. The first feature pointed out pertains to the primary arches in the roof of the forebrain. These are clearly differentiated in an embryo of 10 mm. and are more fully developed in one of 15 mm. The anlage of the paraphysis is marked by a slight thickening in the paraphyseal arch. The pars intercalaris forms an arch of relatively great length as compared with its appearance in lower vertebrates. No trace of the paraphysis could be found in embryos of from 17 to 22 mm., although its anlage was observed in one 15 mm. embryo and two 16 mm. embryos, as well as in several of from 23 to 44 mm. The paraphyseal arch was seen in all embryos studied. The third point of interest refers to the post-velar arch. A striking feature found in many human embryos is a complicated prolongation of the anterior end of this arch just behind the vellum. As the outgrowth becomes more complicated, tubules are given off which may become detached and appear as blind vesicles buried in the midst of this tubular formation.—I. M.

PLURIGLANDULAR SYNDROME accompanying DIABETES INSIPIDUS; efficacy of hypophyseal opotherapy for the polyuria (Syndrome pluriglandulaire ave diabète insipide: efficacité de l'opotherapie hypophysaire sur la polyurie). Crouzon & Bouttier, Bull. et mem. Soc. méd. h. hôp. d. Par., 1920, **44**, 1114-1121.

A report of a case presenting the two fundamental symptoms of amenorrhea persisting for 3.5 years and a diffuse adiposity of simultaneous onset. Other symptoms were polydipsia, polyuria, polyphagia, apathy, tendency to drowsiness, and evident regression of the psychic faculties, temporal hemianopsia of the right visual field, partial paralysis of the right oculomotor nerve, Argyll-Robertson pupil, and, finally, arterial hypotension and thermic instability. Certain of the symptoms indicated the possibility of a **thyroid** disturbance, the whole giving a picture of probable pluriglandular disorder with a certainty of a **hypophyseal** or juxta-hypophyseal lesion. The only treatment given was the daily injection of extract of the posterior lobe of the hypophysis, equivalent to 0.05 gm. of the dry

powder; other medication contemplated was prevented because of removal of patient from hospital. As a consequence of the administration of the extract the polyuria was markedly relieved.—F. S. H.

(PROSTATE) Enlargement of MAMMARY GLAND after prostatectomy (Vergrösserung der Brustdrüse nach Prostatektomie). Kondoléon (E.), Zentralbl. f. Chir. (Leipzig), 1920, **47**, 1098.

In a man of 70 prostatectomy was carried out. After some weeks it was observed that the right mamma was swollen. The swelling disappeared later on without treatment. In another case (also a man of 70) both mammae became larger after prostatectomy, but the swelling did not disappear.—J. K.

PROSTATECTOMY. Bugbee (H. G.), Boston M. & S. J., 1920, **183**, 41-47.

Refers to previous works which deal with the results of castration and vasectomy upon the hypertrophied prostate. Nothing new of endocrine interest.—H. W.

(STATUS THYMICOLYMPHATICUS), Idiopathic hypertrophy of the heart in young children. Howland (J.), Contributions to medical and biological research dedicated to Sir William Osler. Hoeber (New York), 1919, **1**, 582.

Howland reports five cases of idiopathic hypertrophy of the heart in children ranging in age from 10 to 48 months. Four of these were diagnosed clinically and one was followed over a period of three months before exitus. No anatomical cause for the condition was found. The thymus varied in weight from 8 to 22 gm. in the different cases, but Howland points out the extreme normal variability in the weight of the thymus and the absence of cardiac hypertrophy in the usual clinical cases of status thymicolymphaticus. Microscopically the heart muscle in these cases showed no essential change from the normal. In a critical review of the literature Howland is content to reemphasize the obscurity of this condition. (See Riesenfeld. Abst. in this issue).—C. H. G.

STATUS THYMICOLYMPHATICUS, Primary cardiac hypertrophy in early childhood and its relation to—(Über primäre Herzhypertrophie im frühen Kindesalter und ihre Beziehung zum Status thymico-lymphaticus). Riesenfeld (A.), Jahrb. f. Kinderh. (Berlin), 1917, **86**, 419.

Riesenfeld reviews the literature on the congenital idiopathic hypertrophy of the heart in detail and gives a general discussion of the earlier hypotheses in regard to the origin of this condition. He reports an additional five cases in infants, ranging from 9 to 18 months old. These cases were all seen in the acute terminal stage of this disease. The clinical diagnosis of the hypertrophy was possible in all cases and in three it was confirmed by roentgenograms. According to the author the only constant factor present in all five cases was a well marked status lymphaticus. Unfortunately the autopsy protocols are all given in abstract and in only one case was the actual weight of the thymus mentioned; it was 14 gm. in an 11 months old boy. In addition to the gross pathological findings microscopic examination showed diffuse lymphocytic infiltration of the heart muscle. Riesenfeld feels that the hypertrophy may in part be due to the mechanical effect of the enlarged thymus, but that the casual factors more probably are to be found in the endocrine disturbances associated with the status thymicolyphaticus. In this connection he remarks upon the hypoplasia of the adrenal medulla found in one of his cases.—C. H. G.

(TESTES) The man young at fifty. Periodicities, cycles of energizing organic rhythyms. II. Critical epochs in the reproductive cycles. Taylor (J. M.), Med. Times (N. Y.), 1920, **48**, 235-238.

An interesting article in which the author attempts to show that men have a more or less well defined sexual cycle and that they demonstrate phenomena which are the equivalent of the climacteric period in women. New data to support such a view are not offered.—H. W.

Experiences in TESTICLE transplantation. Stanley (L. L.), Calif. State J. M., (San Fran.), 1920, **18**, 251-253.

The author reports the results of 11 transplants of human testes and 21 of young rams into men. Such transplants seemed to have an invigorating effect upon the recipients, sexually and psychically. The implant (entire testes) does not live but becomes necrotic; however, in the process of necrosis certain unknown potent substances are probably released into the system. The glands of rams seem to be as effective as those of man. These glands may be kept for a week or longer by immersion in vaseline and freezing. Slices of testes placed in the abdominal cavity do not show the same tendency to slough as do entire glands when placed in the scrotum.—H. W.

TESTICLE transplantation. Stanley (L. L.) & Kelker, (G. D.), J. Am. M. Ass. (Chicago), 1920, **75**, 1501-1503.

These authors report the result of eleven cases of testicle transplantation. In five cases only one testicle was implanted into the scrotum; in six cases two testicles were implanted. In one case, the testicle of a ram transplanted to man, began to slough in sixteen days. In three cases, one-half of the ram's testicle began to slough in seven days. In three cases human material was placed in a bed made in scrotal tissue, and in seven cases the testicle was grafted on the atrophied testicle of the recipient. In the case of one patient 25 years of age, who was dull mentally and inactive physically, mental acuteness improved and he became a better laborer after having a double graft from a man 27 years of age. In a case of a man 72 years of age, who had never had normal sex impulses, after a double graft from a 19 year old boy, improvement physically, a lower pitched voice and more mental activity resulted. Judging from their limited number of cases, the authors concluded that the transplantation of the human testicle has a decided beneficial effect on the well-being of a patient. They do not believe that the transplant lives. Their experience shows that the beneficial results probably last more than one year.—F. C. P.

The behavior of the interstitial cells of the TESTIS toward vital dyes. Addison (W. H. F.) & Thorington (J. M.), Anat. Rec. (Phila.), 1916, **11**, 318-319.

Vital staining with trypan blue reveals two types of cells in the intertubular structure of the testis. One type is elongated in the form of fibroblasts, while the other is rounded or polyhedral in shape. Both types, according to the definition of Evans, are to be considered as macrophages and are not, as Goldmann interpreted them to be, identical with the interstitial cells of Leydig which represent the testicular organ of internal secretion. The vital staining with counterstain makes it possible definitely to differentiate between the interstitial cells and the macrophages.—I. M.

(TESTIS) Hypertrophy of the interstitial tissue of the testicle in man. Goddard (T. R.), J. Anat. (Lond.), 1920, **54**, 173-176.

Examination of five undescended testicles showed a distinct hypertrophy of the interstial tissue accompanying atrophy of the seminal epithelium. The testis of a man of 78 years also showed hypertrophy of the interstitial tissue.—W. J. A.

Enlarged THYMUS GLAND in infancy and its treatment by radium. Brayton (H. W.) & Heubelin (A. C.), Bost. M. & S. J., 1919, **181**, 740-743.

The symptoms of enlarged thymus gland are divided by the authors into the two classes, general and local. The first group is characterized by faulty endocrine function, such as flabbiness of the tissues, lack of resistance to acute infections, liability to frequent convulsions, eczema and mental retardation. The local symptoms on the other hand are referable entirely to the mechanical effects of pressure on adjacent vital structures enclosed with the organ in the upper part of the rigid chest cavity. These are laryngeal spasm, heart shock, pulmonary engorgement and tracheal compression, with cough, dyspnea and cyanosis. There may be no general symptoms in a given case, but, where thymic enlargement is suspected, the diagnosis is made from the history of pressure symptoms, substernal dullness on percussion and the x-ray shadow. While it has been demonstrated by Friedlander and others that properly standardized x-ray therapy is successful in a high percentages of these cases, the authors were the first to employ radium in this connection. Every one of 34 cases treated by radium was promptly cured by the first exposure, as shown by disappearance of symptoms and by x-ray findings at varying intervals after treatment. The technique used is as follows: 100 milligrams of radium element in its 0.3 mm. silver capsule is wrapped in sufficient gauze to hold it at a distance of about one-half inch from the skin surface. Four marks are then made in the form of a rectangle over the area of thymic enlargement. The radium is applied over each mark in succession for a period of two hours, making a total dose of 800 milligram hours. This mode of treatment has several advantages over x-ray therapy. One application only is required for cure; complicated apparatus, skilled operators and the bad psychical effects of the x-ray technique are avoided.—I. M.

(THYMUS) Microscopic analysis of the thymus in 14 cases of so-called thymus deaths (Mikroscopische Analyse der Thymus in 14 Fälle sogenannten Thymustodes). Hammar (J. A.), Ztschr. f. Kinderh. (Berlin), 1916, **13**, 152-217.

See Endocrinology, 1917, **1**, 88.

(THYMUS) Hirschsprung's syndrome and diffuse spinal gliosis; Bartel's status hypoplasticus (Sindrome de Hirschprung, gliosi spinali diffusa e stato ipoplastico). Pende (N.) & Fici (V.), Riforma Med. (Napoli), 1920, **36**, 504-597.

A case history of the simultaneous occurrence of the 3 disorders named in the title. The authors attempt to coalesce the varied syndromes under one caption, i. e., status hypoplasticus, basing their conception on the wider meaning given by Bartel to the status lymphaticus as an indication of organic immaturity. The gliosis as found at the post mortem examination is explained as a congenital abnormality of the spinal cord which proceeds after birth with proliferation of the epithelium of the ependymal canal and of the glial tissue. The megalocolon, though it brought the patient to death because of an acute ileus at the age of 36, can be easily classified as a congenital abnormality, as it would belong to those abnormal developments of the gastro-enteric canal, such as diverticula, congenital atresia, abnormal length of the intestine, etc., forms found very often accompanying status thymus-lymphaticus and status hypoplasticus.—G. V.

THYMUS function in growth (La funcion del timo y el crecimiento). Sans (A. Lorente), Aragon med. (Zaragoza), 1920, 38, 241-243.

A general review without original points of view.—G. M.

(THYMUS THYROID) Ligation of the superior pole of the thymus in operating for goitre. Stewart (L. F.), Penn. M. J. (Athens), 1917, 20, 751-755.

The opinions of surgeons concerning abnormalities in the thymus as a factor in exophthalmic goitre are summed up and the conclusion is drawn that, while in some cases both thymus and thyroid are responsible, there is no satisfactory proof that the thymus is ever the sole factor. From ten special dissections it was found that the inferior thyroid artery gives an important branch to the superior lobes of the thymus in the majority of cases. The author believes that the ordinary ligation of the inferior thyroid artery near the gland leaves an increased blood supply to the upper pole of the thymus, thereby causing this portion of the gland to become congested and enlarged to the great detriment of the patient. He therefore, dissects into the carotid sheath and ligates the inferior artery behind it in order to include the thymus branch in the ligation and thereby cut off the blood supply from two toxic glands at once.—I. M.

Experiments with feeding **THYMUS GLAND** to frog larvae. Swingle (W. W.), Biol. Bull (Woods Hole), 1917, 33, 117-133.

The experiments recorded were undertaken in an attempt to repeat some of the work of Gudernatsch who found that

feeding fresh thymus gland to tadpoles stimulates the growth processes and inhibits the onset of metamorphosis. A rather extensive review of the literature is given.

In one set of experiments fresh gland was fed and in a second series thymus powder was given. The control animals were fed beef liver in equivalent quantities. Rana pipiens, R. catesbiana and one undetermined species were employed in the study. The author's results are at variance with those of Gudernatsch in that no acceleration of the growth processes was produced by feeding either fresh or powdered thymus. Some of the observations recorded indicate that thymus feeding may have a slight inhibitory effect upon limb development but even this may be only apparent since the normal variability of frog larvae in this respect is so great. The author suggests the possibility that the digestive enzymes may destroy the growth-accelerating principle of the gland so that feeding is not the best test of the gland's activity.—I. M.

Does the THYMUS GLAND of mammals when given as food to amphibians exert any specific influence upon the organism? Uhlenhuth (E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1917, **15**, 37-40.

A report is presented of experiments undertaken to answer this question. Several species of amphibians (A. tigrinum, A. opacum and A. punctatum) were employed in the study, the individuals being divided into two groups, one of which received an exclusive diet of mammalian thymus gland while the other or control series were given the regular diet of earthworms It was shown that the thymus diet exerts no specific growth promoting influence on the salamander larvae so fed. The apparent faster growth of amphibians following thymus feeding, reported by other workers, is explained in the present communication as being due to the greater quantity of food contained in a given weight of thymus gland as compared with that in an equal weight of earth worms. The earth worm contains a great deal of indigestible matter, i. e., soil, cuticle, etc. As regards the effect of thymus on metamorphosis the different species of the same genus vary greatly; e. g., A. tigrinum showed no acceleration whereas in A. opacum it was greatly accelerated. Individuals of the same species also differ in this respect as in a few cases of A. opacum, metamorphosis was unusually late. Low temperature was probably a factor in the cases noted. In these experiments it was noted that larvae receiving an exclusive diet of thymus showed convulsions which continued until about the time when the **parathyroids** first appear.—I. M.

A case of THYROID insufficiency (Un caso de insuficienca tiroidea). Abasanez (E.), An. de la Acad. med-quir. de Madrid. 1919, **6**, 367-369.

Case report of no especial interest.—G. M.

(THYROID) Case of urticaria of eight years duration with hyperthyroidism. Barber (H. W.), Guy's Hosp. Gaz. (Lond.), 1920, **34**, 115-118.

This interesting case of hyperthyroidism associated with urticaria arose as a result of chronic tonsillar infection. Removal of the tonsils brought about improvement.—J. H. L.

(THYROID) An emergency technic for thyroidectomy. Bartlett (W.), J. Am. M. Ass. (Chicago), 1920, **75**, 169-175.

Of technical surgical interest.—F. C. P.

(THYROID) Acute thyroiditis. Beilby (G. E.), N. York M. J., 1919, **109**, 876; Albany M. Ann., 1919, **40**, 173.

Data published elsewhere. See Endocrin. **3**, 409.

(THYROID) Surgical treatment of hyperthyroidism—relation existing between the amount of gland removed and the permancy of relief. Beilby (G. E.), N. Y. State J. M. (N. Y.), 1920, **20**, 230-231.

If sufficient of the thyroid gland is removed the toxic symptoms of hyperthyroidism disappear and the patient has permanent relief. To accomplish this result the author removes from five-sixths to nine-tenths of the gland. The removal of a single lobe will often give relief but it will not cure. A portion of a lobe, the blood supply of which is not disturbed, may later hypertrophy and produce symptoms. For these reasons the glandular tissue left should be scattered and small.—H. W.

(THYROID) The treatment of hyperthyroidism (Contribucion al estudio del tratamiento de los estados hipertiroideos). Bonilla (E.), Siglo méd. (Madrid), 1919, **66**, 105-108.

A study of conditions of hyperthyroidism is here reported based on the opinion that the greater number of such cases are susceptible to medical treatment. An alimentary regimen is used consisting of carbohydrates (save where glucosuria is present) and fats. Both physical and psychic rest is prescribed, while antithyroid serum is given and in addition **ovarian** substance to the women, since great importance is attached to

gonadal insufficiency in the production of the syndrome. Physicians are warned against the use of iodine in these disorders. —G. M.

(THYROID) Some pitfalls in the diagnosis of exophthalmic goiter. Bram (Israel), Ann. med. (N. Y.), 1919, **n. s. 25,** 266-268.

A review containing no new data.—J. H. L.

(THYROID) Delayed hereditary lues (Lues hereditaria tardia: Endocrinopatias. II. Tiroides). Castex (M. R.), & Waldorp (C. P.), Prensa Med. Argentina (Buenos Aires), 1920, **7,** ——, (July).

The stigmata of hereditary syphilis are in large part due to thyroid dystrophy. The nasal hydrorrhea often has as its cause a hypo- or dys-thyroidism. Mongolism is a dystrophy of endocrine origin produced by syphilis.—B. A. H.

(THYROID) Development of myxedema after treatment of Graves' disease with x-rays (Ueber die Unwandlung des Morbus Basedowii in Myxoedem durch die Röntgenbehandlung). Cordua (R.), Mitt. a. d. Grenzgeb. d. Med .u. Chir. (Jena), 1920, **32,** 283-295.

A woman of 38 showed all symptoms of classical Graves' disease. As treatment with rest and drugs had no effect, x-ray treatment was tried. After five or six applications rapid improvement occurred. After some time she complained of loss of hair, dullness and diminished perspiration. Menstruation remained regular The skin showed the typical symptoms of myxedema. Thyroidin was then given and caused much improvement, without complete cure, however. These cases are very rare; the opposite, myxedema changing into Graves' disease has also been described. This case must certainly be attributed to the x-rays, as in spontaneous cases progress is much slower. It is necessary to be very careful to measure the dose of x-rays with exactness.—J. K.

(THYROID) Practical points in goiter surgery. Cottis (G. W.), N. Y. State J. M. (N. Y.), 1920, **20,** 290-294.

Of surgical interest.—H. W.

(THYROID) Special consideration of the adenoma in relation to exophthalmic goitre. Crile (George W.), Ann. Surg. (Phila.), 1920, **72,** 141-144.

The author makes no differentiation between exophthalmic goitre with hyperplasia and thyrotoxicosis from adenomata. He summarizes the special points in his treatment of these cases. This is based upon a personal experience of 2477 thyroidectomies. The last series since the foregoing plan has been routinely employed consists of 562 thyroidectomies. No case was refused and the mortality rate in cases of exophthalmic goitre was one per cent.—J. F.

(THYROID) Hyperthyroidism and iodides (Mecanismo de la acción terapéutica del yoduro en los estados de hipertiroidismo). Delgado (Honorio F.), Crón. Méd. (Lima, Perü), 1919, **36**, 155.

Excellent results from the use of potassium iodid are claimed by Delgado in certain cases of hyperthyroidism. The mechanism of its action is not clear, he states, but the fact of the efficiency of potassium iodide in his cases was beyond question. In the case reported, the enlargement of the thyroid, tachycardia and exophtalmos had developed with hallucinations and distress, after a period of emotional stress and financial worry. Delgado used psychotherapy and gave daily 4 gm. of potassium iodide, and in two days nearly all the symptoms had disappeared.—J. Nerv. & Ment. Dis., **52**, 34.

(THYROID)—Advantages of local anesthesia in thyroid operations. Eastman (J. R.), J. Am. M. Ass. (Chicago), 1920, **75**, 166-169.

This excellent paper describes in detail the advantages of local anesthesia in operations on the thyroid gland and gives details of the author's method of removal of this gland under local anesthesia.—F. C. P.

(THYROID) Superficial percussion of the apices of the lungs in goiter (Schallverkürzungen über den Lungenspitzen bei bestehender Struma). Elias (H.) & Pick (R.), Wien. klin. Wchnschr., 1920, **33**, 674-676.

The author discusses the problems of differential diagnosis between inflammation of the pulmonary apices and goiter. The article is of technical but not immediate endocrine interest.
—J. K.

Cancer of the THYROID. Eliot, Ann. Surg. (Phila.), 1920, **72**, 381-382.

Eliot presented before the New York Surgical Society a woman, thirty-two years of age, who had been admitted to the hospital in December, 1916, complaining of a lump in her neck about the size of a hen's egg. It was of three years duration and of gradual growth. This had been her sole complaint until five months before admission, when she noticed dyspnoea on walking. Resection of the right half of the thyroid was made without difficulty. Pathological study, however, revealed a true carcinoma of the gland. The symptoms were entirely different from those of malignancy and the author is of the opinion that the carcinoma was a recent development.—J. F.

THYROID dyspepsias (Dispepsias tiroideas). Escudero (P.), Rev. españ. med. y cir. (Barcelona), 1920, —, 355-366.

The author discusses in this extensive and interesting work the conjunction of gastric alterations observed with thyroid processes. In hypothyroidism, as Hernando, Levi and Rothschild and others have noted, hypochylous conditions predominate. According to Escudero the greater part of the hypochylias and functional achylias have such an origin. In hyperthyroidism, on the contrary, there is a tendency toward high gastric values. Marañon has shown the frequency with which hyperchlorhydria accompanies hyperthyroidism. According to Escudero the first symptoms in these disorders are the painful phenomena; then the motor reactions (gastric hypertonicity, pyloric spasm) and, finally, the secretory (hypersecretion). Thyroid opotherapy in cases of the first group and anti-thyroid serum in those of the second are very useful. The article ends with interesting descriptions of 18 clinical histories.—G. M.

(THYROID) Graves' disease and goitre with heart complications (Basedow und Struma mit Herzstörungen). Fahr, München. med. Wchnschr., 1920, **67**, 884.

In 24 cases of Graves' disease or goiter, perivascular and interstitial lymphocytic infiltration of the cardiac muscle was found. In three cases there were only pathological changes of an older date. Status thymolymphaticus or persistent **thymus** was often encountered. Pathological changes in the heart may occur in goiter without symptoms of Graves' disease.—J. K.

(THYROID) Hysteric chorea and hyperthyroidism (Corea histerica e hipertirodismo). Fernandez Sanz, Medicina y libros (Madrid), 1919, **4**, 158-160.

This article refers to the case of a young female who was affected with continuous and diffuse motor alterations distinct

from all ties and systematized choreas. The author considers these alterations as a species of functional psycho-neurotic manifestation. When these attacks occurred there appeared a small lump on the middle lobe of the thyroid. The author supposes that moderate hyperthyroidism is connected with pseudochoreic disturbances.—G. M.

(THYROID) The management of toxic goitre from the surgical point of view. Frazier (Chas. H.), Ann. Surg. (Phila.), 1920, **72**, 155-160.

A brief resumé of the current literature and a discussion of the management of these cases based upon 339 cases with a mortality after resection of about one per cent. The author emphasizes the importance of making a determination of the metabolic rate and the limitations of the x-ray in the treatment of these patients. The author has applied the Goetsch test routinely during the past few months but has found it of little aid. —J. F.

(THYROID) A "tourniquet" operation in toxic and other goitres. Freeman (Leonard), Ann. Surg. (Phila.), 1920, **72**, 161-163.

Of technical interest to surgeons.—J. F.

(THYROID) Tachycardiac neuroses and abortive Graves' disease (Quelques remarques sur les névroses tachycardiques et la maladie de Basedow fruste. Gallavardin (Louis), Arch. d. mal du Cœur (Paris), 1916, **9**, 45-64.

When cases of tachycardia are encountered which are not otherwise accounted for, one should always think of subacute thyroidism. The symptoms of this condition and of "nervous tachycardia" are identical. In both conditions the same variability of heart acceleration is seen, as well as the same type of matutinal tachycardia and the same clinical forms, with the tachycardia intermittent or episodic. The whole picture amounts, in effect, to intense excitability of the sympathetic system, not only the cardio-accelerator fibers, but also the vasoconstrictors with consequent vascular hypertension.—R .G. H.

Recent advances in the diagnosis and treatment of THYROID disease based on the use of the epinephrin hypersensitiveness test. A. The differentation of tuberculosis and hyperthyroidism due to "diffuse aderomatosis." Goetsch (E.), N. Y. State J. M. (N. Y.), 1920, **20**, 282-286.

This same subject is covered in an article by Goetsch which appeared in Endocrin. 1920, **4**, 389-402.—H. W.

(THYROID OVARY) Cure of goitre and cardiac insufficiency by radiation of the ovaries. (Beseitigung einer Struma und Heilung einer Herzinsuffiziens durch Röntgenbestrahlung der Ovarien). Groedel, München. med. Wchnschr., 1920, **67**, 882-883.

A woman of 28 suffered from a large goitre, cardiac insufficiency and a pulsis irregularis perpetuus. When she was 40 she was suffering from a myoma of the uterus and lost enormous quantities of blood. An intensive treatment of the ovaries with x-rays was tried. Not only the goiter disappeared but the cardiac disturbance was also cured. It would be of interest to study the thyroid in women during and after sterilization with x-rays. In cases of myoma of the uterus and hyperfunction of the thyroid, sterilization with x-rays must be warmly recommended. It is necessary exactly to measure the quantity of x-rays used.—J. K.

(THYROID) Hyperplasia of the SALIVARY GLANDS and diseases of the ENDOCRINE ORGANS (Speicheldrüsenhyperplasie und Erkankung endokriner Drüsen). Hämmerli (A.), Deutsch. Arch. f. klin. Med. (Leipzig), 1920, **133**, 111-124.

Diseases of the salivary glands associated with affections of the endocrine organs have been rather frequently described, but this is the first instance reported in which a histological examination was carried out. The author describes the combination indicated, in an insane individual of 50 years. Autopsy showed both parotid and submaxillary glands enlarged and a goitre weighing 1050 grams. The enlargement of the submaxillary glands was due to hypertrophy of the glandular tissue. The **adrenals** were large as was also the **pancreas**. The **testicles** were small and brown.

The combination of hyperplasia of the salivary glands with goitre is not so very rare. Often **status thymolymphaticus** is also present. There may be also found in the literature descriptions of combined disease of the salivary glands and of the gonads or the **hypophysis**. The author thought there may possibly exist a relation between the thyroid and the salivary glands. Therefore, he regularly weighed the thyroid and submaxillary glands at every autopsy performed for some time, and found that their weight is always absolutely parellel. A heavy thyroid is always accompanied by large salivary glands and vice versa. May not the submaxillary glands, therefore, be regarded as endocrine organs? Though many authors have

written on this subject, this question is not yet settled; it is probable that these glands have a certain endocrine function. —J. K.

(THYROID) Improvements in the surgical treatment of goiter (Ueber Fortschritte in der operativen Behandlung des Kropfleidens). Hartert, München. med. Wchnschr., 1920, **67**, 948.

Of technical interest to surgeons.—J. K.

(THYROID) Successive transplantation of thyroid tissue into the same host. Hesselberg (Cora) & Loeb (L.), J. Med. Research (Boston), 1918, **38**, 33-53.

The results of the successive homoiotransplantation of thyroid tissue into guinea pigs leads the authors to the tentative opinion that while the transplanted thyroid resembles certain tumors in the lymphocytic reaction brought about, there exists a difference in the behavior of the second transplantation in the case of these tumors and of thyroid, in that the latter did not appear to develop a markedly accelerated lymphocytic reaction. The lymphocytic reaction which develops because of the thyroid depends upon the relation of transplant and host, a change in either modifying the result. The transplanted thyroid develops definite structural peculiarities which differ from those of the normal thyroid, e. g., the development of solid strands of acini. The lymphocytic reaction is not prevented by pregnancy, loss of weight, dying state, or greater age. Much of the colloid in the acini is destroyed through phagocytic action, and if fat tissue is transplanted with the thyroid the adjacent acini usually become necrotic.—F. S. H.

The effect of administration of small amounts of THYROID gland on the size and weight of certain organs in the male white rat. Hewitt (J. A.), Quart. J. Exper. Physiol. (Lond.), 1920, **12**, 347-354.

In view of the conflicting results of thyroid feeding on the various organs by Herring and by Hoskins on the one hand, and by Kuriyama on the other, it seemed advisable to investigate the matter further. The work of Kuriyama is reviewed critically. Male rats were used and the change in weight of the organs after feeding 0.1 gm. fresh thyroid per day is given as percentage of the corresponding organs of the standard rats of Donaldson. In general the results of Herring and of Hoskins are confirmed. There is hypertrophy of the heart, liver, spleen, kidneys, **suprarenals,** and possibly the **pituitary.** The thyroid is diminished. There is a tendency for the organs to

resume their normal proportions after resumption of the ordinary diet, the alteration in size becoming less marked according to the length of time elapsed after cessation of thyroid feeding.—T. C. B.

(THYROID) Experimental goiter induced by water from the Cerrillos (Salta) [Goitre expérimental provoqué par l'eau de Cerrillos (Salta)]. Houssay (B. A.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1244.

There is much discussion in South America whether certain waters can produce goiter. Experiments were made at Buenos Aires, with waters from goitrous regions. The water was transported in sterile demijohns and was 3 days in transport. In spite of the unfavorable circumstances, 2 white rats developed goiter after four and a half months of experiment and eighty-two days' ingestion of water from the Cerrillos. The water was mixed with bread and milk. It is suggested that the experiments should be repeated under better conditions.
—T. C. B.

(THYROID) Thyroidectomy in the horse (La thyroïdectomie chez les chevaux). Houssay (B. A.) & Hug (H.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1242-1243.

The experiments were made on 8 horses. Their ages varied between 2 months and 2 years. Three colts died of cachexia 5 or 6 months after the operation. Retardation of growth was very marked in the 6 young animals. Five of the animals developed marked synovial edema. Diphtheria toxin injected in some of the horses provoked a marked edema. There was retardation in the development of the permanent teeth. Nearly all were excessively tranquil and docile in disposition.—T. C. B.

(THYROID) Hyperthyoidism and pseudohysteria (Hipertiroidismo y pseudo histerismo). Juarros (C.), Plus Ultra (Madrid), 1919, **2**, 350-354.

The author remarks upon the frequency with which diagnosis confounds hysteria and hyperthyroidism in women, due, he supposes, to an equivocal conception of the former affection and lack of clinical exploration. In order to avoid this confusion, Juarros insists on the necessity for the presence of a perfectly defined hysterical mentality before diagnosing hysteria, and that symptoms of hyperthyroidism should be sought for in all women apparently suffering from this disorder. In those cases in which the result of the clinical examination is

not characteristic, this author recommends employment by way of proof, of antithyroid medication and laboratory methods such as the determination of the basal metabolism according to Benedict, and the glucose tolerance or alimentary glycosuria test.—E. B.

(THYROID) The result of surgical treatment of exophthalmic goitre. Judd (E. S.), N. Y. State J. M. (N. Y.), 1920, **20**, 287-290.

Subtotal thyroidectomy actually removes changed tissue; as a result the metabolic rate is reduced approximately to normal and the symptoms subside rapidly in a great majority of cases. X-ray and radium treatments modify the severity of the hyperthyroid state, but do not cure the disease. The paper is based upon the results of 100 consecutive goiter cases. Of this number 60 per cent were dismissed cured; 13.5 per cent with marked improvement; 5.5 per cent with slight improvement; 15 per cent died. The average blood pressure before operation was: systolic 145.2, diastolic 75.6. The average pulse rate before operation was 122.6 per minute.—H. W.

(THYROID) Results of operations for adenoma with hyperthyroidism and exophthalmic goitre. Judd (Edward S.), Ann. Surg. (Phila.), 1920, **72**, 145-154.

This study of the operative results in these two diseases of the thyroid is based upon two selected groups of one hundred cases each. One hundred consecutive cases of exophthalmic goitre were chosen from the 1914 series at the Mayo Clinic and one hundred consecutive cases of adenoma with hyperthyroidism from the 1917-18 series. The analysis revealed that 65 per cent of the patients suffering from exophthalmic goitre were free from all evidence of the disease six years after operations, while 15 per cent were dead from all causes. Most of the others were benefited. More than 80 per cent of the patients with adenoma with hyperthyroidism were relieved of their toxic symptoms and a cure obtained by thyroidectomy. It is the opinion of the author that a higher percentage of cures would undoubtedly obtain if the patients were all operated upon before there was any evidence of edema or terminal degeneration.—J. F.

(THYROID) Seven cases of nocturnal shaking of the head (Sieben Fälle von nächtlichem Kopfschütteln). Kalmus, München. med Wchnschr., 1920, **67**, 883.

The above mentioned symptom was observed in a girl of 11 years with symptoms of myxedema. Since by **thyroid** treatment the shaking of the head disappeared it was also tried in 6 other children with complete success.—J. K.

(THYROID) Present status of non-surgical treatment of Graves' disease (Der jetzige Stand der nictoperativen Behandlung der Basedowschen Krankheit). Klewitz (F.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 971-973.

Cases of goitre with symptoms of malignancy, or with compression of the trachea or oesophagus, must always be operated upon, as must also chronic cases or cases in which the goitre shows colloid or cystic degeneration. Internal treatment is indicated in the "formes frustes" and in the acute or subacute cases; also in patients with a complication which will not allow surgical treatment, and in convalescence after operations, though of course in these cases the prognosis is never good. It would be desirable to exclude patients with status thymolymphaticus from operation but it is nearly always impossible to diagnose these cases during life.

Non-operative treatment consists of drugs, physiotherapeutic measures, and diet. Bromides and arsenic are recommended. Sodium phosphate, as recommended by Kocher, in the hands of the author never has given good results. Iodine in extremely small quantities, as recommended by Neiszer, may be tried. From the milk or serum of thyroidectomized animals and from **thymus** or **ovary** preparations not much may be expected. As regards physical methods, electrical treatment with constant currents is recommended, but much better effects are obtained from deep radiation of the thyroid. It is dangerous to submit every patient to this treatment, but the author does not indicate which patients are suitable for it. It is absolutely necessary to choose the quantity of x-rays exactly. In cases of Graves' diseases caused by the **thymus** this gland also may be radiated. These cases may perhaps be recognized by an enlarged shadow of the mediastinum on the Roentgen screen, myasthenic symptoms on electrical stimulation of the muscles, symptoms of vagotonia, very marked lymphocytosis, and a positive Abderhalden test against thymus. Another good physical method is CO_2 baths or indifferent baths. Rest in bed during the first weeks of treatment is necessary. Diets during treatment must be rich in calories. It is not necessary to forbid all meat. Many small meals ought to be given. After this combined treatment exophthalmus and goitre may remain unaltered but the nervous symptoms, the tachycardia, and the loss of weight disappear and the patients are again able to go about their work.—J. K.

(THYROID) Diagnosis and management of intra-thoracic goiters. Lahey (F. H.), J. Am. M. Ass. (Chicago), 1920, **75,** 163-165.

Lahey emphasizes the importance of the x-ray in the diagnosis of intra-thoracic goiters and describes the surgical technique for their removal.—F. C. P.

The histology of tadpoles fed with THYROID. Lim (R. K. S.), Quart. J. Exper. Physiol. (Lond.), 1920, **12,** 303-316.

A brief abstract has already been given (See Endocrin., 1920, **4,** 174 The paper is chiefly concerned with the histology of the organs after thyroid feeding. All the organs appear more adult in character. Metamorphosis is induced and hastened. There is a rapid absorption of the tail, the caudal muscles being disintegrated, partly by phagocytes and partly by autolysis. The alimentary tract is the first to be affected by thyroid treatment, the large thin-walled larval type being replaced by a thick-walled type. The stomach and intestines have well developed glands in the mucous membrane. Masses of pigment accumulate in the mucosa and may be seen breaking through. In general the normal processes have been hastened and exaggerated by excess of thyroid hormone.—T. C. B.

Ligation of the four THYROID arteries in operating for goiter Ueber die Unterbindung der vier Schilddrüsenarterien bei der Kropfoperation). Madlener (M.), Zentralbl. f. Chir. (Leipzig), 1920, **47,** 949-951.

Of technical surgical interest.—J. K.

(THYROID) Adenoma with hyperthyroidism. Mayo (Chas. H.), Ann. Surg. (Phila.), 1920, **72,** 134-140.

A resumé of data presented elsewhere upon this subject by Plummer, Kendall, Boothby and Sandiford of the Mayo Clinic.—J. F.

(THYROID) Basedow's syndrome and tuberculosis (Sindroma de Basedow y tuberculose). Mieres (J. F.), Semana med. (Buenos Aires), 1920, **27,** 507-508.

Tuberculosis is often an etiological factor in Basedow's disease.—B. A. H.

(THYROID) Myxedema after operation for Graves' disease. (Myxödem nach Basedowoperation). Munk, München. med. Wchnschr., 1920, **67,** 945.

A case of Graves' disease in a woman of 19 occurring after the death of her father. The left lobe of the goiter was removed with complete success. Later her mother became insane and the patient nursed her. During this nursing a polyglandular insufficiency with symptoms of myxedema developed.—J. K.

Some structural modifications of the THYROID gland in compensatory hypertrophy (Sur quelques modifications structurales de la glande thyroïde dans l'hyperthrophie compensatrice). Parreira (H.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1193-1194.

Of histological interest.—T. C. B.

(THYROID PARATHYROID) Serum changes following thyroparathyroidectomy. Peterson (W.), Jobling (J. W.) & Eggstein (A. A.), J. Exper. M. (N. Y.), 1916, **23**, 499-505.

A study of the serum changes in the tetany produced by thyro-parathyroidectomy. The ferment-antiferment balance, the non-protein nitrogen, the amino nitrogen and the proteose content of the blood were determined in fifteen thyroparathyroidectomized dogs before and at various intervals after the operation. It was found that the protease activity of the serum was increased with a resulting increase in the non-protein nitrogen, the amino-nitrogen and the proteoses. At the same time the lipase titre remained at a very low level in all except one case, in which there was a slight rise. The onset of tetany was found to bear no relation to the ferment-antiferment balance, but the amino nitrogen of the serum was usually increased at the time when tetany was most marked.—I. M.

(THYROID) Goitre, a clinical study of one hundred and thirty-nine cases. Porter (Miles F.), Ann. Surg. (Phila.), 1920, **72**, 129-133.

A summary of the author's experience with goitre since November, 1912.—J. F.

Carcinoma of the THYROID. Rogers (J.), Ann. Surg. (Phila.), 1917, **66**, 222.

This is a note on the author's presentation of cases of cancer of the thyroid gland before the N. Y. Surgical Society. The author said that in his experience carcinoma of this gland has been comparatively rare. In the one dozen cases of which he has records there are two distinct varieties. In one, the new growth develops extensively throughout the greater part of

the gland while in the other it apparently originates and remains confined in some localized portion of the organ. The lymphatics tend to become involved much earlier in the diffuse type.—I. M.

(THYROID) Corneal ulcer of exophthalmic goitre. Rogers (J.), Ann. Surg. (Phila.), 1917, **66**, 222-224.

This is a description of a case of corneal ulcer in exophthalmic goitre. Because of the extreme degree of exophthalmos and edema of the conjunctiva various procedures were attempted to relieve the pressure and to protect the cornea from further erosion. Ligation of the inferior thyroid arteries and section of the lower filaments of the cervical sympathetic and treatment with **adrenal** extract gave little or no relief. The lateral bony walls of the orbit were then partially removed and the eyelids were sutured together after longitudinal incisions were made in each. This last procedure alone gave relief and protection to the cornea.—I. M.

(THYROID) The signs and treatment of thyroidism. Rogers (J.), Med. Rec. (N. Y.), 1917, **92**, 961-962.

This is a short discussion of thyroid disease from the point of view of its physiology, symptomatology and treatment. The author has aimed in all of his operations to protect and save rather than to excise or destroy thyroid tissue, because of his belief that every kind of thyroid disorder is preceded or accompanied by circumstances which involve fatigue. The fatigue state, according to his idea, is followed by a compensatory hypertrophy which later develops into some one of the ordinary diseases of the gland. For treatment, instead of thyroidectomy the author recommends ligation of thyroid arteries for hyperthyroidism and enucleation of all diseased tissue whether the case be one of hyper- or hypo-thyroidism. Rest and appropriate organotherapy should precede and follow operation in every case.—I. M.

Basal metabolism in THYROID diseases as an aid to diagnosis and treatment with notes on the utility of the modified Tissot apparatus. Rowe (A. H.), Calif. State J. M. (San Fran.), 1920, **18**, 332-334.

From a consideration of 36 cases of actual and supposed hyperthyroidism, the author shows the importance of basal metabolism determinations as a means of differentiating thyroidal disturbances and nervousness. The modified Tissot apparatus is highly recommended.—H. W.

THYROID administration in dementia precox (Proeven met toediening van schildklierstof bij dementia praecox). Schnitzler (J. G.), Psychiat. en neurolog. bladen (Amsterdam), 1916, **20,** 292-302.

Though it is quite probable that there exists a relation between endocrine organs and dementia precox, we know extremely little about this. The author treated some patients with thyroid (as had been recommended in previous literature) without any success.—J. K.

Syphilis as a factor in diseases of the THYROID gland. Simonton (T. G.), Penn. M. J. (Athens), 1917, **21,** 293-296.

Syphilis was found to be the cause of disease of the thyroid gland in five cases observed by the author. All of these cases showed a positive Wassermann reaction and four of them received specific treatment with successful results. Numerous cases studied by others have given similar results. The author concludes, therefore, that a Wassermann test should be made in all cases of tumor or disturbance in function of the thyroid before operation is resorted to.—I. M.

Changes in the THYROID gland following intoxication by toxic protein derivatives. Tatum (A. L.) & Sweet (J. E.), Proc. Path. Soc. (Phila.), 1917, **37,** 22.

The thyroid glands of animals killed by obstruction of the duodenum or by intravenous injection of material found in the intestinal loops were studied histologically The following changes were observed: There was frequently rupture of the alveolar walls with passage of colloidal material into the extra-acinar tissue; desquamation of the epithelium with enlargement of certain cells was common and hyperemia was marked in many instances. The parathyroids and thymus, studied for comparison, appeared quite normal except for a variable degree of hyperemia. A few cases of acute experimental pancreatitis and general peritonitus gave similar results. It is assumed that the poisonous material liberated in these morbid conditions is a product of protein elevage.—I. M.

(THYROID) Surgery of toxic goitre. Terry (W. I.), Ann. Surg. (Phila.), 1920, **72,** 152-154.

The author emphasizes the surgical treatment of toxic adenomata because he finds that they are not curable by medical means. He feels that it is the work of the hygienist to prevent the occurrence of simple goitres. He presents his personal ex-

perience with goitre which is based upon 748 operations. Of these 527 were for toxic goitre in 504 patients. The mortality in this group was 4.3 per cent. The mortality in the group of simple goitre was less than ½ per cent.—J. F.

(THYROID) The heart in goiter (Das Kropfherz). Urban, Wien. klin. Wchnschr., 1920, **33**, 832.

A short note. The operation for goiter is dangerous when there is a typical goitrous heart, which has not been stimulated before the operation.—J. K.

(THYROID) An observed epidemic increase in juvenile goitre in the environs of Budapest (Über eine vorwiegend im Kindesalter beobachtete epidemische Verbreitung des Kropfes in der Hauptstadt Budapest bezw. in deren Umgebung). Vas (J.), Jahrb. f. Kinderh. (Berlin), 1919, **90**, 243-254.

Analysis of the statistics of the Budapest clinics showed a great increase in goitre in children during the war. The incidence the first year of the war was 0.03 per cent, the second year it was 0.08 per cent, the third 0.20 per cent, and the fourth year of the war 0.61 per cent. In July, 1918, the incidence had increased until over 1 per cent of the patients seen in the clinics were affected. Of these cases 70 per cent were females and 85 per cent were over 7 years of age. These cases were studied further from the standpoint of the group and familial incidence of the goitre, and especial attention was paid to underfeeding, occupational factors, and local mechanical causes. Unfortunately this analysis was made largely through the medium of a spot map of the city rather than by a detailed statistical study. However, it led Vas to the belief that there was but a single causal factor involved. He felt that the recent spread of goitre in the city showed an epidemic character similar to an infectious disease especially affecting girls at puberty. This infecting agent perhaps was brought to the capital during the war by the great influx of soldiers, refugees, prisoners, etc., many of whom came from areas of endemic goitre.—C. H. G.

(THYROID) Hyperthyroidism and mental disorders. Walker (W. K.), Penn. M. J. (Athens), 1917, **21**, 300-305; N. York M. J., 1918, **107**, 391-394.

This paper deals with the clinical manifestations of hyperthyroidism which have to do with the central nervous system. The exaggerated symptoms of exophthalmic goitre are compared with those of a violent septic intoxication in which all of the bodily symptoms are overshadowed by mental symp-

toms. From the mental aspect the clinical picture here is characterized by a more or less violent confusion. The association mechanism is prevented from performing its functions properly. Delays and interruptions occur along associative tracts between areas of special sense perception and feelings of strangeness and unreality, bewilderment and oppression with excitement or depression result. Illusions and hallucinations are also comparatively frequent. Milder cases show similar tendencies and in long continued cases various morbid moods appear and suspicional attitudes with mild delusions are observed.

Cases of hyperthyroidism showing a preponderance of mental over physical symptoms are explained by a relative vulnerability of the cortical cells to the toxic products circulating in the blood stream. There is said to be in such cases some destructive alteration of cerebral cortical cells and their intercommunicating fibers.—I. M.

(THYROID) Clinical studies in hyperthyroidism. Watson (L. F.), Med. Rec. (N. Y.), 1917, **91**, 411.

The present paper is the second by the same author on the employment of urea-quinine injections in cases of hyperthyroidism. A few experimental injections of quinine-urea into the thyroid glands of dogs and several hundred injections in 150 human cases of simple and toxic goitre led the author to the following conclusions: 1.—That strong solutions of this substance when injected properly into the thyroid glands are effective in relieving the hyperthyroidism. 2.—Such solutions cause definite destruction of some of the cells and of the colloid present in the alveoli, whereas weak solutions have but little or no effect. 3.—That, while quite harmless in skilled hands, the method offers two dangers when carelessly employed, viz., the possibility of making the injection into the trachea or other neighboring organs and the proneness for myxoedema to follow excessive doses injected directly into the thyroid tissue. 4.—Preliminary injections of isotonic saline solution and distilled water every other day for a short period, before the quinine-urea injection is attempted, raises the patient's threshold to sensory stimuli and so averts an acute attack of hyperthyroidism in the more serious cases.

The method is recommended in special cases of mild toxic goitre and as a preliminary to surgical treatment in cases too severe for immediate operation, but not in cases where large simple goitres are to be removed for cosmetic effects only.

—I. M.

(THYROID) A case of exophthalmic goitre. Welt-Kakels (Sara), Med. Rec. (N. Y.), 1917, **91**, 1161.

A case of a boy 14 years of age who showed striking signs and symptoms of exophthalmic goitre. The case was of special interest because the condition is a rare one in young boys of this age. There was tachycardia, increased blood pressure, exophthalmos, defect in convergence, von Graef's sign and a fine tremor of the fingers. There was a history of emotional shock.—I. M.

(THYROID) The surgery of exophthalmic goitre. Williams (L.), Lancet (Lond.), 1917, **ii**, 950.

In a note to the Editor the author cautions against the statement of Dunhill in a previous issue of The Lancet to the effect that an operation on the thyroid gland is not only justified but obligatory when the symptoms become urgent. The author points out that a large percentage of such cases could be successfully treated by medical measures and that for permanent results in such cases foci of infection such as a diseased appendix, diseased tonsils or gall bladder should be sought and if found removed before thyroidectomy is attempted. When the latter operation is performed without removal of such contributory or underlying factors, the benefits from it can only be temporary. McCarrison is quoted at some length in support of the argument for the more conservative methods of treatment.—I. M.

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DIABETES INSIPIDUS AS A HYPOPITUITARY SYNDROME

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In a recent book (1920) I have presented my clinical and experimental experience on diabetes insipidus. Data more recently acquired induce me to publish in this review the results of later observations on this problem, which in recent years has become one of much interest to pathologists.

The careful study, from the endocrine point of view, of 32 cases of diabetes insipidus collected during the last few years, has convinced me that this syndrome is, at least in a large majority of cases, a consequence of an insufficiency of the posterior lobe of the hypophysis. All clinicians, practically without exception, are agreed to this interpretation of the problem. On the other hand, among the physiologists there are a certain number of investigators who will not admit the hypophyseal pathogeny of diabetes insipidus: Among these are Camus, Roussy, Houssay, Leschke and others. But that is due, in my opinion, to the fact that they have not given to the clinical and anatomical-pathological data the biological value which they really possess, and which is often considerably superior even to that of physiological experimentation. When, after the studies of Fröhlich, of Lannois and others, the idea appeared in medicine that the origin of obesity lay in the hypophysis, there also appeared discussions which were almost identical with those which the problem of diabetes insipidus now presents. The difference between the data

obtained in the clinic and by experimentation were also noted; then the physiologists invoked the existence of a nervous centre at the base of the brain, which was said to be responsible for obesity; and they said, as now, that in cases of hypophyseal lesions accompanied by obesity, the latter depended on the indirect lesion of the nervous centre on account of the production of a tumor of the hypophysis, and not on the insufficiency of the secretion of this gland. At last, an agreement was reached and today the hypopituitary origin of obesity is a fact as solidly established as is that of the thyroid origin of myxedema (Marañón, 1920, b.)

The clinical argument is decisively in favor of the hypopituitary theory since in the great majority of cases of diabetes insipidus, clinical examination shows the existence of symptoms of hypophyseal lesions. And the analysis of the symptoms nearly always shows us an insufficiency in the functioning of the posterior lobe* of the gland, either primary or secondary to lesions of the anterior lobe. Our 32 cases† have given us the following results, from the endocrine point of view:

I. A boy of 15 years of age. Fröhlich's dystrophia adiposo-genitalis. Normal sella turcica. Voids 5 liters of urine per day, which is very dilute and without abnormal substances.

II. A boy of 13 years of age. Fröhlich's dystrophia adiposo-genitalis. Normal but rather deep sella turcica. Voids from 6 to 7 liters of urine per day.

III. A boy of 14 years. Fröhlich's dystrophia adiposo-genitalis syndrome and exceptionally low stature. Clinical symptoms of a hypophyseal tumor, which is confirmed by the radiograph. Urinates from 12 to 14 liters per day.

IV. A girl of 19 years, with normal menstruation, vitiligo, marked abdominal adiposity, normal sella turcica. Urinates 4 liters per day.

V. A girl of 26 years. Low stature, great abdominal adiposity, somnolence. The radiographic image shows a very small sella turcica, the anterior clinoid processes appearing in contact with the posterior. Urine, 6 liters per day, which is dilute and without abnormal substances.

VI. A boy of 19 years. Very neurotic; marked cachexia, without any lesion which would account for it. Small, elongated sella turcica, accompanied by polyuria of 7 to 8 liters per day. He died in cachexia, and we were unable to perform an autopsy.§

*When speaking of *posterior lobe*, we always refer also to the so-called pars intermedia, the functional separation of which from the posterior lobe seems to us to be, for the moment, arbitrary.

†In our book mentioned above (1) the clinical history, with photographs and radiographs of 24 of the cases, is presented in detail.

§In all of these cases, for the sake of brevity, we do not give details of the analyses of the urine, but it is understood that in all of them there were the usual characteristics of diabetes insipidus, e.g., low density, dilution of the normal constituents, absence of abnormal constituents, etc.

VII. A boy of 22 years. Very neurotic. Leanness of the cachexia type, voids 3 liters per day. Thirst, etc. Without symptoms of hypophyseal tumor. Radiograph of the head not taken.

VIII. A man of 50 years. Suddenly complains of marked asthenia, impotentia coiundi absoluta, became very thin without any apparent reason (tuberculosis, hyperthyroidism, neurathenia, cancer, etc., absent), thirst and polyuria of 3 and a half or 4 liters per day. Radiograph of the sella turcica normal.

IX. A girl of 15 years. At the age of 9 years she was greatly frightened and began to urinate from that time onwards from 9 to 10 liters per day. Stature almost dwarfish; infantilism, has not menstruated; sella turcica indistinct, giving the impression of an enlarged hypophysis.

X. A boy of 16 years. General and genital infantilism clearly marked. The radiograph showed a slightly but certainly increased sella turcica. Polyuria of 3 to 5 liters per day, thirst, etc.

XI. A boy of 15 years. From the age of 6 years, his growth has been retarded, and he now manifests a very accentuated type of infantilism and dwarfism. Urinates 8 to 10 liters per day, great thirst, etc.

XII. A girl of 15 years. From the age of 5 years she has been backward in growth; at the moment her stature is small with excessive adiposity which reminds one of Fröhlich's syndrome. Normal menstruation since 12 years of age. Silhouette of the sella turcica showed enlargement. Slight goitre and symptoms of thyroid insufficiency. Urinates from 9 to 10 liters per day.

XIII. A woman of 31 years. Shorter than all her brothers and sisters and very stout (Fröhlich's type). Very irregular menstruation, which does not appear for many months at a time. Urinates from 8 to 10 liters per day.

XIV. A boy of 13 years. Eunuchoid type, very long legs, cryptorchidic, etc., severe headaches with vomiting attacks. Urinates 7 to 8 liters per day.

XV. A man of 32 years. His aspect is that of a man of 50 years or more, his teeth have fallen out, hair becoming grey, wrinkles on his face, etc., atrophied genitalia and absence of the secondary sexual characteristics. Urinates 5 to 6 liters per day, has great thirst, etc.

XVI. A boy of 13 years. Shot in the cranium, and in consequence has been developing a typical adiposo-genital syndrome with a polyuria of 9 to 11 liters per day. The radiograph, surgical intervention and autopsy confirmed the existence of the shot at the extremity of the third ventricle, dividing the tuber cinereum.

XVII. A boy of 16 years. Marked traumatism in the head, serious concussion of the brain, and appearance of an intense polyuria which attains 18 liters per day.

XVIII. A man of 40 years. Marked cerebral traumatism with serious concussion. Since then polyuria of 14 to 16 liters per day has appeared and a tendency to adiposity and giddiness.

XIX. A man of 37 years, with acromegalic habitus since puberty, and considerable tendency to urinate, but within normal limits. Twenty years before he had contracted syphilis, which had been badly treated. Three years ago he developed a gumma in his leg and soon afterwards thirst and polyuria of 7 to 8 liters per day appeared, both of which ailments began to disappear with the anti-syphilitic treatment. Sella turcica plainly increased in size.

XX. A woman of 39 years. At 29 years of age, she was seriously eclamptic after giving birth to a child and since then a rapid in-

crease in weight, thirst and polyuria of 9 liters daily appeared, which has disappeared spontaneously in 5 or 6 months. At present she has glycosuria.

XXI. A man of 54 years. He was always much taller than his brothers, with very large feet and hands and mandibular prognatism. During the last year he had worried a great deal and since then had suffered from neurasthenia, a tendency to grow fat, thirst and polyuria of 4 to 5 liters per day.

XXII. A woman of 27 years. All her brothers are very tall, but she is taller than any of them. She has a marked development of the lower jaw. Her menstruation is always scanty and she has a tendency to fatness, especially of the abdomen and the hips. From the age of puberty to 18 years, she suffered from a polyuria of 5 to 7 liters daily which desisted spontaneously.

XXIII. A woman of 39 years. Much taller than all her brothers and than her parents. Menstruation always scanty; sterile; tendency to great fatness. From the age of 11 to 16 years she suffered from diabetes insipidus (6 to 7 liters of urine were voided per day). Quite nervous. Cured spontaneously.

XXIV. Woman of 28 years. Had a very intense Graves' disease for many years. Her father manifested a typical case of gigantism with acromegaly. She has slight mandibular prognatism, intense headaches, an enlarged sella turcica and very scanty menstruation. In spite of the hyperthyroidism, there is a tendency to put on fat. Great thirst and diabetes insipidus (4 to 5 liters) during the past three years.

XXV. A woman of 33 years, with a normal constitution and without any apparent symptom of an endocrine nature. Since she was a child she has suffered from diabetes insipidus (6 to 8 liters of urine daily). When we thought the examination from an endocrine point of view to be negative, we found on examining the abdomen that the whole anterior wall was covered completely with a thick hairy down, which she had not wished to show us. Besides this, she has a very scanty menstruation. Her voice becomes thick at times, and the face has become puffy in appearance in later years.

XXVI. A man of 32 years. Ten years ago, after an intense emotion and great physical fatigue, he suffered from polyuria which reached 15 to 20 liters. Great development of the frontal sinus, giddiness, sudden loss of sight; diminishing of the sexual libido and increase of epigastric adiposity. His attention was attracted by a considerable increase of hairy down on the abdomen, from the pubis to the umbilicus.

XXVII. A boy of 19 years. Diabetes insipidus (4 to 7 liters of urine daily) for the last 5 years. Little development of the genitalia, with absence of hairy down on the whole body save the abdomen, which had an abundance.

XXVIII. A woman of 31 years. Cancer of the breast with a great number of metastases in different organs. Headaches and polyuria of 5 to 6 liters per day during the latter months of her life.

XXIX. A man of 64 years. Cancer of the stomach in the last two months of his life, headaches, tendency to sleep, rapid loss of weight (in spite of the fact that he ate enough and did not suffer from digestive complaints); accompanying this he had a marked polyuria of 8 to 9 liters daily.

XXX. A woman of 45 years. Accompanying a large number of circulatory and nervous disturbances of the climacteric type and the disappearance of the menstruation, she suffers from great thirst and

polyuria of 4 to 6 liters per day. A great tendency to lay on adipose tissue.

XXXI. A woman of 48 years. A year ago she went through the menopause accompanied by a strong hyperthyroidic reaction, and since then has had diabetes insipidus (6 to 7 liters of urine daily) with great thirst, etc.

XXXII. A man of 38 years with moderate diabetes insipidus (3 to 5 liters daily); very intense thirst. He presents no morphological or functional symptom which can be related to the alterations of the endocrine glands, or symptoms of hypophyseal tumor. Ten years before he had had syphilis which was badly treated, and latterly had had an attack of purpura.

As can be seen, almost all these cases confirm the hypofunctional theory of diabetes insipidus. In cases I, II and III, it is a question of the typical Fröhlich adiposo-genital syndrome, now definitely considered as the clinical expression of the hypofunction of the posterior lobe of the hypophysis. In cases IV and V, this adiposity was limited to the abdomen, which, as we have seen, often occurs in lesions of the hypophysis, and in these cases it is confirmed by the disappearance of the adiposity, simultaneously with the polyuria, under hypophyseal opotherapy.

Cases VI, VII and VIII are typical of the hypophyseal cachexia, well known since the studies of Cushing, Pende, Simmond, Luzzato, Marañon (1920, b.), and others. The frequency with which one reads in old clinical histories of progressive cachexia in diabetes insipidus, is easily explained by the common origin of both processes (cachexia and polyuria) and not, as was formerly believed, because the excessive loss of water determined the loss of weight. Considering the frequency with which hypophyseal metastases are produced in cancers of the breast and certain abdominal cancers, it is possible that the cachexia of cancer is hastened in some cases (as in our observation XXIX, by a marked insufficiency of the posterior lobe of the hypophysis.

Cases IX, X, XI, XII and XIII, are either examples of pure dwarfism or are cases of dwarfism combined with infantilism and sometimes with adiposity of Fröhlich's type. At present the hypophyseal origin of dwarfism and the participation of the hypophysis in the polyglandular disturbance which causes infantilism, is admitted by all. It is certain that the anterior lobe of the gland appears in both cases to be directly responsible for the disturbance in growth, but it is easily understandable that the atrophic or sclerotic process, which has a tendency to invade

several endocrine glands, also invades the posterior lobe, united to the anterior lobe without solution of continuity, and then the polyuria, the adiposity, etc., appear.

In case XIV it was a question of an isolated example of genital insufficiency, with eunuchoid morphology and without a known etiology. Tandler and Grosz and other authors have shown clinically the participation of the hypophysis in these states of genital insufficiency, which are apparently primary. It is in fact very possible that in many of them a hypophyseal insufficiency exists which gives rise to the genital disturbance; and this case, with its symptoms of hypophyseal tumor (headaches and attacks of vomiting) would confirm it. Unfortunately the radiograph of the head did not come out well, and the patient went away so that it was impossible to repeat it.*

Case XV belongs to the syndrome called "insuffisanse pluriglandulaire" by the French authors, "gerodermia genitodistrofica" by Rumo and Ferranini and other Italian authors, and "Multipleblutdrüssensklerose" by the Germans. It is probably, as a matter of fact, a sclerotic condition which affects the whole endocrine system, comparable to that which physiologically appears in old age and, like this, is responsible for the aspect of senility of the patient. According to Lereboullet, syphilis is often the origin of this sclerosis. When the lesion affects the posterior lobe of the hypophysis, polyuria will result, as it resulted in the cases of Lereboullet and in ours. In this patient, we observed another phenomenon, which was also probably of hypopituitary origin: Slight attacks of intestinal paralysis with considerable meteorism, which rapidly yielded to pituitrin.

Case XVI has the value of a laboratory experiment, as the shot penetrated between the two cerebral hemispheres without producing the least nervous disturbance in the patient and settled in the parahypophyseal region, causing the adiposo-genital syndrome and diabetes insipidus. The fact that the shot did not wound the hypophysis itself, but the extremity of the middle ventricle, could be interpreted to their advantage by the partisans of the nervous theory of diabetes insipidus. But the histological examination of the gland showed that with section of

*In other cases of genital insufficiency of the eunuch type (without polyuria) that we have observed, we have obtained good results on the genital development with hypophyseal opotherapy; and in one case with the grafting of two hypophyses of sheep into the tibia.

the pituitary stem occurred cicatrization, which invaded the posterior lobe of the hypophysis. In addition, apart from the polyuria, there were in this case adiposo-genital changes which undoubtedly depended on the endocrine insufficiency of the hypophysis. In cases XVII and XVIII, we suppose that the traumatism produced a hemorrhage of the posterior lobe of the hypophysis, which caused the transitory insufficiency, expressed by diabetes insipidus. In post-mortem examinations of persons dead through traumatisms of the head, falls, collisions, etc., we have been able to confirm, in the Judicial Deposit of Madrid, the ease with which these hypophyseal hemorrhages can be produced. In case XVIII the tendency to obesity confirmed the diagnosis of the hypophyseal lesion. In both cases the admirable result of the injection of pituitrin pointed also to this etiology.

Case XIX was, from birth, an example of attenuated acromegaly. Probably this abnormal state of the hypophysis favored the fixation or stay of the syphilitic organism. Moreover, Bernario has shown the frequency with which gummas of the neurohypophysis give rise to the diabetic syndrome.

In case XX, the puerperal infection probably attacked the hypophysis, as is proved by the polyuria coinciding with the rapid increase in weight. According to Massalongo and Piazza post-infectious obesities are almost always of hypophyseal origin* and Motzfeldt attributes to the hypophyseal insufficiency, not only the cases of post-infectious diabetes insipidus published recently, but also even the transitory polyurias which are frequently observed after infections.

Cases XXI, XXII and XXIII are very similar. All three are examples of hyper-hypophyseal constitution, actual attenuated acromegalies, as in case XIX. One can suppose that in them the hypertrophy of the anterior lobe, characteristic of acromegaly, compressed the posterior lobe within the sella turcica, and provoked the polyuria. Creutzfeld and Pittaluga also give this explanation for their cases of acromegaly with polyuria. Sometimes other symptoms of insufficiency of the posterior lobe accompany the polyuria, such as obesity and genital insufficiency

*One of our recent cases which will shortly appear in the Revue Neurologique, of Paris, showed that the hypophysis not always intervenes in these cases, although it may appear to do so clinically.

(Case XXIII). This compression of the posterior lobe may be transitory, as probably occurs in these predisposed cases, during the pubescent reaction of the anterior lobe, which is responsible for the rapid growth which many youths undergo during this period. This would be the explanation of many cases of diabetes insipidus of the pubertal period, which are cured spontaneously (XXII and XXIII). In the case of observation XXIV, this same mechanism can be invoked to explain the polyuria: hypertrophy of the anterior lobe, large sella turcica, physiognomical acromegalic features, inherited from a father, and compression of the posterior lobe (polyuria, adiposity and scanty menstruation).

Cases XXVI and XXVII are very interesting, as, in them the hypophyseal change is manifested almost exclusively by the symptom of increased hairy down on the abdomen, almost monstrous in case XXV, and less intense, but also very marked in cases XXVI and XXVII. This symptom of the acromegaly, quoted by various authors—Falta, Barker and Hodge, and others, was found by us in almost all the cases of that illness, and we do not know if it is due directly to the hypersecretion of the anterior lobe of the hypophysis or, as Falta believes, to a hyperfunctional reaction of the cortex of the adrenal glands which frequently accompanies acromegalic conditions. The fact is that its presence allows us to suspect strongly the existence of a change in the anterior lobe of the hypophysis, of which there were evident symptoms in cases XXV and XXVI. The insufficiency of the posterior lobe (polyuria) is explained by the mechanism noted above.

Cases XXVIII and XXIX are probably instances of cancerous metastases in the hypophysis. Simmond and Sekiguchi have shown the frequency with which polyurias appear, as in my case XXVIII, in the course of cancer in the breast, without other symptoms of hypophyseal lesion; and the post-mortem examination showed that it was a question of a small metastasis in the posterior lobe. Arnstein has described a similar case in a cancer of the digestive apparatus, resembling our case XXIX.

Cases XXX and XXXI are instances of diabetes insipidus appearing in the course of the climacterium. We have shown (1919) the frequency with which one can find manifestations of hypophyseal insufficiency at the climacterium, which are respon-

sible for many of the disturbances which women usually suffer at this period of life.* Among these disturbances diabetes insipidus may be reckoned, since it occurred in these cases. In case XXX the polyuria coincided with a sudden tendency to adiposity; in case XXXI there were no other hypophyseal symptoms, but there was a strong reaction of the thyroid. Case XXXI, which could be considered as one of climacterium virile, could be added, in a certain way, to the former cases.

There remains only case XXXII, of all those collected by us, which does not present direct or indirect symptoms permitting us to suspect a hypophyseal lesion. As we saw the patient only once, we were unable to examine the condition of the sella turcica and determine if anti-syphilitic treatment would diminish the polyuria (which would have allowed us to correlate this with case XIX).

In any case *our clinical experience overwhelmingly demonstrates that diabetes insipidus is, almost without exception, connected with a disturbance of the hypophysis; and more exactly, to a disturbance of the posterior lobe of the hypofunctional type.* It is very important to note that the majority of our cases (and the same thing occurs with those published by other authors) *are absolutely opposed to the hypothesis that it is a matter of tumors of the gland which, by secondary pressure on the neighboring nervous centres, and not by an endocrine disturbance, produce the polyuria;* since in nearly all cases the *lesions were not tumors* but were sclerosis, atrophy, hemorrhage, etc., as was proved by the clinical and radiographic examination.

Great value is also attached in this regard to the favorable result of hypophyseal opotherapy. I do not understand how one can doubt the biological significance of the fact that the injection of the extract of the *organ which the clinical and post-mortem examination shows to be diseased in diabetes insipidus*, is *the only therapeutic means*, among so many which have been used through the ages, which in a *certain and safe manner* suppresses the polyuria. One cannot suppose that it is a question of a general action of these extracts, as *other polyurias, such as that of chronic nephritis* or *that of diabetes mellitus, are not influenced*

*This interpretation contradicts that of Culbertson in which many of the symptoms of the menopause are attributed to hyperfunctioning of the hypophysis. This point of view has been discussed at length in our book.

by pituitrin, or are influenced to a very slight degree, as we have proved repeatedly. In consequence of the combined evidence of the curing of the polyuria of diabetes insipidus and not the other polyurias; and the efficacy of the extract being precisely that of the gland which is found to have a lesion in this disease and no other extract or inorganic substance whatever having a like effect —I think one can assert, with Hoppe-Seyler, that the curative action of pituitrin in diabetes insipidus has the same value as that of thyroidin in myxedema; that is to say, that, even in the absence of other clinical symptoms, it is sufficient that the polyura diminishes or disappears after the injection of the drug for one to decide upon the hypophyseal origin of the disease.

Of our 32 cases the therapeutic test was made in 19 (observations I, III, IV, V, VI, VIII, IX, X, XII, XIII, XIV, XV, XVI., XVII, XIX, XXI, XXIV, XXV, and XXVI), and in all but two cases it was positive; moreover these can be eliminated as cases of negative tenor, since they were precisely two patients who certainly had hypophyseal disturbances (Observation I: dystrophia adiposo-genitalis; and XXIV, Graves' disease and slight acromegaly, with a large sella turcica, in a daughter of an acromegalic giant.) In order to judge with exactitude the inefficiency of pituitrin, it would have been necessary to repeat several times the proof with other samples of the medicament, because, as Hartman has pointed out, not all extracts have the same composition, and they are sometimes decomposed. As a matter of fact, in case V we obtained no diminishing of the polyuria with the first injection; but one month afterwards a fresh injection lowered the quantity of urine from 5 to 3 liters in 24 hours. In case XXVI, the first injection with old pituitrin diminished the 10 liters which were originally voided daily by only 1 or 2 liters; while fresh pituitrin diminished it by 6 liters per day.

A very interesting fact, to which some authors have called attention, but which I think has not been sufficiently emphasized, is that pituitrin, used in the same dose for different cases, (0.5 or 1 cc. of the commercial solution) produces in various patients a different effect, inversely proportional to the intensity of the polyuria.* That is to say that in patients with great polyuria, the effect is greater than in those with less polyuria; and in

*Recently F. Brun has insisted on this fact in a work which we have read whilst writing the present article.

both the former and the latter, whatever the dose given, the quantity of urine is never less approximately than normal. For example, 1 cc. of pituitrin lowered the quantity of urine in case III, from 12,000 cc. to 1,900 cc.; in cases XII and XIII, from 9,000 cc. to 2,000 cc.; in case XVI from 9,600 cc. to 1,300 cc., while in observation IV, the diminution was only from 3,500 cc. to 1,600 cc.; in observation VIII, from 4,000 cc. to 1,700 cc.; in XXI from 4,100 cc. to 2,000 cc. In no case was the reduction less than 1,500 cc. It appears then, *that pituitrin is only able to act on pathological polyuria, by reducing it to normal, but without reducing it below this limit.* This effect is obtained almost equally with a dose of 0.5 cc. as with 1 cc. of the commercial pituitrin. *Doses greater than 1 cc. do not increase the oliguric capacity of the drug.* As a confirmation of these points of view, we have observed that in normal man and animals, the injection of pituitrin acts very slightly, or not at all on the quantity of urine; but if we take a polyuric rabbit, and make it imbibe an excessive quantity of water (Motzfeldt) or inject it with physiological salt solution (Marañon and Rosique), we then observe clearly that the urine output falls to the normal values. An increase in the quantity of pituitrin injected in the rabbit is not followed, as is true also in cases of diabetes insipidus, by a proportional diminution in the quantity of urine; only when the dose is very excessive and frequently repeated, do *oliguric* phenomena induced by acute nephritis occur. In such cases are noted albuminuria and marked lesions of the kidney, as I have demonstrated with Pascual.

For all these reasons, we think that the internal secretion of the posterior lobe of the hypophysis exercises, physiologically, a controlling action on the elimination of water through the renal filter and that, through the disturbance of this controlling mechanism, diabetes insipidus is produced. We cannot discuss here what this mechanism may be (see Marañon, 1920, a), but we will say that, in our opinion, the hypophyseal *oliguric* hormone may perhaps act, partly directly on the renal cell (either increasing its power to concentrate dissolved matter, or increasing its capacity to retain water), and partly by means of the nervous system, collaborating with the *oliguric* centers at the

base of the encephalon as postulated by Pende. The modifications of these centers would be transmitted to the kidney, probably by way of the sympathetic, as some of our experiments and especially those of Motzfeldt seem to show.

It is very probable, as Cushing and Biedl have suggested, that the hypophyseal hormone ascends by the tuber cinereum to act on the proximal mesencephalic centers. Our observation, XVI, which we have presented in detail elsewhere (Marañon and Rosique, 1917) is, in this sense, very important, as the lesion producing a very intense diabetes insipidus was, as the histological examination confirmed, the fibrous scar which was produced around the shot which separated the hypophysis from the nervous tissue of the infundibular region.

The role of the cerebrospinal fluid in this mechanism is not made clear by our experiments. Some authors suppose that the internal secretion of the hypophysis passes to and is diffused in it. But we have shown (Marañon and Gutsinger, 1919) that the *cerebrospinal fluid does not possess the the slightest oliguric action*, either in cases of normal individuals, nor in those of diabetes insipidus patients. Moreover, according to this hyphothesis, the injection of pituitrin directly into the spinal canal should be much more efficacious than when injected intravenously; but in four of our observations on diabetes insipidus (XIV, XVII, XXV, and XXVII) we injected pituitrin (0.5 cc. and 1 cc.) into the spinal canal *without obtaining a greater diminution than when intravenous injections were made.*

However, *hypertension of the cerebrospinal fluid is a constant phenomenon in diabetes insipidus, and the extraction of a certain quantity of the fluid diminishes the polyuria,* as is shown by the cases of Graham, Williams, Motzfeldt, Costagli and three of our four patients on whom the experiment was made (observations XIV, XVII, XXVII). In observation XIII, on the other hand, the diminution was insignificant (150 cc.). It is difficult to explain this phenomenon, except by supposing that the hypertension, distending the base of the middle ventricle, opposes the supposed ascent of the hypophyseal hormone from the gland, through the pituitary stem. As to the origin of the hyper-

tension, it is difficult to fix it in cases where there are no hypophyseal tumors, as occurred in some of our cases.*

Finally, I wish to insist on the importance, according to my experience, of the emotions in the pathogeny of this disease. Lereboullet, Van der Heijden and Germani all report an initial terror in the clinical history of their polyuric patients. In several of our observations the origin of the polyuria also coincided with an emotional state which was either brusque (fall in cold water in observation IX, as in the cases of Van der Heijden and Lereboullet, serious quarrels with parents as in observation XXVI), or slow and depressing (a period of great intellectual effort and fear of an examination, as in observation VI; serious matrimonial troubles which led to divorce as in observation XXI). Besides, in all the cases, the polyuria increased considerably during emotional states. It is obvious that in these cases there was an easily demonstrable predisposing factor (infantilism, obesity, IX; great development of the sinus frontalis, giddiness and sudden loss of sight, epigastric adiposity and abdominal down in observation XXVI; abnormal smallness of the sella turcica in observation XXVII; great height and acromegalic characteristics in observation XXI). But the fact is interesting, when bearing in mind the role which the internal secretions certainly play in the mechanism of the emotions. One of the proofs of the intervention of the endocrine system in the development of the emotions, is precisely the frequency with which, in predisposed individuals, are produced certain diseases of the glands of internal secretion, due to the emotional states; for instance, Graves' disease, which is often a pathological prolongation of the vegetative modifications of the emotions (exophthalmus, tremor, perspiration, diarrhoea, tachycardia, palpitations, etc.). In the same way one can imagine that diabetes insipidus is related to emotional polyuria, which is transitory in individuals not predisposed.—September, 1920.

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*Weed and Cushing admit a stimulating action of the internal secretion of the hypophysis on the choroid plexus. But this hypothesis cannot be applied to cases of diabetes insipidus in which there is a pituitary hyposecretion and, in consequence, a lesser stimulus.

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HYPOPHYSIS TUMOURS IN DOMESTIC ANIMALS

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After thyroidectomy, hypertrophy of the pituitary body, with obvious formation of colloid substance has been repeatedly described. In rabbits, Stieda found that nine weeks after the extirpation of the thyroid gland, the weight of the hypophysis had doubled. Also after castration, enlargement of this organ has been observed in man, the rabbit and in birds. Exceptions have, however, been reported. Hans Kühn came to the conclusion that castration is of no influence on the dimensions and the weight of the pituitary body in horses (Dissertation, Bern, 1910). Pathological enlargement of the hypophysis can take rise in three different ways: (1) originating from rests of the hypophysis vesicle, (2) originating from the ependyma of the infundibular canal, (3) by hyperplasia of the glandular part.

Rests of the hypophysis vesicle are often met with in quite normal hypophyses as small cysts, lined with epithelium. These occur regularly in ruminants, pigs and carnivores, but not in horses. When they can be demonstrated, they indicate the development of the glandular part as a vesicular body, isolated from the dorsal pharyngeal wall. Among the vertebrates, only in Ammocoetes, the larvae of Petromyzon, the direct communication between the hypophysis vesicle and the pharynx persists during life; in all other vertebrates it is fully isolated in a very early period of embryonic development and placed in the cranial cavity, before the basis cranii is closed. In several mammals a permanent cranio-pharyngeal canal has been seen, not seldom quite accidentally during a section, in cases in which no clinical symptoms had indicated its existence during life. In such instances the sphenoid is perforated and filled up with a continuation of the pharyngeal mucous membrane.

Originating from the epithelium of the hypophysis vesicles or rests of these in the glandular part of the organ, and from the epithelium of a canalis cranio-pharyngeous persistans, malignant tumours may destroy the pituitary body. A striking example of this manner of development of hypophysis tumours in

the horse has been described by Wolff (Dissertation, Bern, 1916). On the base of the brain of a horse of six years, Wolff found a tumour weighing 80 grams (the normal weight of the hypophysis of a horse is about 2½ grams.) This tumour had extended through a slit in the sphenoid into the sphenoidal sinus, which was fully filled up with the tumour tissue.

In our domestic animals the infundibular canal extends into the nervous part of the pituitary body in a variable way. In the horse, no extension of this canal is to be found; in ruminants we can trace a small continuation of the canal in the pars nervosa; in pigs this continuation is more distinct, but in carnivores the infundibular canal may extend throughout the length of the nervous part. Malignant tumours can also take origin in the epen dyma of this canal. Of this way of development of hypophysis tumours, too, examples are known in the veterinary pathology. In the "Bulletin Centrale de Mèdicine vétérinaire," 1890, Mollereau describes a hypophyseal tumour in a horse 9 years old, which, microscopically was found to be only epithelium of the pars nervosa. It was gray in color, friable and the size of a hazelnut. It lay quite centrally. In the horse, the nervous part of the pituitary body, incidentally, does not lie behind the glandular part, as is the case in man, but is wholly surrounded by the glandular part, so that it is to be seen only in cross section.

In his dissertation (Bern, 1911) Valenta describes a hypophyeal tumour in a cow. This neoplasm weighing 62 grams had caused an enormous dilatation of the sella turcica and had also grown out from the centre.

Hyperplasia of the glandular part has been seen by myself in two horses and in a goat. In a mare of 8 years I found a large, hard hypophysis tumour of the shape and the size of a small hen's egg, weighing 36.6 grams. The tumour lay in a pit in the base of the brain at a depth of 1.8 centimetres. The corpus mammillare, the medial parts of the pedunculi cerebri and the corpus cinereum were totally destroyed. On cross section a strong fibrous capsule and, on the cerebral side, large hemorrhages were found. This tumour was constructed wholly of eosinophil cells in which fine and thick bundles of connective tissue and cysts, more or less filled with a colloid substance, could be observed. A second case of eosinophile hypophysis tumour I saw in an old horse. It was round in shape and the size of a

hazel-nut. Remains of old hemorrhages were also in this case to be seen on the cerebral aspect.

Attention may be drawn to the remarkable fact that, in the case which Wolff described and in the first case observed by myself, the clinical symptoms were characterized by a high degree of somnolence, which under the same circumstances is also observed in man.

In a hermaphroditic goat that during life, had not shown any symptom whatever of cerebral disease, I found a large hypophysis, which reached the pons cerebri; it had five times the weight of the normal organ. In the pars intermedia, enormous colloid cysts occurred, and also, but in a minor degree, in the markedly hyperplastic glandular part.

I regret that I had no occasion to examine the thyroid gland of this animal.

PHYSIOLOGICAL HYPERTHYROIDISM*

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Physicians everywhere are now intensely interested in every sort of disease and disturbance of the ductless glands. Probably no other one subject is just at this time receiving so much attention. As a result of this, a better understanding of the disturbances of the ductless glands is becoming very widespread, both in the profession, and unfortunately, perhaps, also, among the laity. As the result of this last, encouraged largely by the now popular pseudo-medical reports in the general magazines and the public press, the practitioner is frequently brought into contact with cases in which this small sum of knowledge is working out quite other than beneficially for those so instructed. Some of the medical profession also are becoming obsessed with the idea that these interesting structures are concerned only with the production of disease and that they exist but for the purpose of causing work for the physician and surgeon.

In this short paper it is my aim chiefly to point out a condition under which symptoms of thyroid disturbance appear, symptoms mistakenly regarded as indicating serious and permanent disease. The interesting fact, of course, to be deduced from these cases, is that treatment should not be directed to prevent or circumvent these efforts on the part of the gland, but that, while in many instances it may be necessary to direct or guide nature's efforts, it is unwise to attempt measures, and particularly radical measures, which inflict changes or limitations of a permanent character on the gland in question.

Doubtless there is no more familiar example of physiological hyperthyroidism than is frequently seen in the developing youth. In fact, many of the characteristics which we regard as a part of youth itself are but probable evidences of thyroid activity.

The full necked youth is so because of the prominence which the thyroid begins to assume at about this age, and a study of

*Read before the Williamsburg Medical Society, Brooklyn, January 10th, 1921.

the work of the greatest artists, ancient and modern, illustrates this fact most graphically: note the young girls of Greuze and the wonderful singing boys of Donatello.

There are many conditions which, particularly in youth, are met only by an active secretion on the part of the thyroid; in fact, very many of the so-called youthful characteristics are really manifestations of thyroid activity. The alert, aggressive attitude of the healthy young man and the similar, though feminized, pose of the healthy young woman are in large part an evidence of thyroid activity. The tremor and blushes, the sentiment of the young woman, the nervous apprehension of the young man under emotional stimulation, are also largely, though not exclusively, evidences of thyroid activity. The blushing of the sensitive young girl or boy is but a neuro-circulatory reflex, exaggerated, through an over-activity of the thyroid, into the neuro-circulatory instability of the definitely hyperthyroid patient.

The tachycardia of the pronounced hyperthyroid patient is represented in the physiological hyperthyroidism stage by that condition of palpitation in which, in the words of the poet, "His heart went pitti-pat and hers went pity 'Zekial."

In the teens and early twenties new tissues are being builded with tremendous rapidity, particularly in the more complex mechanism of the female. Such being the case, the physiological demand for an increased thyroid secretion is often met by an increase in the size as well as in the activity of this gland, and in most instances this is induced by a hypertropy or hyperplasia, as well as by a mere hyper-secretion of the gland. The large and prominent thyroid is frequently, then, at this period of life and genesis, as typical a normal phase as the appearance of straggling hairs on the chin and upper lip of the youth, and the inclination of the mentality and emotional side of both boy and girl toward the development of sex characters and full maturity. The more charming the young woman, the more virile and attractive the youth, the more constantly will it be found that a large gland is present and the more certainly will it be noted that, under normal conditions, such a person responds to emotional and mental stimuli with a quick, aggressive and ap-

propriate reaction, which, after the manner with impetuous youth is frequently over-action.

Still another physiological evidence of thyroid activity or over-activity in the youth, and purposed doubtless by the great need at this period of growth and development, is an increased demand and utilization of food. The healthy and attractive young man and young woman at this period of life are possessed of good appetites, and the basal metabolism should be high at this period.

Again, at this time, artistic perceptions are most keen. In this so-called "formative period" of life, the young musician is most open to the development of his art and to the rapid acquisition of its technic; the young artist, actor or writer, particularly the young poet, is most capable of flights of imagination and of artistic conceptions, though, of course, the mature artist is better able to express and to elaborate his dreams. All these traits are dependent, at least to a considerable extent, upon a certain degree of thyroid flexibility and over-activity, and a study of the portraits of notable people at this period of their lives will commonly show that there is a large thyroid gland present.

It will also be found that in youth, and to a lesser but still perceptible extent among adults, periods of great emotional output, such as courtship, early months of marriage, and the more active phases of an artistic career, are accompanied by enlargements, though perhaps temporary, of the thyroid. The tremor, characteristic of both the hyperthyroid and the enthusiast, may be present, and even exophthalmus may become evident or accentuated.

This tendency is shown particularly in the pregnant young woman, in whom an increased emotionalism is quite likely to be present, especially in earlier pregnancies. In these there is also, according to many obstetricians, an increase in the demand for hypernourishment. An increase of thyroid activity is also necessary at this time because of the demands incident to the building of the new fetal tissue. Many of the activities of the body are noticeably exaggerated under these conditions in perfectly normal and normally reacting individuals. This fact is well illustrated in the madonnas of the great masters of painting. Besides

the enlargement of the thyroid gland there is also normally present in most pregnant women a quite definite enlargement of the fingers and hands, together with many alterations in the facial lineaments which perhaps the artist has been better able to recognize than has the physician. There is a certain beauty which appears in the face of the normal woman during and after her early pregnancies which causes pregnant or recently delivered women to be chosen invariably by great artists for their models of madonnas.

There is also, beyond doubt, something closely allied to a diminished action of the thyroid gland that renders the old maid less generous and self-sacrificing, less spiritually beautiful than the pregnant or parturient woman. That this trait is by no means a cultural one, is shown by the well recognized fact that the same spiritual and facial evolutions are also manifest in the highly bred horse or dog, and probably also in many of the other animals, even among the widely diversified and most savage of the cat family.

Very similar, though far less marked, and, of course, much less permanent alterations are noticeable in the thyroid during the menstrual periods. As a rule, and this has been observed by many intelligent lay women, the thyroid enlarges during the early days of the menstrual epoch, again showing the very close association which exists between the activities of the sexual functions and those of the thyroid. It is doubtless because of this that we find so consistently variations in the thyroid activity, and coincidentally in the thyroid bulk, in association with the sexual waves and doubtless for this, more than for any other reason, disturbances of the one gland are quite likely to be associated with abnormal reactions on the part of the other.

In many courtships, especially those of a highly dramatic or emotional type, thyroid enlargement takes place, even to a pathological degree. Under such circumstances the hyperactivity of the thyroid may become so manifest that marked neuro-vascular instability, exophthalmus, severe tremor and thyroid tumor of even a disfiguring degree may rapidly develop. When such a courtship terminates in a happy and normal marriage relation all these abnormal manifestations, as a rule, lessen or disappear.

A young woman of twenty years, who had been under my observation for some time, was brought to me with a definite picture of mild exophthalmic goiter which had developed during a period of not over two months. She had always been of an emotional type, was an excellent musician, fond of art, dancing, and sports of all kinds. Because of her beauty and charm she was very much sought after, and at times was considerably imprudent on account of her social desires and obligations. She had, however, remained a very healthy and active girl, due largely no doubt to her interest and skill in outdoor sports.

She had required very little medical attention and represented a very delightful example of attractive girlhood. She had never apparently been in love before, nor did she appear to have much conception of physiological love, preferring usually for her intimate associates her girl friends.

A chance meeting with a young army officer developed on both sides into a very rapid and fervent love affair. The young man's expected early order to active service abroad, with all the dramatic elements then stirring, profoundly affected the girl, and she rapidly developed a quite unmistakable case of hyperthyroidism of sufficient degree to be classed as early Graves' disease. She was then referred to me for advice as to the advisability of immediate operation, either the tying of the arteries or the probable removal of a segment of thyroid tissue.

Knowing the mother to be likewise of an intensely emotional type, and herself possessing a notably large thyroid, I advised that the patient be isolated from all outside influences, put to bed, and submitted to a long medical course of treatment before surgical treatment was resorted to. Little was accomplished during the two weeks this method was being enforced, although I believe that I had the thorough cooperation of the patient. At the end of this time, the sympathy of the mother and, I believe, her dramatic impulse which she has subsequently aptly and characteristically referred to as her "maternal comprehension," caused her to side with her daughter and an immediate marriage was consummated. My late patient then proceeded to her husband's station in company with him. The marriage proved happy and was shortly followed by an uneventful pregnancy, the delivery of a fine, healthy child, and the ap-

parently complete cure of the young mother, who is now more happy and content than ever.

Other instances of a similar character have occurred in my experience, though none has been quite so definite and pronounced in its effect. The lesson for me, I hope, has been a better understanding of the relationship between the emotionalism of youth and the effects of its thwarting on the thyroid gland, and also the effect of a perfectly normal and human outcome in the cure of this state.

My experience has been in no way different from that of any other physician, and I have, like many others, come to look for the cause behind hyperthyroidism, and when the condition has been of a physiological nature, have tried to act along physiological lines in the attempted cure, rather than to assume it a pathological condition demanding drastic or eliminative measures.

Very many cases of hyperthyroidism also appear to be due to too deep a drain on the emotionalism along mental rather than physiological or physical lines, as indicated in the case above cited. I have seen examples of this in temperamental young girls in their relation to school and studies, particularly in schools of music and art. I have observed, for instance, many examples of mild hyperthyroidism, occasionally approaching a Graves' picture, in a group of young women of a certain art center in which the conditions of life are very intense and highly competitive. Almost without exception, a withdrawal from competitions, an application of art to outdoor life or an arrangement so that sufficient rest and physical diversion are supplied, have sufficed to check or cure these cases without, at the same time, precluding a normal ambition and interest in life. I am told that a colleague has had a very similar experience among young actresses and singers.

Nor are such experiences limited solely to young women. There is rarely a graduating class at the medical college in which I have taught for the past twenty-five years that does not present one or more examples of similar conditions. As a rule, these manifestations do not appear in these young men before the third or fourth year of their studies, but it is quite unusual for the season to pass without several of them consulting me, either as physician or friend, because of hyperthyroid disturbances that

have usually been fully recognized as such by the students themselves. Palpitation of the heart, neurovascular instability, and over-excitability are the most frequent manifestations complained of; but in some, sweating when under nervous strain, inability to concentrate, insomnia and abnormal apprehensions are the striking symptoms. As a rule, on examination the young man displays a rapid and ofttimes irregular heart action which is checked or mitigated, to some degree at least, by moderate physical exercise and diminished by rest and sedatives, and also by psychic assurance, etc.

Many of these young men are made very miserable by these symptoms; some of them are brought to consent to operative or x-ray treatment of the thyroid, or consider giving up their studies, perhaps permanently. I myself was at first inclined to feel that many if not most of these young men were poorly fitted for the strain and rigor of a physician's life, but a broader experience has decided me against such a serious conclusion.

The young men who are most likely to develop these symptoms and signs of hyperthyroid activity are among the most desirable and brilliant of the students. Very frequently, however, they are men who, through over-ambition, poor antecedent education, poorly chosen nourishment, or insufficient rest and relaxation, have excited the condition by their habits of life and of study. I have noted the fact that many of these students suffered considerably from apprehension in regard to their studies and examinations and my experience has been such that I now have no worry about the results of examination in case of the boys who worry about them themselves, for they have always been among the highest in standing, not only in their examinations, but also in their professional after-life.

One such young man, I remember with especial vividness, because I now frequently see patients with him and have therefore become well acquainted with his success, and I feel also that I now understand the elements which led up to it. When he first came under my observation as a second year student he was twenty years of age. He came of poor, uneducated, but ambitious and intelligent parents, and during his entire course was obliged to support himself in large part by outside work. This resulted in insufficient rest, irregular and poor food, and con-

siderable strain. In addition, he was quite apprehensive as to his ability to pass his examinations, because of the unfair conditions under which he worked as compared with his fellow students. This anxiety was groundless, however, for he was recognized throughout his course as one of the most promising of the students, and while his conditions of life prohibited his sharing many of the pleasures of his fellows, he was one of the best liked and most popular men of his class.

The boy first came under my profesional care during his third year, and at this time was fully aware of his condition. He suffered extremely from attacks of tachycardia, associated with hot and cold flashes, profuse perspiration, tumultuous heart action, great nervous apprehension, a tremor which seriously interfered with his laboratory technic, and increasing insomnia. He was unable to eat sufficiently or properly and was losing weight rapidly.

Physically he presented marked enlargement of the thyroid, a considerable degree of exophthalmus, marked tremor, dermographia, and many other indications of unstable neurovascular control. His scholarship, however, still remained of a very high standard. The serious questions which presented themselves were: Was he able to continue his work as a medical student? Must be give up medicine as a career? Should he receive the classical medical treatment for his condition, namely, confinement to bed, prolonged rest, etc., or should he be at once operated upon? Compliance with either of the last two conditions practically meant for him the giving up of medicine as a career, and his apprehension was such a striking feature of the case that I concluded finally that the mental trauma inflicted, were he entirely withdrawn from his chosen work, would be so great as perhaps to do him as much harm as a continuance of the work under modified conditions.

He was directed to give up study, to attend his lectures, clinics and recitations, to go to bed at a regular time each night, and to force his nourishment to the full. He was given large doses of bromide until sleep became excellent and apprehension as to his work and standing was quieted. Notwithstanding these restrictions, he was able to pass his examinations very satisfactorily at the end of the year and was then directed to spend the

summer entirely away from medical work. His necessary occupation during the vacation was largely a matter of physical strain only and the work was so easy nervously for him that he was advised to continue it, but to eat regularly, play baseball, and to go to entertainments as much as circumstances permitted.

He returned to school in the fall much improved, though under mental excitement, considerable degrees of tachycardia still developed. His work during the fourth year was almost entirely practical and clinical, and was much enjoyed. He was again advised to study as little as possible, but to attend his clinics and all class exercises regularly, to go to bed early, and to eat as generously as possible. He gained steadily throughout his fourth year and graduated high in his class, making easily the hospital to which he aspired. Bromides had long ago been discontinued and he gained constantly in flesh and self-assurance while in the hospital, though it was occasionally necessary for him to curb himself when he was tempted to work too hard or for too long hours.

After leaving the hospital he entered independently into general practice, switching his chief attention toward surgery. His practice developed rapidly and in the hospital to which he had attached himself he rapidly passed the periods of assistant and assistant attending surgeon and now, at the age of twenty-seven years, he is a full visiting surgeon, with his entire work given over to surgery in which he is doing quite all that he is able to do. He is robust, happy in his work and success, enjoying life immensely, and no signs of disease of the thyroid are now evident unless it be a very quick emotional response and an almost abnormally quick acquisition of knowledge and technic.

I consider this case a typical example of hyperthyroidism excited by an abnormal demand placed on the gland by the conditions of life, as a result of which pathological symptoms developed. With a cessation of the abnormal demand a diminution in secretion took place and with the resumption of a relatively normal life, at least as much as a busy practitioner can expect, a return to normal followed. I am also of the opinion that the winning personality, tremendous capacity and virility of this young man are to a considerable extent the natural results of a very quick thyroid response. Many similar, though few so

marked, examples have come under my notice as a teacher of medical students. One further example only will be cited.

At the conclusion of my lectures on the endocrine organs the last college year, a young man came to me for advice as to his own condition. His history in general was uneventful except that since early childhood he had been a confirmed and successful student. Though fond of outdoor sports and a typical boy in every respect, mischievous, alert, and attractive, he had given most of his time to study and had rapidly passed his regular college course and entered medical college, where he found his work so absorbing and interesting that he "found little time to get into trouble," as he himself expressed it.

When he came to me he was suffering very much from tachycardia, especially when under nervous stimulation; and though fully aware of his ability, he was very apprehensive when called upon to recite. He showed an asymetrical goitre, which he asserted was increasing in size. He was losing flesh rapidly, had ceased to sleep normally, had marked periods of depression and of nervous incoordination, marked dermographia, and he felt himself fast slipping into a condition which he described as "neurasthenia."

Much the same regime as in the previous case was instituted; the boy was advised to accept neither operation, x-ray exposure nor even medical treatment, except the use of bromides at night, to have as much diversion as possible, music, play, plenty of sleep, outdoor exercise, and as much neglect of his studies as was possible, while attendance at classes, recitations and especially his clinics was urged. He succeeded in passing his final third year examination satisfactorily, but was forbidden to enter a hospital, as he had expected to do that summer. He was urged instead to go to the country and work on a farm or ranch until college reopened in the fall, giving his entire time and attention to physical activities and to recreations along the same line. He had gained rapidly in weight during the last semester, the tachycardia had greatly diminished, both in severity and in frequency, he had been again able to sleep normally and was greatly improved in all respects. Meanwhile the goitre had diminished so much in size that it now entirely failed to attract attention. He returned from his vacation this fall apparently

a well-balanced, healthy young man, and will, I fully believe, be entirely able to "carry on" in the medical profession.

I have also observed frequent instances of this syndrome among young women, particularly in finishing schools of the better class and in women's colleges. In most of them, however, there appears to have been an association of sexual and emotional factors which could not be elicited with the young men. I believe the condition to be the same precisely in both, but with girls at this period the disturbances of maturation are more striking and dominant than with young men. The chief concern of the latter at this period of life is usually occupational ambition or sports, while the young woman is wittingly or unwittingly thinking of love and maternity. This I believe to be the only essential difference.

By no means all of the cases of this class which I have observed have gone on to recovery and a successful life. Many have broken nervously and become neurotics; several have developed typical and persistent Graves' disease, which has responded only to aggressive treatment. The deciding factor, so far as I can judge, is very largely the intelligence with which the case is first managed.

One of my young women, whom I had considered as a very promising case and in whom the condition had apparently developed as a direct result of great sorrow, lack of affection on the part of a remaining parent, became entirely disoriented with the sane and proper school atmosphere under which she had been placed. Gifted, as most of these people are, with very considerable artistic understanding (temperament, if you like), this young woman adopted the career of a motion picture actress in which she displayed decided ability. Later, however, she developed a condition of melancholia, interspersed with emotional and temper outbursts which ruined her life and caused her, in the early twenties, to become a disagreeable, unhappy, embittered, and useless person.

Other instances of young women who have had unfortunate love affairs or contracted unhappy marriages, or in whom elected or enforced sterility has finally caused obsessions of all sorts to develop, have become hopeless misanthropes and neuroties, anathema to their physicians. Some embittered by disappoint-

ments and grief, unhealthy and unhappy, unable to find rest and satisfaction anywhere, have become the sort of old maids described in story books.

In so far as I have observed these cases, I am convinced that in very few, if any, do Freudian impulses figure to any extent. They have been simply temperamental and unusually capable and acquisitive young persons in whom an unbalanced or improper habit of life has caused an unusual demand upon the thyroid and doubtless also on other glands as well. Once established, this increased thyroid demand becomes more or less a gland habit and persists until it becomes a pathologic condition. I believe that most such cases can be brought back to normal by proper management, which must include both social and medical, and to a certain degree mental readjustments, provided, of course, these attempts receive the cooperation of the patient and are established sufficiently early before the body habits have been fully developed and fixed.

I would separate these instances very sharply from those of neurocirculatory asthenia, with which they have doubtless been often confused. I would base the essential distinction on the fact that the subject of neurocirculatory asthenia is abnormal in many other respects and these cases are undoubtedly of familial or congenital origin. There is usually associated with them a distortion of the moral perceptions, in many instances, a timorousness almost pathological, and almost without exception, there are sexual inadequacies or perversions and disinclination toward a normal physical expression in all channels. While I am convinced that in all of these cases a hyperthyroidism exists, either as an etiological factor or a sequence, it certainly is not the sole endocrine abnormality, nor the basic one. This, on the contrary, I believe to be the essential factor in the condition of physiological hyperthyroidism which I have been attempting to describe. I have never seen typical neurocirculatory asthenia develop into Graves' disease, but this is the legitimate outcome of improperly managed cases of the condition to which I am now calling attention.

I think that I have made clear my conception of this condition: that it is brought about by an abnormally great demand on the thyroid as the result of developmental growth associated

with too much emotional output. When these factors are either diminished within normal limits or directed into other channels, automatically the over-action of the gland, together with other secondary factors that may be associated with it, drops toward the normal; but if the urge is too long continued, or if fixed habits of demand and response be established, the condition will develop either into Graves' disease or take on a neurasthenic phase likely to ruin the life of the individual. It appears, then, to be but a normal response to an exaggerated or abnormal demand, with the final establishment of a tissue habit.

My purpose in presenting this study has been to point out that these instances of thyroid activity do not call for surgical or other radical treatment. On the contrary, I believe that when these are enforced serious permanent harm is likely to result, — either a subsequent hyperthyroidism or an alteration or holding in abeyance of natural and normal tendencies which, when compared to mediocrity, in their full efflorescence lie very close to genius. A failure to comprehend and correctly manage these cases leads to Graves' disease, to neurasthenia or eventual nervous and physical inadequacy.

DEGENERATIVE CHANGES IN THE SEMINAL EPITHELIUM AND ASSOCIATED HYPERPLASIA OF THE INTERSTITIAL TISSUE IN THE MAMMALIAN TESTIS

(With 5 figures in text)

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INTRODUCTION

Degenerative changes in the mammalian testis, due to a wide variety of causes, have been described by a number of observers. Such changes involve primarily the seminal epithelium. However, not infrequently degenerating testes also show hyperplasia of the interstitial tissue, and such hyperplasia has been interpreted as an accompaniment or a result of the degeneration of the seminal epithelium. The writer ('19) has recently described degenerative changes in the seminal epithelium and associated hyperplasia[1] of the interstitial secretory tissue in the testis of the dog, following elimination of the sympathetic nerve supply to the testes and unilateral ligation and resection of the ductus deferens.

The present paper embodies the results of further experimental studies undertaken in an effort to determine whether the degenerative changes which occur in the testes following operative procedures are the direct results of these operations, or whether, in some instances, they may be but an expression of the physiological state of the experimental animal. The results of these studies also throw some light on the problem of the compensatory hyperplasia of the interstitial secretory tissue and the relationship of the hyperplasia of this tissue to changes going on in the seminal epithelium. As recorded in the previous paper referred to above, bilateral degeneration of the testes followed both the elimination of the sympathetic nerve supply to these

[1] The word, hypertrophy, has been commonly employed to designate the increase in the interstitial tissue in the testis. It was employed in the same sense by the present writer in his earlier paper. Inasmuch as the increase in the interstitial tissue which is associated with degenerative changes in the seminal epithelium involves an actual increase in the number of cellular elements it is more correctly designated as hyperplasia. The word, hyperplasia, will be employed in this sense in the present paper.

glands and the unilateral ligation and resection of the ductus deferens. A priori, there is no ground for the assumption that degenerative changes in one testis may occur as either a direct or an indirect result of degenerative changes in the other.

The dogs used in the first series were confined in relatively close quarters during the experimental period. Their diet, though ample in caloric value, was somewhat deficient in its protein content. The influence of such environment and diet can not be disregarded. For the purposes of the present study a series of rabbits and another series of dogs were subjected to operation[2] and kept under conditions as favorable as circumstances permitted. The diet of the rabbits consisted of oats, bran and alfalfa. The diet of the majority of the dogs was similar to that of the dogs used in the previous study; that of the others consisted largely of fresh meat.

RESULTS IN RABBITS

Five rabbits were subjected to operation under ether anesthesia. One of these (No. 1) was unilaterially castrated, three (Nos. 2, 3, and 4) were subjected to ligation and resection of the right ductus deferens, and one (No. 5) was subjected to resection of the right ductus deferens without ligation. The animals were allowed to live 29 to 38 days following operation. In all cases both testes, when removed, were fixed in 10% formalin and prepared for microscopic study.

In the case of the rabbit which was unilaterally castrated, preparations both of the testis which was removed at the time of operation and of the other, which remained in situ 38 days following operation, presented similar microscopic pictures. Both glands were entirely normal in all respects. There was no evidence of any increase in the interstitial tissue in the testis left in situ after unilateral castration; consequently, compensatory hypertrophy or hyperplasia of this tissue did not take place.

In all three rabbits which were subjected to ligation and resection of the right ductus deferens, the seminal epithelium of the right testis underwent degeneration with accompanying hyperplasia of the interstitial secretory tissue, while the left testis

[2]The operative work involved in this study was carried out by Dr. J. E. Thomas, to whom the writer desires gratefully to acknowledge his indebtedness.

suffered no apparent change. Spermatids and spermatocytes were still present in small numbers in some of the tubules while they were absent in others. The spermatogonia were materially reduced in number in all the tubules. The nuclei of the majority of the sustentacular cells remained in situ. The interstitial secretory tissue was markedly increased and showed evidence of heightened functional activity. Some of the sections also showed evidence of a slight increase in the interstitial connective tissue.

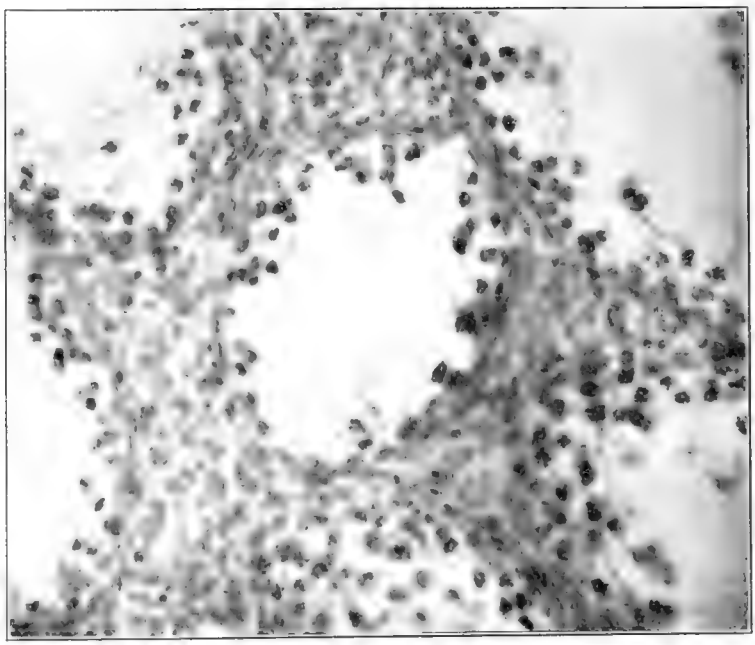


Fig. 1. Photomicrograph (x 230) of an area of a section of the right testis of rabbit No. 4 which was removed 31 days after ligation and resection of the right ductus deferens, showing degeneration of the seminal epithelium and hyperplasia of the interstitial tissue.

Limited areas of sections of the right and and left testis respectively of rabbit No. 4 are illustrated microphotographically in figures 1 and 2. This animal was allowed to live 31 days following operation until the other testis was removed. As illustrated in figure 1, the seminal epithelium of the right testis underwent advanced degeneration, accompanied by marked hyperplasia of the interstitial secretory tissue and less marked hyperplasia of the interstitial connective tissue. The relatively

small amount of interstitial tissue present in the normal testis of the rabbit is illustrated in figure 2. The testis on the unoperated side, in these rabbits, was not apparently affected by the degenerative changes going on in the testis on the operated side.

In the rabbit (No. 5) which was subjected to resection of the right ductus deferens without ligation the proximal portion of the ductus remained patent; consequently, the right testis did not undergo degenerative changes. Microscopic preparations of both testes in this case indicate that the glands were normal in all respects.

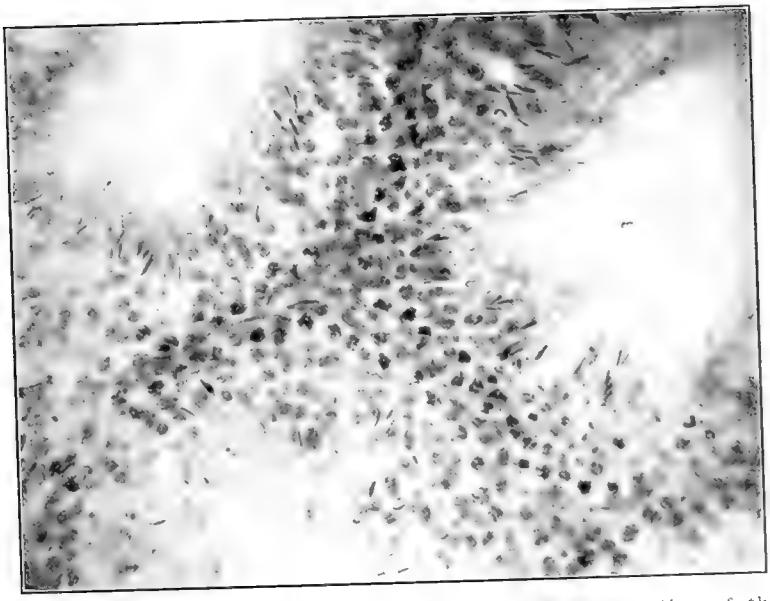


Fig. 2. Photomicrograph (x 230) of an area of a section of the left testis of rabbit No. 4 which was removed 31 days after operation on the opposite side, showing normal condition.

In this series of rabbits degenerative changes occurred only in those testes of which the outflow of the seminal secretion was prevented. The intraglandular pressure caused by the occlusion of the ductus deferens doubtless is the direct cause of degeneration in these glands. Inasmuch as none of the other testes suffered degenerative changes there is no evidence which indicates that other factors played any part in the results observed in these cases. Degeneration of the seminal epithelium is in every

instance accompanied by hyperplasia of the interstitial secretory tissue. The degree of such hyperplasia obviously is correlated with the degree of degeneration of the seminal epithelium.

RESULTS IN DOGS

The series of dogs used in this study consisted of ten animals which were subjected to operation under anesthesia and several controls. Four (Nos. 3, 7, 9, and 11) were unilaterally castrated, four (Nos. 2, 5, 10, and 12) were subjected to unilateral ligation and resection of the ductus deferens, and two (Nos. 1 and 6) to unilateral resection of the ductus deferens without ligation. These dogs were allowed to live 28 to 142 days following operation. In all cases both testes were fixed in 10% formalin and prepared for microscopic study.

In two of the dogs which were unilaterally castrated (Nos. 9 and 11) no degenerative changes took place in the testis which was left in situ following the operation. One of these dogs (No. 9) was operated under novocain anesthesia and given a diet consisting largely of fresh meat until the testis left in situ was removed 35 days later. Microscopic preparations of both testes in this case indicate that they were normal in all respects at the time of removal. The other dog (No. 11) was operated under ether anesthesia and was kept and fed with other laboratory animals for 142 days, when the right testis, which had been left in situ, was removed. Microscopic preparations of the left testis in this case show that it was entirely normal at the time of its removal, but that spermatogenesis was at low ebb. Microscopic preparations of the right testis show that it also was entirely normal at the time of its removal and that spermatogenesis was going on actively. No changes involving the seminal epithelium could be observed. Neither was the interstitial secretory tissue more abundant than in the left testis. Although this gland alone remained in situ for an interval of 142 days, no compensatory hypertrophy or hyperplasia of the interstitial secretory tissue took place.

Both the other dogs which were unilaterally castrated suffered testicular degeneration. One of these (No. 7) was killed 48 days after the right testis had been removed under ether anesthesia. Microscopic preparations of the right testis indicate

that it was normal in all respects and that spermatogenesis was going on actively. Microscopic preparations of the left testis, which was removed at autopsy, showed advanced degenerative changes in the seminal epithelium with accompanying hyperplasia of the interstitial secretory tissue. Spermatogenesis had ceased in this gland. Many of the tubules showed complete absence of spermatids and material reduction in the number of spermatocytes. Relatively few spermatids were still present in some of the tubules, but all the tubules showed unmistakable evidence of degeneration. The other dog (No. 3) was killed 36 days after the right testis had been removed under morphine and ether anesthesia. Microscopic preparations of the right testis in this case showed some evidence of degenerative changes. Apparently spermatogenesis was at very low ebb. The majority of the tubules showed very few spermatids and a material reduction in the number of spermatocytes. Sloughed epithelial cells also were present in the lumina of the seminiferous tubules and the ductus epididymis. There was no evidence of any hyperplasia of the interstitial secretory tissue. Preparations of the left testis, which was removed at autopsy, showed advanced degenerative changes in the seminal epithelium accompanied by marked hyperplasia of the interstitial secretory tissue. The evidence also indicates a slight increase in the interstitial connective tissue. Obviously, testicular degeneration was initiated in this animal before he was subjected to operation; however, the process advanced rapidly in the testis left in situ following operation. Inasmuch as the animal was apparently in good physical condition at the time of operation as well as throughout the experimental period, no cause for the early initiation of testicular degeneration can be assigned.

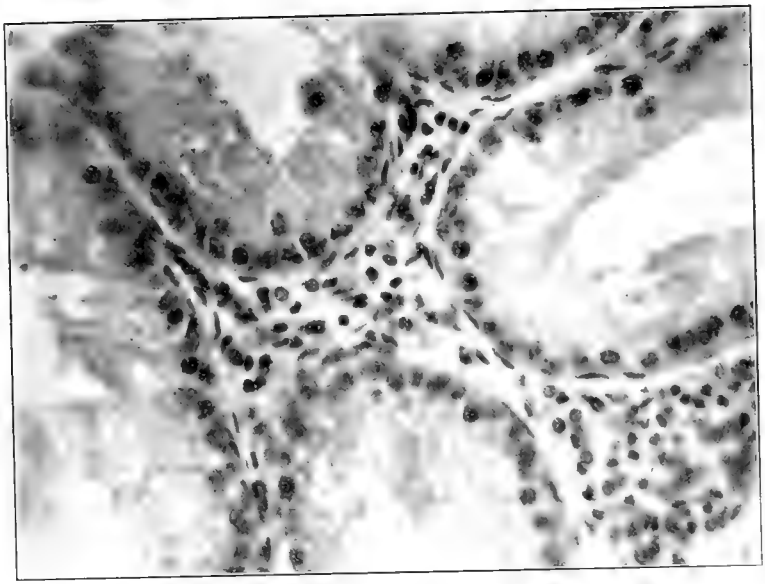
In all but one of the dogs which were subjected to unilateral ligation of the ductus deferens the testis on the corresponding side underwent degenerative changes. In the two cases in which the ductus deferens was not ligated it nevertheless became occluded. In the single case (No. 5) in which testicular degeneration did not occur following resection of the ductus deferens, although the latter was ligated, an outlet for the seminal secretion was restored. In three cases the testis on the opposite side

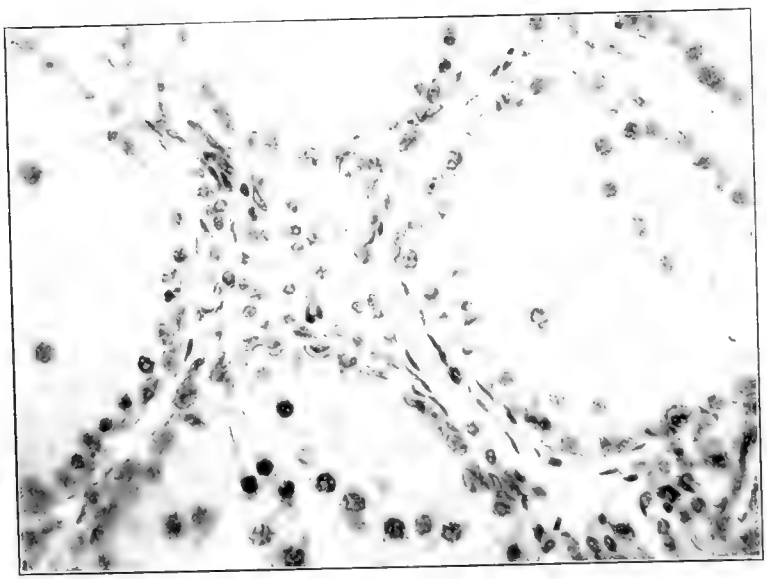
also underwent degenerative changes. In one case the evidence is not unmistakable. In the remaining two cases the testis on the opposite side suffered no degenerative changes.

In two of these animals (Nos. 1 and 6), in which both testes were removed at autopsy 28 and 42 days respectively after operation, advanced degenerative changes in the seminal epithelium with accompanying hyperplasia of the interstitial secretory tissue had taken place in both testes. Microscopic preparations showed absence of spermatids and spermatozoa in the majority of the tubules and material reduction in the number of spermatocytes in all the tubules. The degenerative changes in the seminal epithelium, as well as the hyperplasia of the interstitial secretory tissue, were not appreciably less marked in the testis on the opposite side than in the one of which the ductus deferens was occluded. The conditions observed in the right and left testis respectively of dog No. 1 are illustrated microphotographically in figures 3 and 4.

One of the dogs (No. 10) which were subjected to unilateral ligation and resection of the ductus deferens was among those whose diet following operation consisted largely of fresh meat. Active spermatozoa were expressed from the resected ductus deferens at the time of operation. Both testes were removed 35 days later. Microscopic preparations of both testes showed almost entire absence of spermatozoa and some degeneration of the seminal epithelium. The epididymis on the operated side was greatly distended. The lumen of both the right and the left ductus epididymis contained masses of sloughed cells. The degenerative changes were less advanced in the testis on the unoperated than in the one on the operated side, but hyperplasia of the interstitial secretory tissue was apparent in both.

In one case (No. 2), although the animal was allowed to live for 60 days following operation under morphine and ether anesthesia and the resected ductus deferens remained occluded, very little degeneration of the seminal epithelium and no hyperplasia of the interstitial secretory tissue occurred. However, spermatogenesis was at very low ebb. This condition probably obtained at the time of operation; consequently, the intraglandular pressure due to occlusion of the ductus deferens did not become sufficiently great to induce pressure atrophy.





Figs. 3 and 4. Photomicrographs (× 220) of areas of sections of the right and left testes respectively of dog No. 1 which were removed 28 days after resection of the left ductus deferens, showing degeneration of the seminal epithelium and hyperplasia of the interstitial tissue.

One dog (No. 12) was allowed to live 142 days following ligation and resection of the right ductus deferens under ether anesthesia. Both testes were removed at autopsy. That the outlet for the seminal secretion on the operated side had not been restored was indicated by the great distension of the ductus epididymis on that side. Nevertheless, microscopic preparations of both testes indicated active spermatogenesis and appeared entirely normal in all respects except that the interstitial secretory tissue in the testis on the operated side was markedly increased.

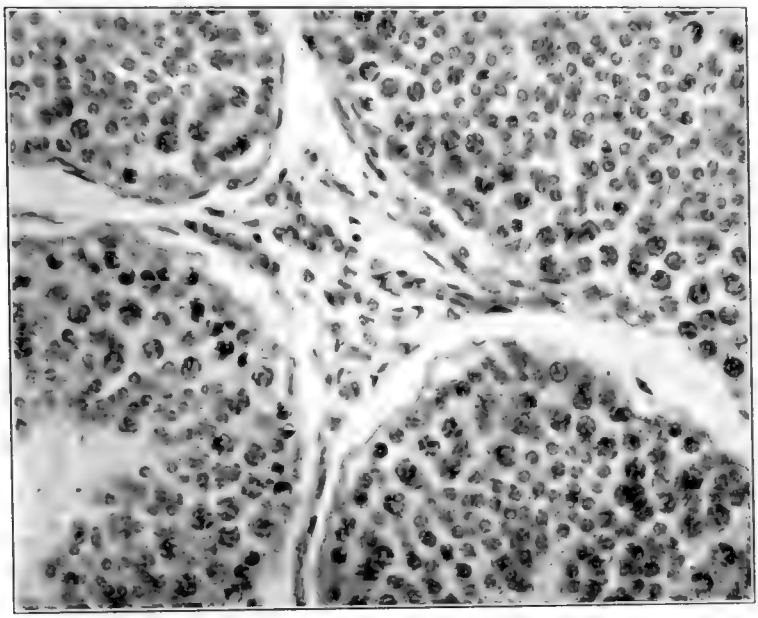


Fig. 5. Photomicrograph (x 230) of an area of a section of the right testis of dog No. 12 which was removed 142 days after ligation and resection of the right ductus deferens, showing restoration of the seminal epithelium.

Obviously, in this case regeneration of the seminal epithelium followed degenerative changes in this tissue with accompanying hyperplasia of the interstitial secretory tissue. The conditions observed in the testis on the operated side in this case are illustrated microphotographically in figure 5.

One unoperated dog, kept for one month with some of the operated dogs as a control animal, showed degenerative changes in both testes. Another dog was subjected, under ether anes-

thesia, to an operation not involving the genital organs and kept under essentially the same conditions as the other experimental animals for four months following operation, when both testes were removed and prepared for study. Preparations of both testes in this case showed advanced degenerative changes in the seminal epithelium; however, spermatogenesis was not entirely suspended. They also showed evidence of hyperplasia of the interstitial secretory tissue. None of the other control animals showed any evidence of testicular degeneration.

DISCUSSION

That the degenerative changes in the seminal epithelium following ligation or occlusion of the ductus deferens differ somewhat from the degenerative changes in this tissue due to other causes is well known. Degenerative changes due to occlusion of the ductus deferens involve first the spermatids and spermatocytes. Some of these cells become necrotic and gradually slough; others slough before they become necrotic. Degenerative changes due to other causes also involve first the spermatids and spermatocytes, but sloughing is a less important factor. The great majority of the cells become necrotic before they slough. This difference was discussed by the writer in the earlier paper referred to above and need not be considered further at this time. As degeneration of the seminal epithelium advances the spermatogonia also become involved. The distal portions of the cytoplasm of the sustentacular cells become involved relatively early, but the basal portions of these cells, including their nuclei, remain intact until relatively late. Indeed, in many of the tubules in which the seminal epithelium has suffered advanced degenerative changes, the nuclei only remain, either in their normal position or somewhat farther removed from the basement membrane.

The writer was led, in his earlier studies, to conclude that the degenerative changes observed in the testis on the opposite side, following unilateral ligation and resection of the ductus deferens, are identical with those observed in the testis of which the ductus deferens was occluded, and that degeneration in the former is "associated with and conditioned by" degeneration in the latter. The present study does not justify these conclusions.

The material upon which it is based shows clearly that when degenerative changes in both testes follow unilateral ligation and resection of the ductus deferens these changes are not identical in both glands. The same differences which are commonly recognized between the degenerative changes in the seminal epithelium due to occlusion of the ductus deferens and those due to other causes which do not involve pressure atrophy may be observed. The testis on the opposite side did not undergo degenerative changes synchronously with the one of which the ductus deferens was occluded in any of the rabbits nor in several of the dogs included in the present series of experimental animals. In those cases in which testicular degeneration occurred bilaterally, following unilateral occlusion of the ductus deferens, the changes observed in the testis on the unoperated side doubtless are an expression of the physiological state of the experimental animal.

The causal factors involved in testicular degeneration which is not the direct result of an operative procedure or traumatic injury may be exceedingly complex. Diet is an important factor. Testicular degeneration in rats, due to a diet deficient in the water-soluble vitamine, was recently described by Allen ('19). McCarrison ('19) also described testicular degeneration in fowls fed on milled and autoclaved rice. However, these fowls suffered from deficiency disease and showed degenerative changes also in other organs. Testicular degeneration under these conditions probably was a direct result of the disease, which was caused by the deficiency in the diet. The diet of the majority of the dogs included in the present series of experimental animals was somewhat deficient in its protein content. Some of these dogs suffered degenerative changes in the testis on the unoperated side; others did not. On the other hand, the diet of one of the dogs which suffered degenerative changes in both testes following unilateral ligation and resection of the ductus deferens consisted largely of fresh meat. This dog was in good physical condition at the time of operation and apparently remained so throughout the experimental period. Spermatogenesis also was going on actively at the time of operation, as indicated by the fact that viable spermatozoa were expressed from the resected ductus deferens. Indeed, testicular degeneration occurs

under such a wide range of conditions that it is quite impossible in many instances to determine a direct cause. It is not improbable that any condition which materially affects the physiological state of the animal may be a factor in testicular degeneration.

Seminal epithelium which has suffered even advanced degenerative changes may be restored and may resume its normal activity. Steinach ('20) has pointed out that in rats the seminal epithelium may be quite completely restored 6 to 8 months after ligation and resection of the ductus deferens. Regeneration of the seminal epithelium is indicated also in one of the dogs included in the present series. Both testes of this dog showed normal seminal epithelium and evidence of active spermatogenesis 142 days after unilateral ligation and resection of the ductus deferens. The great distension of the ductus epididymis on the operated side in this case indicates that the ductus deferens remained occluded. Inasmuch as in all other cases in which the ductus deferens remained occluded the seminal epithelium underwent degeneration, it is highly improbable that degeneration should not have occurred in this case. An appreciable hyperplasia of the interstitial secretory tissue also suggests that the seminal epithelium had undergone degenerative changes. Obviously this gland became adjusted to the new conditions of intraglandular pressure resulting from occlusion of the ductus deferens.

Throughout the entire series of experimental animals used in this study hyperplasia of the interstitial secretory tissue was observed as a constant accompaniment of advanced degenerative changes in the seminal epithelium. On the other hand, hyperplasia of this tissue did not occur in the testis left in situ in any of the animals which were unilaterally castrated, unless the seminal epithelium suffered degenerative changes; i. e., compensatory hyperplasia of this tissue due to the absence of the testis on the opposite side did not occur, although much more time was allowed than is required for the hyperplasia of this tissue to become well marked in glands in which the seminal epithelium undergoes degenerative changes. Hyperplasia of the interstitial secretory tissue in a cryptorchidic testis, in animals from which one normal testis has been removed, has been interpreted as a compensatory process. That cryptorchidic testes commonly show degenerative

changes in the seminal epithelium is well known. Such changes in the seminal epithelium with accompanying hyperplasia of the interstitial secretory tissue in a cryptorchidic testis doubtless have been observed frequently in animals from which a normal testis was not removed. This phenomenon was observed by the writer in both the rabbit and the dog. Biedl ('13) cites with apparent approval the work of Bouin and Ancel, in which they interpreted the enormous hyperplasia of the interstitial secretory tissue following unilateral castration and ligation of the ductus deferens on the opposite side in rabbits as a compensatory process. The present study shows clearly that hyperplasia of the interstitial secretory tissue follows ligation of the ductus deferens no less promptly in the presence than in the absence of a normal testis on the opposite side. As suggested by the writer in his earlier paper, hyperplasia of the interstitial secretory tissue in all such cases as those cited above is probably not a compensatory process, but an accompaniment of degenerative changes in the seminal epithelium. Indeed, it is quite improbable, in the light of the present study, that hypertrophy or hyperplasia of the interstitial secretory tissue in the testis ever occurs as a compensatory process. On the other hand, hyperplasia of this tissue doubtless is a constant accompaniment of advanced degenerative changes in the seminal epithelium.

Although no active hormone produced by the interstitial tissue in the testis has been isolated, the theory that this tissue produces an internal secretion which is an important factor in the development of the secondary sexual characters, and that it plays an important part in the sexual life of the individual, is quite generally accepted. The work of not a few investigators affords at least circumstantial evidence in support of this theory. Histological evidence of the secretory character of the interstitial cells (cells of Leydig) is not wanting. Whitehead's ('08) studies, which are based on preparations of the testes of mammals of several types, including man, are quite conclusive on this point. His findings are corroborated by those of not a few more recent investigators. The present study also affords histological evidence of the secretory character of these cells. The results of experimental studies as well as observations on the behavior of animals with an undescended testis, the normal

descended testis having been removed, strongly suggest that sexual excitability is conditioned by the functional state of the interstitial tissue. The recent work of Steinach ('20) indicates furthermore an important relationship between the functional condition of the interstitial tissue in the testis and the sexual behavior and potency, as well as the physical vigor, of the individual, as manifested especially by senile animals in which hyperplasia of the interstitial secretory tissue is experimentally induced. Although none of the animals included in the present series had reached the age of senility nor had manifested any lack of physical vigor, several of the dogs in which hyperplasia of the interstitial secretory tissue had taken place in one or both testes showed unmistakable evidence of heightened sexual excitability.

SUMMARY

Of five rabbits which were subjected to operation under ether anesthesia, one was unilaterally castrated, three were subjected to ligation and resection of the right ductus deferens, and one was subjected to resection of the right ductus deferens without ligation. Testicular degeneration occurred following operation only in the right testes of the three animals which were subjected to ligation and resection of the right ductus deferens. Degeneration of the seminal epithelium in these cases was accompanied by hyperplasia of the interstitial secretory tissue.

Of ten dogs which were subjected to operation under anesthesia, four were unilaterally castrated, four were subjected to unilateral ligation and resection of the ductus deferens, and two were subjected to unilateral resection of the ductus deferens without ligation. Testicular degeneration occurred following operation in two of the dogs which were unilaterally castrated, but not in the others. In the two dogs which were subjected to resection of the ductus deferens without ligation the ductus became occluded. Degenerative changes in the testis on the operated side occurred in all but one of the dogs which were subjected to unilateral ligation of the ductus deferens. In the animal in which testicular degeneration did not occur following operation, the outlet for the seminal secretion was restored. In three cases degenerative changes in the testis on the opposite side occurred synchronously with those in the testis of which the ductus deferens was occluded. In the one dog which was

allowed to live 142 days following ligation and resection of the ductus deferens the seminal epithelium was restored.

Degenerative changes which occur in the testis on the unoperated side following unilateral occlusion of the ductus deferens or unilateral castration probably are an expression of the physiological state of the experimental animal.

Hyperplasia of the interstitial secretory tissue probably is a constant accompaniment of advanced degenerative changes in the seminal epithelium. It probably does not occur in any case as a compensatory process.

Dogs in which the interstitial secretory tissue in one or both testes had undergone hyperplasia showed evidence of heightened sexual excitability.

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THE SPECIAL SERVICES RENDERED TO THE HUMAN ORGANISM BY THE SYMPATHETIC AND PARASYMPATHETIC SYSTEMS

INCLUDING BOTH NERVES AND GLANDS OF INTERNAL SECRETION

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With the increased interest which is now being manifested in the study of endocrinology and vegetative neurology, it is well for us to consider these vegetative systems in their broadest relationships to medicine and not to narrow down to the study of any single phase of the subject, no matter how interesting such phase may be.

In the endocrine glands and vegetative nerves we have the normal control of those functions of the body which are essential to the life and growth of the individual and the perpetuation of the species. These systems are interdependent and supplementary in their action, as is evident from their evolution. If we go back in the scale of evolutionary life to the point where there was no nervous system and where all body control was carried on by chemical products, we find nothing but the simplest of organisms. But as the organism became more complicated its sustenance and preservation became a matter of greater concern and complexity. Then a nervous system was developed, and this divided into two distinct components, one the somatic or voluntary system, presiding over the animal's relationship to the outside world, and the other the splanchnic or vegetative system, presiding over his internal mechanisms. The former is more or less under the control of the will; the latter not only acts independently of the will, but is able to functionate, though imperfectly, when entirely separated from the central nervous system. With this arrangement of physiological control, the functions essential to animal life can go on undisturbed, while the voluntary system adjusts the organism to its external environment.

While the voluntary nervous system, on the one hand, and the vegetative systems (composed of the endocrine glands and vegetative nervous system) on the other, are separate and distinct in their functions, they are, nevertheless, not wholly independent; neither of them can be considered alone. Sensory impulses which reach the spinal cord and brain over the somatic nerves influence the vegetative as well as the voluntary structures and the psychical system; and impulses which arise in the vegetative structures influence the somatic structures and psychical system. Furthermore, impulses arising in the physical system influence both somatic and vegetative functions. Therefore, all nervous, endocrine, and psychical impulses are more or less interdependent and interactive.

In the study of the internal secretions considerable progress has been made in those very definite diseases which are due to frank hypofunction, or hyperfunction of the thyroid and pituitary and to deficiency in the secretion of the pancreas. A considerable literature has also grown out of study of the adrenals and gonads. There remains, however, much still to be discovered, which, when in hand, should prove to be of great aid to the clinician. So far the studies of internal secretions have been directed with greatest zeal toward the relationship of these glands to growth, development and metabolism. Some investigators have fixed their attention upon the effect of increased and decreased secretions upon the mental and psychical states of the individual. The very interesting and very important relationships which the endocrine glands bear to the vegetative nervous system, however, have not appealed to endocrinologists as strongly as they should. This relationship is basic and should be most carefully studied.

Both the vegetative nerves and the endocrine glands are vegetative systems and are closely related developmentally, as well as in the functions which they perform for the animal economy. In the skeletal structures we have flexor and extensor muscles innervated by different nerves; but the vegetative structures are provided in a different manner with action and counteraction, or action and inhibition. In some structures the same nervous system produces action and inhibition of action. In those structures which are supplied by both the sympathetic and parasympathetic

systems, one of these activates and the other inhibits action. In the glands of internal secretion, too, we have glands that work in harmony and glands that oppose. The adrenals, thyroid and pituitary act in harmony, at least in the production of certain effects, and in their effect upon sugar metabolism they are opposed by the pancreas.

There can be but two kinds of results of stimulation in the muscles and glands which make up the vegetative structures: one activation, the other inhibition. It matters not whether the action be produced by the neurons of the sympathetic and parasympathetic nervous systems or by the chemical substances produced by the glands of internal secretion; there can be no other action produced. Recognizing this fact, investigators have divided the vegetative nervous system into two distinct components, and have been able in a measure to assign to each of these the sympathetic system and the parasympathetic system the particular function which it mediates. They are also attempting to divide the endocrine glands in the same manner and have made considerable progress, although there are still many gaps to be filled. It is widely accepted that the adrenals, thyroid and pituitary are glands which act with the sympathetic system; and many observers believe that the parathyroids, pancreas, and *secretin*-producing glands of the duodenum act with the parasympathetics.

This study and classification should be furthered by any conception which will add definiteness to the action of the sympathetic and parasympathetic systems.

If we liken the body to a tube we can graphically present the distribution and function of these two divisions of the vegetative system. The outer side of this tube comprises the skin and subdermal musculature and the tissues related to it; the inner side of the tube is the gastro-intestinal canal and the structures embyologically related to it; while the middle portion consists of the tissues which form the bulk of the body through which blood vessels course.

That part of the body which is under the control of the will, the skeletal muscular tissues, has to do with providing food for the organism and protecting it from danger. These structures would be helpless, however, were it not for the vegetative struct-

ures which make the providing of food and escape from danger possible by supplying the energy necessary for the purpose.

Although it may not be at once apparent, the subdermal vegetative structures (pilomotor muscles and sweat glands) belong to the protective mechanism of the body. The pilomotor muscles in some animals, such as the porcupine, have a very important protective function, as may be readily imagined. The sweat glands act along with the vessels of the skin in aiding the mechanism of defense by allowing heat to be given off during physical effort and in the presence of infections. Were it not for their heat-regulating power the organism would often be overcome during struggle.

These subdermal structures, most of the urogenital structures (which Gaskell calls the *urogenitodermal structures*, to show their relationship to the dermal structures proper) and the blood vessels are innervated by the sympathetics alone, action and inhibition of action being produced through the same system. The sphincters of the intestinal tract and bladder and the trigone are activated by the sympathetics and provided with inhibitory fibers by the parasympathetics. The glands and musculature of the enteral system, including the gastro-intestinal canal, except the oesophagus and cardiac end of the stomach, and all structures developed from it (lungs, liver, pancreas and body of the bladder) are given inhibitory fibers from the sympathetics. The parasympathetics activate the entire enteral system, including the respiratory tract, liver, pancreas, and body of the bladder, and send inhibitory fibers to the heart and sphincters. It also sends a few to the genito-urinary system.

By grouping together the structures supplied on one hand by sympathetic nerves and the sympathicotropic glands of internal secretion, and on the other by the parasympathetic nerves and parasympathicotropic glands of internal secretion, and by analyzing the effect upon the organism of their action in these structures, one can bring some order out of what otherwise seems to be chaos.

The sympathetic and parasympathetic systems, when viewed in their broad relationships, have separate and distinct functions to perform for the organism. Cannon, Crile, Brown and others have discussed certain phases of this subject. The sympathetic nervous system, with the glands allied to it—the adre-

nals, thyroid, pituitary, and possibly also the gonads—have to do particularly with growth, metabolism, and defense. This is the protective system which reacts against such conditions as pain, shock, fear, anger, rage, injury, and infections. It protects the individual against outward enemies, prepares him for resistance or flight, and sustains him during the effort. It provides the means for defense against injury, heat and cold, and infections. It is the protective system of the body and, as such, presides over the expenditure of energy.

The parasympathetic system, on the other hand, provides sustenance for the individual. It presides over the appetite and the digestion and absorption of food. It supplies all the necessary juices for digestion—salivary, gastric, intestinal, pancreatic, and biliary—and provides the digestive tube with motor power for bringing the ingested food into intimate contact with the secretions, for propelling them onward, and, finally, for ejecting the refuse from the body. Besides this, the parasympathetics, through their action on respiration, influence the oxygen supply of the body, a fact which indicates the intimate relationship which exists between respiration and digestion. The respiratory system develops as a diverticulum from the gastrointestinal tract and, aside from the latter, is the one system of the body which is activated by the parasympathetics.

There are also certain glands of internal secretion which seem to bear a more or less intimate relationship to the parasympathetic system, among which are mentioned the parathyroids, pancreas, and the duodenal glands, which produce *secretin*.

It can thus be appreciated that the parasympathetics have the activating control of digestion and the production of energy, while the sympathetics preside over the expenditure of energy. The former are largely anabolic, the latter catabolic. The former supply a limited number of tissues while the latter are widely distributed, and through the blood vessels reach every tissue in the body.

It is impossible for us, with our present knowledge, to assert that these functions of the two systems do not dovetail into each other. In fact, we should assume that they do. Both food and oxygen must be carried to the tissues where oxidation takes place, and various waste products resulting from tissue action

must be carried to their respective points of elimination by the blood vessels which are sympathetically innervated.

It might, at first thought, seem strange that a protective mechanism such as the sympathetic system, which provides the individual with the means for escape from or combat with an enemy, resisting an infectious disease or overcoming an injury, should exercise an inhibitory action upon the gastro-intestinal functions which are necessary to provide the nourishment which is the basis of the energy used for protection. This can be understood, however, in its relation to the struggle for survival which has ever gone on in animal life. There have been times when nothing but a supreme struggle was able to save the individual. To make this supreme effort all activity, which for the time being was not essential to defense, was checked that the energy might be utilized to preserve life. While digestion is essential for the maintenance of the organism and to store up energy for future combat, yet it can be stopped during severe struggle without resulting in harm unless the struggle is too long.

In combating infection we see this same inhibitory action on the part of the sympathetics in the gastro-intestinal canal: appetite lags, digestive juices are lessened in amount, and the muscle tonus throughout the stomach and intestines is lowered, with the result that digestion is slow and stagnation of the bowel contents takes place.

Nature has even provided a way for combating this inhibitory action on digestion in some instances, as may be illustrated in pulmonary tuberculosis. This is a chronic infection which, even in the active inflammatory state, often lasts for months. If such a state were accompanied by inhibition of the gastro-intestinal action during all the time that the disease is active, it would be extremely difficult to keep the patient from dying of inanition. But the lung is also supplied by the vagus of the parasympathetic system which affords reflex stimulation to the branches of the vagus supplying the gastro-intestinal tract and the glands belonging to it, such as the liver and pancreas, with the result that the inhibition exerted upon the gastro-intestinal tract is opposed and sometimes overcome to such an extent that during the severe infection with marked toxemia digestion goes on normally or with little embarrassment.

The parasympathetic nerves have little or no power to inhibit the action of the sympathetics in their defense program, but the pancreas, which is a parasympatheticotropic gland, seems to antagonize to a certain extent the adrenals and thyroid in some of their functions. This inability of the parasympathetics to antagonize the sympathetics in the mechanism of defense is evident from the fact that the principal structures of defense are not innervated in any way by the parasympathetics. The latter have no connection with the sweat glands and cutaneous circulation, which governs to so great a degree the dissipation of heat from the body and has to do with maintaining temperature. They have no influence upon the pilomotor muscles and little on the circulatory system, except that exerted upon the heart, salivary glands, tongue and penis. Furthermore, they play no part in the activation or inhibition of the adrenals, pituitary and thyroid; and probably have no control over stored glycogen that has been forced out of the liver by the sympathetics to be utilized by the defensive mechanism in case of struggle. So we may say that, while the parasympathetics provide the organism with food and oxygen, they apparently have no veto upon its use when once converted into potential energy.

While, as previously mentioned, there is a stage in the development of animal life when the organism is provided with energy only by means of internal secretions, and another in which it is supplied by both internal secretions and nerves of simple and comparatively rudimentary action, yet, as the organism becomes more complex, a complicated central nervous system is developed which is presided over by the higher centers, whose particular function it is to correlate and integrate all body activities. When this stage is reached the vegetative control by the vegetative nervous system and endocrine glands is linked with the higher centers in such a way that, while they are able to carry on their activities when wholly separated from the central nervous system, yet as long as they are connected with it they are closely and sensitively influenced by it. They are affected by physical stimuli which are transmitted to them through the somatic sensory nerves and by ideas and emotions which arise from psychical stimulation.

It is a long way, developmentally speaking, from the movements of the amoeba, the opening and closing of the oscula of

the sponge in response to the movements of the sea water, or the response to outward stimuli of the earth worm, with its simple nervous system; to the fine adjustments of man with his highly developed and minutely adjusted central nervous system. Yet, throughout all this wide gap, the same vegetative functions have been cared for in the same general manner, at first by response to chemical products resulting from glands of internal secretion and later by these and the vegetative nerves combined.

We shall now discuss briefly some of the functions which are performed for the organism by the vegetative systems as a whole.

Defense Against an Enemy. It is now evident that stimuli which affect the human body may be either of physical or of psychical origin. In defending the body against danger from without, stimuli of both types come into play, as will be evident in analyzing the process which results when the mechanism of defense is called into action. A man sees a source of danger, he is imbued with fear and decides either to defend himself or make his escape. Whichever course he decides upon he wills to bring the necessary muscles into action. This decision would be entirely useless, however, were it not for the vegetative nerves and endocrine glands. Muscles can not perform work unless they are provided with dextrose and oxygen for its oxidation. Six or eight times as much blood must pass through the muscles when they are in action as when they are at rest, in order to supply the needed energy. A certain amount of glycogen is stored up in the tissues, particularly the muscles and the liver, ready to be used at any time. If struggle be of short duration this stored supply may be sufficient for the purpose; if not, more must be provided by the ingestion and digestion of food or by transforming the body tissues into fuel substances. All of this requires oxygen, and the tissues at a given time have only about enough oxygen for their actual needs; therefore, pulmonary ventilation increases from a normal of 5 to 8 liters per minute to 30 or 50 liters per minute, or, if the struggle be exceedingly severe, to 100 liters or more per minute. This preparation is accomplished by a combination of the spinal and vegetative systems.

It may be necessary that this defense be called into action at once. This is accomplished through the higher centers. The emotion of fear and the desire for self-preservation cause

psychical impulses to be transmitted to the proper centers in the brain and cord, and, even before the individual moves a muscle in the struggle impulses are sent by way of the sympathetic centers in the brain through his sympathetic system (nerves, adrenals and thyroid), as a result of which his heart beats rapidly, carrying more blood to the muscles and brain, the glycogen is forced from the liver so it can be delivered to the muscles, the blood pressure rises to insure a more rapidly flowing stream, the coagulation power of the blood increases, ready to check the flow of blood in case of injury, his pupils dilate, his hair stands on end, and his sweat glands become active in order to eliminate the excess of heat produced in the struggle. At the same time there is an inhibition of action in the gastro-intestinal tract so that all energy may be directed for the time being to the brain, heart and muscles, which require all possible energy for the conflict. When the struggle begins these conditions are maintained as long as is necessary, or until the mechanism of defense is exhausted and the individual is overcome. As energy is used up and acids are formed in the blood, these stimulate the respiratory center and cause pulmonary ventilation to keep pace with the demand for oxygen.

Infections. So is it in infections; the struggle for the destruction of toxins, as it affects vegetative structures, is manifested through the sympathetic system,—a dry skin, lessened elimination with increased production of heat, resulting in a rise of temperature, rapid pulse, increased thyroid and adrenal action, and an inhibitory effect on the gastro-intestinal tract, as shown in a loss of appetite and a decrease in secretory and motor power of the stomach and intestines, producing slow digestion and constipation. The combat of infections is also accompanied by psychical stimuli, but these are of little or no importance in starting action in the defensive mechanism.

It will be appreciated that there is a marked difference between the body's reaction to the severe acute infections and the more chronic and milder ones. In both of these the defense may eventually break down, but we can sometimes study it more readily in the acute cases, in which the patient goes into collapse with rapid, inefficient heart muscle, low blood pressure, sweating and falling temperature. In some severe infections recovery is followed by marked asthenia. This was seen often fol-

lowing influenza during the recent pandemic. In this, as a part of the injury done to the sympathetic system, there is probably a hypoadrenia, the glands failing to recover quickly from the injury. This same condition of exhaustion of the mechanism of defense is a part of the picture in chronic infections such as tuberculosis.

Shock. Shock is another condition in which there is marked disturbance of the sympathetics. This is favored by the fact that the individual receives an injury at a time when his defensive mechanism is already weakened by such conditions as fatigue, excitement, exposure, or infection. The condition of the control of the vessels in shock is such as to stimulate a sympathetic paralysis. Blood pressure falls, fluid transudes into the tissues, and the capillaries are found dilated and filled with corpuscles.

Injury and Asphyxia. In conditions of injury and asphyxia it is the sympathetic system that bears the brunt of the struggle.

High Blood Pressure. Certain high blood pressures met with, particularly in women, may be due to sympathetic stimulation, and it is quite possible that prolonged harmful stimulation of the sympathetics might result in arterial degeneration.

Anaphylaxis. Anaphylaxis affords an example of a general stimulation which predominantly affects the parasympathetics. Mild anaphylaxis shows the following symptoms: Bronchial spasm and increased bronchial secretion, nausea, vomiting, diarrhea, and itching of the skin. Severe anaphylaxis shows increased motility of the intestinal tract with relaxation of the anal sphincter resulting in involuntary discharge of feces; increased activity of the bladder musculature with relaxation of the sphincter, causing incontinence of urine; perspiration; low blood pressure; fall in temperature and collapse. From this we conclude that the symptoms of anaphylaxis, except in severe cases in which the higher centers are predominantly affected, belong to the parasympathetic syndrome.

Local Parasympathetic Syndromes. Local syndromes of parasympathetic stimulation are common: hay fever, due to hyperirritability of the fifth and seventh cranial nerves; asthma, due to hyperirritability of the pulmonary branches of the vagus; hypermotility and hyperchlorhydria which may be due to hyperirritability of the gastric vagus and increased motility and secre-

tion in the intestine; and spastic constipation, due to hyperirritability of the sacral innervation of the colon. It must also be remembered, however, that a simulated hyperchlorhydria may be due to a marked stimulation of the sympathetics controlling the pylorus, which causes a contraction of the sphincter muscles thus interfering with the emptying of the acid contents.

SUMMARY

1. Physiological action in smooth musculature and secreting glands is controlled by the vegetative nerves and the glands of internal secretion, and is influenced by stimuli either of physical or psychical origin.

2. The vegetative nerves are divided into two systems, the sympathetic and parasympathetic. The glands of internal secretion may in a measure likewise be divided into those which act with the sympathetics and those which act with the parasympathetics.

3. The sympathetic nerves and the sympatheticotropic glands of internal secretion aid in the defense of the organism against such conditions as enemies from without, infection, pain, anger, injury, heat, cold, asphyxia, and shock. The parasympathetic nerves and parasympathicotropic glands of internal secretion provide the body with an appetite and the secretions—salivary, gastric, biliary, pancreatic, and intestinal—for the digestion of food, and motor power to the gastro-intestinal tube, for mixing the food with the secretions and propelling it onward, and for expelling the refuse from the body.

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CHANGES IN THE ENDOCRINE GLANDS OF A TUMOR-BEARING FEMALE ALBINO RAT

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A female rat nearly two years old and the mother of nine litters died, apparently from the effects of a large abdominal tumor. External examination showed the growth to be about 9 cm. in diameter and to be situated in the caudal portion of the abdominal cavity. An incision through the abdominal wall pierced the capsule of the tumor from which there escaped a large amount of sanguineous fluid which failed to clot on standing. Most of this fluid was unfortunately lost so that the weight of the tissue and fluid within the capsule cannot be given. The matrix of the growth was loose and spongy and easily friable under manipulation with the forceps. The interstices of the mass were filled with the sanguineous fluid. The tumor was encapsulated by a thick fibrous covering. Portions of the matrix were embedded and sectioned by the courtesy of Doctor Damaso Rivas, who is of the opinion that the growth was a non-malignant hematoma with a rather myxo-cavernous type of hemangioma.

On removal of the tumor the abdominal contents were seen to be greatly displaced cephalad and no point of intraabdominal attachment could be found. The uterine cornua were free and their distal extremities as well as the ovaries were colored a greenish black. The intestines near the liver were stained a greenish yellow, apparently by bile, while in the liver an encysted parasite was found, the nature of which was not determined. The pancreas was not obtainable. The spleen was enormously enlarged and blackened for about one-third of the distance from its superior pole. The adrenals were enlarged, soft and discolored. The kidneys were blackened in spots and friable. The thyroid was absent, though there appeared to be present a small amount of residual edematous thyroid tissue that was too small to be weighed. The femur was much shorter and thicker than the normal. This may have been due to an adaptive change

to the increased burden or to the evident lack of parathyroid tissue. In view of the general findings for the bones, the latter alternative is preferred.

The observed weights of the organs are given in the table, and for purposes of comparison the weights normally found in female rats of the same body length. The percentage difference of the observed values from the normal figures is given.

A comparison of the observed weights of the organs of a female albino rat bearing an abdominal tumor with those obtained from standard female rats of the same body length.

It will be noted that the brain and cord are much heavier than normal. Although King has found that these tissues tend to increase in water content some hours post-mortem, the changes noted here can hardly come under this category, since the animal was dissected shortly after death and the increases are much larger than those obtained by her. The increase in the weights of the lungs and heart might at first be attributed to the toxemia induced by the growth were it not for the fact that the liver and kidneys show no such changes. There was slight evidence of pneumonia. The enormous enlargement of the spleen taken together with the quantities of hemoglobin-containing fluid in the tumor indicate an extra activity of this organ.

The hypophyseal enlargement may be interpreted in part as either due to the lack of thyroid secretion, if we accept such lack as a cause of compensatory hypophyseal hypertrophy, or it may be allied with the findings of Houssay and Sekiguchi that mammary carcinoma is frequently accompanied by disorders of the hypophysis commonly associated with hyperfunction, and with the observation of Inglis of the simultaneous occurrence of acromegaly with a mediastinal tumor. Moreover, since Robertson and Burnett have shown that tethelin, the active substance of the anterior lobe of the hypophysis, tends to accelerate the growth of carcinomata, it is not beyond the range of probability that the tumor here observed was stimulated to increased growth by the possibly increased activity of the hypophysis. The alteration in the thymus can also be correlated with the growth of the tumor through the report

TABLE

Organ	Obsvd. wts. gms.	Stand. wts. gms.	Per cent diff. %
Body L. cm.	204	.....	.....
Tail L. cm.	185	180	2.8
Body Wt.	389.8	224.5	73.6*
Brain	2.080	1.868	10.1
Cord	0.743	0.609	22.1
Kidneys	1.908	1.891	0.8
Spleen	2.044	0.596	243.0
Lungs	2.330	1.298	79.4
Heart	1.508	0.876	72.1
Thymus	0.0887	.....	.....†
Adrenals	0.0718	0.0388	82.1
Pancreas	.....	.....	.....
Thyroid	0.0000	0.0352	100.0
Liver	9.66	10.94	11.7
Submax	0.433	0.424	2.1
Hypophy.	0.0175	0.0155	12.9
Ovaries	0.0248	0.0497	49.2
Humerus	0.2202	0.2645	16.7‡
Femur	0.4927	0.5740	14.2‡
Length—			
Humerus	21.7	26.9	19.3
Femur	24.4	34.6	29.3
Water Content—			
Humerus	35.6%	34.7%	0.9%‡
Femur	45.1%	37.4%	7.7%‡
Water Content—			
Brain	78.51%	78.02%	0.49%§
Cord	72.64%	69.94%	2.68%§

*Tumor included.

†No weight given in standard tables for this body length.

‡All values calculated on standard body weight.

§Corrected.

of Kaminer and Morgenstein, who claim that there is a relation between the condition of the thymus and the destruction of cancer cells by serum.

The peculiar fact that neither thyroid nor parathyroid tissue residues could be found supports the opinion that the former is one of the contributing causes to the marked increase of the epidermal fibrous tissue simulating myxedema in certain of its aspects, and that the latter had something to do with the considerable lack of development of the calcareous portion of the bones as shown by their lesser weight and length and greater water content. The lower weight of the ovaries may possibly be correlated with the hypophyseal changes (See Arai, 1920).

In cases such as this it is difficult to distinguish between cause and effect. Nevertheless the most logical assumption to be made with the data at hand is that the alterations observed are due in major part to the systemic toxemia resulting from the pathological growth; particularly since Farrant has shown that certain symptoms of endocrine disturbance in the insane can be traced to toxemias of one sort or another, and from the clinical observations of Hofbauer and Smith that both pregnancy and the toxemias of pregnancy produce hyperplasia of the thyroid, adrenals and hypophysis. Although neither kidneys nor liver gave by hypertrophy evidence of the existence of such a condition, nevertheless, we cannot deny that a toxemia was present as a product of the tumor and that it had caused the marked alterations in the endocrine glands found at autopsy.

SUMMARY

A case is described of a tumor-bearing albino rat in which marked alterations in weights of all of the endocrine glands were observed at dissection. The hypo—or hyper—function of these several tissues serves to explain some of the abnormalities observed in the other tissues, and can be correlated in part with certain clinical observations reported on man.

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FURTHER OBSERVATIONS ON THE PIGMENT CHANGES FOLLOWING REMOVAL OF THE EPITHELIAL HYPOPHYSIS AND THE PINEAL GLAND IN THE FROG TADPOLE

(With 4 figures in text)

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That the early removal of the epithelial hypophysis in the frog tadpole results in the production of an individual with a greatly disturbed pigmentary system has been shown by P. E. Smith, B. M. Allen and the writer. The operated animal exhibits a much lighter color than its normal mates and has been termed a "silvery" individual or an "albino." Apparently considerable difference of opinion has existed concerning the nature of this pigmentation change and the altered condition of the various types of pigment cells which may be responsible for it. Since the publication of a previous brief contribution bearing on these points additional observations have been made and the total results are now presented in a more comprehensive form, together with photomicrographs from the living animal.

HISTORICAL

Smith ('16) states that the differences in color begin to be noticeable in the operated tadpole before a length of 15 mm. has been reached. In his paper Smith holds that "these pigment differences are referable chiefly, if not solely, to the condition of the epidermis." Counts of the melanophores of corresponding areas in the 'albino' and in the controls showed that in the epidermis the number of these cells was reduced in the former. It was further observed that the melanophores of the albino specimens contain fewer pigment granules than do those of the controls, and thus have a distinctly lighter appearance. Smith states that "the melanophores are equally expanded in the two types, consequently the lighter appearance of the albinos cannot be due to the con-

tracted condition of the chromatophores." The free pigment granules which are so noticeable in the superficial layer of the epidermis in normal animals are much reduced in the operated tadpole. The deeper or subcutaneous pigment is present in as great quantity, if not greater, than in the normal animals.

Allen ('17) noted that the color change occurs when the operated tadpole is about 8 mm. in length. He also records the observation that only a few pigment cells are to be found in the epidermis of the operated animal. It is suggested that the pigment cells have migrated to deeper positions. As regards the deeper chromatophores, he states that "there is a constant difference in that they are expanded in the normal tadpoles and much contracted in the operated ones."

At this stage of an apparent controversy the writer ('19) obtained evidence, of an experimental nature, which strongly supported Allen's contention that the lighter color of the operated tadpole is due largely to an altered state of contraction of the melanophores, rather than to a reduction in the amount of pigment material present. This evidence consisted, briefly, in the ability to darken appreciably the silvery tadpole by subjecting it to extracts or emulsions of pars intermedia, coupled with the direct observation in both living and fixed material that the deeper melanophores, which in the silvery tadpole are contracted, expand under this treatment.[1]

Smith ('19) strongly controverted the statement that the silvery tadpole may be darkened by treatment with appropriate pituitary solutions, stating that "albinous larvae have never in the hands of the writer been appreciably increased in depth of pigmentation." And in regard to the view of Allen and the author that the deeper melanophores are contracted in the silvery animal he stated: "In the experience of the writer no constant deviation exists from the various stages of relaxation or expansion which may occur normally in the subepidermal or deeper melanophores as contrasted

[1] At the time of this former brief article the writer failed to recognize that any controversy existed concerning the role of the light-colored pigment cells, the xantholeucophores. By use of the low powers of the binocular microscope their changed condition in the operated tadpole as compared with the normal is readily apparent, even to the casual observer. All statements in the previous article refer only to the melanin-bearing chromatophores.

with normal larvae." At this time he directed attention to the role of the silvery, or light-colored pigment cells, the xantholeucophores.[2] These cells, which are contracted and inconspicuous in normal tadpoles, are widely expanded in the operated animal. They are responsible for the metallic lustre which the silvery tadpole displays. They are held to mask, to a considerable degree, the deep melanophores and thus to reduce to a minimum any color effect which might be produced by the latter.

In his recent memoir Smith ('20) has considerably modified the views expressed by him in previous writings. In fact, he is able to confirm the writer in both of the points formerly controverted by him, admitting that "the deep melanophores exhibit a contracted condition" at least in the young albino, and further agreeing "as pertains to the darkening of these larvae and the expansion of the corial melanophores when placed in the pars intermedia solution." He states also that in the albino tadpole darkened by immersion in pars intermedia solutions the xantholeucophores suffer a great contraction.

The prolonged feeding of albinos[3] with posterior lobe substance was found by Smith to result in a considerable degree of darkening. So far as analyzed by him, this darkening is to be accredited to the restoration of melanin granules in the epidermal chromatophores and epithelial cells. The xantholeucophores were found to be refractory and were not reduced to their normal state of contraction. The condition of expansion or contraction obtaining in the deep melanophores is not recorded.

McCord and Allen ('17) found that the normal frog tadpole is made very transparent by immersion in solutions or emulsions

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[2]The term 'xantholeucophore' as used by Gaupp ('04) has been objected to recently by Schmidt ('19-'20) who finds that the two pigments (xanthin and guanin) exist separately in two kinds of cells, xanthophores or lipophores, and guanophores or leucophores, respectively. In the present article xantholeucophore is used to designate the pigment cell, or cells, containing light-colored pigments, without attempting to analyze the varieties. The 'interference cell' of Biederman is homologous.

[3]The continued use of the term 'albino' (Smith) seems confusing and undesirable. It is probably to be considered a relic from the time when the light color of the hypophysis-free tadpole was believed to be due principally to a reduction in the amount of pigment material. Such reduction is now known to be confined to the pigment of the epidermis. Hereafter in this article the term 'silvery' will be employed as being more accurately descriptive.

of beef pineal substance in water. A study of the pigment cells showed that the epidermal chromatophores are not perceptibly modified, but the deep melanophores undergo a very striking contraction. The effect is transitory, passing off in a few hours unless pineal material is repeatedly added. Smith ('20) confirms most of the results obtained by these observers. He notes further that the xantholeucophores are not changed from their usual state of strong contraction.

OBSERVATIONS

Pineal Solutions. Treatment of normal frog tadpoles with pineal solutions or emulsions, first done by the author in the spring of 1918, following McCord and Allen, gave results which confirmed those writers. The change by which the normal dark tadpole becomes transparent is accomplished in a short time, usually 15 minutes to one hour. The condition is transitory and disappears within two to four hours, or sooner if the tadpole is removed to fresh water. While the animal is in the transparent state the eyes, which apparently do not suffer reduction in pigmentation, are very distinct, as are also the liver and other large viscera. The animal does not display the silvery metallic lustre so characteristic of the hypophysectomized tadpole. The appearance of the animal is dull and drab and the term *ashen* has been chosen to designate it.

A critical examination of the pigment cells in the ashen tadpole discloses the following points which may be briefly summarized:

(1) The free epidermal melanin is not changed.

(2) The epidermal melanophores apparently are not changed from their normal, expanded, dark condition.

(3) The deep melanophores are reversed from their normal expanded condition to one of very strong contraction.

(4) The xantholeucophores are not modified from their normal state of marked, pin-point contraction.

Pineal Gland and Hypophysis Removal. Removal of the pineal gland alone in the frog tadpole was found to produce no change in the depth of pigmentation. Epiphysectomy under chloretone anesthesia was performed when the larvae were about 8 mm. in length. It was found that previous to this stage the cavity of the pineal is in open communication with

the third ventricle. Consequently earlier removal of the gland results in a temporary cerebral fistula. Shortly before a length of 8 mm. is attained the gland closes off from the brain and, if care is exercised, it may be removed without perforating the brain wall. Such an accident rarely proved fatal, however. Epiphysectomized tadpoles responded to treatment with beef pineal quite as readily as the unoperated.

Having in mind the effect of pineal solutions on the pigmentation of normal larvae, it was assumed, subject to experimental determination, that perhaps the main factor in the production of the silvery tadpole following hypophysectomy was an unrestrained activity of the pineal. It was held that if this be true removal of the pineal, as well as the hypophysis, would prevent the characteristic silvery condition of the hypophysis-free animal. Accordingly the double operation was performed: first the removal of the hypophysis at the stage of 3.5 to 4 mm. and six or seven days later, when the animal was approximately 8 mm. in length, the removal of the pineal. The hypothesis on which the double operation was undertaken was entirely disproved, since these tadpoles turned silvery, as well as those which had undergone hypophysectomy alone.

Condition of the Chromatophores in the Silvery Tadpole. Repeated observations made on both living and fixed material confirm the previous observations of the writer as regards the condition of the melanophores in the silvery or hypophysectomized tadpole. The amount of pigment in the epidermal melanophores is reduced as is apparently also their actual number. Some of them are contracted, or at least the pigment material is concentrated in them. The pigment granules of the epithelial cells are reduced in number, as stated by Smith. The deep melanophores exhibit various stages of contraction. They are not so uniformly or so strongly contracted as in the case of the temporary transparency of the ashen larva (normal tadpole under influence of beef pineal).

In the silvery tadpole the xantholeucophores are readily seen to be so widely expanded that the neighboring cells are almost contiguous; in the normal they are contracted to minute points. That they do not mask entirely the deeper melanophores may be seen by reference to fig. 1, which was photo-

graphed from a living tadpole 15 mm. in length. Many of the melanophores may be seen as rounded black spots. These are particularly noticeable in the vicinity of the eye and at the root of the tail. The xantholeucophores appear in this figure as relatively large irregular white spots. Their arrangement in two layers becomes more distinct when the tadpole has at-

Fig. 1. Living, unanesthetized, silvery tadpole, 15 mm. in length, photographed through one tube of the binocular microscope. The deep melanophores, strongly contracted, may be seen as rounded black spots in the vicinity of the eye and at the root of the tail. The expanded xantholeucophores show as larger, irregular white spots.

tained a length of 25 to 30 mm. It is not so apparent in the younger stages.

Objection has been made to the tail as a site for study of pigment cells, on the ground that this region is atypical. It has been our observation that the midrib (not the fin) of the tail contains the different varieties of chromatophores found in the skin of other regions of the body, that they exist in the

same relative states of contraction or expansion, and respond, to certain stimuli at least, in the same manner as those of other parts of the body. True, they are not nearly so numerous nor so richly branched as on the dorsum of the body, but this is an advantage rather than otherwise, especially in observations with high power objectives. Figure 2 represents a photomicrograph, taken by reflected light, from the midrib of the tail of a living silvery tadpole while held in a Clark chamber and immobilized by a 1:5000 solution of chloretone. Previous observations had shown that chloretone of itself does

Fig. 2. An area from the mid-rib of the tail of a 16 mm. silvery tadpole, held in the Clark chamber under chloretone anesthesia; photographed with 16 mm. objective and reflected light. Deep melanophores, contracted; xantholeucophores, expanded.

not bring about the contraction or the expansion of the chromatophores, nor prevent the reactions ordinarily obtained by the use of other agents. Figure 2 shows the deep melanophores and the xantholeucophores. The former are the more numerous and exist as dense rounded spots, showing marked contraction. The latter are relatively scanty and exhibit great expansion. Their processes are often more delicate than those found in the coresponding cells of the dorsal body region. From these observations, combined with the study of *toto* skin

mounts prepared after careful fixation, the condition of the various types of pigment cells in the silvery tadpole may be summarized as follows:

(1) The free epidermal pigment is reduced in amount.

(2) The epidermal melanophores are reduced in number and apparently in pigment content. Contraction of the cells, or concentration of pigment in them, is often apparent.

(3) The deep melanophores are in various stages of contraction. They are not all in such complete contraction as may be induced by such agents as pineal gland solutions, for example, but they are definitely contracted when compared with the same cells in the normal dark tadpole.

(4) The xantholeucophores are widely expanded.

The Darkening of the Silvery Tadpole by Action of Pituitary Extracts. That the silvery tadpole may be made considerably darker for a short time by treatment with certain pituitary solutions was reported previously by the writer. Although denied by Smith at that time ('19) confirmation has recently been given by that author ('20). Further observations have verified our earlier results. It has been possible to obtain a darkening with pars intermedia substance of the beef hypophysis, with aqueous extracts of the posterior lobe prepared according to a method described elsewhere (Atwell and Marinus), and with 'oral' pituitrin (Parke, Davis and Co., serial number 2413685). Darkening did not result from dilute extracts of the anterior lobe of the beef hypophysis. It was sometimes obtained by the use of very strong anterior lobe extracts, but these proved rapidly fatal. It is possible that when the stronger extract was employed there was sufficient contamination from the posterior lobe to cause the effects seen. It was ascertained that when an appropriate strength of anterior lobe extract failed to produce darkening, the effect could always be produced by use of posterior lobe extract of the same strength. This seems to give support to the assumption that the posterior lobe is the part responsible for color changes in the silvery tadpole.

Critical observation of the living animal, unanesthetized, under the binocular miscroscope, shows that in the darkened tad-

pole the deeper melanophores are expanded. A limited, partial contraction of the widely expanded xantholeucophores has been observed in some cases. This has not in any case been great enough to be considered reciprocal to the expansion of the deep melanophores. In these temporary periods of darkening the epidermal pigment, both that found free in the epithelial cells and that contained in the epidermal melanophores, is not restored. Confirmatory results were obtained by examination of the living tadpole in the Clark chamber. It was possible to select a certain field and to study it while the animal was in the

Fig. 3. From the mid-rib of tail of a silvery tadpole; same as figure 2.

silvery state and later when darkened by a 1:100 solution of 'oral' pituitrin. Photographs by both transmitted and reflected light were obtained. Transmitted light does not differentiate well the xantholeucophores from the melanophores, but reflected light brings out the two types of chromatophores in a beautiful manner. Photographs obtained with a 16 mm. objective, showing the same field before and after darkening, are presented in figures 3 and 4. The field chosen was from the midrib of the tail. Epidermal melanophores are not shown, being for the most part out of focus. In figure 3 the deep melano-

phores may be seen as numerous dense, rounded spots. The xantholeucophores are less numerous and are seen in the figure as widely expanded white cells. In figure 4, taken after the silvery tadpole had been darkened by 'oral' pituitrin, the same deep melanophores and xantholeucophores shown in figure 3 may be identified. The melanophores are seen to have expanded by sending out numerous processes. The xantholeucophores have changed but very little, although perhaps a slight degree of contraction may be noted. This is not marked enough to be considered reciprocal to the expansion of the melanophores. The condition of the several kinds of pigment cells in the silvery

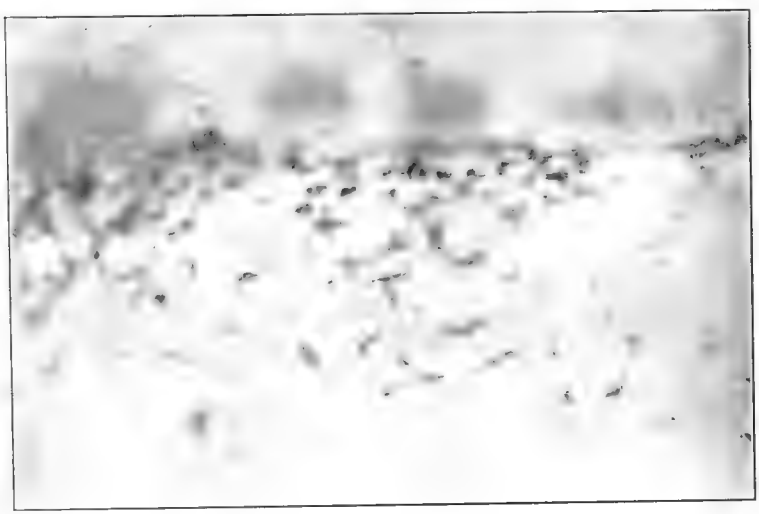

Fig. 4. Same field as in figure 3, showing change in pigment cells when animal is darkened by action of 'oral' pituitrin. Same cells shown in figure 3 may be identified. Deep melanophores are expanded; xantholeucophores not greatly changed.

larva which has been darkened by the action of pituitary extracts may be summarized briefly as follows:

(1) The free epidermal pigment is not restored.

(2) The epidermal melanophores are not restored.

(3) The deep melanophores are expanded, but ordinarily not so completely as in the normal untreated control.

(4) The xantholeucophores are perhaps somewhat contracted. This reaction is not so marked as the expansion of the melanophores.

DISCUSSION AND SUMMARY

It is evident that the appearance of a lighter color in the frog tadpole following removal of the epithelial hypophysis, is not a simple phenomenon. It is not due to the reaction of any one type of chromatophore alone. As concerns the melanin-bearing type of cell, of which there are two varieties, epidermal and deep, reduction and contraction (or concentration) occurs in the former and contraction in the latter. It is also to be noted that reduction of the amount of 'free' melanin in the epithelial cells takes place. The light-colored pigment cells or xantholeucophores become widely expanded.

In attempting to evaluate the roles of the different chromatophores in the causation of the characteristic appearance of the hypophysis-free tadpole, experimental methods have been of much value. It has been shown that when the normal dark tadpole is treated with a pineal solution the principal reaction is a contraction of the deep melanophores. The animal in this condition presents a light colored, semitransparent appearance which has been described as *ashen*. The silvery tadpole, in addition to being light colored, possesses a characteristic metallic lustre. This latter feature is due, without doubt, to the expansion of the xantholeucophores which may be observed in the silvery but not in the ashen tadpole. That the condition of the deep melanophores is of importance is amply shown by the fact that these cells are not by any means completely obscured by the expanded xantholeucophores. If the deep melanophores were not contracted the silvery tadpole would be considerably darker. In fact just such a darkening takes place when posterior pituitary extract is used. The principal reaction is found to be an expansion of the deep melanophores. The writer cannot agree with Smith that the xantholeucophores contract sufficiently to be largely responsible for the darkened appearance.

The reason why the darkened silvery tadpole is not so dark as the unoperated control is the fact that the xantholeucophores do not markedly contract, as well as the fact that the epidermal melanin is not restored in so short a time. Authors are pretty well agreed that the xantholeucophores are more refractory to the action of agents than are the melanophores. This is clearly shown by the use of pineal substance. Furthermore, the long-

continued feeding of silvery tadpoles with posterior lobe substance results in the restoration of the epidermal melanin but does not produce contraction of the xantholeucophores (Smith .

CONCLUSIONS

1. The silvery tadpole is light-colored because of the condition of its melanophores, and lustrous because of the condition of its xantholeucophores. The light color is due to the fact that the deep melanophores are contracted and the epidermal melanophores and free melanin are reduced in amount. The metallic silvery appearance is due to a wide expansion of the xantholeucophores.

2. When the silvery tadpole is temporarily darkened by the action of posterior lobe extracts the deep melanophores expand. There is in some cases a slight contraction of the xantholeucophores, but this is never complete. The epidermal melanin is not restored.

3. Removal of the pineal gland alone does not produce a pigmentary disturbance in the frog tadpole.

4. Removal of the pineal gland soon after the removal of the epithelial hypophysis in the frog tadpole does not prevent the silvery reaction characteristic for the removal of the hypophysis alone.

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Book Reviews

INNERE SEKRETION UND DEMENTIA PRAECOX. By Oscar Lessing, Berlin, 1920. S. Karger, 63 p.

The first 35 pages of this little book are devoted to the symptomatology of dementia precox. In the last 28 pages the author tries to prove the polyglandular origin of the disease. It is a well known fact that schizophrenics may lose weight more rapidly than other patients. Even in patients who eat normally, the loss of weight may be enormous. The involuntary nervous system is often disturbed. The reaction after injection of atropin or pilocarpin is not the same as in normal subjects. The pupils are often larger than normal. Many of these patients acquire tuberculosis; this disposition is, according to Lessing, also due to endocrine disturbances. The injection of adrenalin does not cause an increased blood pressure; in 50 per cent of the cases no effect is seen when 1 cm. of a solution of 1:1000 is injected; in the other 50 per cent the blood pressure is lowered. When the serum is subjected to Abderhalden's test the reaction is positive with brain, with **testicle** in men, and with **ovary** in women. The test is often positive with **thyroid**. The coagulation of the blood is retarded; this is a symptom of hypothyroidism. Many authors state that thyroid treatment gives good results in this disease. The book is very readable but the author postulates as absolute facts various statements that have been denied by other investigators. For example, most medical men have never seen any significant effect from organotherapy in dementia precox.—J. K.

DIE MEHLFRÜCHTEKUR BEI DIABETES MELLITUS. By Prof. Dr. W. Falta, 1920, Berlin and Vienna. Urban & Schwarzenberg, 388 p.

The title of the book is not very well chosen, since many other subjects besides that indicated in the caption are treated. The term "Mehlfrüchte" is given by the author to the treatmen of diabetes by a diet rich in farinaceous elements but poor in protein. It is not essential what kind of flour is given —in fact, many different kinds can be given together. In this respect the treatment differs from the oats diet and the

diet of rice, potatoes, etc., in which only one kind of carbohydrate is given. It also differs in the fact that Falta gives his carbohydrate treatment for a long time, with an occasional fasting day or vegetable day. This treatment has been found to be suitable, not only for serious, but also for light cases. In the latter, however, more proteins may be given. The results of the treatment appear to have been very good. One case in particular is worthy of mention. A woman was brought to the hospital in coma. She rallied from this and was given Falta's treatment. Some time later she became pregnant and during pregnancy fell into coma and again recovered under the same treatment. At term she was delivered of a normal child.

The book is well written and readable, and will be found of interest to any one devoting himself to the treatment of diabetes.—J. K.

THE PIGMENTARY, GROWTH AND ENDOCRINE DISTURBANCES INDUCED IN THE ANURAN TADPOLE BY THE EARLY ABLATION OF THE PARS BUCCALIS OF THE HYPOPHYSIS. By P. E. Smith, University of California. American Anatomical Memoirs, No. 11, 1920, 112 p. and 19 plates, one in color.

The operation for the early and complete removal of the epithelial hypophysis from the amphibian tadpole as perfected independently by Smith and Allen in 1916 has provided an excellent material for the study of a vertebrate which presumably has never possessed a functioning pituitary gland. Evidence of an altered metabolism in the operated animal is the development of a characteristic silvery or "albinous" appearance. The present monograph has afforded the author opportunity not only for presenting the results of his own extensive studies on the altered anatomy and physiology of these pituitary-free "albinos," but also for a consideration of the related researches of Allen, E. R. and M. M. Hoskins and Atwell. Changes in the pigmentary system, growth disturbances and modifications in the size and structure of the other endocrine organs resulting from the operation receive thorough consideration in this comprehensive and well-illustrated memoir.

As now stated, Smith's views as to the altered condition of the pigment responsible for the "albinous" appearance of the operated tadpole are considerably modified from those set forth in his earlier articles. He finds that an actual reduction of pigment material in the "albino" as compared with the normal tadpole occurs only in the "free" epidermal pigment

and the epidermal melanophores. He also finds that the deep melanophores are contracted, at least in the younger animals, which he had apparently previously denied. The silvery pigment cells, or xantholeucophores, are widely expanded and are held to be largely responsible for the characteristic "albinous" condition.

Striking evidence that the color change is due to hormone action and not to nervous influences was obtained by effecting reciprocal epidermal transplants between "albinous" and normal tadpoles. The chromatophores of the skin area thus transplanted quickly assume the state of contraction or expansion characteristic of the corresponding cells of the host.

Of a variety of diets tried only one—posterior pituitary substance—accomplished a permanent darkening of the "albino." Confirming a previous observer Smith finds that a temporary darkening is obtained by immersion of the silvery tadpole in a pars intermedia solution. This proved to be the only physiological or pharmacological agent which would cause the return of the pigment cells to a condition approximating the normal. The evidence thus acquired indicates that the pigmentary disturbances are due to the absence of a functional posterior lobe (neural lobe plus pars intermedia).

The "albino," when maintained on a "standard" diet consisting of liver and boiled lettuce, exhibits a retarded growth curve when compared with his normal mate on a similar diet. A continuous diet of fresh anterior lobe of the beef pituitary was found to replace the growth-"maintaining" substance lost by buccal hypophysectomy and so to effect a nearly normal rate of growth in the "albino." As the author points out, the readiness with which the operated tadpole responds to the growth-"maintaining" substance of the anterior lobe makes it possible to test in a particularly efficacious manner any hypophyseal fraction for the presence or absence of this principle. Applying this test it was found that the growth-"maintaining" substance is absent from aqueous and alcoholic extracts of the anterior lobe and from the intra-glandular colloid, but that it is present in the residue remaining after ether method of extraction.

With the absence of one member of a group of organs so closely inter-dependent as the endocrine system, it is necessary to conceive that a new relationship must arise among the remaining organs of the group if the animal is to survive for any considerable period. That such a readjusted endocrine balance exists in the typical albino is suggested by the definite modification in size and structure of the thyroid, the neural portion of the hypophysis and the interrenal and

chromaphil components of the adrenal. Changes of a lesser degree are exhibited by the epithelial bodies and the fat organ.

The thyroid is greatly reduced in bulk, due to a reduction in the size of the follicles and in their colloid content. The evidence for believing that this reduction of the thyroid is responsible for the failure of the "albino" to undergo metamorphosis is summarized.

The neural lobe of the hypophysis makes its appearance but exhibits a profound reduction in size, an atypical shape and an abnormal position in the operated tadpole. It would seem, then, that while the presence of the epithelial lobe is not necessary for the early formation of the neural portion, its absence is responsible for the failure of this lobe to attain its normal size, shape or position.

The cortical material of the adrenal gland is diminished in amount in the "albino" while the medulla appears to be increased and its individual cells enlarged. The epithelial bodies (of Maurer) seem to be diminished in size, while the fat organ, a structure which normally is largely exhausted at metamorphosis, persists in the "albino" even in conditions of extreme inanition. This latter is suggestive of the adiposity which follows hypophyseal insufficiency in mammals.—W. J. A.

BEZIEHUNGEN ZWISCHEN NEBENNIEREN UND MÄNNLICHEN KEIMDRÜSEN. By E. Leupold, Jena, 1920. Gustav Fischer, 62 p.

In this instructive little book the author discusses the relations between the adrenals and the testicles. First he weighed the adrenals and the testicles obtained at autopsies and found a constant relation between the two values. When the weights did not correspond there probably was atrophy of the testicle or hyperplasia of this organ. This hyperplasia combined with hypoplasia of the adrenals is observed when a persistent thymus is present. When the adrenals contain much fat the quantity of fat in the testicles also is generally high. All causes giving rise to a decrease of fat in the adrenals tend to diminish also the quantity of fat in the testicles. The testicle, however, generally contains less cholesterol than do the adrenals, and when cholesterol diminishes in the testicle and in the adrenals it generally is first decreased in the testicle; this proves that the adrenals have a higher function than the testicle. When saponine is injected subcutaneously into cats the cholesterin is partly removed from the cortex of the adrenals and from the interstitial cells of the testicles. In animals, extirpation of both adrenals produces, if the animal survives for some days, degeneration of

the secretory cells of the testicle. All the above mentioned facts are found in adults. In young children the relation between the gonads and the adrenals seems to be less intimate.

—J. K.

LAS GLANDULAS DE SECRETIÓN INTERNA Y LAS ENFERMEDADES DE LA NUTRICIÓN. Teoria y Practisca del Tratamiento Oporterapico de las Enfermedades del Metabolismo. By. G. Marañón, Madrid, 1920. Librería Gutenberg de José Ruiz. 3 ed., 437 p. 8°.

To those who are able to read the Spanish literature, this book of Marañón's is well known and hence calls for no extended review. The fact that it has reached a third edition in six years speaks for itself. Its contents are accurately indicated by the title. It contains a great mass of data presented in an entertaining and readable fashion. The monograph is written from a physiological point of view and is to be accordingly commended.

The question may be raised, however, whether the author is not over hospitable toward the claims of various investigators whose work has been quoted, and accordingly over optimistic as regards present-day endocrine therapy. The ultimate standing of hormone therapeusis will undoubtedly be enhanced by a rigidly critical attitude upon the part of writers in this field. That brilliant successes are often achieved cannot be doubted, but the fact should be equally emphasized that flat failures are also unfortunately common. The outstanding need in the field of clinical endocrinology is the development of clean-cut diagnostic criteria and much greater precision in therapeusis. Until these are achieved many conservative clinicians—men who are temperamentally averse to skating on thin ice—are likely to hold the entire field as unworthy of their much needed attention.

But in stressing the deficiencies of endocrinology as a branch of scientific medicine one must recognize that there is no lack of sheer ignorance of the solid data already accumulated. Illuminating is a recent article by Anders* in which the fact is pointed out that even so well marked an endocrinopathy as that of myxedema had passed unrecognized by one or more clinicians in 74 per cent of 55 cases studied.

R. G. H.

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*Diagnosis of myxedema. Anders (J. M.), Am. J. M. Sc. (Phila), 1920, **160**, 801-808.

VERJÜNGUNG DURCH EXPERIMENTELLE NEUBELEBUNG DER ALTERNDEN PUBERTÄTSDRÜSE. By E. Steinach. Berlin, 1920. J. Springer, 68 p.

Rarely has a book on a scientific subject become as popular as this. Steinach's theory is that the sex gland increases in activity when the vas deferens is ligated. As an individual advances in age the sex gland gradually loses its internal secretion, and in order to increase the diminished function ligation of the vas deferens is necessary. There are other possible methods of stimulating function in the senile sex gland (chemical stimulation or x-ray treatment), but the surgical method is considered the easiest and most reliable. The author experimented upon rats. In ligating the vas deferens it is of great importance not to include the blood vessels of the testicle. It is therefore better (in rats) to ligate between the testicle and the epididymis. When the operation is performed in this way the effect can be observed more quickly than when the vas deferens is ligated. It may be recommended that the operation be performed by laparotomy, since only in this way can the vesiculae seminalis and the prostate before and after operation be compared. After the operation the cellulae seminalis atrophy and the organ shows the same histologic picture as a transplanted testicle. The effect of the operation is that the symptoms of senility disappear, the penis, vesiculae seminalis, and the prostate increase in size, the metabolism becomes more intense, the animals eat more, their sexual desires reappear, the potentia coeundi and generandi (sic!) is as in young animals. The thyroid and the hypophysis show a picture as seen in young animals. Unilateral ligation is sufficient to produce this effect. The same technic was employed in three old human patients who did not know the purpose of the procedure, which was performed in combination with another operation. In all three cases the effect was very good. Whether it is possible to obtain the same results in women is not yet known. Perhaps x-ray treatment in case of the latter may be useful.—J. K.

Abstract Department

Hereditary endogenous ADIPOSITY (Hereditäre endogene Fettsucht). Arnoldi (W.), Deutsche med. Wchnschr. (Berlin), 1920, 46, 1154.

Published elsewhere and abstracted Endocrinol. 5, 132.—J. K.

ADRENAL tumor (Tumor der Nebenniere). Ambrozic (M.), Deutsche med. Wchnschr. (Berlin), 1920, 46, 1324.

Demonstration of the left adrenal of a girl of 3, with a tumor consisting of epithelium. The child had shown all the symptoms of macrogenitosomia praecox.—J. K.

Case of phäochromocytoma of the ADRENAL gland with hypertrophy of the left myocardium (Ein Fall von Phäochromocytoma Glandulae suprarenalis mit Hypertrophie des Myocards des linken Herzens). Bergstrand (Hilding), Hygiea (Stockholm), 1920, 82, 321-335.

The tumor was an accidental finding at autopsy of a fifty-year-old woman who had died of influenza; it was two hundred grams in weight and lay in the upper part of the right adrenal. It was encapsulated by tissue enclosing the rest of the adrenal cortex. The tumor cells were, in spite of their variability, all of the same fundamental type, like epithelia (polygonal). They contained chromaphil and colloid-like globules. It is of especial interest that the heart showed a highly significant myocardial hypertrophy of the left side which weighed five hundred grams. All other organic alterations which such an enlargement of the heart might account for were lacking, from which it is conceivable that this condition was caused by a chronic hyperadreninemia as a consequence of the secretion from the tumor.
—J. A. H.

Treatment of spasms by removal of the ADRENALS (Die Extirpation der Nebenniere zur Behandlung von Krämpfen). Bruning (A.), Zentralbl. f. Chir. (Leipzig), 1920, 47, 1314-1317.

Fischer has discovered that when both adrenals are removed from an animal no spasms occur when the animal is poisoned with amylnitrite. There is a close relation between the adrenal system and muscle tonus. He, therefore, advises the removal of one of the adrenals in spasms. Bruning has tried this treatment, removing the left adrenal from nine patients. He preferred the left since in operating on the right side one may meet with adhesions of the gall-bladder.

He noted a marked improvement in all cases, but no cures. The time between operation and publication is not yet three months. It is doubtful whether in this short time it is possible to speak of a result. It would not be the first disillusionment in the treatment of epilepsy.—J. K.

Hydrocephalus and atrophy of the ADRENALS (Hydrocéphalie et atrophy des glandes surrénales). Cosmettatos (G. F.), Grèce méd. (Athens), 1920, **22**, 17-19.

According to Cosmettatos, who records a case of hydrocephalus and atrophy of the adrenals in a child who died twenty-four hours after birth, cases of co-existence of malformation of the brain and suprarenals may be divided into two groups, namely, those in which the congenital anomalies occur at the commencement of development of the nervous system and congenital anomalies which occur later, that is, after the appearance of the sympathetic ganglia and the chromaphile substance. In the first group the arrest of development of the nervous system entails an arrest of development of the sympathetic ganglia and consequently of the chromaphile substance also. In the second group, some morbid condition in the parents, such as syphilis, tuberculosis, or alcoholism, is responsible for the congenital anomalies in organs embryologically allied, namely, the brain and the suprarenal medulla.—Med. Sc. Abst. & Rev., **3**, 218.

(ADRENAL) Addison's disease following renal tuberculosis (Syndrome d'Addison fruste consécutif a une tuberculose rénale). Damade (R.), J. de méd. de Bordeaux, 1920, **91**, 303.

Damade records the case of a man, aged 58, who presented intense asthenia, low blood pressure, the phenomenon of the white line, digestive disturbances, and lumbo-abdominal pain accompanied by very slight pigmentation of the skin and mucous membrane. Treatment consisted in two subcutaneous injections of ½ mg. of adrenalin and 10 c.c. of glycerinated suprarenal juice by mouth. Immediate improvement resulted and the adrenalin was stopped in two days' time, but a relapse occurred a few days later and death took place after a comatose period of five to six hours. Although the kidneys were studded with gross tuberculous lesions, it was only by microscopical examination that slight inflammatory lesions were found in the medulla of the suprarenals.—Med. Sc. Abst. & Rev., **3**, 218.

ADRENAL infarction (Ueber Apoplexie der Nebennieren). Freudemann. Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1275-1276.

Report of a soldier of 20 who had been gassed. He complained of headache and giddiness. As he did not improve much he was sent back to Germany after three weeks. Then he did light military service during seven weeks, complaining now and then of abdominal pains. He became suddenly ill with severe abdominal pain, abdominal spasms,

but no "defense musculaire." On the fourth day after this fever he developed herpes labialis, albuminuria, spasms in the region of the kidneys, rapid and feeble pulse, and constipation, but no vomiting. On the eighth day he lost consciousness and showed rigidity of the muscles of the neck. A diagnosis of meningitis was made. Death followed on the tenth day. The autopsy showed: endocarditis, embolism in the left hemisphere of the brain, embolism in the left branch of the pulmonary artery, and infarction of both adrenals with thrombosis of both adrenal veins.—J. K.

(ADRENAL) A case of cure of Addison's disease (Un cas de guérison de maladie bronzée d'Addison). Giraudeau (R.), Thèses de Paris, 1919-20, 31.

A case of recovery from Addison's disease is reported by Giraudeau. The patient, a man aged 39, the subject of chronic alcoholism, was admitted to hospital in November, 1901, with pronounced asthenia, pigmentation of the skin and buccal mucous membrane, diarrhoea, abdominal pains, and a feeble pulse. On January 4, 1902, he was given his first injection of suprarenal extracts, and the injections were continued for twelve days. Improvement took place in the general condition and there was a rapid increase in weight. The injections were resumed on January 27, when the abdominal pain and diarrhoea were very violent. On February 1, the pigmentation in the face had considerably diminished, and in the next two months it had disappeared from the rest of the face and from the buccal mucous membrane. In the summer of 1902 the general condition had so much improved that the patient was discharged. Apart from an attack of alcoholism, for which he was interned in an asylum in June, 1904, he was lost sight of until February, 1913, when he was admitted to the asylum again with another attack. Death took place on March 13, 1913. Apart from carcinoma of the pylorus with metastases in the liver, the only lesion found at autopsy was some scar tissue in the right adrenal, indicating the occurrence many years previously of some inflammatory condition the nature of which could not be determined. There were no signs of tuberculosis or syphilis. The case thus illustrates how a small suprarenal lesion is sufficient to give rise to the melanodermic syndrome. Giraudeau concludes that in cases in which transient suprarenal incompetence is the result of a localized inflammatory lesion, treatment may be effective, whereas it is of no avail in ceaseous tuberculosis of the suprarenals.—Med. Sc. Abst. & Rev., 3, 217.

(ADRENALS) Bilateral paralysis of the plexus femoralis with changes of the skin, as in Addison's disease, caused by an abdominal tumor (Dubbelzijdige verlamming van den plexus femoralis met huidveranderingen als bij zeikte van Addison ten gevolge van eengezwel in de buikholte). Klessens (J. J. H. M.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1920, 64 (II), 787-796.

A woman of 50 years complained of fatigue and pain in the right leg. Some months later all the symptoms of a thrombosis of the vessels developed; the leg became paralyzed. At the same time the other leg became affected in like manner. The whole body showed brown pigmentation, and in a few months the patient's hair had turned absolutely white. There were no symptoms of Addison's disease. There was a large tumor in the abdomen, perhaps a hypernephroma. Opportunity to determine this at autopsy was not obtained.—J. K.

The interrenal and ADRENAL system as one organ. The adrenal as a homogeneously functioning organ (Die Vereinigung von Interrenal und Adrenalsystem zur Gesamtnebenniere. Die Nebenniere als einheitlich funktionerendes Organ). Löwenthal (K.), Berl. klin. Wchnschr., 1920, 57, 807-811.

It has been the custom of many authors to consider the medulla of the adrenal as the only part of physiological importance and to neglect the cortex. Embryology makes it highly probable that cortex and medulla belong together. In general infectious and other diseases medulla and cortex are generally affected together (the lipoids in the cortex decrease, the medulla fails to give the characteristic color reaction). After stimulating the splanchnics by "piqure" of the fourth ventricle glycosuria occurs, adrenin disappears nearly completely from the medulla and the quantity of lipoids (when examined immediately after operation) is diminished. It seems possible that a "pre-adrenin" is formed in the cortex, that it passes by the capillaries into the medulla and is transformed there into adrenin. It is said that the cortex produces the lipoid for the body, but this has not been confirmed. On the contrary, the quantity and distribution of the lipoids in the cortex depend on the quantity of lipoids in the blood. After removal of one adrenal the other shows hypertrophy, but though the blood at once contains more cholesterin after the operation, the adrenal at first contains less than before the operation, and it takes some time before the quantity of adrenin becomes normal again. The function of the cortex is to form a depot of cholesterol. Cholesterol is one of the most important substances in the defense of the body against infections. Perhaps the cortex has thus an anti-toxic function. However, this substance is not excreted. So the function of the cortex is to produce a local immunity and to protect in this way the medulla against infections. Löwenthal observed at autopsy that only in those cases in which the cortex contained lipoids did the medulla contain adrenin, though he states that not all investigators agree upon this. If, however, this is true it will be important to prescribe in serious infections cholesterol, as has formerly been done, particularly in France.—J. K.

(ADRENAL) Results of the operative treatment of hypernephromas. Michaelsson (Eric), Hygiea (Stockholm), 1920, 82, 220-232.

The author discusses thirty cases which have been observed on the average for at least four years since operation. Seven were living from four to fifteen years after operation, four died as the result of the operation. There died from recurrences and metasteses: six within and three more than three years after the operation; ten died of other diseases, etc., five within the first year and a half. The histological picture afforded no valid indication of the biological value of the growth in question.—J. A. H.

(ADRENALS) The origin of hemangiectases. Moise (T. S.), Johns Hopkins Hosp. Bull. (Balt.), 1920, **31**, 369-373.

This paper presents the first description of diffuse hemangiectases of the liver in association with a similar process in the kidney and adrenals. The adrenals in the case reported here showed a diffuse telangiectasis. The process involved the cortex extensively and the medulla to a lesser degree. There was definite evidence of blood formation as shown by the presence of nucleated red blood cells and young cells of the myeloid series. The specimens were recovered at the autopsy of a case of general carcinomatosis from a primary tumor of Bartholin's gland.—J. F.

Histochemical researches on the ADRENAL cortex in cases of death by scalding (Ricerche istochimiche sulla corticale delle surrenali nella morte da scottatura). Righi (U.), Pathologica (Geneva), 1920, **12**, 331-332.

Death from scalding follows the loss of a certain amount of the skin—one-fourth of the surface for the rabbit, one-third for man—yet besides the lack of function and protection caused by the partial destruction of the skin, a severe strain on the organism is brought about by the absorption of the products of cellular destruction (from skin, aponeuroses, muscles and blood). Such a deep change must perforce act on the adrenal cortex, as its function is not only connected with the nutrition and development of the nervous system, but with the general metabolism. The author is not aware of any post-mortem examination of human adrenals in such caes; but some of Moschino's experimental researches have shown regressive alterations of the cortex in death after 24 hours; these are more marked in cases dying 48 hours after the burn. His technique (staining by hematoxylin-eosin) would not tend to give satisfactory results, however, with respect to the nuclei. No conclusion has been drawn by Moschino concerning the medullary substance. Righi repeated Moschino's experiments, using Nile Blue, Sudan III and other stains, and studied the results of death of rabbits 24 to 36 hours after scalding. Using control animals he came to the conclusion that scalding produces a marked swelling of the spongiocytes and increase of cholesterin and cholesterin esters. He did not study the medullary substance. The article ends by a citation from Landau's researches,

who, while agreeing with Righi as regards the final findings, states that the cortex, instead of undergoing an increase of function, is only the recipient of the increased amount of lipoids, which can no longer be normally eliminated.—G. V.

The differential white-cell count of the blood before and after surgical reduction of the ADRENALS (Ueber das Verhalten des relativen morphologischen weiszen Blutbildes vor und nach der operative Nebennierenreduktion bei Krampfkrankheiten nach H. Fischer). Schlund (F.), Deutche med. Wchnschr. (Berlin), 1920, **46**, 1273-1274.

The influence of adrenin on the blood picture has been repeatedly discussed. The contrary condition, however, the influence of subadrenalism, has not been studied. Fischer has described a new operation for the treatment of spasms. He removed one of the adrenals. Schlund examined the blood picture after this operation. He observed that the number of neutrophil leucocytes is increased and the number of lymphocytes diminished. There are fewer eosinophil cells after the operation than before. In one case the eosinophil cells disappeared temporarily.—J. K.

Hypernephroma of right ADRENAL (Hypernephrom der rechten Nebenniere). Schopper, Wien, klin. Wchnschr., 1920, **33**, 718.

A woman of 23 died suddenly without having shown any pathological symptoms. At autopsy a hypernephroma of the right adrenal was found. The tumor had grown through the vena suprarenalis into the inferior vena cava. During defecation a part of the tumor had been torn off, producing a fatal embolism of the pulmonary artery. —J. K.

Hypo- or dys-function of ADRENALS (Hypo- oder Dysfunktion der Nebennieren). Steinert, Wien. klin. Wchnschr., 1920, **33**, 765.

Demonstration of a case of retarded development in a girl of 5 years. There was hyperkeratosis of the nose with dark pigmentation. Whenever the patient was wounded the scars showed pigmentation. The skin was of a brownish color. The Pirquet reaction was negative. The mucous membranes were not pigmented. The author believes that during birth there occurred a hemorrhage into the adrenals. There are two types of cachectic children, a white and a dark type. The last-named type may be due to a hypofunction or dysfunction of the adrenals.—J. K.

Tumor of the ADRENALS in a congenital dystopic kidney (Nebennieren-tumor in einer kongenital dystopen Niere). Stephan. Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1233.

Not of immediate endocrine interest.—J. K.

Some observations on ADRENIN apnoea (Algunas obervaçoes sobre a apnea adrenalinica). de Almeida (M. Osorio), Arch. de esc. sup. de agric. e med. Veter. (Nichteeroy), 1919, **3**, 65.

The intravenous injection of adrenin produces almost fatal apnoea when the dose is large. Preliminary ligation of the carotid and vertebral arteries does not prevent the appearance of apnoea.—B. A. H.

Action of iodine and ADRENIN on living surviving cells. Cervello (V.) & Levi (G.), Arch. di fisiol. (Firenze), 1917, **20**, 219-228; Arch. ital. de biol., 1919, **69**, 70-71.

Tissue cultivated in fowl plasma grows as readily in this plasma after it has been treated with iodine. In plasma treated with adrenin growth ceases sharply at the end of the second day. If the cultures are then removed to plasma containing no adrenin, activity revives in 24 hours and cell division in 48 hours.—Chem. Abst., **14**, 762.

The antagonism of ADRENIN and quinine (Adrénaline et quinine, leur antagonisme). Clerc (A.) & Pezzi (C.), Compt. rend. Soc. de biol. (Paris), 1919, **169**, 1117-1118.

From experiments on a dog the following conclusions are stated: There is complete antagonism in the cells of the bulbar vagus center between adrenin which excites and quinine which paralyzes. The drugs act in a similar way upon the heart. Upon arterial pressure adrenin is hypertensive, quinine hypotensive, but adrenin determines the hypertension by a combined cardiac and vascular action; whereas quinine causes hypotension by its cardiac depressive action which overcomes the vaso-constrictor influence characteristic of the two substances.—Chem. Abst., **14**, 3725.

(ADRENIN) A study of the cardiovascular reaction to epinephrin. Clough (Paul W.), Johns Hopkins Hosp. Bull. (Balt.), 1920, **31**, 266-273.

Clough finds that there is a marked difference in the cardiovascular reaction of different individuals to a subcutaneous injection of 1 mg. of epinephrin. The reactions observed have been classified arbitrarily, according to their intensity as, negative, moderate, marked and very marked. In a moderate reaction there was: (1) a rise of from 15 to 30 mm. in systolic blood pressure, associated usually with, (2) a fall of from 10 to 20 mm. in diastolic pressure. The striking feature of the reaction was (3) the increase in pulse pressure, which was often doubled. There was usually (4) a slight tachycardia. Other symptoms were usually mild. In marked reactions the systolic pressure rose from 30 to 100 mm. There was usually a slight rise in diastolic pressure also, and a marked rise in pulse pressure. There was sometimes glycosuria, and very often tachycardia, palpitation, pallor, mydriasis, tremor, nervousness, and anxiety. Atrophin fre-

quently exaggerated the response to a subsequent injection of epinephrin. Of 32 normal individuals, 82 per cent gave a slight or moderate response. Patients with hypertension often showed severe reactions to 1 mg. or less of epinephrin. Marked responses were obtained in 68 per cent of 22 cases, whereas they occurred in only 18 per cent of 32 normal individuals. This epinephrin sensitiveness occurred irrespective of the cause, the degree, or the duration of the hypertension. None of these patients showed evidences of significant endocrine disturbance. It seems probable that this epinephrin sensitiveness in hypertension may be only one manifestation of a general abnormal reactivity of the cardiovascular system to stimuli of all kinds, and that it need not be attributed to a hyperactivity of either the chromaphil system or of the thyroid.—J. F.

(ADRENIN) The point of attack of certain drugs acting on the periphery. II. Action on the retractor penis muscle of the dog. Edmunds (C. W.), J. Pharm. & Exper. Therap. (Balto.), 1920, 15, 201-216.

Adrenalin caused a marked contraction, but after treatment with ergotoxin relaxation was observed.—R. G. H.

Blood changes produced by ADRENIN. Kägi (Adrienne), Folia Hematol, 1920, 25, 107-152.

In man no constant blood changes were observed after subcutaneous injection of ½ to 1 mg. adrenalin. The most constant finding was a leucocytosis involving cells of both lymphoid and myeloid origin, but the leucocytosis was relative rather than absolute.—Chem. Abst.

(AUTONOMIC NERVOUS SYSTEM) (Zur Anatomie und Pathologie des vegetativen Nervensystems). Spiegel. Wien. klin. Wchnschr., 1920, 33, 975.

There exists a morphological difference between the ganglia of the sympathetic system and the ganglia of the cranial autonomic system, as may be proved by the fact that the former are markedly pigmented in old age, while the latter never are. Graves' disease may be caused by a primary disease of the thyroid or by a disturbed nervous or chemical regulation. The constitution of the patient plays also an important part. In two cases of Graves' disease the author found inflammation of the cervical sympathetic.—J. K.

AUTONOMIC NERVOUS SYSTEM. The blood picture in diseases of the—and how it is influenced by drugs (Das Blutbild bei Störungen des vegetativen Nervensystems und seine pharmacologische Beeinflussung). Schenk (P.), Deutsche med. Wchnschr. (Berlin), 1920, 46, 1192-1193.

In vagotonia often a relative as well as an absolute increase of the lymphocytes may be observed. Sometimes there is a slight in-

crease of eosinophiles. In sympathicotonia there are no typical changes in the blood picture. Injection of pilocarpine is sometimes followed by a very light temporary lymphocytosis without an increased eosinophilia. Injection of adrenalin in sympathicotonia is followed by a very marked increase of the lymphocytes during the first half hour. This is followed by a neutrophil polymorphonuclear leucocytosis. The number of eosinophils does not change. The hypo- or an-eosinophilia that is observed in animals under these circumstances is never seen in man.—J. K.

(BRAIN) Experimental studies on growth. XVI. The influence of brain tissue, freed from cholesterol, upon the growth of the white mouse. Robertson (T. Brailsford) & Ray (L. A.), J. biol. chem. (Baltimore), 1920, 44, 439-453.

There are many observations, hitherto isolated, which when taken together, point towards the nervous system as the source of very decisive stimulant of the growth of parenchymatous tissues. Two possible alternatives are offered: either the nervous system promotes the anabolism of parenchyma by the conduction of stimuli to it—the so-called "trophic influence" of nerves, or the nervous system promotes the anabolism of parenchyma by the elaboration of a catalyzer which is liberated from the nervous tissues and functions as a growth hormone.

The authors fed white mice with decholresterinized brain tissue and found that such material in doses of 36 mg. daily is without effect upon the growth of the mice. Moreover, it had been previously shown that cholesterol modifies the growth of mice by stimulating the growth of parenchyma so as to modify the time relationships and bring the growth curve for mice towards the form of the growth curve for human beings, in whom the ratio of brain weight to body weight is much higher. But the effect of cholesterol is much less even in high doses than the effect of a high ratio of brain weight to body weight. Hence if the nervous system does affect growth through the agency of a specific catalyzer or hormone, this substance must be more potent than cholesterol and must be extracted by acetone from the brain tissue together with cholesterol.—F. S. H.

CHOLIN as paristaltic hormone (Cholin als Hormon der Darmbewegung—II). le Heux (J. W.), Arch. f. d. ges. Physiol. (Bonn), 1920, 179, 177.

With the isolated intestine atropin gives varying results. This is due to the presence or absence of cholin, "the hormone of intestinal movement." If it is present, the antagonistic action of atropin produces inhibition, but if cholin has been removed by repeated washing, atropin produces its ordinary characteristic effect, namely, stimulation.—Physiol. Abst., 5, 236.

The lipins of human CORPUS LUTEUM. Rosenbloom (J.), Scientific Proceedings, Am. soc. biol. chem., XIV., J. Biol. Chem. (Baltimore), 1920, 41, lxxi.

Given by title only.—F. S. H.

Consideration on syphilitic DIABETES (Considérations sur le diabète syphilitic). Beguier (G.), Thèse de Paris, 1919.

Though a combination of diabetes and syphilis is frequently seen, syphilitic diabetes is exteremly rare. There are very few cases in the literature of diabetes caused by syphilitic sclerosis of the pancreas. The author first gives a review of the literature on the subject, referring frequently to the "islets of Langerhans," and reports a case himself of a diabetic woman in whom complete sclerosis of the pancreas was found at autopsy. This case does not appear very convincing. The syphilitic infection was not definitely proved; the Wassermann test in blood and cerebrospinal fluid was negative, and infection was denied. The pancreas was not examined histologically, or at least no report of a histological picture is given. Many of the neurological symptoms, such as loss of reflexes, may be observed also in non-syphilitic diabetes. Diabetic neuritis and the pseudotabes diabetica are well-known clinical pictures. On the other hand, the diabetes, as described by the author, was certainly not a classic case. Such a serious one, dying in coma but never showing any signs of acidosis, can not be identified with the ordinary diabetes ending in coma diabetica.—J. K.

The influence of work on the sugar of blood and urine in DIABETES (Ueber die Wirkung der Arbeit auf Blut und Harnzucker beim Diabetiker). Bürger, München. med. Wchnschr., 1920, 67, 1278.

In diabetes muscular activity increases the blood sugar. It depends on the amount of glycogen in the liver. Women show hyperglycemia more than men; young people sooner than adults. When 10-20 grams of sugar are injected intravenously then the increase in sugar in the plasma of the blood is higher at rest than when the injection has been preceded by muscular activity. Glycosuria does not depend upon the amount of blood sugar. The author observed six cases in which a rise of blood sugar was accompanied by a disappearance of sugar from the urine.—J. K.

Cholesterinemia in DIABETES (Cholesterinaemie bij diabetes mellitus). Boom (B. K.), Inaug. Diss. (Amsterdam), 1920.

From numerous observations the author concludes that there is no relation between acidosis and the quantity of cholesterol in the blood plasma. In patients younger than 40, the amount of cholesterol is generally much higher than in older patients. No relation was found between the tolerance for carbohydrates and the quantity of cholesterin. Diet was noted to have no influence—even after pro-

longed fasting the cholesterol content may remain high. Similarly, no relation is found between xanthosis and cholesterol; the xanthosis is due, supposedly, to the high concentration of lipochrome in the plasma. Whether a high concentration of cholesterol is of bad prognostic significance is not definitely established. The fact, however, that this concentration is high in younger subjects in which, in general, the prognosis is poor, suggests that some relationship may exist.—J. K.

(DIABETES) Critical glycemia. Charbanier (H), J. phar. chim., 1920, 21, 177-183; Presse méd., 1920, 28, 222.

Parallel determinations of the degree of glycemia and of acetonuria, both in normal and diabetic persons, put upon a non-carbohydrate diet (the coagulum of 3 l. of milk deprived of serum), show that upon decreasing glycemia a point will be reached, called critical glycemia, at which the corresponding acetonuria rises suddenly. Upon giving carbohydrates again acetonuria returns to normal values. This work supplements Ambard's hypothesis that hyperglycemia is a mechanism, which in the diabetic compensates the disturbance in carbohydrate metabolism.—Physiol. Abst, 5, 216.

Pancreatic DIABETES and disturbed pancreatic function (Pankreas Diabetes und pankreatische Resorptionsstörung). Dresel, Deutsche med. Wchnschr. (Berlin), 1920, 46, 1154.

The patient was a man of 30. From the 18th to the 24th years he had used alcohol excessively. At the age of 25 sugar was found in his urine. After four weeks' feeling ill he came to the hospital. The feces showed typical steatorrhoea, creatorrhoea and bulkiness. The Schmidt-Kashiwado test was positive. The duodenal contents did not contain trypsin. The urine showed about 5% sugar, with traces of maltose. The blood sugar was 0.362%. The curve of blood pressure after the injection of adrenalin was the same as in sympathicotonia; this may have been caused by the loss of pancreatic function. Injection of adrenalin raised the blood sugar but little.—J. K.

The decrease of sugar in blood and urine by x-ray treatment of the adrenals in DIABETES (Ueber Herabsetzung des Blut und Harnzuckers durch Röntgenbestrahlung der Nebennieren beim Diabetiker). Dresel (K.), Deutsche med. Wchnschr. (Berlin), 1920, 46, 1240-1241.

Stephan exposed the pancreas to stimulating doses of x-ray and observed in two cases of diabetes an increased tolerance for carbohydrates and a diminished quantity of excreted sugar. That it is possible to expose the adrenals to x-ray without any harm to the other organs is proved by the experiments of Zimmern and Cottenot, who treated patients with high blood pressure in this way, often with success. Dresel tried the influence of x-ray treatment of the adrenals in diabetes. He observed that the blood sugar showed a marked de-

crease; sometimes the sugar in the urine disappeared. The treatment is harmless. Its result, however, is temporary.—J. K.

(DIABETES) Xanthosis diabetica. Hannema (L. S.), Nederl. Maandschr. v. Geneesk. (Leiden), 1920, 1, 318-325.

The author observed a case of xanthosis diabetica. The serum was dark yellow. There was no increase in the amount of bile pigment, the color being due to a very large quantity of lutein.—J. K.

(DIABETES) Our internal sugar shortage. Hutchinson (Woods), Saturday Eve. Post. (Phila.), 1920, 193, 16.

An interesting and popular review of the subject of diabetes.
—F. S. H.

(DIABETES) Xanthelasma diabeticorum. Van Leeuwen (T. M.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1920, 64, II, 2085-2086.

Report of a case.—J. K.

Severe case of DIABETES mellitus with multiple endocrine disturbances. Lindblom (Sven), Hygiea (Stockholm), 1916, 78, 721-764

In a 16-year-old boy, besides symptoms of diabetes there were also symptoms of thyroid insufficiency, e. g., poor growth of hair. The growth of hair was improved by thyroid treatment. Near the end, a high-grade lipemia of 17.55 per cent fat set in. Death occurred in coma. At autopsy there was found a marked pancreatic atrophy with decided quantitative and qualitative alterations of the neck; significant thyroid and hypophyseal atrophy, particularly the pars infundibularis of the latter; the adrenals were of normal weight, but in their cortex changes were seen which were indicative of a hyperfunction. The author expresses the opinion that, although hormones of the pancreas and the thyroid function antagonistically, yet the organs themselves, whether by their hormones or by way of the vegetative nerves, stimulate one another. Various observations of diabetes, Basedow's disease and acromegaly permit this assumption.—J. A. H.

The modern treatment of DIABETES (Der heutige Stand der Diabetestherapie). Richter (P. F.), Deutsche med. Wchnschr. (Berlin), 1920, 46, 1197-1200.

A general review. The author points out three differences between modern and former methods of treatmnt. Over-nutrition is now avoided; proteins are restricted and carbohydrate "cures" are administered. Of these latter Falta's "Mehlfrüchtekur" is recommended.
—J. K.

DIABETES INSIPIDUS. Stenström (Thor), Allm. sven. Lakartidn. (Stockholm), 1916, 13, 876-888; 893-901.

Presentation of a case of diabetes insipidus in a man of 20 years with a positive blood Wassermann reaction, to whom anti-luetic treatment was given together with **pituitrin** injections four different times. The diuresis was diminished each time and the molecular concentration showed a parallel rise. Sodium chloride and nitrogen were in general excreted in smaller amounts, although their percentage was increased.—J. A. H.

(DIABETES) Experiments on intermediate carbohydrate metabolism in man. I. (Studien über den intermediären Kohlehydratestoffwechsel. I.). Stepp (W.) & Lange (H.), Deutsch. Arch. f. klin. Med. (Leipzig), 1920, **134**, 47-58.

If the quantity of acetone in the urine is determined and then the urine is heated with oxide of silver and after this the quantity of acetone is again measured, it is found to be less. Since acetone is not itself oxidized by silver oxide this proves that what we call acetone in urine is a mixture of two substances: a substance oxidized by silver oxide together with actual acetone. This substance is volatile, reduces Fehling's solution and gives iodoform with iodine and sodium hydrate. It reduces ammoniacal silver solution. It is certain that this substance is an aldehyde and probably acetaldehyde. It is found in urine only when acetone and diacetic acid are present, and especially when acidosis is becoming more marked.—J. K.

(DIABETES) Experiments on intermediate carbohydrate metabolism in man. II (Studien über den intermediären Kohlehydratstoffwechsel. II.). Stepp (W.) & Zumbusch (H.), Deutsch. Arch. f. klin. Med. (Leipzig), 1920, **134**, 112-118.

Stepp has previously shown that normal blood contains formic acid (Ztschr. f. physiol. Chem. (Berlin), 1920, **109**, 99). In diabetes the amount of formic acid is diminished or entirely absent.—J. K.

Value of the lactone form of glykoheptonic acid in the treatment of DIABETES mellitus (Om vardet af glykoheptonsrelation vid behandlingen af diabetes mellitus). von Wendt (Dora), Finska Läkares. Handl. (Helsingfors), 1916, **58**, 664-675.

A testing of the material named in four cases of diabetes mellitus. The glycosuria was stopped—in one of the cases, however, only during the first day of the treatment. The acidosis was not influenced to a definite degree. The material is of greatest efficacy in mild cases of diabetes, when it quickly makes the patient sugar-free.—J. A. H.

Starvation treatment of DIABETES. Widmark (E.), Allm. sven. Läkaretidn. (Stockholm), 1916, **13**, 1140-1144.

Mainly bibliographical.—J. A. H.

Experiments on carbohydrate metabolism and DIABETES. III. The permeability of blood corpuscles to sugar. Wishart (Mary B.), J. biol. chem. (Baltimore), 1920, **44**, 563-587.

An extensive tabular presentation of experiments on dogs, goats, sheep and a pony, tending to throw light on the question of the permeability of the red-blood corpuscles for sugar. No specific alteration of the distribution of sugar between the plasma and corpuscles was found in experiments with different amounts and modes of glucose administration, different degrees of **pancreatectomy**, and **diabetes**, lipemia, acidosis, exercise, cold, or different levels of the renal threshold.—F. S. H.

Experiments on diminished immunity against purulent infection in patients with DIABETES (Untersuchungen über die verminderte Immunität Zuckerkranker gegen eitrige Infektionen). Wolfsohn, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 986.

The author determined the opsonic index of patients with diabetes. The phagocytic count against staphylococcus in diabetics is distinctly lower than in normal individuals. After infection the number of leucocytes in the blood is lower than in healthy individuals. Vaccine therapy in diabetes is of considerable value in cases of infection.—J. K.

(ENDOCRINE ORGANS) Diseases of ductless glands. Anon., Med. Sc., Abst. & Rev. (London), 1920, **3**, 212-223.

In this article is presented an interesting digest of some of the more recent literature on diseases and therapy of the endocrine organs. The glands treated are the thyroid, parathyroids, suprarenals, hypophysis, and pineal, together with pluriglandular syndromes. Several paragraphs have been quoted as abstracts in this number of Endocrinology.—R. G. H.

(ENDOCRINE THERAPY) L'opothérapy en thérapeutique infantile. Apert (E.), Presse méd. (Paris), 1920, **28**, 341-343.

Apert remarks that except for thyroid treatment in myxedema, very little use is made of organ extracts in pediatrics, and yet this is a particularly fertile field for them. The children's clinics, fetal findings and the results of experimental research all confirm that the suprarenal cortex, like the thyroid, stimulates the nutritional processes. But, with thyroid excessive stimulation, there is emotionalism and a tendency to lose weight, while with suprarenal cortex excessive stimulation, the tendency is to obesity and virilism. Apert advises that organ extract treatment be begun with small doses for three days each week, watching the pulse, the weight and the excitability. With uniform backward growth, he has obtained the best results with a combination of thyroid and suprarenal powder, especi-

ally in the thin, anemic and frail. If the sexual development is precocious, he associates pituitary with the other extracts, with or without suspension of the suprarenal extract. In mongolism, or depressed vitality from any cause, this associated organotherapy often whips up the sluggish development and renders the children easier to teach. He insists that administration by the mouth is as effectual as by subcutaneous injection. The powder can be given with a mouthful of food. Calcium seems to promote the action of thyroid extract, and magnesium that of the suprarenal extract. The indications for pituitary treatment will be found among the short and stout, hairy subjects, with precocious puberty; for suprarenal treatment, among the overtall, weak and apathetic, and among boys, in those with a tendency to feminine characteristics; for thyroid treatment, among those with uniform backward growth, gait, speech and intelligence and delayed development of the sexual organs.—J. Am. M. Ass., 75, 208.

(ENDOCRINE ORGANS) Increase of agglutinins after organotherapy as a proof of the stimulating action of organ preparations (Erhöhung des Agglutininspiegels durch Organpräparate als Ausdruck leistungssteigernder Wirkungen in der Organotherapie). Borchardt (L.), Therap. Halbmonatsh. (Berlin), 1920, **34**, 536-541.

The author has previously reported that when anti-typhoid inoculations are accompanied by injections of adrenalin or hypophysin the agglutin titre is increased. In this article a similar increase is reported to follow the injection of spermin and of "asthymolysine." Thyroid administered by mouth has a similar influence.—J. K.

A case of multiple sclerosis of the ENDOCRINE ORGANS (Di un caso di sclerosi multipla della glandole endocrine). Bussi (A.), Gazz. d. Osp. (Milano), 1920, **41**, 715-716.

A description of a patient of 50, who first lost his hair and whose testicles then became smaller and smaller. His sexual desires diminished and he became sexually impotent. Then he lost his pubic and axillary hair as well as his beard. He always complained of feeling cold; his skin was very dry. The heart beat was slow, the blood pressure was 57, the nails were fragile. Prostate and thyroid were exceedingly small. The skin and the mucous membrane showed brown pigmentation. From time to time there was polyuria. The patient showed all symptoms of asthenia cordis.—J. K.

(ENDOCRINE ORGANS) A case of pluriglandular sclerosis with clinical picture of Addison's disease (Ein Fall von multipler Blutdrüsensklerose unter dem klinischen Bilde eines Morbus Addisonii). Donath (J.) & Lampl (H.), Wien. klin. Wchnschr., 1920, **33**, 962-964.

A woman of 24, who during childhood suffered from several infectious diseases, became suddenly ill with intestinal symptoms, debility, pigmentation of the skin and mucous membrane of the mouth,

hypertension, loss of pubic hair and cessation of menstruation. The post-mortem showed a small **thyroid** and liver, with marked increase of connective tissue. Symptoms of infantilism (narrow aorta, infantile uterus), were also present. In the **adrenals** the medulla was changed into a mass of connective tissue, while in the cortex there was a chronic inflammation. Sclerosis of the **hypophysis** was also found.—J. K.

(ENDOCRINE ORGANS) **Pathology and therapy of the so-called "constitutional adiposity" (Pathologie und Therapie der sog. "Konstitutionellen" Fettsucht).** Grafe (E.), Deutsch. Arch. f. klin. Med. (Leipsig), 1920, **133**, 41-63.

A careful study of the metabolism of ten cases of adiposity. Two cases were due to a **thyroid** disturbance, three to **ovarian** insufficiency, and two were of **hypophysial** origin. The three other cases did not show any special endocrine abnormalities. Only in one case of thyroid adiposity, in one case of dystrophia adiposo-genitalis and in one without endocrine disturbance was there a lowered metabolism. In the other seven cases the metabolism was normal. It is probably not true that adiposity is caused by a defective oxidation of fat. It is well known that patients with adiposity retain much water in the tissues. The studies of Eppinger have shown that thyroid preparations are excellent diuretic drugs in edema. This may be one of the reasons why thyroid therapy is indicated in adiposity.—J. K.

(ENDOCRINE ORGANS) **A case of dystrophia myotonica (Beobachtungen an einen Fall von Dystrophia myotonica).** Mann (O.) & Zondek (H.), Berl. klin., Wchnschr., 1920, **57**, 788-789.

A report of the case of a patient who had an enormous nose, large lips and polyuria. These symptoms may be attributed to a disturbed function of the **hypophysis.** The low blood pressure and the extremely low amount of blood sugar (0.04%) may be caused by **adrenal** insufficiency. The protein metabolism was retarded and the nitrogen excretion was very slight as it is in **myxedema.** The electrocardiogram showed an extra long A. V. interval.—J. K.

ENDOCRINE GLANDS and syphilis (Syphilis e glandulas endocrinicas). Nonohay (U.), Arch. Rio Grand. de med. (Porto Alegre, Brazil), 1920, **1**, ——, (May).

The author proposes a conception which in his judgment revolutionizes the ideas concerning syphilis. He thinks that the disorders of syphilis of the adult and particularly all hereditary phenomena are due to the selective attack of the treponema on the endocrine glands, the functions of which are accordingly destroyed.—B. A. H.

(ENDOCRINE ORGANS) **A case of idiocy with marked adiposity (Intorno ad un caso di idiozia con notevole obesità).** Pedercini (E.), Morgagni (Milano), 1920, **62**, 253-264.

A description of a woman of 25, weighing 95 kilos. Menstruation began at 15, but was always irregular. She suffered from epilepsy and had mental disturbances (attempted suicide, smeared with feces, etc.). The temperature was sub-normal. Her face was cretinous. The author believed that this disease is caused by endocrine disturbances. He tried thyroid and hypophysis medication. This had a remarkable effect; the weight was rapidly diminished and the number of epileptic attacks was markedly reduced.—J. K.

Physiological action of different extracts of ENDOCRINE ORGANS in myxedema [De l'action physiologique de différents extraits de glandes à sécrétion interne chez les myxoedémateux (application au diagnostic de l'insuffisance thyroïdienne fruste)]. Porak (R.), Ann. de méd. (Paris), 1920, **6**, 469-476.

Porak has found that injection of thyroid extract in myxedema does not have a definite physiological effect, whereas in normal subjects it causes hypotension and acceleration of the pulse. In two myxedematous patients, who were still under the influence of treatment, there was a suggestion of physiological reaction, which was completely abolished when the treatment was discontinued for a longer period. He also found that adrenalin and extract of the suprarenal medulla had a more powerful action in normal subjects than in myxedema. On the other hand, extract of the posterior lobe of the hypophysis had a much more active effect on the blood pressure of myxedematous patients than of normal subjects, as was shown by a sudden and prolonged fall of blood pressure. By application of these glandular tests to various complex syndromes, Porak shows that it is possible to confirm or exclude the diagnosis of thyroid insufficiency.—Med. Sc. Abst. & Rev., **3**, 216.

(ENDOCRINE ORGANS) The biochemistry of the adrenals, thyroid and hypophysis (Zur Biochemie der Nebenniere, Thyreoidea und Hypophysis). Richter, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 954-955.

According to the author, the **chromaphil system**, the **thyroid**, and the **hypophysis**, together, form a reducing system with the function of producing reducing substances. Diabetes is due to a hyper-function of this reducing, or a hypo-function of the oxidative system. It is possible to prepare the reducing substance from the organs and the blood. They should have an influence on the coagulation of the blood, on the quantity of calcium in the bones, etc. The oxidative system comprises the lymphatic system. The **thymus** has an "antagonistich-komplementierende" relation to the thyroid. The vagus is the nerve of oxidation, the sympathetic that of reduction. (See also Endocrinology, 1919, **3**, 533.—J. K.

(ENDOCRINE ORGANS) Dwarfism (Ueber Zwergwuchs). Sternberg (C.), Wien. klin. Wchnschr., 1920, 33, 764.

Of no immediate endocrine interest.—J. K.

(ENDOCRINE ORGANS) A quantitative method for the determination of vitamine in connection with determinations of vitamine in glandular and other tissues. Swoboda (Frederick K.), J. biol. chem. (Baltimore), 1920, 44, 531-551.

Having developed William's biological test for the detection of small amounts of water-soluble-B vitamine, the method was applied to various organs and tissues. A table is given of the so-called vitamine number of the organs studied and it is evident that this specific vitamine is present in large amounts in most of the glands of internal secretion which are of developmental importance, while it is generally low in the other organs examined, with the exception of the liver and kidney. Tissues high in nuclear material such as the **thymus** and lymph glands, were low in vitamine content. Fresh **pancreas** is also low. **Thyroid** in high concentration has a toxic effect on the method, but by proper regulation is shown to contain the water-soluble-B. The order of the endocrine glands as expressed in their vitamine number is: **testes, pineal, pars intermedia** of the hypophysis, **hypophysis** as a whole, **anterior lobe** of the hypophysis, **thyroid, adrenals, ovaries, thymus, posterior lobe** of the hypophysis, **pancreas.**

—F. S. H.

(ENDOCRINE ORGANS) The influence of the several parts of the human body on each other (Over den invloed van verschillende deelen van het menschelijk lichaam op elkaar). de Vries Reilingh (D.), Geneesk. Blad. (Haarlem), 1920, 22, 161-178.

A good general review of the correlation of the endocrine glands.

—J. K.

The heart in diseases of the ENDOCRINE ORGANS (Herzbefunde bei endokrinen Erkrankungen). Zondek (H.), München. med. Wchnschr., 1920, 67, 793; Deutsche med. Wchnschr. (Berlin), 1920, 46, 1239-1240.

In **acromegaly** tachycardia is observed, with a decided inclination towards arteriosclerosis. Very often there exist cardiac insufficiency and, especially in cases without gigantism, dilation of the heart. In chondrodystrophy the heart is enlarged (probably dilated) and the blood pressure is low. In myotonia there is increased irritability of the heart with brachycardia, dilation, and low blood pressure. In the electrocardiogram the period between the atrial wave and ventricular interval is longer than normal. In myxedema there is often cyanosis combined with dilation of the heart. The electrocardiogram is remarkably flat, as many individual waves are lacking. When **thyreojodin** is given, the electrocardiogram resumes its normal outline.

As "formes frustes" of myxedema are very frequent, in cases in which digitalis gives no results thyreojodin should be given a careful trial. —J. K.

(GONADS) Contribution to the physiology of the glands. 43. Studies of the respiratory metabolism of castrated rabbits (Beiträge zur Physiologie der Drüsen. Leon Asher. 43. Untersuchungen über den respiratorischen Stoffwechsel kastrierter Kaninchen). Bertschi (H.), Biochem. Ztschr. (Berlin), 1920, 106, 37-55.

Using Haldane's apparatus to determine the respiratory exchange B. was unable to detect any changes from the normal in rabbits from which the ovaries or the testes had been removed. Moreover, the injection of freshly made ovarian extracts or of testicular extracts into the animals, whether normal, castrated or spayed, had no evident effect on the respiratory exchange. Consequently, there is at present no direct evidence that the gonads exert any influence of a direct nature upon respiratory metabolism.—F. S. H.

(GONADS) Steinach's operation on man (Steinachsche Tierversuche auf die Menschen übertragen). Lichtenstein, Deutsche med. Wchnschr. (Berlin), 1920, 46, 1211.

Data reported elsewhere.—J. K.

(GONADS) Steinach's studies on rejuvenation (Zu den Steinachschen Verjüngungsversuchen). Liek (E.), Deutsche med. Wchnschr. (Berlin), 1920, 46, 1167-1168.

In general the work of Steinach is commended. The author, however, does not believe that mere ligation of the vas deferens or Roentgen radiation of the gonads will bring about rejuvenation. Both these procedures have been repeatedly carried out for other purposes in clinical practice, but it has never been observed that patients get younger. The cases cited by Steinach prove merely that in sexual matters suggestion plays an important role.—J. K.

Studies on the GONADS of the fowl. I. Hematopoietic processes in the gonads of embryos and mature birds. Nonidez (J. F.). Am. J. Anat. (Phila.), 1920, 28, 81-113.

The connective tissue of the gonads of the fowl is found at times to contain centres of hematopoietic activity. Certain of these blood- and lymph-forming cells, according to Nonidez, have been termed interstitial cells and an endocrine function ascribed to them. Such, he believes, are the granule-laden cells described by Boring and Pearl.—W. J. A.

(GONADS) Treatment of large malignant growths of the male and female generative organs with x-rays (Behandeling der uitgebreide

kwaadaardige gezwellen van de mannelijke en vrouwelijte geslachtsklieren met Röntgenstralen). Orbaan (C.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1920, **64** (II), 787-796.

Of no immediate endocrine interest.—J. K.

(GONADS) The experiments of Steinach on rejuvenation (Steinach's Verjüngungsversuche). Romeis (B.), München. med. Wchnschr. 1920, **67**, 1020-1021.

Steinach has described experiments on old rats in which ligation of the funiculus spermaticus (on both sides) caused a marked increase in vitality. Lichenstein operated in the same way on three elderly men and, so he states, with success. The author discusses the experiments of both of these investigators and reaches the conclusion that no great confidence can be placed in the efficacy of these operations. The time for observation, especially in men, is too short. Some years ago resection of the funiculi spermatici was frequently done for hypertrophy of the prostate, and it is a noteworthy fact that in none of the cases was there any indication of rejuvenation of the patient. Romeis himself saw a patient in whom the sexual desires returned after a simple operation for hydrocele. Great caution is needed in the interpretation of such an experiment..—J. K.

(GONADS) The skeleton in hermaphroditism (Das Skelett eines Teilzwitters). Stieve (H.), Arch. f. Entwckslngsmech. d. Organ., 1920, **46**, 38-84.

Stieve points out that Steinach's views on hermaphroditism hold, if proof is obtained that the formation of germ cells is dependent upon interstitial cells. He describes a case of scrotal hypospadia associated with anus praeternaturalis scrotalis, in which examination of the generative glands showed that it was completely male. On the basis of the skeletal measurements, which are given, it was decided that the case was one of partial hermaphroditism. Ber. ü d. ges. Physiol., **1**, 24.

(GONADS) The practical value of Steinach's operations (Die praktischen Aussichten der Steinachschen Verfahrens). Stutzin (J. J.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 966.

The author points out that it is difficult to obtain testicles for transplantation. We have no right to take them from healthy individuals, and cases of cryptorchism in which a testicle has to be removed, are rare. It would be better never to perform castration except in cases of malignant tumors. In nearly all cases of tuberculosis it is necessary to remove the epididymis only. The results in homosexuality may be due to suggestion, and even if this were not true, it is impossible to foretell which cases would be suitable for this treatment. The operation of ligating the vas deferens for the

purpose of restoring youth is to be regarded with suspicion, as during many years this procedure has been followed in hypertrophy of the prostate without ever having given rise to rejuvenation of the patient. Until we know more about the matter, surgeons should not resort to these operations.—J. K.

X-ray treatment of the HYPOPHYSIS in bronchial asthma (Irradiazione dell ipofisi nell' asma bronchiale). Ascoli (M.) & Fagiuoli (A.), Gazz. Osp. (Milano), 1920, 41, 696.

The authors tried to find out whether it was possible to stimulate the endocrine glands with x rays. First they tried x-ray treatment of the **hypophysis** in a case of dystrophia adiposo-genitalis, and of the **thyroid** and hypophysis in a case of scleroderma with success. Then then treated five patients with bronchial asthma exposing the hypophysis to small doses of x-ray with good results. The authors suggest the study of the function of the endocrine glands by submitting them to small stimulating doses of x-rays.—J. K.

Case of tumor of HYPOPHYSIS, acromegaly and bitemporal hemianopsia. Behse (Emil), Finska Läkares. Handl. (Helsingfors), 1920, 62, 382-395.

The case is reported of a 47-year-old carpenter who, in his youth, had suffered from recurrent attacks of severe headaches four or five times a year. For the past fifteen years there has been a gradual overgrowth of different parts of his body, especially the hands and feet. Impairment of vision also occurred. For two years tiredness and somnolency have been general, accompanied by profuse sweating and severe thirst, as well as heat sensations in the extremities and acroparesthesia in the finger and toe tips. Potency and libido sexualis were completely lost. Diabetes mellitus, exopthalmus, sluggish pupillary reaction, almost complete amaurosis of the left side, right temporal hemianopsia (V:6-15) and bilateral optic atrophy were present. Enlargement of the sella turcica was evident. Treatment first with **thyroidin** tablets and potassium iodide, then with hypophysis tablets (Merck) 3-10, was initiated. During the two and a half months' period of observation there was a continued improvement of the eye symptoms.—J. A. H.

Products from the HYPOPHYSIS gland. Flaecher (F.) & Reuter (B.), U. S. patent 1,296,063, March 4th, 1919.

The well ground infundibular portion of the hypophysis is extracted with slightly acidulated water and the extract so obtained is freed from albumin and concentrated by evaporation. The concentrated extract is acidulated with sulfuric acid and then treated with an aqueous solution of phosphotungstic acid as long as a precipitate is produced. The precipitate thus formed is washed with water, acidi-

fied with sulfuric acid and then stirred into a thin magma with water and treated with barium hydroxide until a distinct alkaline reaction is produced. The barium phosphotungstate thus formed is filtered off, the filtrate is freed from dissolved barium by the addition of dilute sulfuric acid and then evaporated in vacuo to the point of crystallization; or the base may be precipitated by the addition of alcohol or acetone and washed and dried in vacuo. The base thus obtained is soluble in water with an alkaline reaction, is difficultly soluble in alcohol, ether, ethylacetate and acetone; it is soluble in alkalies and acids. It is stable in air. With acids the base forms crystalline salts, which, like the base itself, possess the physiological properties of the hypophysis and may be used for hemostatic, astringent, pressor or oxytocic effect. The compound is precipitated by alkaloidal reagents such as picric acid, tannic acid, phosphotungstic acid, bichloride of mercury, mercury potassium iodide, potassium periodide, platinic chloride, or potassium bismuth iodide. It gives the biuret reaction and does not yield, on addition of iron chloride, the green coloration characteristic of **adrenalin.** U. S. patient 1,296,064 relates to the manufacture of the salts of the base. The sulfate is formed by combination of the base with sulfuric acid in aqueous solution and concentrating the solution in vacuo until crystallization is effected. It is slightly yellowish, stable, crystalline powder which decomposes at 160 to 161°. It is readily soluble in water and difficultly soluble in alcohol, ether, ethyl acetate and acetone. The base also forms salts with the following acids: hydrochloric, nitric, boric, succinic, oxalic, citric, tartaric, benzoic and salicylic acids. Chem. Absts. 13, 1517.—F. S. H.

(HYPOPHYSIS) Recklinghausen's disease with acromegaly (Coexistencia da doenca de Recklinghausen com acromegalia). Castro (A. de), Rio de Janiero, 1920. F. Briguiet, ed.

Castro, in 1912, reported a case of co-existing cutaneous neurofibromatosis and acromegaly (N. icon. Salpêtriére). In 1915 the case came to autopsy. A tumor of the hypophysis was found. Histological examination was not made.—B. A. H.

(HYPOPHYSIS) Acromegalia e tabes. Notes e observaçoes clinicas. Castro (A. de), Rio de Janiero, 1920, F. Bruguiet, ed.

The author reports the simultaneous occurrence of acromegaly and tabes in a patient.—B. A. H.

(HYPOPHYSIS) Syndroma Thyreo-Hypophysaria. Notes e observaçoes clinicas. Castro (A. de), Rio de Janiero, 1920, F. Bruguiet, ed.

In 1912 Castro reported a case (Encephale, 1912, 329) as **thyrotesticulo-hypophyseal** syndrome. More recently he has concluded that the testicle did not figure etiologically and that the patient had typical acromegaly with slight goiter.—B. A. H.

(HYPOPHYSIS) Distortions of the visual fields in cases of pituitary tumors. Josephson (Arnold), Nord. med. arkiv. (Stockholm), 1616, F. 3. 16. Afd. 2. 1-5.

A claim for priority since the author in 1903 distinctly showed in his work on acromegaly and pituitary tumors the distortions of the visual field in case of pituitary tumors described in 1905 by Cushing and Walker in BRAIN.—J. A. H.

(HYPOPHYSIS) The cause of diabetes insipidus (Zum Wesen des Diabetes insipidus). Hecht (E.), Ztschr. f. klin. Med. (Berlin), 1920, 90, 126-145.

A man contracted syphilis and was treated with inunctions of mercury until a negative Wassermann reaction was obtained. Some years later, after a single injection of salvarsan, diabetes insipidus immediately appeared, and gradually the condition of dystrophia adiposo-genitalis developed. Further treatment with salvarsan had no effect. The skiagram revealed no abnormality of the sella. From his observations on this patient the author is led to conclude that in diabetes insipidus the diuresis is due merely to increased permeability of the kidney to water. Veil's contention that the anti-diuretic effect of pituitary extract is due to the retention of water by the tissues is controverted. Although, when extra amounts of NaCl are administered, the elimination of this is brought about by an increase in the quantity of urine, it is also true that the concentration of NaCl in the urine is higher than when an equal degree of diuresis is produced by the ingestion of water. It follows, then, that the concentrating power of the kidney still exists. In fever, during thirst, or after injections of pituitary extracts, in diabetes insipidus, the concentration of the urine may be increased, although it does not reach the normal. Often the polyuria of diabetes insipidus is considered as a simple compensatory mechanism for the loss of concentrating power of the kidneys. That such is not the case is indicated by the fact that in true compensation polyuria the epithelial cells of the renal tubuli are found to be flattened, whereas this is not true in diabetes insipidus. It is not possible to consider polyuria as compensatory when the concentration of the urine is lower than that of the blood plasma.—J. K.

(HYPOPHYSIS) Diagnosis of hypophyseal asthenia (Zur Diagnose der Hypophysenschwäche). Fliess (W.), Med. Klin. (Berlin), 1920, 16, 778-781.

Fliess describes a syndrome characteristic of insufficiency of the anterior lobe of the hypophysis and consisting of five principal manifestions, viz., (1) general fatigue; (2) lack of power of concentration; (3) polyuria, occasionally accompanied by enuresis; (4) occipital neuralgia, not infrequently accompanied by a backache and sciatica;

(5) disturbances of menstruation, especially menorrhagia. The first four symptoms, though most frequent in women, especially during pregnancy, may also be found in the male sex at puberty. All the symptoms may be caused to disappear by administration of tablets made from the anterior lobe. Fliess emphasizes the importance of examining all the other members of the family to which the patient belongs for similar disturbances.—Med. Sc. Abst. & Rev., 3, 219.

(HYPOPHYSIS) Late acromegaly (Acromegalie à début tardif). Hamant (A.) and Caussade (L.), Rev. méd. de l'est., 1920, 48, 446-448.

Acromegaly of late onset is exceptional. Examples of the kind have been recorded by Widal, Ballet and Laignel-Lavastine, to which may be added the case recently reported by Hamant and Caussade. The patient was a woman, aged 53, the mother of three children, in whom the first symptoms, enlargement of the hands and feet, had appeared at the menopause four or five years previously. Subsequently the skin of the face and neck grew thick. Deformities of the trunk, visceral signs, and symptoms of compression were absent, but the diagnosis of acromegaly was confirmed by the x-rays, which showed enlargment of the sella turcica.—Med. Sc. Abst. & Rev., 3, 218.

(HYPOPHYSIS) A case of suspected tumor of the pituitary body. Hansell (H. F.), Ophth. Rec. (Chicago), 1917, 26, 275-278.

A case is recorded presenting interesting eye findings, dilatation of the pupils, concentric contraction of the right field and complete left hemianopsia. The x-ray plate of the skull suggested a tumor in the region of the sella turcica. Neurological examination revealed nothing abnormal. There were no indications of acromegaly. The eye grounds were normal. The headache and vomiting seemed to be relieved by pituitrin and thyroid extract.—H. L.

(HYPOPHYSIS) Exhibition of a case of gigantism in a girl 12 years of age. Heuer (G. J.), John Hopkins Hosp. Bull. (Balt.), 1917, 28, 96.

Heuer presented before the Johns Hopkins Medical Society, Oct. 16, 1916, a girl of 12, whose height was 6 feet 1 inch and whose weight was 117.5 lbs. The extremities were abnormally long and the hands and feet very large, but not acromegalic. There was a beginning bitemporal hemianopsia. The x-ray plate of the skull showed an enlarged sella turcica with atrophy of the posterior clinoid processes. There were no signs of thyroid disturbance, adrenal disease, or pineal involvement. No gynecological examination was made. Menstruation had not begun. The response to adrenalin and atropin were normal, as was the blood sugar curve.—H. L.

The histological structure of the HYPOPHYSIS and hypophyseal adenomas together with their relation to acromegaly. Kalmeter (Gunnar), Hygiea (Stockholm), 1916, 78, 609-627.

A single case of hypophyseal tumor without acromegaly is reported. The tumor was shown to be a so-called chief-cell adenoma. The individual cells agreed completely with the "chromophobic" chief cells of the normal hypophysis; acidophile cell granules could not be found at any place. Cell polymorphism and other evidence of malignancy were lacking. The finding gives rise to the opinion that the acidophile granules are the effective secretion product of the hypophysis and that an overproduction of such secretion leads to acromegaly.—J. A. H.

(HYPOPHYSIS) Dystrophia adiposo-genitalis. Hoffmann. Deutsche med. Wchnschr. (Berlin), 1920, 46, 1266.

A demonstration of a boy of eleven with this disease and a "forme fruste" of Recklinghausen's disease (general neurofibromatosis). There was a bilateral atrophy of the optic nerve which may have been caused by a neurofibroma of the chiasma.—J. K.

(HYPOPHYSIS) Relation between diabetes insipidus and disturbances of hypophyseal functions. af Klercker (Kj. Otto), Allm. sven. Läkartidn. (Stockholm), 1916, 13, 909-918.

After a review of the literature on the question the author comes to the conclusion that one is not justified in considering as satisfactory the theory of hypophyseal genesis of diabetes insipidus. The not infrequent association of this disorder not only with acromegaly but also with the still rather uncertain dystrophia adiposo-genitalis, is not conclusive. In the last analysis the question reduces to a "non liquet."—J. A. H.

(HYPOPHYSIS) Acromegaly. Kraus (E. J.), Deutsche med. Wchnschr. (Berlin), 1920, 46, 932.

At the autopsy of a patient dying with acromegaly there was found a large eosinophile adenoma of the hypophysis. The heart weighed 950 grams, the liver 3220 grams, the spleen 650 grams, the thyroid 150 grams, the pancreas 150 grams, and the adrenals 25 grams. Pineal, parathyroids and testicles were of normal weight.—J. K.

Tumors of the HYPOPHYSIS (Hypophysisgezwellen). Kuijjer (J. H.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1920, 64, 1971-1979.

A report of five cases treated with x-rays:

1. A man of 23, with headache, vomiting, giddiness, almost complete blindness and adiposo-genitalis. After x-ray treatment the headache was slightly less intense. He died a year later. No post-mortem was held.

2. A woman of 52, with headache, disturbances of speech, and almost complete blindness. After treatment all symptoms disappeared. The sight was very much improved.

3. A woman of 49, who was tired, giddy and nearly blind, the right eye being completely so. After treatment she was much improved. The sight became better.

4. A woman of 40, with pains in arms and legs, headache, poor vision, amenorrhea and symptoms of dystrophia adiposo-genitalis. After treatment there were no complaints and the vision was perfectly normal.

5. A man of 26 had headache, bad sight and protrusion of the left eye. He was sexually impotent. After treatment there was no complaint; the protrusion disappeared. He remained impotent.

In all these cases the diagnosis of hypophyseal disturbance was absolutely sure. The improvement in the last four cases has lasted now for over two years.—J. K.

(HYPOPHYSIS) A case of symmetrical lipodystrophy (Ein Fall von symmetrischem Fettschwund). Mosse, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 985.

A short note. The respiratory quotient was normal. The blood showed only a relative lymphocytosis. The hypophysis was normal. About twenty-five such cases have been reported in the literature. The etiology is unknown.—J. K.

(HYPOPHYSIS) Dystrophia adiposogenitalis (Zur Dystrophie adiposogenitalis). Pfeiffer (R.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1302.

The patient was a girl of 17 with dystrophia adiposo-genitalis and polyuria. The x-ray pictures showed an enlarged sella turcica. Death occurred 48 hours after operation. Autopsy showed the ependyma of the third ventricle partly changed into a number of layers of epithelium with the formation of a solid benign tumor in the infundibulum, consisting of layers of epithelial pearls (so-called Hypophysengangsgeschwülst of Erdheim). The pars intermedia and the anterior lobe of the hypophysis were normal.—J. K.

HYPOPHYSIS and Raynaud's disease (Hypophyse und Raynaudsche Krankheit). Pribram (B. O.), München med. Wchnschr., 1920, **67**, 1284-1286.

A man of 42 developed Raynaud's disease. There was no loss of nails but a gradual loss of teeth; no ocular symptoms or acromegaly. There was obstruction of the nose. When the skin was examined it was seen that the blood in the capillaries intermittently ceased circulating for a short time. This symptom was due to local angiospasms. There were also symptoms of latent tetany (Chvostek's symptom was

positive). The x-ray pictures showed an enlarged sella. Hypophysis preparations met with marked success, and it was therefore deemed probable that hypophysis extract exerts a regulating influence upon blood-vessel tone. In Raynaud's disease periods of achylia gastrica are observed. The author supposes that these periods are due to vasomotor disturbances in the stomach.—J. K.

(HYPOPHYSIS) Hypophyseal cachexia (Hypophysäre Kachexie). Reye, München. med. Wchnschr., 1920, 67, 1302.

A short note on a patient with syphilis and hypophyseal cachexia. Treatment with mercury, salvarsan and asthmolysin was followed by improvement. The patient became less dull and the pubic hair and eyebrows, which had previously been lost, began to grow again. —J. K.

(HYPOPHYSIS) Tumors of squamous epithelium of the infundibulum, their structure and position in the oncological system (Plattenepithelgeschwülste des Infundibulums, ihr Bau und ihre Stellung im onkologischen System). Siegmund, München. med. Wchnschr., 1920, 67, 827.

The author examined four of these tumors, which were originally described by Erdheim. Their structure is complicated. They always contain cysts. The epithelium resembles in its morphology that of the tissue from which the enamel of the teeth is derived. The stroma of the tumor consists of connective and glial tissue. Masses of necrotic columnar epithelial cells, surrounded by giant cells, and often containing a large quantity of calcium, are characteristic. In three out of four cases the tumors were invasive; in two cases, clinically resembling dystrophia genitalis, the hypophysis was unchanged. The tumors are not teratomata, but probably originate from the ectoderm of the buccal cavity, from rests of the fetal ductus hypophysis. In two of the cases dystrophia genitalis without adiposity occurred. It is possible that the adiposity in such cases is not related to the hypophysis, but is secondary to the atrophy of the gonads.—J. K.

A case of tumor of the HYPOPHYSIS (Een geval van hypophysegezwel). de Stella (H.), Vlaanischgeneesk. Tijdschrift (Ghent), 1920, 1, 440-449.

A report of a case of a boy of 19, who complained of severe headaches and vomiting. After a month the pain disappeared, but the boy gradually became very fat and blind. There was but little hair in the axillae and on the pubes. The testicles were atrophied. Goitre, exophthalmos and tachycardia were present. The x-ray showed an enlarged sella turcica. The patient was first treated with thyroid with good result. The adiposity disappeared and the general health improved. Hypophysis preparations gave still better results. The

exophthalmus nearly disappeared, but the sight did not improve. Nevertheless, the tumor gradually became larger, organotherapy ceased to be successful and the adiposity again returned. X-ray treatment will be initiated and if this fails, operation will be attempted.—J. K.

(HYPOPHYSIS, THYROID) A case of diabetes insipidus changed to myxedema (Uebergang eines Falles von Diabetes insipidus in Myxödem). Strausz (L.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 939.

An intelligent boy of 9 years developed polyuria (seven liters daily) and polydipsia. When he was 13 these symptoms had disappeared, but he became dull and very stupid. When he was 15 he had typical myxedema, but no symptoms of diabetes insipidus. The patient died of pneumonia when he was 20. No autopsy was performed.—J. K.

(HYPOPHYSIS) (Technik der Hypophysealoperation). Tiefenthal, München. med. Wchnschr., 1920, **67**, 794.

Of technical surgical interest.—J. K.

(HYPOPHYSIS) Extract titration by the isolated uterus method (Titrierung von Hypophysenextrakten am ausgeschnittenen Uterus). Trendelenburg (P.) & Borgmann (E.), Biochem. Ztschr. (Berlin), 1920, **106**, 239-253.

This paper is a report of a study of the assay of some 20 commercial preparations of the extract of the posterior lobe of the pituitary as compared with extracts made by the authors from fresh glands. They found that adult virgin guinea pigs weighing no less than 200 nor more than 250 grams are the animals most suited for the work. Using such animals it was found that while the freshly prepared posterior lobe extracts had an average titer of 0.17 gram β-imidazolylethylamine, the commercial extracts were very much weaker and equivalent to but 0.00025 to .008 grams per 1 gram posterior lobe, as a basis of calculation.—F. S. H.

(INTERNAL SECRETIONS) Paracer a respeito. Barbosa (Renato), Arch. Rio Grand. de med. (Porto Alegre, Brazil), 1920, **1**, ——, (May).

Polemical, concerning a previous report.—B. A. H.

Influence of the glands of INTERNAL SECRETIONS on gastro-intestinal pathology (Influencia das glandulas de secreçao interna na pathologia gastro-intestinal). Dias (Annes), Arch. Rio Grand. de med. (Porto Alegre, Brazil), 1920, **1**, —— (May).

Enthusiastic exposition of the importance of endocrine disturbances in diseases of the gastro-intestinal tract.—B. A. H.

Polycythemia as a hereditary disorder of the INTERNAL SECRETIONS (Ueber Polyzythämie als vererbbare Störung der inneren Sekretion). Engelking (E.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1140-1142.

The author reports the study of a family manifesting polycythemia for three generations. The condition was observed in the grandmother, the mother, and five children. The characteristic age of the appearance of polycythemia is from the 35th to the 55th years. In the family studied, however, the grandmother had died at 24, and one of the children developed the condition at 5. All the children of the family are infantile. The older children showed symptoms of endocrine abnormalities. A daughter of 19, as well as the mother, began menstruation very late, and this function was always irregular. The second child, a girl of 15, has not yet menstruated. Some members of the family were goitrous. The author discusses the question as to whether the formation of red corpuscles is under the influence of the internal secretions. In this connection he cites the observations of Bertelli, Falta, and Schweeger, that in dogs subcutaneous or intravenous injections of adrenalin resulted in an enormous increase in the number of corpuscles (40 to 100 per cent). This influence of adrenalin and other hormones on the blood has been repeatedly confirmed. On these grounds the author believes that hereditary endocrine perturbations may be responsible for polycythemia.—J. K.

INTERNAL SECRETIONS (Innere Sekretion). Kestner (O.), Ztschr. f. ärztl. Fortbild. (Jena), 1920, **17**, 573-581.

A general review. The author states that all endocrine glands are closely related. The most intimate relation exists between the **hypophysis** and the **thyroid.** Growth depends upon the hypophysis and is completed at puberty; therefore most women are smaller than men because puberty in women begins earlier; and the men in southern countries are generally smaller than those in northern regions.
—J. K.

On the cause of the hypertrophy of the surviving OVARY after semispaying (albino rat) and on the number of ova in it. Arai (H.), Am. J. Anat. (Phila.), 1920, **28**, 59-79.

After semispaying in the young albino rat the compensatory hypertrophy of the remaining ovary occurs independently of copulation or pregnancy. The hypertrophy is produced by a greater abundance of well developed normal and degenerate follicles, and by an excess of corpora lutea. The number of ova is only slightly decreased Semispaying neither hastens nor delays the appearance of the first ovulation.—W. J. A.

The specific hormone of the OVARY (Ueber das spezifische Overialsekret). Fellner (O. O.), Zentralbl. f. Gyn. (Leipzig), 1920, 44, 1133-1138.

Esch (Zentralbl. f. Gyn., 1920, 44, 561) has stated that no hormone of the ovary is known. According to the author, this is not true, for he considers the "sexual-lipoid," which he prepared years ago, as the specific hormone. It can be prepared from placenta, "Eihäute," corpus luteum, the interstitial cells of the ovary and the testicle, but from no other organs. When injected into female animals it causes hypertrophy of the uterus, the vagina, and the mammae. In the male animal it causes an enlargement of the breasts. It is not identical with the lipamin described by other investigators, for lipamin causes hemorrhage when injected; sexual-lipoid does not. Lipamin is a mixture of substances; perhaps there are traces of sexual-lipoid in it. The corpus luteum has no relation to bleeding in menstruation, for this may be observed now and then after double ovariectomy. The function of the sexual-lipoid is to prepare the mucous membrane of the uterus for menstruation. In an alcohol-ether extract of ovary and placenta poisonous substances may be found. Therefore, one should use only the author's sexual-lipoid.—J. K.

(OVARY) The treatment of the symptoms caused by a loss of ovarian function with the organo-preparation "Ovobrol" (Die Behandlung der ovariellen Ausfallserscheinungen unter Anwendung des sedativen Organpräprarates "Ovobrol"). Guttmann (E.), Deutsche med. Wchnschr. (Berlin), 1920, 46, 1255-1256.

A recommendation of "ovobrol," one tablet of which contains one cc. of ovoglandol and one gram of sodium bromide with some aromatic plant extracts.—J. K.

The influence of iodine on the OVARY (Ueber die Einwirkung von Jod auf die Ovarien). Jastram (M.), Mitt. a. d. Grenzgeb. Med. u. Chir. (Jena), 1920, 32, 460-466.

Tiersch has asserted that large doses of iodine have an unfavorable influence on the ovaries of young persons. Jastram has tried to confirm this experimentally. He gave potassium iodide to young dogs of 4, 6 and 7 weeks (up to three grams daily). He observed growth of connective tissue in the ovary, but even after very large doses no changes in the follicular elements could be found. Nevertheless, the author advises care in the use of iodine in young women. —J. K.

MYOTONIA combined with dystrophy (Myotonie in Kombination mit Dystrophie). Rülf, Deutsche med. Wchnschr. (Berlin), 1920, 46, 1178.

The most common symptoms in this disorder are, according to Rülf, dystrophy of the muscles, cataract, testicular atrophy with sex-

ual impotence, loss of hair, and dermographia. The disease is in all probability a pluriglandular endocrine disorder.—J. K.

(PANCREAS) Cytological studies of Langerhans' islets, with special reference to the problem of their relation to the pancreatic acinus tissue. Saguchi (S.), Am. J. Anat. (Phila.), 1920, **28**, 1-57.

A detailed study of the frog's pancreatic islets by means of the more recent cytological methods is reported. Three types of granular and two of non granular cells are described. The cells of the islets are derived according to Saguchi from the acini.—W. J. A.

PINEAL tumor (Epiphysentumor). Frank, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 900; Wiener klin. Wchnschr., 1920, **33**, 743.

A man 20 years of age died with symptoms of brain tumor. At autopsy a teratoma of the pineal gland was found. The tumor included intestinal tissue, alveoli of lung, connective tissue, muscle, cartilage, epithelium, and neuroglia. In addition, a relatively large amount of pineal tissue remained. It is probably due to this fact that the patient failed to show any symptoms of pineal disease during life.—J. K.

(PARATHYROIDS) A case of peripheral pressure neuritis in tetany (Ein Fall von peripher Druckneuritis bei Tetanie). Beth (H.), Wien. klin. Wchnschr., 1920, **33**, 701-703.

A patient with pneumonia suddenly developed clonic spasms in both arms with all symptoms of tetany. The spasms continued for four days. On the third day trophic changes were observed in the nails and there was edema of the arms. The spasms gradually subsided but the edema and the Trousseau phenomenon remained; there were ulcers between the fingers and the finger joints were swollen. Gradually these symptoms disappeared but the right hand was weaker than the left and showed atrophy of the small muscles, especially of the thumb and the little finger. The nails of both hands and feet became brittle and after some time the patient lost all of her nails. —J. K.

(PARATHYROIDS) Tetanie. Elias (H.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1236.

Report of a patient of 27 with tetany who was successfully treated with intravenous injections of sodium carbonate solution. As it is known that the administration of acid may produce tetanic symptoms, the author believes that acidosis plays an important part in the pathogenesis of tetany.—J. K.

(PARATHYROIDS) Experiments on tetany (Experimentelle Untersuchungen über Tetanie). Farner (E.), & Klinger (R.), Mitt. a. d. Grenzgeb. Med. u. Chir. (Jena), 1920, **32**, 353-373.

The authors used more than 100 rats in their experiments. The parathyroids were removed and after some time the animals were killed and the thyroid and thymus examined histologically to see whether or not parathyroid residues remained. Many animals, but not all, within ten to twenty hours after the operation, showed a rigidity, especially of the hind-legs; the fore-legs were bent, and there were tremors of the limbs. These symptoms rarely lasted for more than three hours. The animals developed normally and the sexual functions and pregnancy were also normal. Cachexia as described by other observers was not obtained in these studies. The incisor teeth of the lower jaw always became opaque as has been described by other workers, particularly Erdheim; the teeth often became fragile. Ulcers or necrosis of the bones were not observed. When the animals were frightened they often went into spasms and sometimes died. These symptoms do not depend upon diet, since change of food had no influence. As other authors obtained more typical symptoms, it is possible that different kinds of rats show a different susceptibility to tetany. Farner and Klinger found no differences between wild and tame rats. The technic of the operation had no influence. In animals with and without goiter, the results were the same.—J. K.

Transplantation of PARATHYROIDS in post-operative tetany. Flörcken (H.) & Fritzche (G.), Zentralbl. f. Chir. (Leipzig), 1920, 47, 1005-1007.

The patient, a woman of 23, was operated upon 11 years ago for goiter. Three years later she developed attacks of tetany at regular intervals during the cold months. The attacks returned every year at the same time, accompanied by convulsions with loss of consciousness and biting of the tongue; gradually the patient became mentally dull. In 1919, parathyroid tablets were given but without success. (The dosage is not mentioned.) In February, 1920, a piece of thyroid and one parathyroid from another patient were transplanted into the musculus obliquus internus. There was no further recurrence of the spasms after the operation, and the symptoms of Chvostek and Trousseau became much less marked. While it is impossible to call this a positive cure, it cannot be denied that the improvement was important.—J. K.

(PARATHYROIDS) New investigation on the relations between otosclerosis and tetany and on the constitution of patients with otosclerosis (Weitere Untersuchungen über die Beziehung zwischen Otosklerose und Tetanie sowie über die körperliche Konstitution der Otosklerotiker). Frey (H.) & Orzechowski (K.), Wien. klin. Wchnschr., 1920, 33, 697-700; 734-736; 754-757.

In 1917 the authors published an article in which they proved that patients with otosclerosis often show signs of latent tetany. They now give the history of ten other cases. In five of the patients latent tetany was obvious, in four very probable. In only one patient, not completely examined, were no symptoms of tetany found. These cases nearly always show hypogenitalism (habitus infantilus, obesity, small testicles, few hairs, especially few pubic hairs, short penis, etc.) and symptoms of so-called asthenic constitution.—J. K.

(PARATHYROID) The blood picture in a case of post-operative tetany Blutbildbeobachtungen bei einem Falle von post-operativer Tetanie). Haas (W.), München. med. Wchnschr., 1920, 67, 781-783.

In a case of post-operative tetany the author observed a diminution in the number of neutrophylic polymorphonuclear leucocytes, an increase in the number of leucocytes, and some eosinophilic leucocytes. The total number of white corpuscles was diminished during the first few days of the illness but soon became normal again.—J. K.

(PARATHYROIDS) Manifestations of tetany in adults (Manifestazioni di tetania negli adulti). de Paoli (N.), Gazz. d. Osp. (Milano), 1920, 41, 899.

A short description of four cases. The first is of tetany in a pregnant woman, which was cured after the birth of the child. The second was a patient in whom tetany occurred during lactation. When feeding was discontinued the tetany stopped. The third case is of the occurrence of tetany after influenza. In the fourth there was present a goiter. Classical tetany gradually developed. In this case there was exophthalmos but no tachycardia. The author believes that the goiter had an influence on the parathyroids embedded in the thyroid.—J. K.

A case of tetania gravidarum cured by implantation of PARATHYROIDS (Durch Epithelkörperimplantation geheilter Fall von Tetania gravidarum). Roth (N.), Wien. klin. Wchnschr., 1920, 33, 886-887.

The subject, a woman of 32, was in her fifth pregnancy, the first four having been normal. She entered the hospital in the sixth month of the pregnancy because of having had various attacks of tetany in the earlier weeks. During these attacks calcium was administered intravenously with temporary benefit. A parathyroid gland obtained from a patient undergoing strumectomy was then implanted. The first three days following the operation no attacks were observed; then three mild attacks occurred. Following these the patient was restored to perfect health and suffered no further symptoms of tetany.—J. K.

PITUITRIN as stimulant to parturition (Ueber die Anwendung minimaler Dosen von Pituitrin zur Einleitung der Geburt am Ende der Schwangerschaft). Stein (A.), Zentralbl. f. Gyn. (Leipzig), 1920, **44**, 1152-1153.

When pituitrin is injected two or three weeks before term it has no effect whatever as a uterine stimulant. During the last days of pregnancy, however, it is possible in about 60 to 70 per cent of the cases to initiate labor by the injection of small doses of pituitrin. The author advises the use of this drug at this time in doses of 0.12 to 0.18 c.c., administered three times at hourly intervals in the muscles of the leg. If ineffective, the procedure may be repeated the next day. Labor so initiated is generally completed within twelve hours. The use of large doses is not advisable.—J. K.

The influence of PITUITRIN on diuresis (Ueber diuresehemmende und diuretische Wirkung des Pituitrins). Brunn (F.), Zentralbl. f. inn. Med. (Leipzig), 1920, **41**, 674-679.

When a given subject ingests a large quantity of water and receives also a hypodermatic injection of 1 c.c. of a 20 per cent extract of hypophysis, the quantity of urine excreted is diminished in the relation of 10 to 1 as compared with excretion following the taking of the same quantity of water without the extract. Similarly, the quantity of NaCl excreted bears the relation of 3 to 1. When, with a given large quantity of water, the subject ingests at different times gradually increasing amounts of NaCl, the quantity of urine gradually diminishes. If, however, pituitrin is injected under these conditions the quantity of urine is increased. This fact was observed in case of normal subjects and of two patients with thyroid disorders. One of these patients had frank Graves' disease and the other a "forme fruste" of the malady. The quantity of NaCl in the blood plasma is not changed when a large amount of water is taken; but when NaCl is ingested it appears in the plasma in increased concentration. This is true whether pituitrin is injected or not. With the refractometer the plasma gives a higher reading after the administration of NaCl and pituitrin than after the NaCl alone. The more dilute is the urine the greater anti-diuretic effect has pituitrin. The author reports some interesting observations upon the isolated kidney of the frog. When hypophysis is injected into the aorta the permeability of the kidney becomes materially less than when the same quantity is injected into the renal vein. Since, in the frog, the blood supply of the glomeruli is from the arteries, while that of the tubuli is from the veins, the observation would indicate that hypophysin acts primarily on the glomeruli.—J. K.

(TESTES) Dystrophia myotonica. Gunther, Deutsche med. Wchnschr., 1920, **46**, 1131.

Case report of a man of 36 with atrophy of the masseters, the sternocleidomastoids, and the muscles of both arms and hands, cataract of both eyes, loss of hair, and marked atrophy of both testicles.—J. K.

(TESTES, THYROID) Dystrophia myotonica. Hauptmann, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1132.

In this case the symptoms were atrophy of the face, the forearms and the hands, paralysis of the peronei, loss of hair, cataract, increased salivation, very small soft testicles, and goiter. In the blood were found lymphocytosis and eosinophilia—J. K.

(TESTES) Abnormal sexual desires (Abnormer Geschlechtstrieb). Lichtenstern, Wien. med. Wchnschr., 1920, **33**, 893.

The patient was a man of 44 with greatly increased sexual desire. He had symptoms of sadism and suffered from severe headaches. One testicle was removed and successfully implanted into a homosexual. The patient himself, however, was not improved. The second testicle was removed also. All sexual desires then disappeared, as also the sadistic perversion. The second testicle was transplanted into a eunuch with good results.—J. K.

(THYMUS) The modern view of status thymico-lymphaticus and its relation to other diseases (Der jetzige Stand der Lehre vom Status thymico-lymphaticus und seine Beziehung zu anderen Krankheiten). Henke (F.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1257-1259.

A general review without new facts.—J. K.

Congenital cataract binocular, complicated by a large persistent THYMUS gland. Tivnen (R. J.), Surg. Clin. Chicago, 1920, **4**, 943-958.

A case report. The patient, 20 months old, was presented for operation. The child was a "blue baby," with the cord once about the neck; resuscitation required two minutes. Weight of child at birth was 6 pounds, 8 ounces; length, 50 cm. For forty-eight hours following birth the child was apparently normal. Early on the third day the nurse found it in a cyanotic condition, with irregular respiration—Cheyne-Stokes in character—and pulse rapid but regular. Examination during this attack disclosed both anterior fontanel and the wide median suture bulging without pulsation; right eyelid edematous, completely closing eye; left eye negative; knee-jerks normal; no contractures or spasms present. For three days following, the baby had almost daily attacks of this character, after which its respiratory and cardiac system gave no further trouble. Two weeks later an oculist made a diagnosis of binocular congenital cataract and recommended deferring operative procedure until the baby was one or more years of age.

The so-called "cyanotic spells" continued at irregular intervals to the twentieth month. The baby never became unconscious; the duration of the attacks was from three to five minutes; slight noises, hunger, fatigue, and undue excitement were the usual exciting factors. A radiogram of the chest disclosed a very large persistent thymus gland. Physical examination disclosed cerebral palsy ascribed to defective glandular secretion and probably also to a cerebral hemorrhage at birth; the chest examination failed to disclose the thymus enlargement. The Wassermann reaction was negative.

The patient was placed on roentgenotherapy at weekly intervals for a period of twelve weeks in order to decrease the size of the gland. A radiogram taken after the last treatment showed practically complete disappearance of the hypertrophied thymus gland shadow. The roentgenotherapy produced a very marked beneficial effect upon the child's general condition. His mentality was greatly stimulated and developed, his vocabulary increased, locomotion, which had previously been absent, was established, and in particular, the "cyanotic spells" were strikingly diminished both as to frequency and severity.

In this patient the clinical history fits perfectly the diagnosis of a large persistent thymus gland. The attacks of dyspnoea, the spells of cyanosis, the delayed development, the mental status, and to some extent the congenital cataracts, are characteristic. In addition the radiogram corroborates the clinical history and the reduction of the hypertrophied gland, as shown by the skiagram, under roentgenotherapy is coincident with the striking improvement in the child's development, mentally and physically and the marked diminution in the severity and frequency of the attacks of dyspnoea.

In connection with the report of this case the author presents a comprehensive review of the anatomy and physiology of the thymus gland. He directs especial attention to the fact that patients with enlargements of the thymus gland are undeniably distinct hazards as candidates for surgical procedures where an anesthetic, local or general, is contemplated, and expresses the opinion that the only safe course to pursue in such cases when an operative procedure is contemplated, particularly in infants and the young and especially when they present lesions attributable to some vagary of evolutionary character is definitely to determine the condition of the thymus gland before the operation is undertaken. In his own practice he has advocated and adopted this plan for some time past as a regular routine of pre-operative investigation. In this connection he refers to the case of an infant of two and a half years, upon whom in the course of several months he was to perform a tonsillectomy and adenectomy, whom the parents one morning found dead in its crib. It had suffered no previous illness of any character and was regarded as in excellent health. Autopsy disclosed a large persistent thymus gland with associated general adenopathy.

In the author's experience, physical examination alone of the chest is neither satisfactory nor conclusive and he has come to regard the x-ray when properly taken by an experienced roentgenologist, as the most reliable and dependable method of investigation. In one of his cases physical examination of the chest by an experienced and skilful diagnostician proved negative, while the x-ray showed a large persistent thymus gland.

Roentgenotherapy is advocated as a satisfactory and useful agent in properly selected cases in reducing the thymus enlargement and improving the general condition and development of the patient. The indiscriminate use of roentgenotherapy, however, is not advisable, particularly in cases where the enlarged thymus has been rendered deficient through focal degenerative changes, with secondary cretinism, myxedema, or Addison's disease. In such cases more harm than good results.—Author's Abst.

(THYROID) The treatment of goiter by the Roentgen ray. Boggs (R. H.), Interstate M. J. (St. Louis), 1917, 24, 362-367.

Boggs explains the beneficial effect of roentgen rays on hyperthyroidism and malignancy by their power to inhibit proliferation of embryonic cells through their direct action on the nuclei of epithelial cells. He stresses the importance of radiating not only the thyroid, but also the thymus and ovaries in Graves' disease, pointing out that resection of the thyroid gland does not always cure the disease, because the thymus and ovaries are still over-active. In grave thyroid autointoxication, radiation should be very carefully begun, since stimulation of the gland with increase of symptoms sometimes results at first. The roentgenologist must be careful not to overtreat or myxedema will result. A decrease in pulse rate is the first sign of improvement, usually followed by gain in weight and subsidence of nervous symptoms; reduction of the size of the gland and of the exophthalmos comes later or not at all. The author very briefly reports three typical cases of Graves' disease cured by roentgen rays and remaining well for 7 to 10 years after treatment. Boggs advocates judicious roentgen treatment of the adolescent goiter as a prophylactic measure and has found the patients to be distinctly improved in health even though none of the obvious signs of hyperthyroidism were present.

He also insists that radiation should not be attempted except by an expert familiar with the technic and thoroughly versed in the physiology, pathology and clinical aspects of endocrin disease. Better cosmetic results and lower mortality than can be expected from surgical methods are claimed for the roentgen therapy. [It would be safer if the patient treated with x-rays be systematically watched by an experienced internist and controlled also by basal metabolism studies.]—H. L.

The discovery of the active principle of the THYROID (Ueber die Entdeckung des wirksamen Bestandteiles der Schilddrüse). Widmark (Erik M. P.), Sven. Lärkartidn. (Stockholm), 1920, **17**, 241-246.

Refers to Kendall's research on the composition of "Thyroxin." The point of view is taken that this substance approximates tryptophan in composition and the idea is expressed that tryptophan-poor food should be tried out in cases of hyperthyroidism.—J. A. H.

(THYROID) Contribution to the physiology of the glands. 44. The behavior of normal, thyroid-fed and thyroidless rats to oxygen deficiency (Beiträge zur Physiologie der Drüsen. M. 44. Leon Asher. Das Verhalten von normalen, mit Schilddrüsen-substanz gefütterten und Schilddrüsenlösen Ratten gegen reinen Sauerstoffmangel). Cao (M. D.), Biochem. Ztschr. (Berlin), 1920, **106**, 254-274.

White rats were put under the bell-jar of a vacuum pump and the air partially exhausted. The removed gases were replaced by hydrogen and the behavior of the animals studied. Extensive protocols are appended, the data from which lead to the conclusion that both hypo- and hyper-thyroidism in rats conduces to an increased susceptibility to oxygen deficiency. These facts contribute to an understanding of the behavior of the respiratory metabolism under the influence of pathological conditions of the thyroid.—F. S. H.

Relationship of the THYROID gland to Graves' disease. Crile (G. W.), Can. M. Ass. J. (Toronto), 1917, **7**, 727-731. J. Med. Soc. N. Jersey (Orange), 1917, **14**, 180-182.

Hyperplasia is not a necessary characteristic of Graves' disease, because excision of a sufficient amount of a colloid goiter or of an adenoma in a typical case improves or cures the disease just as it is cured or improved by the excision of a hyperplastic gland. The degree of surgical relief is independent of the histology of the gland. In most pregnant women, in many adolescent girls, in a large proportion of advanced cases of tuberculosis, and in numerous cases of intense pyogenic infection the thyroid is not only hyperplastic but the histological picture is identical with the hyperplasia of Graves' disease. On the other hand, in from only 50 to 75 per cent of cases of Graves' disease is the thyroid hyperplastic. Crile, therefore, concludes that hyperplasia of the thyroid cannot be the cause of Graves' disease any more than it is the cause of pregnancy or of tuberculosis or of adolescence—it is an end effect, not a cause. But resection of thyroid tissue does mitigate or cure Graves' disease, whereas such a procedure would not end pregnancy, cure infection or assist adolescence. The cases of Graves' disease which were not entirely cured or which partially relapsed after resection did so for the following reasons. (a) Psychic drive—"The more intense the struggle of man against man, the more difficult it is to cure Graves' disease

completely." Crile points out that the disease is rarely found in the degenerate, in idiots or in moral defectives. Sudden emotional or physical shock, great worry or strain, etc., will cause relapse. (b) Acute infections are also a cause. (c) Intestinal auto-intoxication will prolong the disease. (d) Pregnancy may cause it; with its termination the relapse subsides. (e) Adolescence is another cause and one which cannot be controlled. The interesting conclusion follows that the thyroid changes are end effects and not the cause of Graves' disease, but that resection of the thyroid breaks "a link in the kinetic chain," and that maximal improvement demands a combination of surgical and medical measures.—H. L.

(THYROID) Malignant goitre. Crotti (A.), Ohio M. J. (Columbus), 1917, 13, 807-809.

Malignant goitre develops in an already existing goitre in 90 per cent of the cases; a malignant tumor developing in a normal thyroid is rare; the tumor is nearly always of connective tissue origin, as sarcoma, etc.; malignant degeneration of goitre occurs mostly between 40 to 60 years of age. Sarcoma occurs mostly in young people, cancer in old. Malignant goitre is more common in women, and most frequent at the menopause. It may develop very acutely and is then difficult to differentiate from acute woody thyroiditis. It may be latent and the gland may hardly be modified in appearance, but numerous metastases may occur in lungs and bones. The thyroid origin is usually discovered at autopsy; this type is rare. Usually malignant goitre is subacute, and develops from a goitre which has been stationary for years. Crotti gives an excellent clinical picture of the symptoms and physical signs present in these cases, all of which is so detailed that it cannot be abstracted. Cancer metastases in bones are most frequently due to thyroid cancer; a prostatic origin comes second. The skull is the most common site for thyroid cancer metastasis, then the pelvis, sternum, femur, clavicle, lower jaw and shoulder blades. Malignant goitre does not necessarily produce hyper- or hypo-thyroidism. Interference with respiration and deglutition, in a patient with a goitre which has becomes irregular and peculiarly hard, accompanied by shooting pains, strongly suggests the presence of malignant goitre. Crotti insists that the only therapy deserving consideration is surgery, and that if the high mortality is to be reduced, it rests with the family physician to diagnose cases sufficiently early before the neoplasm has burst through the capsule. "An alarming pessimism" is the best state of mind for the general physician, so that he may suspect malignancy early.—H. L.

(THYROID) Acute febrile epidemic myxedema (Mixedema acuto febbrile epidemico). Ditelli (S.), Gazz. d. Osp. (Milano), 1920, 41, 696.

A short note. A mild epidemic of myxedema, beginning with a swelling of the head, the neck and the thorax was observed in Nicosia, Italy. The patients became normal again after a few weeks without any treatment.—J. K.

(THYROID) Case of severe hemorrhage in a cystic goiter with danger of suffocation (Su di un caso di grave emorragia in gozzo cistico con imminente pericolo di soffocazione). Dossena (G.), Morgagni (Milano), 1920, 62, 291-296.

Report of a case caused by strumectomy. Two good illustrations.—J. K.

(THYROID) Direct muscular protection to the goiter residue in primary closing of the wound after strumectomy without drainage (Die direkte Muskeldeckung des Kropfrestes beim primären Wundschlusz nach Strumektomie ohne Drainage). Dubs (J.), Zentralbl. f. Chir. (Leipzig), 1920, 47, 1294-1296.

Of technical surgical interest.—J. K.

(THYROID) Surgical goitre. Else (J. E.), Northwest Med. (Seattle), 1917, 17, 16-20.

The author considers the indications for operation upon the thyroid to be: (1) cosmetic, (2) mechanical, (3) toxic, (4) malignancy. Only the second and third are considered in this paper. The mechanical indications are all due to pressure, either upon the trachea, esophagus, nerves or adjacent blood vessels. Pressure upon the trachea may result in deflection, lateral compression, cough, interference with expiration producing emphysema, edema of the mucosa and, rarely, complete occlusion with death. Else refers to the various types of intrathoracic goitre which may cause compression. He then mentions the varieties of toxic goitre—exophthalmic or hyperplastic, and toxic or cardiovascular, which in turn are due to adenoma, adenomatosis, and regeneration or compensatory hyperplasia. Attention is called to the lack of correlation between the clinical findings and pathological changes. Depending upon the quantity of colloid present Else speaks of foetal, adult and mixed adenoma. One cannot tell from the microscopic appearance whether toxic symptoms were present or not. Eye signs are absent in adenomas. The author follows closely the classification and ideas of Wilson and Plummer. Preliminary ligation of the superior thyroid artery is urged in severe toxic cases, to be followed shortly by lobectomy.—H. L.

(THYROID) The heart in 17 cases of Graves' disease and 7 cases of goiter (Herzuntersuchungen an 17 Fällen von Morbus Basedow und 17 Fällen von Struma). Fähr, Deutsche med. Wchnschr. (Berlin), 1920, 46, 1178.

Data reported elsewhere.—J. K.

(THYROID) Abnormal goat milk. Grimmer (W.), Milch. Zentralbl., 1920, **49**, 67-69; Physiol. Abst., **5**, 427.

Milk from thyroidectomized goats was found over a considerable period of time to be abnormal. Such milk has a relatively high specific gravity, low caseinogen and sugar content and a notable increase in the weight of the non-fat solids. Calculations based on the Fleischmann and Babcock formula yielded high values, not in harmony with the analytical results.—R. G. H.

(THYROID) Basedow und THYMUS. Haberer. Mitt. a.d. Grenzgeb. Med. u. Chir. (Jena), 1920, **32**, 329-353.

In cases of Graves' disease or simple goitre, treated surgically, it is often not enough to reduce the thyroid, but it is necessary, when possible, to reduce the thymus also. This is not a proof that there is a thymic factor in Graves' disease. It is very doubtful whether this exists. Haberer treated 35 cases with reduction of both thyroid and thymus. Three patients died. One of them was a woman with a very weak heart who was in the last months of pregnancy. The two others showed nervous tension after the operation; the pulse was too rapid to be counted; there was fever and cyanosis. In both cases it was found at autopsy that a large part of the thymus had been left in the body. In most other cases after the operation nervousness disappeared at once and the pulse became regular and quiet, although in two the heart symptoms and the nervousness persisted for some time. In both cases a relatively large part of the thymus had been left. One patient was at the point of death on admission to the hospital. He had repeatedly undergone strumectomy without success. After strumectomy and thymectomy complete recovery occurred. In 10 patients the goitre returned, but the other symptoms of Graves' disease never came back. If thymectomy is not performed but only a part of the thyroid removed, Graves' disease often shows real recurrences. Some cases are still healthy seven years after operation.—J. K.

(THYROID) War diet and hypothyroidism (Kriegsernährung und Hypothyroidismus). Hinz (C.), Med. Klin. (Berlin), 1920, **16**, 313-315.

Hinz, of the University Medical Polyclinic, at Rostock, quotes cases to show that there is a close relationship between hypothyroidism and war edema. He alludes to the success obtained by administration of thyroid extract in many cases of war edema, and mentions the autopsy findings of Oberndorfer, who found marked atrophy of the thyroid. He also alludes to Adler's experiments on hibernating animals as illustrating the connection between diminution of food metabolism and the function of the thyroid. By injecting hibernating animals in which respiratory movements and temperature are reduced to a minimum, Adler succeeded in waking them after one to three hours, and raising their temperature from 8 degrees

C. to 35 degrees C. Hinz suggests that in war edema the insufficiently nourished organism endeavors in like manner to protect itself by a diminution of thyroid function.—Med. Sc. Abst. & Rev., 3, 215.

(THYROID) A new pair of scissors for operating for goitre (Ein neue Kropfschere). Hofmann (A.), Deutsche med. Wchnschr. (Berlin), 1920, 46, 1257.

A new surgical instrument.—J. K.

(THYROID) Myxedema. Kaspar, München. med. Wchnschr., 1920, 67, 1190.

A typical case in an infant of three months.—J. K.

(THYROID) Demonstration of four cases of cretinism (Demonstration von 4 Fällen von Kretinismus). Kellner, Deutsche med. Wchnschr., 1920, 46, 1130.

After the demonstration the author discusses the mortality of mentally deficient children. This is always much higher than in normal persons, but during the war the ratio was increased. The bad hygienic conditions in Germany, the increased number of alcoholics and patients suffering with syphilis are the causes of the rapid increase in the number of mongoloids, myxedemas, and cretins.—J. K.

Ligation of the THYROID arteries in operation for goiter (Zur Frage der Unterbindung sämtlicher Schilddrüsenarterien bei Kropfoperation). Kreuter (E.), Zentralbl. f. Chir. (Leipzig), 1920, 47, 1317-1318. Lobenhoffer, Ibid., 1319-1322.

Of technical surgical interest.—J. K.

(THYROID) Goiter (Struma). Linhart, Wien. klin. Wchnschr., 1920, 33, 763.

A short note on a very large retrosternal goiter and the way in which it was removed.—J. K.

(THYROID) Mistakes in one hundred thyroidectomies; with description of a new method of thyroid cauterization in treating exophthalmic goiter. Mason (J. Tate), J. Am. M. Ass., (Chicago) 1920, 75, 160-162.

A report of a series of 100 thyroidectomies covering a period of eight years. Fifty-eight patients were operated upon for toxic adenomas; one patient died. Forty-two patients were operated upon for exophthalmic goiter and five died. The symptomatology of the two types of cases is briefly discussed. The one death in the first series was due to refusal of the patient to undergo preliminary rest treatment. Mason feels that the most serious mistakes are due to lack of a full appreciation of the dangers of the crisis in exophthalmic

goiter, and to attempting too much in extremely bad cases. As to technic, local anesthesia is begun by pressure for 30 seconds with a cotton applicator frozen with ethyl chloride, upon the point chosen for the first needle puncture. Procain is then infiltrated as usual, the goiter exposed, and small portions cauterized. This is repeated every two or three days until the patient is considered a safe risk for ligation or thyroidectomy. This fractional cauterization may replace ligation in time.—F. S. H.

(THYROID) Mongoloid idiocy. Meltzer, Berl. klin. Wchnschr., 1920, 57, 791-792.

Although the thyroid is frequently asserted to be at fault in mongoloid idiocy, this is certainly not true in all cases. Post-mortem examinaitons often do not show that changes have taken place in the thyroid and often iodine has no effect upon the disease.—J. K.

(THYROID) A case of myxedema after operation for Graves' disease (Ein Fall von Myxödem nach operiertem Morbus Basedow). Munk, Deutsche med. Wchnschr. (Berlin), 1920, 46, 1154.

Previously abstracted from the München. med. Wchnschr.—J. K.

The treatment of THYROID toxicosis with iodine (Ueber Jodbehandlung bei Thyreotoxicose). Neisser (E.), Berl. klin. Wchnschr., 1920, 57, 461-463.

Most authorities consider the administration of iodine as extremely dangerous in cases of Graves' disease. Neisser has seen cases in which iodine cured the patient almost at once. One of his patients was a man of 45, who had a simple goiter. After x-ray treatment the goiter became smaller, but symptoms of Graves' disease (tachycardia), great loss of weight, diarrhoea, perspiration, and exophthalmus developed. Potassium iodide in small doses (three times daily, 10 drops of a solution of 1:20) cured the patient in a very short time. Six other cases are described, one a young woman in whom Graves' disease followed **ovariotomy.** In this case, also, the iodine treatment was successful. The author points out how we may distinguish the cases to be treated with iodine. According to him, there are four classes of patients in whom iodine treatment is advisable; those in whom the loss of weight has reached the maximum and whose weight is therefore stationary; those with small or diminishing goiters; those without exophthalmus; and those with tachycardia but without dilation of the heart. For these cases the author recommends the use of a solution of sodium or potassium iodide, 1:20, beginning with 2 to 5 drops three times daily, and increasing gradually to 20 drops three times daily.—J. K.

(THYROID) Goitre exophthalmique et syphilis. Pfeiffer (C.), Progres méd. (Paris), 1920, 3.s., 35, 187-188.

Pfeiffer, of Dijon, records three cases of acute Graves' disease in which the causal emotion, which was insufficient in itself to produce a permanent anatomical change, was accompanied by an important factor, viz., active syphilitic infection. As these three cases were the only examples of so-called exophthalmic goiter which he had met with during eighteen months' observation of several hundred cases of commotion, Pfeiffer is convinced that every case of exophthalmic goiter of so-called emotional origin, occurs on a syphilitic soil.—Med. Sc. Abst. & Rev., **3**, 213.

(THYROID THYMUS) Syndrome polyglandulaire thymothyroïdien avec hydrocéphalie. Sabrazès (J.) & Dupérié (R.), Gaz. hebd. d. sc. méd. de Bordeaux, 1920, **41**, 350-351; 410-415.

The authors report the case of a woman, aged 29, the daughter of a goitrous mother and alcoholic father, who, in addition to hydrocephalus, presented a congenital thyro-ovarian insufficiency which was improved by opotherapy. But a deep goiter and a large thymus were refractory to treatment and contributed to a fatal termination of an attack of typhoid. Examination of the glands of internal secretion at autopsy showed normal parathyroid tissue and a hypophysis which was in a state of excessive activity. Sclerotic changes in the choroid plexus and various ependymal changes appear to have played an important part in the mechanism of the hydrocephalus.—Med. Sc. Abst. & Rev., **3**, 220.

The relation of THYROID secretion to the condition of the skin—and incidentally to old age. Starr (M. A.), Constrib. Med. & Biol. Research. . . . Sir W. Osler, N. Y., 1919, **2**, 1184-1185.

Starr has found that the dryness of the skin, brittleness of the nails, and the loss of hair usually met with in old age may be stopped by taking small amounts of thyroid (not more than 1 grain of the Burroughs and Welcome extract in divided doses in a day). The patients feel more active mentally and physically, and suffer less from depression and insomnia. Starr concludes that some of the conditions supposed to be due to old age are actually due to a diminution in the activity of the thyroid gland and consequently may be obviated or removed by the constant use of thyroid extract as age advances.—Med. Sc. Abst. & Rev., **3**, 216.

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ADRENAL INSUFFICIENCY

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I. PHYSIOLOGICAL DATA

When both adrenals are removed from most of the ordinary laboratory animals, e. g., dog, cat or guinea pig, death speedily ensues. The fatal result is not evaded, although it may be somewhat delayed, if the operation is performed in two stages and a considerable interval allowed to elapse between the removal of the two glands. The literature is enormous and is extensively cited in the monographs of Biedl (1) and Swale Vincent (2). We shall only refer to a few of the papers, especially as in the more modern work there is a general agreement in the results which particularly concern us.

Abelous and Langlois (3) found that hibernating frogs might live as long as 12 or 13 days after complete ablation of the adrenals, whereas summer frogs on the average never survived more than 48 hours. If the temperature of the room was kept about 22° C. the period of survival of winter frogs was much diminished. If a substantial fraction of one adrenal is left the animals remain entirely normal. If the portion left is very small, death ensues, but not so rapidly as after total adrenalectomy.

Albanese (4) confirmed these results, and from observations on the resistance to fatigue of the decapsulated frogs, concluded that a function of the adrenals is to destroy or transform toxic substances, especially those generated in muscular contraction, a suggestion also made by Abelous and Langlois (5). In another communication Abelous and Langlois (6) found that adult guinea pigs never lived more than 9 hours, and often only 5 hours after double adrenalectomy. Brown-

Séquard (7) in 1856 saw in guinea pigs a minimum period of survival of 9 hours and a maximum of 23 hours. The animals become rapidly weaker, paresis or complete paralysis of the hind legs may be seen and sometimes before death, convulsions. Removal of one adrenal has practically no effect.

Of rats, about 50 cent survive double adrenalectomy. Boinet (8) removed both adrenals in 75 grey rats and found that half of them survived. Many were in excellent condition 5 or 6 months later. The results were quite as good when the two glands were removed simultaneously as when the operation was done in two stages. Similar results were obtained by Stewart and Rogoff (9) in albino rats, although they did not keep them so long. It is astonishing, but characteristic of much of the work on this subject, that in rather recent papers Schwarz (10), Kahn and Starkenstein (11) it should be stated that rats do not survive more than a day when both adrenals are removed at one sitting. It is, of course, important to discriminate between the mortality due to the operation and that due to adrenal deficiency, and this is by no means easy when the animals die within a day or two. The size, age and nutritive condition of the rats are probably not without influence upon the result of removal of the adrenals, certainly as regards the surgical risks in those small animals, and perhaps also as regards the consequences of adrenal insufficiency.

The great majority of rabbits die after double adrenalectomy, but some survive even where the glands are excised at one operation. When the operation is done in two stages, about one in five of the animals survive under good conditions, and after some weeks these rabbits are not distinguished from normal animals by any striking peculiarities. The result of Strehl and Weiss (14), that of 26 rabbits, all died in 8 to 14 hours after double adrenalectomy must have been due to faulty surgery. The rats operated on by them also died in 15 to 19 hours.

Elliott (15) found that 19 out of 21 cats in which both glands were excised at one and the same operation died in from 18 to 48 hours (generally on the second day). Only 2 cats survived to the 9th and 10th day respectively. Of 25 cats from which the glands were removed in two operations 9 died on the 2nd or 3rd day. Thirteen of the animals lived for 6 to 10 days; two survived to the 22nd and 23rd day, and one seemed to have recovered completely when it was killed in the 9th week. These details are quoted because in the question of the time of survival after removal of both adrenals the results of modern work, done with good surgical technique, are much more important than much of the older work, such as that of Strehl and Weiss (14), where some of the deaths attributed to adrenal insufficiency were undoubtedly due to shock (especially in the case of the smaller animals) and others to infection. Elliott attributes the longer periods of survival to compensatory hypertrophy of small accessory adrenals of cortical tissue.

All good observers agree that in practically all dogs double adrenalectomy is incompatible with life. Langlois (16) found that apart from complications connected with the operation all dogs survived removal of one adrenal. Removal of the second gland after an interval of 15 days to 5 months was invariably followed by rapid death (10 to 52 hours, average 28 hours). When both glands were removed at one time the average period of survival was only 17 hours, with a maximum of 26 hours. As is pointed out in the paper, it is impossible to say how much of this slight difference is due to the greater severity of the operation as such. Langlois suggests that observers, like Giliberti and Di Matei (17), Tizzoni (18), and others who saw some dogs sur-

vive for a long period must have left behind a portion of the adrenal tissue owing to faulty technique. The current explanation for the survival of so many rabbits and rats is that accessory adrenal (cortical) tissue is more frequently encountered and is more abundant in these than in the other laboratory animals. In a general way this may be true, but it must be said that in many cases of long survival, such accessory tissue is not discoverable, at least by careful macroscopic examination, nor when discoverable does its total mass often equal the fraction of the total mass of adrenal substance which must be left behind to prevent death in animals like the dog, cat and guinea pig.

A few of the animals which die after removal of both adrenals no doubt, even under the best conditions, in extensive series, succumb to accidental surgical consequences of the operation (shock and infection). With good technique this is a quite unimportant factor. Intercurrent diseases known to affect laboratory stock, sometimes account for a certain number of the deaths. But there can be no doubt that in the vast majority of cases the animals die from "adrenal insufficiency," from the loss, that is to say, of the indispensable something which the adrenals contribute to the functioning of the body. What are the symptoms associated with the extreme degree of adrenal insufficiency caused by the removal of both adrenals in animals? It is disappointing to say in view of the prominence assumed by "suprarenal insufficiency" in the speculations of many clinical observers, who cannot know till after the death of the patient, if then, whether there is any defect in the quantity or physiological quality of the adrenal cortex or medulla, that the symptoms observed by physiologists in animals in which they have purposely produced a known amount of adrenal deficiency, are by no means definite, sharp and characteristic. To be sure, the animal, which may have recovered well after the final operation, and may exhibit a normal temperature, and an appetite and power of muscular effort not sensibly different from that of a control animal subjected at the same time to a similar operation, not involving interference with the adrenals, may rather abruptly begin to show loss of appetite, muscular weakness and a temperature below the normal, and in 24 or 48 hours or less, may be dead. But there is nothing specially pathognomic in such symptoms unless indeed it be the muscular weakness, which may seem to come on with more rapidity than is usually seen in animals dying under other conditions. Elliott (15) says that "all the cats" which survived for the longer

periods "lost weight, and those which survived longest became extremely thin. This was partly due to a loss of appetite. The approach of death was always announced by a very characteristic weakness. The eyeballs lost their tension and became soft as the blood-pressure steadily fell. Special care had to be taken by artificial warmth to check the fall of body temperature, for otherwise the rectal temperature would have dropped from 103° or 104° F. to 85° or 90° F. ere death ensued." We have seen all these symptoms in cats dying after reduction of the total adrenal substance beyond the necessary minimum. But we have no confidence that if shown the animals, without knowing what had been done to them, we could make the diagnosis of adrenal insufficiency. There must, of course, be some profound disturbance of function but the essential manifestations of that disturbance have hitherto remained obscure.

It might be thought that if the process were rendered more chronic by removing only a portion of the adrenal substance, a more definite clinical picture of adrenal insufficiency would be revealed. In the case of the pancreas, it is known that in the dog, so long as a fifth, or even somewhat less, of the total mass is left, no permanent symptoms ensue (Minkowski and von Mering (19)). When one-ninth to one-eighth of the pancreas is left the symptoms come on more gradually and are more dependent upon the character and amount of the food than if the organ is totally extirpated or than if a still smaller fraction (1/10) is spared, and the resemblance of the condition to moderately severe diabetes in man becomes more close (Thiroloix (20), Allen (21)). In the case of the adrenal, however, it has not hitherto proved possible, or only in a very limited degree, to realize a similar gradation in the severity of the symptoms, when varying proportions of the total gland substance are taken away. Trim and pare as he may, the operator either leaves so much of the gland that the animal survives indefinitely in good health, or takes away so much that it dies quickly, as it would have done if the glands had been totally excised. The anatomical line which separates full physiological sufficiency from fatal insufficiency is so narrow that a certain small fraction of this peculiar loaf seems to be, in some cases, so much better than no bread, that it is apparently as good as

the whole, while, in other cases, it seems to be no better than a stone. It must be remembered, however, in comparing the adrenals with the pancreas that from the shape and dimensions of the two objects, it is probably easier in the case of the latter to purposely leave behind a given fraction of the gland substance than in the case of the adrenals. The damage due to interference with the blood supply, including that possibly due to thrombosis, cannot be precisely known, and must vary in each case. The amount of accessory adrenal tissue, hypertrophied in variable degree after the first operation, and the amount of hypertrophy in the portion of the adrenal left, if the animal lives some time, are also factors which cannot well be accurately controlled.

According to Langlois (16) when about 1/6 to 1/11 of the total mass of the adrenal tissue is left in dogs, survival is possible. Far too much emphasis has sometimes been placed on these figures, which, as the author points out, are not to be taken in an absolute sense. They are rough estimates of the amount of tissue unintentionally left behind in a very small number of the animals. Hoskins (22), and Whipple and Christman (23) have supplied better data on this point. The former found that dogs survive after removal of as much as 7/10 of the total mass of the glands, and the latter observers give examples of dogs in which 1/6 or perhaps even a smaller fraction of the adrenal tissue sufficed.

Biedl (1) speaks of one-eighth as the proportion which must be left in dogs, cats and rabbits. Abelous and Langlois (6) stated that the removal of one adrenal had little effect upon guinea pigs, although they might lose weight for a time. After considerable destruction of both glands by the cautery survival was still observed, and even when the amount of tissue destroyed was so great that indefinite survival was not possible the animals lived much longer than after complete adrenalectomy. Elliott mentions that he found it impossible to excise even one adrenal in the English guinea pig at one operation, without causing death, although one adrenal can be removed piecemeal. This, however, does not apply to the variety of guinea pig termed by dealers here the "English guinea pig," in which excision of one adrenal causes no symptoms, even when followed later by removal of a large portion of the other (Stewart and Rogoff). It is not definitely known whether age is a factor in the results of such operations, although susceptibility to shock may be greater in small than in large adult guinea pigs. Gates (24) found that it was possible to remove 3/4 to 7/8 of the adrenal tissue from guinea pigs without causing symptoms of adrenal insufficiency. We can confirm this. In a large series of guinea pigs it was found that even as little as 1/9 or 1/10 of the total mass sufficed. Even after total adrenalectomy (at two sittings) in 7 guinea pigs, 5 of the animals lived 5 to 9 days after removal of the second adrenal. One is still alive after 9 days and another after 14 days.

The results of Rogoff and myself on cats agree with those of previous workers. In the first operation, a varying fraction of one adrenal (usually the right) was removed. When the animal had sufficiently recovered from the effects of the operation, the whole, or, in a few cases, a portion of the remaining adrenal was excised. Of

18 animals, 2 died of distemper after removal of the greater portion of one adrenal, and the experiment could not be completed. Five cats have survived, all in good condition. In one of these the left adrenal and one-third of the right were excised at one operation. In another, 3/5 of the right adrenal was removed and, 18 days thereafter, the whole of the left adrenal. In another 1/3 to 2/5 of the left adrenal, and, 22 days thereafter, the whole of the right were excised. In the fourth cat nearly the whole of the right adrenal (at least nine-tenths, as was judged) was taken away, and 16 days thereafter 2/3 to 3/4 of the left gland. In the fifth cat 2/5 of the right and, 18 days thereafter, all of the left gland was removed. In the eleven cats which died, the interval between the two operations was about the same (16 to 27 days). They usually recovered well after the second operation, took food and showed no symptoms for a time. Then they refused to eat, showed signs of muscular weakness, often a subnormal temperature, became lethargic and died. Some notes are appended.

Cat 4. Male. Excised 3/4 to 7/8 of right adrenal and 24 days thereafter the whole of the left adrenal. Apparently normal for 6 days after last operation, then developed the symptoms mentioned and died 24 to 36 hours after.

Cat 5. Male. Excised 9/10 of right and 17 days thereafter the whole of the left adrenal. Good recovery. Animal seemed well for 5 days, when it was noticed that the hind legs appeared weak, and that food was not being taken. Died in 24 hours.

Cat 6. Male. Excised 7/8 of right, and 17 days thereafter all the left adrenal. Recovered well and was very active for 6 days, when it seemed to be weaker. It lived still more than 5 days, getting continuously weaker and taking very little milk. Rectal temperature the day before death was still 38.4° C., pulse 220, respiration 24.

Cat 7. Male. Excised 2/3 to 3/4 of right and 17 days thereafter the whole of left adrenal. Post-operative recovery somewhat slower than usual, but on second day after last operation it seemed fairly well. On the third day it became lethargic and apparently weak, especially in the hind legs. Temperature 36.2° C., pulse 208, respiration 32. It died 5 days from the last operation.

Cat 9. Female. Excised somewhat more than 3/4 of right, and 21 days thereaafter the whole of left adrenal. Recovery was good for about a day. Then the animal became progressively weaker. On the 5th day after the last operation the temperature was 35° C., pulse too feeble to count, respiration 40. It died the ensuing night.

Cat 10. Male. Excised 9/10 of left and 21 days thereafter all of the right adrenal. The animal became progressively weaker and died 3½ days after last operation. The day before death, the temperature was 35.3° C., respiration 36, pulse too weak to count.

Cat 13. Male. Excised 1/3 to 2/5 of left, and 22 days thereafter the whole of right adrenal. Recovery was excellent, and cat was in good condition till the eighth day, when weakness in the hind legs became apparent and food was taken sparingly. Two days later it died. Temperature on last day 35.1° C., pulse 180, respiration 42.

Cat 16. Male. Excised 2/3 to 3/4 of right, and 18 days thereafter the whole of left adrenal. The day after the last operation the temperature was 34.5° C., respiration 32, pulse too weak to count. The animal died during the night.

Cat 17. Female. Excised 7/8 to 9/10 of the right, and 16 days thereafter about 2/3 of the left adrenal. The animal began to show weakness the second day after the last operation, and died in the night between the 3rd and 4th day.

Cat 20. Male. Excised 9/10 of right adrenal. The animal developed distemper but recovered; 27 days after the first operation excised 2/3 to 3/4 of left adrenal. It was observed that the left adrenal was very large (hypertrophy after the first operation). The animal was in good condition for a day after the last operation, then gradually weakened and died between the third and fourth day. It was confirmed at autopsy, that the remnant of the left adrenal was decidedly larger than the minimum amount which must ordinarily be retained to prevent death. Two possibilities might be suggested. Either the demand on the adrenals was greater than ordinary in this cat, as indicated by the great hypertrophy of the left adrenal after the first operation, because of the paucity or absence of accessory adrenal tissue or for other reasons, or the tissue of the enlarged adrenal did not possess a physiological value in proportion to its bulk. In this connection it may be remarked that hypertrophy of the adrenal is often observed when far more adrenal tissue remains than is necessary for life and health. For instance, when one adrenal is removed the other hypertrophies. This is seen with the greatest constancy in rabbits, but is common in cats. Yet at the original operation a large fraction of the adrenal which is destined to undergo hypertrophy could have been removed without producing symtoms. Elliott (15) has made the interesting observation that in his experiments on total removal of the adrenals, the cats which survived excision of the second gland for the longer periods rarely showed any enlargement of the second adrenal, compensatory hypertrophy having occurred in small accessory adrenals. On the other hand, in the cats which died soon after removal of the second adrenal that gland was hypertrophied.

Hartman and Blatz (25) endeavored to reduce the adrenal function less drastically than by total removal of the glands, by tying the adrenal veins. They found that most of the animals (cats and dogs) lived much longer than after total adrenalectomy, although they eventually died. No specially characteristic symptoms were developed. Several of the animals showed "symptoms of weakness some time before death."

Up to the present, then, it has not been possible to produce experimentally any well characterized symptoms associated with partial adrenal insufficiency. That changes, and profound changes take place when the adrenal tissue is removed below a certain limit is not arguable, for life can no longer be maintained, and changes which render death inevitable are surely important. It is extremely probable that the essential changes are metabolic, but little real progress has been made in discovering definite quantitative or qualitative alterations in the metabolism, or in relating such alterations as have been assumed to occur to the fatal adrenal insufficiency. The too often quoted statement that the blood sugar content is diminished after total adrenalectomy in dogs (Bierry and Malloizel (26), Porges (27)) rests upon the frail foundation of observations on practically moribund animals. The rapidly increasing weakness and the fall of blood pressure in animals

hastening to die, are not sufficiently specific symptoms to make it very safe to link them up with the loss of adrenal function. In animals which survive with a vast anatomical deficiency in adrenal tissue it is very difficult to unveil any signs of corresponding physiological insufficiency. The temporary emaciation noticed by Abelous and Langlois (6) in guinea pigs after partial destruction of both glands or even after removal of one, is also not easy to interpret, (in animals recovering from a considerable operation,) as a sign of the loss of a specific adrenal function. The observations of Whipple and Christman (23) that the excretion of phenol-tetrachlorphthalein in the bile is diminished when three-fourths or more of the adrenal tissue has been extirpated in dogs, and is again increased if the remaining tissue hypertrophies, is suggestive. Pancreatic deficiency is associated with a similar drop in phthalein excretion, and it would be difficult to say whether the change is associated with a general deterioration of the animal or directly with the loss of some specific endocrine function.

Elliott (15) was unable to demonstrate any alteration in the mechanism of the heart beat during the gradual failure of the circulation in cats after total adrenalectomy until death. There was no paralysis of the skeletal muscles or their nerves, and no paralysis of the cardiac vagus fibres. But when the animals had become very weak and were moribund, there was some paralysis of the efferent vasomotor nerves, and only a slight rise of pressure was caused by nicotin. Hoskins (22) observed also in dogs which survived the removal of one-half to seven-tenths of the adrenal tissue that the vasomotor reaction to nicotin was decreased, and concluded that partial adrenal deficiency results in a depression of the excitability of the sympathetic nervous system proper; this depression being probably only one phase of a generalized interference with fundamental metabolism.

The view has been industriously developed by certain writers that the secret of the adrenal function lies in the reciprocal action of the gland and other endocrine organs, particularly the thyroid and the pancreas (Eppinger, Falta and Rudinger (29)). Gley and Quinquaud (30) very naturally express astonishment at the ease with which such theories

gained a considerable degree of acceptance without ever having been subjected to a direct experimental investigation. Lusk and Riche (31) have shown that not one of the statements as to the supposed rôle of epinephrin in metabolism and its action upon the endocrine organs (pancreas and thyroid), upon which the theory of Eppinger, Falta and Rudinger was based, is true, and that the theory is not tenable in any of its particulars. It has been demonstrated by Stewart and Rogoff (9) (32) (33) that contrary to the statements of a number of observers, the adrenals are not essentially concerned in the experimental hyperglycemias caused by piqûre, ether anesthesia and asphyxia, since these hyperglycemias can be well obtained in rabbits which have survived double adrenalectomy and in cats whose epinephrin output has been greatly diminished or abolished by removal of one adrenal and section of the nerves of the other.

Recently Hédon and Giraud (34) have come to the conclusion, that in dogs extirpation of the pancreas is not followed by hyperglycemia if the adrenals are removed either before, or immediately after the extirpation of the pancreas. If the adrenals are partially destroyed the usual hyperglycemia follows pancreatectomy. Contradictory results have been obtained by other observers. As it is the epinephrin given off from the adrenals which has always been considered the important thing in these theories, a much better experiment could be made upon dogs which had recovered completely after the operation for suppression of the epinephrin output (removal of one adrenal and section of the nerves of the other) than in dogs which have just been anesthetised for the performance of two severe operations.

The observation that feeding with thyroid substance is associated with hypertrophy of the adrenals, and a corresponding increase in their epinephrin store (Herring (35)) has not been confirmed by Kuriyama (36), who considers that the variations seen by Herring are not beyond the normal range. Hewitt (37), however, has pointed out that in certain respects Kuriyama's experiments differed from those of Herring. And other observers, (R. G. Hoskins (38) and especially E. R. Hoskins (39)) have also obtained adrenal hypertrophy after

feeding with thyroid. It is necessary to remark, however, that there is nothing specific about the increase in size of the adrenals, since similar hypertrophy is found in other organs, including the pancreas (E. R. Hoskins (38) Kojima (40)). Many infections and intoxications have been shown to be associated with enlargement of the adrenals (Langlois (41), Porak (42) et al.), although enlargement due to edema (and congestion) has not always been discriminated from true hypertrophy. Mulon and Porak (43) found that in animals employed for the production of antibodies of various kinds the adrenal cortex was hypertrophied. Porak (42) says that the largest adrenals seen by him were in rabbits repeatedly injected with sheep's erythrocytes for the production of anti-sheep serum for the Wasserman test in the municipal laboratory at Paris. He remarks apropos of the innumerable researches on the condition of the adrenals in infections and intoxications before his own work, that the existence of the same histological changes in the adrenals in infection and in immunity prove in a definite fashion the excesses of the theory of adrenal insufficiency in infections and intoxications. It is as welcome as it is unfortunately rare at the moment, to find in the French clinical and pathological literature a protest against the fetish of adrenal insufficiency. Gley and his co-workers have given but a cool reception to the complementary doctrine of what may be almost termed "adrenal all-sufficiency" in physiology.

The risk of deducing a special physiological relationship between the thyroid and the adrenals merely because the adrenal hypertrophies under the influence of thyroid feeding, is further illustrated by the fact that removal of the thyroid may be similarly associated with adrenal hypertrophy (Gley (44), Carlson (45), Stewart and Rogoff (46)). The adrenals seem, indeed, to vary much in size, like the thyroid, and under many physiological and pathological conditions. Thus, Guiyesse (47), Watrin (48), Verdozzi (49) and other observers consider their hypertrophy in pregnancy as a normal physiological event. Verdozzi finds a still greater effect during lactation. Mahnert (94) has based on the more than dubious Abderhalden reaction the contention that in pregnancy a de-

rangement of function (dysfunctioning) of the adrenals occurs. This appeal to the Abderhalden reaction recalls Gibbon's famous footnote: "Abu Rafe was an eye-witness, but who will be witness for Abu Rafe?" Hatai (50) has asserted that the adrenals hypertrophy in female rats subjected to prolonged muscular exercise daily for several months. C. A. Stewart (51) observed a progressive increase in the size of the adrenals in young rats underfed for long periods. Jackson (52) has also observed changes in the adrenal in rats during inanition. Byrne (53) states that in 8 soldiers dead from underfeeding in a German prison camp the suprarenals were enlarged to almost 1½ times the normal size. Microscopically the enlargement seemed to be mostly in the cortex. McCarrison (54) has also described enlargement of the adrenals in inanition and on a scorbutic diet, and Vincent and Hollenberg (55) have confirmed his findings. Some observers have noted a reduction in the lipoids of the cortex in inanition. But Elliott (57) states that the lipoids were not reduced in cases of disease associated with practical starvation (anorexia, cancer of the stomach). Grabfield and Squier (56), have recently announced that under the influence of Roentgen rays applied to the locality of the adrenals in the rabbit, hypertrophy occurred.

The question whether experimental adrenal insufficiency is due to the loss of the cortex or of the medulla, or of both has been much discussed. The experimental evidence has tended more and more to show that the cortex is the part of the adrenal indispensable for life. It is the cortical tissue which alone, or at any rate most conspicuously undergoes compensatory hyperplasia, when a deficiency is created by removal of a considerable part of the adrenal tissue. The accessory adrenal tissue, which also undergoes hypertrophy under these circumstances, and which is usually supposed to be responsible for the survival of those animals which do not succumb to loss of both adrenals, consists entirely of cortex. Only the cortical tissue can be successfully grafted. When one adrenal is completely removed and only a small portion (⅓ to ⅕) at one pole of the other adrenal left, it is probable that in many instances the viable portion of the remnant consists entirely of

cortex. Wheeler and Vincent (58) have destroyed practically all of the medulla in dogs without causing death.

In cats, dogs and macaque monkeys it has been seen that great diminution or suppression of the epinephrin output of the adrenals after removal of one gland and section of the nerves of the other, is compatible with indefinite survival of the animal in good health, (Stewart and Rogoff (59)). It is little more than a trick of special pleading to urge that the extra-capsular chromaphil tissue may be sufficient to supply the indispensable epinephrin output. If there is any epinephrin given off from the scattered chromaphil tissue the output must be of a different order of magnitude from that of the adrenal medulla. Kahn (60) has attempted to show that in the dog the abdominal chromaphil body (paraganglion) does give off epinephrin. But the experiment is very difficult to carry out without fault. He used Trendelenburg's method (61) of perfusion of the hind legs of frogs (Läwen preparation (62)), and it is well known that serum contains a vasoconstrictor substance other than epinephrin which makes it difficult to accurately assay the epinephrin content of serum on such an object. Most of Kahn's curves do not show any very great difference between serum from the cava blood and serum from the abdominal chromaphil body. But Kahn himself states that even in the dog, where it is relatively greater in amount than in most other animals, the whole mass of the extracapsular chromaphil tissue is insignificant, compared with the suprarenal medulla. It must be pointed out also that if there is any physiological liberation of epinephrin from the diffuse chromaphil tissue it is highly probable, judging from the analogy of the adrenal medulla, that this liberation is under the control of nerves. If so, in cases where the splanchnics have been cut, or the dorsal cord divided, it would seem practically certain that the innervation of the greater portion of the extracapsular chromaphil tissue must have been interfered with. Yet such operations, even when added to the operation practiced by us for the suppression of the adrenal output, do not cause death, as removal of both adrenals does.

Vincent (63) points out that from the relatively large size of the abdominal chromaphil body in the dog, this animal

might be expected to be more resistant to extirpation of the adrenals than other animals, if the chromaphil tissue were essential. But the dog does not survive the operation, whereas the white rat, in which Vincent failed to find any traces of "extra-suprarenal chromaphil tissue," is the most resistant of all laboratory animals. In the monkey, also, no extracapsular chromaphil tissue has been recognized with certainty. Yet the monkey is not affected by interference with the epinephrin output of the adrenals.

It is a curious thing that while the great bulk of the experimental evidence emphasizes the importance of the cortex without demonstrating any definite physiological value for the medulla, or at least for its epinephrin secretion, the bulk of clinical writers seem almost to ignore the existence of the cortex. "Adrenal insufficiency" in nine clinical papers out of ten, so far as they have come to the notice of the present writer, seems to connote interference with the output of epinephrin and consequent derangement of functions in which epinephrin is assumed to play a leading rôle. Worse still is the confusion between the rate of epinephrin output and the magnitude of the epinephrin store. It is very common indeed to find the conclusion drawn that because the epinephrin store was found smaller than the average, perhaps, many hours after death, the "adrenal function" must have been depressed and the patient must have suffered from adrenal insufficiency during life. It would be just as correct to conclude that if the liver of an animal, kept at rest in a warm room and fed with a definite food ration, contained 5 per cent of glycogen, while the liver of another animal, fed in the same way but allowed, or compelled to move around freely in a cool room contained but 1 per cent, the "hepatic function" of the latter was depressed and it was suffering from hepatic insufficiency. It ought to be recognized once and for all that the stock of epinephrin present at any moment in the adrenal medulla is simply a balance, related no doubt to the relative rates of formation and of liberation of epinephrin, but giving no clue to the rate at which the epinephrin is being given off. A striking illustration of this is the fact discovered by Elliott (64) that after section of the nerves going to one adrenal the store after a day or two is found to be the same

in the innervated and in the denervated gland. Yet the latter, if section of the nerves has been thorough, is giving off no detectable amount of epinephrin, not even one-hundredth or one-thousandth of the amount being liberated by its fellow (Stewart and Rogoff, 59). To those who estimate the activity of "adrenal function" by the magnitude of the epinephrin store, the two glands would be equally active. Yet this they cannot be if their function is concerned with anything which epinephrin liberated from the adrenals can do in the body.

There is no evidence that diminution in the ordinary rate of epinephrin output or even its total suppression can give rise to symptoms, even in such physiological emergencies as have been supposed to increase the demand for epinephrin. For instance, it has not proved possible to demonstrate any incapacity in animals, deprived of epinephrin from the adrenals, to support the fatigue of enforced muscular effort, as compared with normal animals. Although deficiency of cortical substance, carried to a certain point, produces decisive changes leading more or less speedily to death, the essential changes do not lie on the surface, and no definite, clean-cut symptoms characterize the clinical picture of an animal dying from experimentally produced adrenal insufficiency. In the case of the cortex also, when the amount of adrenal substance has been greatly reduced, but not so much as to cause death, the repeated subjection of the animal to such a physiological emergency as severe muscular exertion, does not reveal any difference between these animals and animals with intact adrenals. It is widely believed that muscular weakness is a symptom of adrenal insufficiency, and often assumed that it is deficiency of the epinephrin output which is the important thing. If either the medulla or the cortex is closely related to the proper functioning of the neuro-muscular machine, or exerts any appreciable influence upon the processes underlying muscular fatigue (Gruber, 13), it might be thought likely that repeated spells of severe muscular exertion, in an animal on the borderline of actual anatomical deficiency of adrenal tissue, would suffice to develop a physiological deficiency, where none would have developed in an animal at rest. In our cats, however, no difference was revealed between the normal animal and the

animal with perhaps only 1/6 or 1/8 of its adrenal mass. Boinet (65) also found that rats which had survived double adrenalectomy for 5 or 6 months, withstood extreme muscular exertion quite well. Considering the small number of normal controls employed, and the great variability in the length of time necessary to produce absolute fatigue, it cannot be said that he made out any difference between the decapsulated and the normal rats. We have found a definite deficiency in the epinephrin store of the still innervated adrenal, as compared with its previously denervated fellow, in cats after muscular exertion carried to the point of great fatigue.

On the whole, then, it must be granted that hitherto the attempts made to evoke in animals a well marked syndrome characteristic of adrenal deficiency, have been singularly disappointing. The contrast is great when we leave this desert, where the physiologists and experimental pathologists have wandered, striking many rocks but finding few springs, and pass into the exuberant land of clinical endocrinology, flowing with blandest milk and honey almost suspiciously sweet.

II. SOME CLINICAL VIEWS

It is impossible to mention more than a few of the conditions discussed in innumerable papers, in which adrenal insufficiency has been assumed to play a part. A rank growth of "endocrinological" speculations sprang up during the war, which developed so many novel medical problems, all of course pressing for solution, few of which could be quickly solved. But hypotheses could be quickly framed, especially when the framers were not hampered by any excess of critical faculty or exact physiological knowledge. The most recent "ology," endocrinology, was naturally pressed into the service. Much of this speculation unfortunately found its way into print, in spite of the scarcity of paper, and scarce paper was sometimes ill applied in this service.

Even in the case of Addison's disease, the majority of clinical writers seem still to suppose that it is the loss of the epinephrin secretion of the medulla which is the important thing, although experimental physiology affords no basis for such a view. That the epinephrin store of suprarenal glands

extensively destroyed by tubercular disease, should be deficient or reduced to vanishing point is inevitable, but this fact throws no light upon the production of the syndrome.

Claude and Gougerot (66) put forward in 1908 what they considered as a new conception, that certain complex symptoms are due to primary insufficiency of more than one of the endocrine glands. There is no reason in the world why this should not be true. But the evidence adduced from the clinical study, followed by autopsy, of one case, is singularly unconvincing. We are only concerned here with insufficiency of the adrenals. But they state that insufficiency of the thyroid, of the testicles and of the suprarenals was diagnosed during life and verified at at autopsy. The patient was tubercular, and there was asthenia. A diffuse pigmentation appeared not long before the patient's death, on certain parts of the face. The blood pressure fell to 100 and even to 90 mm. of mercury. The adrenals were found to weigh only 5 grams, less than half the normal weight. Histologically both cortex and medulla were fairly normal, apart from the smaller volume, especially of the medulla. There is certainly nothing here which, so far can be judged from the results of experiments on animals, lends any support to the idea that adrenal insufficiency was the cause of any of the symptoms. In man a very small portion of the suprarenal tissue has sometimes been found intact at autopsy, although the person almost up to the time of death may have been apparently normal and capable of hard physical work. Boyd (67) for instance, describes the case of a soldier who died while on leave of absence. He was apparently well just before he was found semi-conscious in his room. He had been performing his duty in a training camp and showed no signs of Addison's disease. The autopsy showed that the lungs were to some extent affected with tuberculosis. The adrenals were almost entirely converted into "structureless" masses larger than the original glands. On the right side neither cortex nor medulla could be found. On the left side a narrow strip of cortex not more than 2 mm. in width was present at one point, but no medullary tissue. Although the author attributes death to acute adrenal insufficiency, this is, of course, hypothetical, as no signs of adrenal insufficiency (if there are any definite signs) were observed dur-

ing life. The only safe conclusion, which the author does not fail to draw, is that the medulla is not essential to life. This case seems further to illustrate the fact, established by experiments on animals, that the preservation of only a small portion of the cortex may be compatible with apparent health and vigor.

Brock and Kay (68), discussing a clinical syndrome somewhat allied to that described by Claude and Gougerot, come to the conservative conclusion that "Since we regard the white line of Sergent as being a very doubtful sign of hypoadrenia, and with no other certain evidence of deficient suprarenal secretion, the participation of this gland seems very doubtful." Sergent (69), like many other clinical writers, seems to consider hypoadrenia as synonymous with adrenal insufficiency. If by hypoadrenia he means diminished output of epinephrin, there is not one experimental fact which shows that this would produce any symptoms at all. "Arterial hypotension" is not caused even when the epinephrin output is totally suppressed. Fatal adrenal insufficiency is produced in animals in all probability by interference with the cortex. Diminished epinephrin output is not an important part of adrenal insufficiency. The suggestion in a quite recent paper (Byrne (53)) that hypertrophy of the adrenal, mainly of the cortex, in soldiers dead from the effects of underfeeding in a German prison camp was compensatory, in order to restore the blood pressure lowered by the want of food, ignores the two fundamental facts, that the epinephrin is given off from the medulla not from the cortex, and that the maintenance of the normal blood pressure does not depend in any important degree upon epinephrin.

Pende (70) speaks of the hypoadrenal constitution as a clinical and pathological entity first studied in Italy (constitutional angihypotony of Ferranini). In reading this paper and many others by "clinical endocrinologists," especially the French and the Italians, the physiologist can scarcely escape the feeling that here he has broken through into an uncanny fourth dimension of medicine, where the familiar canons and methods of scientific criticism are become foolishness, where fact and hypothesis are habitually confounded, and "nothing is but what is not." "In such temperaments (hyperthyroid status more or

less associated with stigmata of lymphatism or of constitutional hypoadrenalism; 'sympathicotonia' generally prevails and may be associated or alternated with 'vagotonia.'" "In the vagotonic constitutions described by Eppinger and Hess the stress of war frequently leads to frank vagotonia." "People with prevailing 'vagotonic hormones' are liable to a particular type of soldiers' irritable heart of a vagotonic form. In another group of cardiopathies (hypoadrenal types of Satre) in soldiers one is apt to think of hypoadrenalism, and we can accept the hypothesis of a functional inhibition of the adrenals due to the war." "The neuropsychogenic origin of the adrenal insufficiency of these patients, which must obviously come from a certain instability of the glands or from an easy exhaustion of their secretory nerves, explains the peculiar clinical characters of this form and its easy curability by the removal of its psychic causes." There is no evidence of "adrenal insufficiency" in these patients which will stand the test of critical examination for a moment. Nor is it at all obvious that if there is insufficiency, it must come from a certain instability of the glands, on which there are no experimental data, or from an easy exhaustion of their secretory nerves, which hitherto have been only shown to govern the epinephrin output, and which can be completely severed without producing noticeable effects on the health of animals.

Adrenal asystoly (Josué) (71) is the name given to a supposed syndrome in which sudden death from heart failure is apt to occur, associated with the presence of disease or marked diminution in size of the adrenals. There is no real foundation for the view that the heart stops because the adrenals naturally supply a physiological stimulus necessary for its contractions. But it is very probable that if the adrenals are extremely diseased, the profound changes in the metabolism which must be presumed to occur will affect the heart, as well as other organs. The "syndrome of hypoadrenalism described in soldiers suffering from infectious icterus in Italy by Frugoni, Gardeghi, Ancona, Notari and Monti; from typhoid by Frugoni; from dysentery by Izar, Dujarric, Riviere and Fillerval, and from indefinite infections by Carles and Satre," can scarcely be more at present than the product of an undisciplined imagination.

Anti-typhoid vaccination has also been stated by several writers (Loeper (72), Lian (73), Satre (74)) to cause, sometimes, symptoms of adrenal insufficiency (arterial hypotension, etc.) It is a sufficient commentary on this, that arterial hypotension is not a symptom of adrenal insufficiency experimentally produced, at least not a primary symptom. "The adrenal symptoms in these infections are no doubt accentuated in their initial stages by the capsular exhaustion due to the excessive war fatigue. (Sergent)." There is no experimental exidence whatever that fatigue diminishes the output of epinephrin, and, of course, no evidence that the function of the adrenal cortex, whatever it may be, is diminished in that condition. Until we have such evidence, what is the use of a clinical observer looking at a sick man and saying "No doubt he is suffering from capsular exhaustion due to excessive war fatigue," or to so-called shell shock (Carles) (75)?

Adrenal dyspepsia (Loeper, Beuzard and Wagner (76)), adrenopathic hyperchlorhydrias (Kaplan and Greff (77)), and other digestive disturbances have been described as due to adrenal insufficiency, on no other evidence than that the administration of adrenalin seemed to do good. As has been emphasized repeatedly by physiologists, the pharmacodynamic or therapeutic effects of adrenalin cannot be used to prove the existence of a deficiency in the output of epinephrin. Hoskins (78), for instance, asks very pointedly whether because cascara is efficacious in relieving constipation we ought to conclude that this is because the patient is suffering from hypocascarism?

The diagnosis of "suprarenal" forms of malaria in which adrenal insufficiency is supposed to contribute to the clinical picture (Fraga (79), Paisseau and Lemaire (80), Portocalis (81)) is surely risky on the basis of any physiological knowledge at present at our disposal, although the presence at autopsy of lesions in the suprarenals, described by the last named authors is, of course, well worthy of being recorded. That in one of Fraga's cases the parasite was found in the capillaries of the suprarenal cortex would prove little more than that blood was found there. Similar attempts have been made by not a few writers to establish adrenal insufficiency as one of the factors in the clinical picture in certain groups of cases of

influenza (Cowie and Beaven (82), Ricaldoni (83)). The fact that in diphtheria, typhoid and sometimes typhus the adrenals are sometimes small, and contain little adrenalin and cholesterol (Marañon (84)) would not justify the conclusion, that accidents of the nature of collapse occurring in these and other infections are due to adrenal insufficiency. As already pointed out, it has not been shown that a relatively small epinephrin store means "exhaustion" of the gland and a small epinephrin output. Nor does experimental diminution of the epinephrin output or its total suppression entail any serious consequences.

A large, though quite undeserved place has been occupied in the clinical literature of shock and allied conditions by adrenal insufficiency, or one or other of its aliases. (Loeper and Verpy (85), et al.). There is no evidence that any notable change occurs in the epinephrin output in either direction, or that if it does occur it could play any important part in producing cardiovascular shock (Henderson, Price and Haggard (86), Stewart and Rogoff (87)).

Quite as devoid of experimental basis is the theory supported especially by a number of French writers (88), that in cholera the most characteristic symptoms are due to acute adrenal insufficiency. Luckily, neither in cholera nor in surgical shock does this interfere with the therapeutic use of the drug adrenalin, if that should be indicated on physiological grounds.

Delayed death from burns has been attributed to adrenal insufficiency (Kolisko, Lattes (89)). Adrenal insufficiency has also been advanced as the cause of the prolonged asthenia sometimes seen in aviators after flying at high altitudes (Ferry (90)). Even seasickness has been attributed to hypoadrenalism (Naamé (88)) due to inhibition of the adrenals by the rolling of the ship, also to hyperadrenalism (Cazamian (91)) due to stimulation of the adrenals by the rolling of the ship. Curiously enough, both authors recommend adrenalin in this condition, although the advocate of the theory of hyperadrenalism gives atropin also. It is known that atropin does not diminish the output of epinephrin in the least (Tscheboksaroff (92), Stewart and Rogoff (93)). Mankind can apparently be divided into sheep and goats in regard to this matter, that is to say into sympathicotonics and vagotonics, and the vagotonics have

the better chance of escaping seasickness—if vagotonia (95) and sympathicotonia exist in ordinary, tri-dimensional medicine, and if seasickness is due to hypoadrenalism. But "by my troth, Captain," as Mrs. Quickly has it, "these are very bitter words," for the physiologist or the experimental pathologist—these words like vagotonia and sympathicotonia, hypo- and hyperadrenalism, hypo- and hyperadrenalinemia and all their cousins and connections. For he knows that in most cases they are but words, and in science words which conceal or even distort the facts do not leave a sweet savor in the mouth.

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THE MICROSCOPIC APPEARANCE OF TWO TESTES NINE MONTHS FOLLOWING UNILATERAL VASECTOMY.

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In 1915, while studying the effects of castration on the vasomotor responses to nicotine (1), two dogs were standardized to this drug and the right vas occluded and resected. The two animals, A and B, were in excellent condition and weighed 9.5 and 10 kilos respectively. The operations were done in February, and the animals permitted to survive until the following November, at which time their weight was A, 11.5, and B, 13 kilos. The vascular response was again determined and the results of the previous operations carefully examined. The blood pressure readings gave figures practically the same as those obtained nine months previously. In each dog the stump of the resected vas was found bound down by masses of connective-tissue. Bulging of the vas was not present. However, upon opening the lumen of the stump connecting the testis a small amount of fluid material escaped. This fluid was examined microscopically but no living sperm were demonstrable although much cellular material and debris was present. The testis of the unoperated vas was found firm and normal in appearance. On the other hand, the gland of the occluded vas (occlusion determined microscopically) was smaller than its mate and easily compressible.

Histological examination of the glands on the operated side showed them to be in a very much better condition than was anticipated. The seminiferous tubules, although showing the results of destructive processes, contained much spermatic tissue. In many of the tubules sperm heads were readily identified; in places spermatids were seen. The interstitial tissue in each of the two glands seemed to be somewhat in-

creased. The left glands appeared entirely normal and did not show an increase in the interstitial tissue (cells of Leydig).

Until recently it has been pretty generally believed that complete occlusion of the vas results in the ultimate disappearance of the spermatic tissue and an increase or hypertrophy of the interstitial cells. However, the studies of Steinach (2) and the recent results of Kuntz (3) indicate that if degeneration does occur in the spermatic tissue following vasectomy that such changes are probably not permanent. One of Kuntz's dogs which was permitted to run a period of 140 days following vasectomy, showed a practically normal testis. However, other animals of his series which were permitted to survive shorter periods of time did show varying degrees of degeneration of the spermatic tissue and hyperplasia and hypertrophy of the interstitial tissue.

Alterations in the physical and psychical signs of sex did not occur in the two dogs here reported, during the period of observation.

Therefore, unilaterial vasectomy does not appear to alter vascular responses to nicotine, to bring about alterations in the characters of sex, nor to determine complete disappearance of the spermatic cells from the seminiferous tubules as late as nine months following the operation.

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THE INTERNAL SECRETION OF SANDSTROEM'S GLANDS. PARATHYROID HYPOFUNCTION AND ECLAMPSIA

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In 1896, Vassale and Generali (1) demonstrated experimentally that the parathyroids, which were discovered in 1890 by Sandstroem, and which were believed to be an embryonic residue of the thyroid, are indispensable to life, the abolition of their function causing death from tetany. Afterwards Massaglia (2) completed this study. Operating on puppies, he was able to remove the thyroid without disturbing the two external parathyroids (sometimes in the dog these glands are situated at the anterior poles of the thyroid). In these experiments the animal later developed myxedema, but never developed tetany. In the litter control the removal of both the external and one of the internal parathyroids produced no morbid symptoms, and the animal remained normal. The experiment shows clearly that the thyroid and Sandstroem's glands have different functions. The former exerts a trophic action on the metabolic changes of the body; when this function is abolished, myxedema follows. The latter exercise an antitoxic action; when this is abolished, fatal tetany is the result. Eiselsberg (3), before Massaglia, was able to produce myxedema in lambs and in goats; but this experiment did not show the functional independence of the two glands. In herbivorous animals, Sandstroem's glands are situated some distance from the thyroid; consequently Eiselsberg, without knowing it, failed to remove the parathyroids, as Massaglia did purposely in his experiments with dogs.

These findings have proven useful to the surgeon; from them the explanation of post-operative tetany is given; and they have shown that some parathyroid tissue must be left *in situ* that tetany may not develop. Vassale (4) and Massaglia (5) later continued the study of the function of the parathyroids, and were able to demonstrate that this tissue neutralizes

the toxins arising from pregnancy and muscular fatigue. This study gave rise to the hypothesis that a hypofunction of the parathyroids can produce eclampsia. Massaglia and Sparapani found, moreover, that the eclampsia of animals is similar to the experimental tetany which occurs in the female dog during pregnancy, when there is a parathyroid hypofunction.

These data were supported by some authors [Zanfrognini (6), Pepere (7), Vicarelli (8), etc.] but were contradicted by others [Haberfeld (9), Soli (10), etc.]. Finally Massaglia (11) answered:

"Die experimentelle Tetanie, welche nach der teilweisen Parathyroidectomie die Weibchen gewisser Tiergattungen während der Schwangerschaft und Stillung befällt, bietet, wenn man von einigen Unterschieden absiehr, bezüglich dere man die verschiedene zoologische Art berücksichtigen muss, ohne Zweifel ein egewisse Aehnlichkeit mit der Eklampsie der Frauen dar. Die negativen Befund einiger Autoren—kann man;—durch die Annahme erklären, dass die parathyroidale Insuffisenz nicht immer als einsiger Faktor wirke und kein zur Herbeifuhung jenes Zustandes der Autointoxication, welcher das Komplexe, vielgestaltige und schwere Krankheitsbild des eklamptischen Anfalles erzeugt, immer notwendiger Faktor sei."

Since the problem had not been completely solved, it seemed worth while to investigate the matter further and the following studies were made:

A.—The 1st series of the studies treats of the consequences of parathyroid hypofunction in cats and dogs during pregnancy. Twelve experiments were carried out, since eclampsia in women does not always manifest the same symptoms, and since it was hoped to reproduce experimentally several of the various syndromes of this malady, and also to see if it were possible to obtain the same general rules governing the moment of the onset of the malady, its clinical course, its issue, and the consequences incident to delivery, so that a comparison with cases of eclampsia in women could be made. Of these twelve experiments, some have already been published. To these is added a case of eclampsia in a female dog, which was studied with Dr. Sparapani. [Massaglia and Sparapani (5).] Both the external and one of the two internal parathyroids were removed from the experimental animals. Under normal conditions the animals show no morbid symptoms after the operation, except at times a very slight albuminuria. This special state of hypofunction is designated as "latent parathyroid insufficiency," because the remaining parathyroid is able to carry on the para-

thyroid function. When there is an increase in the toxins which normally is neutralized by these glands, the single parathyroid then becomes unable to meet the demand, intoxication ensues, ending in tetany. Evidence that intoxication is not normally present in latent parathyroid insufficiency is given by the fact that when the skull is trephined and a slight irritation of the Rolandic area is caused, we obviate the occurrence of tetany; for the toxic substances which are neutralized by the parathyroids would otherwise exercise their action in the neuraxis.

When the internal parathyroid in dogs were not found, one of the two thyroid lobules was removed, or only the two external parathyroids were extirpated.

B.—The 2nd series embraces 11 experiments in which a state of latent parathyroid insufficiency was associated with renal hypofunction, in order to determine whether a functional correlation exists between these organs, and if some toxic substances not neutralized by the kidneys can cause tetany because of parathyroid insufficiency.

C.—The 3rd series consists of 8 experiments in which an endeavor was made to ascertain whether the parathyroids neutralize the intestinal toxins.

D.—The 4th series embraces 8 experiments, in which the problematic functional correlation between the liver and the parathyroids was studied.

E.—The 5th series of 4 experiments has already been published in part. In these experiments it was shown that the parathyroids neutralize the poisons of fatigue.

F.—The 6th series consists of only 2 experiments, because I failed to secure the desired results. In these an endeavor was made to ascertain whether lead poisoning in conjunction with parathyroid hypofunction causes tetany in animals.

SERIES A.

Tetany in pregnancy and in the first days after delivery caused by parathyroid hypofunction.

The symptoms of tetania parathyreopriva have been so thoroughly discussed by others that no repetition is necessary. The diet of the animals in these experiments was bread and meat; during the tetany they refused food, but were always thirsty. They were given water and milk. For treatment, para-

thyroidin with calcium chloride was used. Sometimes it was not possible to make a microscopic examination of the urine. Twelve female dogs were used and the parathyroids were removed as described. The results of the experiments indicate that the disorders produced have the following points in common with eclampsia:

1.—The animal, after the removal of three parathyroids, continues in good health, providing that it lives in normal conditions. When it becomes pregnant it shows tetany. What is true of the animal applies to woman also, viz.: that while one would not ordinarily expect illness for her, yet she may have eclampsia in pregnancy.

2.—The first indication of the coming attack in women and in my animals, is albuminuria, very light in the beginning. We rarely have an exception to this rule in women or in animals.

3.—The tetanic attack, as does eclampsia, has the prodromata,—some slight symptoms of tetany. Both occur, generally, at the end of pregnancy or during the puerperium. When we have any exception in this rule, it is due to some change from normal life, as dietetic errors, or complications.

4.—Various authors recognize several forms of eclampsia. I believe that I have reproduced in my experiments almost all the pictures of this disease.

5.—The daily amount of urine, its abnormal components, especially albumin, before, during, and after the tetany were the same in my animals as in eclamptic women.

6.—De Lee (12), speaking of the prognosis in eclampsia, says: "Over 20 per cent of women affected with eclampsia die . . . ," and afterwards " . . . for the child the chances are not good, nearly one-half of the children dying." In these experiments almost the same results were obtained, both for the mothers and for the puppies.

7.—In the animals that die, there was found lesions in the liver and in the kidneys. The severity of the lesions varied in the different cases; at times the greatest injury was sustained by the liver, and at times by the kidneys. Several authors have described lesions, especially in the liver, more severe than those I have seen; but we have also cases of eclamptic women which show almost no severe lesions in the kidneys or in the liver.

8.—The meat diet, in these animals, as in women threatened with eclampsia, seemed to favor the onset of the attack; on the contrary, milk seemed to have a preventive and curative action against tetany.

9.—The treatment with parathyroidin and calcium salts gave good results; indeed, the animals died almost always during the night when it was not possible to administrate the treatment. Since the toxin of tetany injures the central nervous system [Uhlenhuth (13)], it is imperative that the treatment be instituted without delay.

10.—The tetany that was caused in these experiments is similar to the eclampsia of animals. Veterinarians [Saint-Cyr e Violet (14), Delmer (15)], have concluded that this condition in animals is the same as eclampsia in women. In a case (female dog), observed by me with Dr. Sparapani [Massaglia (5)], I reached the same conclusion. This fact makes more certain the deductions from the results of the experiments.

SERIES B

Study of the relation between the renal and the parathyroid function.

When a pregnant animal in a state of latent parathyroid insufficiency is affected with tetany, it shows a disturbance in the renal function during the attack, and sometimes before and after the attack. From these data I have endeavored to prove what functional correlation exists between the kidneys and the parathyroids, and also what part the kidneys play in the genesis of eclampsia by parathyroid hypofunction. Therefore, in the experiments in this series I have associated with a parathyroid hypofunction, stenosis of the ureters (5 experiments), stenosis of the renal veins (5 experiments), and stenosis of both renal veins and ureters (1 experiment). Dogs were used as the experimental animals and the parathyroids were removed as previously described.

The results of the series showed that renal hypofunction does not cause the parathyroid hypofunction. When the kidney function in the animal was severely impaired, uremia and death were caused—not tetany. It is true that sometimes it is impossible clinically to distinguish between a case of tetany and a case of uremia with convulsions; but the diagnosis becomes easy enough when it is made on several cases in which it

is possible to follow the course of the disease from the beginning to the end.

A.—As a matter of fact, in the animals of this series, the nervous symptoms sometimes appeared and sometimes did not, just as occurs in uremic intoxication. In intoxication from parathyroid hypofunction, however, the predominant symptoms are always neural.

B.—The nervous symptoms usually developed when the renal function was almost abolished—that is to say, just before the death of the animal.

C.—In these experiments, when the nervous symptoms appeared, they did not give the classic picture of tetany by parathyroid hypofunction.

Now, how can we explain the fact that a renal hypofunction does not directly produce parathyroid hypofunction when, on the contrary, the hypofunction of these latter cause trouble in the function of the kidneys?

The kidneys, as we know, together with the skin, the lungs, and the intestines, exercise the function of eliminating from the circulation the waste materials which have passed all catabolic transformation necessary for them to be excreted. When the renal glands are injured, we have in the circulation a retention of these waste materials; intoxication results, which finally, if severe, causes uremia. [Wells, (16)]. This intoxication can produce lesions in the parathyroids, as in the other organs (lesions were found with some frequency in the liver, in the intestine, etc.), [Dieulafoy (17)], but can not directly produce a parathyroid hypofunction, because the waste materials which remain in the circulation are materials which have undergone every modification necessary to their being excreted, and they probably contain also the poisons formerly modified by the parathyroid secretion.

On the other hand, the parathyroid glands neutralize certain catabolic substances. When these are not neutralized and reach the kidneys, these glands are injured, because the unmodified substances are not able to be excreted. Consequently we have a special intoxication, which, when severe, exercises its action on the nervous system and causes tetany.

SERIES C

Parathyroid function and intestinal toxins

Many disease conditions, such as headache, malaise, lassitude, tetany, epilepsy, and eclampsia, are attributed by some authors to poison of gastro-intestinal origin. This fact is not demonstrated; however, it would seem that toxic substances from the intestine increase the severity of any of the above morbid conditions. [Wells (16)].

The intestinal poisons are augmented by the retention of the intestinal contents, which cause an excessive intestinal putrefaction. Tissier (18), Metchnikoff with his pupils in the "Institute Pasteur," and several other authors have demonstrated that the bacteria of the "flora intestinalis" change in number and in species, according to the ingestion of the different foods; consequently the intestinal poisons change also.

In view of these data, and inasmuch as the observations from the experiments of Series A show that, in the case of animals in a state of latent parathyroid hypofunction and in pregnancy, a meat diet precipitates and increases the violence of the tetanic attack, while a milk diet weakens, if it does not entirely obviate it, I was led to investigate whether the parathyroids exercise some action upon the poisons which enter the circulation from the intestine. Therefore the normal function of the intestine was altered, either by producing intestinal stenosis or by feeding the animal great amounts of meat, or cultures of microbes from the "flora intestinalis."

Five experiments were made with stenosis of the intestine, and three with ingestion of great quantities of meat or of cultures of bacteria from the "flora intestinalis." The normal diet of the animals under experimentation was bread and meat. Cats and dogs were used and the parathyoids removed as previously described. In some of the animals, in a state of latent parathyroid hypofunction, I abolished the external pancreatic secretion by ligature and resection of the pancreatic ducts. A normal diet of bread and meat did not cause any symptoms of tetany.

The results of this series showed that, taken together with those of series A, a derangement (especially when the animal is fed on flesh) in the function of the intestine which produces an increase of the toxins, either by stenosis or by the ingestion

of a large quantity of germs or meat, causes tetanic symptoms in an animal in a state of latent parathyroid hypofunction; viz., that the insufficiency from being latent becomes apparent, and from this it is concluded that the parathyroids neutralize some intestinal poisons, especially those which come from a meat diet.

In some animals in a state of latent parathyroid hypofunction, I abolished the external pancreatic secretion by ligature and resection of the pancreatic ducts. A normal diet of bread and meat did not cause any symptoms of tetany.

SERIES D

The antitoxic function of the liver in relation to the antitoxic function of the parathyroids.

It seems that all, or a great part of the protein absorbed by the intestine reaches the liver by means of the capillaries; likewise the toxic substances are carried to the hepatic gland for neutralization. To these poisons, indeed, we attribute many cases of non-alcoholic cirrhosis of the liver and of acute yellow atrophy of the liver when of idiopathic origin. [Wells (16)].

Hahn, Massen, Nencki, Pawlow (1892), as reported by Luciani (19), studied the antitoxic function of the liver by means of Eck's fistula in dogs. In the few animals which survived the operation, these authors observed, after about ten days, some tonic-clonic convulsions followed by coma. These attacks followed the eating of a great amount of meat and the intoxication was caused by ammonium carbamate, which is probably an important precursor of urea and which in dogs with Eck's fistula could not be converted into urea. The ammonium carbamate, indeed, being a substance of considerable toxicity, is considered, when free in the blood, an important factor in the production of uremic symptoms. The liver normally decomposes carbamic acid into water, carbonic acid, and urea. In the animal dead from Eck's fistula, the liver showed atrophy and fatty degeneration. Furthermore, later the studies of Bisso (1895) [see Luciani (19)] demonstrated by a method of progressive stenosis of the portal vein that the liver destroys the toxic substances which come from the intestine and, when the function of the liver is impaired, the kidney suffers. Therefore there exists an indirect functional relation between these organs. From these data, and having found lesions in the liver

in my animals dead from tetany caused by parathyroid hypofunction during pregnancy, it was thought that, although in hepatic diseases which produces atrophy of the gland we do not usually have convulsive symptoms, it would be useful to study the consequences of the association of a parathyroid hypofunction with hypofunction of the liver.

Two methods were used in producing hypofunction of the liver:

A.—Progressive stenosis either of the common bile-duct or of the portal vein.

B.—By producing a severe lesion in the gland. As a matter of fact it is known that with phosphorus poisoning we obtain lesions similar to acute yellow atrophy of the liver, the same lesions that are sometimes found in cases of eclampsia. Orth (20), Giacosa (21).

The normal diet of the experimental animals was bread and milk.

The results of these experiments lead to the conclusion that the hypofunction of the liver which follows stenosis either of the common bile duct or of the portal vein (a method which offers some difficulty), or poisoning with phosphorus, associated also with a state of latent parathyroid insufficiency, does not usually cause symptoms of tetany.

Hahn, Massen, Nencki, and Pawlow obtained tonic-clonic convulsions in the few dogs surviving the operation of Eck's fistula. But in these animals the hepatic function was abolished, and the convulsive symptoms developed after a heavy meat diet and when the dogs were about to fall into a state of coma. Considering these data and those I obtained from the experiments of this series and those of Series A and C, I conclude that the liver neutralizes the poisons which, after a meat diet, enter into the circulation from the intestine, and that the parathyroid glands probably help the liver in this important function.

SERIES E

The muscular fatigue in dogs in a state of parathyroid hypofunction.

In 1906 Massaglia (5) demonstrated by means of experiments on dogs that the toxins of muscular fatigue are neutralized by the parathyroids. When the parathyroids are insuf-

ficient to carry on their function, we have albuminaria in the animal, and, if the parathyroid hypofunction becomes more pronounced, we have symtoms of tetany. In that series of experiments dogs were made to run in a treadmill for various periods of time until partial or complete muscular exhaustion was produced. The results of the studies demonstrated that the parathyroids have the function of neutralizing the poisons of muscular fatigue. We know that in pregnancy the muscular fatigue is great during labor, and that it is greater in primaparae than in multiparae.

The experiments wherein exhaustive muscular activity in the dogs was produced demonstrate: 1.—That the parathyroids have the function of neutralizing the poisons of muscular fatigue. We know that in pregnancy the muscular fatigue is great during labor, and that it is greater in primiparae than in multiparae. De Lee (12) says: "Primiparae are affected by eclampsia oftener (3 to 1) than multiparae, and in about 20 per cent of the cases the convulsions begin during pregnancy, in 60 per cent during labor, and in 20 per cent after delivery." In the animals of the experiments of Series A, tetany was more frequent during labor than in any other period. Also at the end of pregnancy, the organs which exercise the antitoxic function (among them the parathyroids, with a vital function) have a heavy burden on account of the great increase of waste products. A sudden appearance of the poisons of muscular fatigue in the circulation as a consequence of labor can easily determine a parathyroid hypofunction with all its consequences.

The kidneys also suffer from a parathyroid hypofunction. If the renal hypofunction has no direct action on the function of the parathyroids (experiments of Series B), parathyroid hypofunction, on the contrary, has a direct injurious action upon the kidneys. This fact explains: A.—Why, in pregnancy, at the beginning of a parathyroid hypofunction, one of the first alarming symptoms is albuminuria. B.—Why sometimes in a state of latent parathyroid insufficiency, and with good health, we have faint traces of albumin in the urine. The only internal parathyroid which remains is not always able, even in normal conditions, to accomplish its function completely.

SERIES F

Lead poisoning in animals in a state of latent parathyroid hypofunction.

As we all know, lead poisoning causes lesions in the liver, in the kidneys, and in the nervous system. Among the morbid symptoms accompanying saturnism, we have many nervous troubles, with sometimes a true convulsive form. [Dieulafoy (17)]. Therefore I tried to prove whether lead poisoning in an animal in a state of parathyroid hypofunction would cause tetany. Two dogs were poisoned slowly with sulphate of lead; both animals, after about 6 months of chronic poisoning, died, but without ever showing symptoms of tetany. The studies were not continued since I was convinced that lead poisoning does not produce a parathyroid hypofunction.

DISCUSSION AND CONCLUSIONS

The results of the experiments may be summarized as follows: The parathyroid glands appear to have the function of neutralizing or of breaking down into waste products of simpler chemical composition the complex bodies of catabolic changes, or toxic substances derived from pregnancy and puerperium, from the intestine, and from muscular fatigue. They also demonstrate that an intoxication from a parathyroid hypofunction injures, more or less, the kidneys, the liver, and the nervous system; that there exists between the liver and the parathyroids an indirect functional correlation in neutralizing toxic substances which arise from the intestine. A parathyroid hypofunction in pregnancy or in puerperium is then certainly a pathogenic factor of eclampsia. This factor, as has already been stated, does not exclude other factors in the pathogenesis of eclampsia.

How can we explain the pathogenesis of eclampsia and its different syndromes? We know that uremia is the consequence of the retention in the circulation of waste products of metabolism which have passed through all the catabolic phases necessary for their excretion by the kidneys. A lesion in these glands can cause a retention of these waste products, which, when they exceed a certain amount, cause uremia. [Wells (16)]. The morbid pictures in this condition may differ widely, since there are a number of different catabolic substances which may remain in the circulation, and the resistance of the different or-

gans to these substances is not constant. Eclampsia, on the contrary, is an intoxication due to retention in the circulation of a certain amount of waste products, part of which is derived from the common metabolism, and part from the fetus and the placenta. [Wells (16)]. I wish to emphasize here, however, in view of what I shall later prove, that the symptoms of the eclamptic attack are similar to those of a uremic attack in the cerebral form of uremia. Indeed, it is possible to differenitate between the two conditions only through the etiology of the case, and from the fact that (if the woman does not die) with the issue, because, overcoming the eclampsia, the kidneys, as a rule, become normal again; on the contrary after the uremic attack nephritis generally remains.

Why do these waste products remain in the circulation? The data which I have gathered from my experiments, in which I reproduced a syndrome entirely similar to eclampsia, induced me to formulate the following theory: In pregnancy and in puerperium we have an increase of the waste products in consequence of an increase of the metabolic changes; this is in addition to the waste products derived from the fetus and the placenta. The result is the added work for these organs which normally keep the body free of these catabolic substances. The parathyroids have the function of neutralizing some or all of the waste products and the poisons derived from the fetus, the placenta and from the muscular fatigue—this is great during labor—and also in part from the intestine. Very frequently there are troubles in the intestinal function during pregnancy. If the parathyroids are not able to carry on their function, we have in the circulation some metabolites not converted into products which could be eliminated normally in the urine. These produce in the liver, in the kidneys, in the nervous system, and in other organs, lesions more or less severe, the degree of severity depending upon their nature and extent and the resistance of the organs affected. The organs which normally keep the body free of waste products are able, for a time to eliminate them from the circulation, but finally, because of injury, they are no longer able to accomplish this, and we have a severe intoxication, and, in the end, an eclamptic attack.

But what special part have the kidneys and the liver in the pathogenesis of eclampsia? Normally, the kidneys have the

function of eliminating many converted catabolic products. In pregnancy and in puerperium the renal glands eliminate these in an increased quantity, together with some waste products from the placenta and the fetus. If we have parathyroid hypofunction, the waste products not converted by the parathyroid secretion go to the kidneys, which, for a time, eliminate them also (indirect functional compensation). But these catabolic substances easily injure the renal glands. As pregnancy advances, the catabolic substances in the circulation increase, and consequently the parathyroid hypofunction increases also; then the lesions in the kidneys become more severe. The time comes when these poisons can not be eliminated from the body. It is at this time that the very dangerous intoxication arises as a result of the retention of catabolic products not converted by the parathyroids and of an increase in the common catabolic substances which are normally eliminated by the kidneys. Eclampsia is the final result of this condition. My conception explains the cases in which we have marked anuria before the eclamptic attack as well as the autopsy findings of severe lesions in the kidneys. Therefore renal hypofunction is a very important factor in eclampsia resulting from parathyroid hypofunction.

But the kidneys may sometimes be the primary factor in eclampsia. The great burden of eliminating the waste products (perhaps some trouble in the circulation of the gland, or a compression of the ureters) can cause injury to the kidneys, or make it easier for one to become ill from exposure to cold, from some flagrant error in the diet, or with some infectious disease. One develops, in this case, an acute nephritis with convulsions. [De Lee (12)]. Clinically, we can not differentiate these symptoms from those of cerebral uremia, but we call this condition eclampsia, and not uremia, because it is caused principally by intoxication from the waste products of pregnancy. Indeed, when the uterus is emptied of its contents, rapid improvement often follows. This does not occur in common nephritis, and the lesions in the kidneys are often accompanied by lesions in the liver.

It now seems certain that the hepatic gland has the function of neutralizing poisons. To the action of these poisons several authors [Wells (16)] attribute some severe lesions of

the liver, as acute yellow atrophy and non-alcoholic cirrhosis. Now, when we recall that in pregnancy the intestinal poisons are often greatly increased, since intestinal troubles are very common in this condition [De Lee (12)], that there are in the circulation many waste products from the material change, and that the liver very easily suffers from renal and parathyroid hypofunction, we find the reason why the hepatic gland is so often injured in eclampsia, and also an explanation of the nature of the lesions it sustains. [Orth (20)]. Then the liver is a secondary, but a very important and frequent factor in the pathogenesis of eclampsia.

But some of the causes cited above may cause lesions in the liver before any other organs. In this case the hepatic hypofunction may become the primary factor in eclampsia. As a consequence of hepatic hypofunction, we have in the circulation some amino-acids, not converted into urea, which have a toxic action, some intestinal poisons, and probably other products not neutralized by the liver. These poisons exercise an injurious action, especially upon the nervous system and on the kidneys, causing a dangerous hypofunction of these organs; finally, they may also determine a hypofunction of the parathyroids, which are overworked at this time in neutralizing many other catabolic products. The final consequence of this intoxication is eclampsia. These are probably the eclamptic cases [De Lee (12)] in which the patient has, among other symptoms, jaundice, petechiae, and, in case of death, very severe lesions in the liver.

Treatment—De Lee (12) says of eclampsia: "One can speak of rational prophylaxis only when the cause of disease is known. Since we do not know the cause of eclampsia, our treatment is all empiric."

These studies have, I hope, thrown some light upon the causes of eclampsia. It is necessary, after the diagnosis is made, to discover what organ has yielded first in its antitoxic function, and so to determine the nature of the poisons causing the intoxication. Then it is possible to obtain good results by instituting an immediate antitoxic treatment with special reference to the organs first affected. I know that this etiologic diagnosis is not easy to establish, especially when the attack occurs almost without warning. But eclampsia is most often

caused by a parathyroid hypofunction, and, for this reason I believe it wise always to use the opotherapic treatment (parathyroidin). Moreover, this treatment should be instituted before the appearance of any strong convulsive symptoms, because, as I have said, when the nervous system is severely injured, it recovers with great difficulty. When medical treatment is without effect, it is the part of the obstetrician to determine when it is time for emptying the uterus.

I wish to thank Professor F. C. Becht for assistance and advice in my work.

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HYPOPITUITARISM—FROEHLICH TYPE

In an Infant—Nine Month's Old

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Baby J. S.—Age, nine months; weight, twenty-one pounds, was admitted to the Out-Patient Department of the Children's Free Hospital, July 29th, 1920, the mother seeking medical advice because the neighbors had told her that her child was "crazy." This opinion was based upon the facial aspect of the baby, which was that of marked stupidity.

The family history is not remarkable except for the fact that the mother has had two miscarriages, one at the third month, and one at the fourth month of pregnancy. No case of mental deficiency has occurred in either branch of the family; the one other living child being quite normal.

The child herewith reported was a full term baby; delivery was easy; weighed seven pounds and was entirely healthy at birth. It has always been breast fed and has suffered from no acute illnesses. Development was apparently in no way remarkable until the third month, at which time it was noticed that the weight began to increase rapidly. The mother also noticed that from this time on the mentality of the child was regressing; its stupidity becoming more and more pronounced. Sleep was almost continuous, and the waking moments were devoted almost entirely to feeding. The child did not sit up until the eighth month and at the ninth would not sit alone, and supported his head with difficulty. The feedings are taken quite well and there is a mild constipation. A very marked polyuria is present, the mother stating that she cannot keep the child dry. (I have recently seen a child with a glandular dystrophy that passes its urine almost continuously, the act being involuntary, though the child has passed the age of incontinence. The enormous polydypsia which accompanied this condition was the interesting factor. The child, though less

than two years old, drank three quarts of milk daily, besides water in a like quantity, as far as I can figure from the parents' statements. In all about six quarts of fluid were consumed daily.)

EXAMINATION: A very stupid appearing child; the skin is uniformly clear, warm, moist and velvety; the general appearance is that of a very fat child, of the Fröhlich type, with the characteristic enormous abdomen and thighs.

HEAD: The circumference is 18.5 inches; the hair is scanty and soft. The eyes show an evident divergent squint and there is a slight nystagmus. The tongue is continuously protruded from the mouth (this is not macroglossia) and a constant dribbling of saliva is evident. There are no teeth. Nothing noteworthy is found in the throat.

CHEST: Very fat, but in no way remarkable, except for the presence of a large thymus gland; the heart and lungs reveal no adventitous sounds. The circumference of chest is twenty inches.

ABDOMEN: This is of interest on account of the distribution of the sub-cutaneous fat. Although the entire abdomen is quite fat it is found that the greatest distribution lies below the level of the umbilicus; here the circumference is twenty-two inches . The abdominal organs are found to be in no way remarkable.

EXTERNAL GENITALIA: They are exceedingly small. Upon first inspection the impression is given that the penis is buried in the excessive fat, but upon trying to express the organ only a rudimentary condition is found to be present. The testicles are also quite small.

HIPS: Ponderous; their circumference is 22.5 inches.

EXTREMITIES: The arms are quite fat, the hands are broad, the fingers, tapering though not unusually short. The legs are very fat; the thighs measure fourteen inches in circumference.

OPHTHALMOSCOPIC EXAMINATION: Pale disc, but not atrophic; the muscular regions are reported as normal.

URINE AND BLOOD EXAMINATIONS: Normal.

TEMPERATURE: Though a uniformly subnormal temperature might be expected in this condition, only once was the rectal temperature below 98° F. On one occasion following the injection of one mil of antuitrin, it rose to 100° F., after twenty-four hours.

CARBOHYDRATE TOLERANCE: This was quite high, as shown by the following observation: In addition to other foods, the child received daily for three successive days, 150 grams of cane sugar. A specimen of urine obtained at the end of this period and on successive days, failed to reduce Fehling's solution. (The blood sugar was not determined because the mother would not allow the withdrawal of a specimen of blood.)

TREATMENT AND PROGRESS: Treatment was started with thyroid extract (P. D. & Co.) one quarter of a grain, three times a day, whereupon the polyuria immediately disappeared, the protrusion of the tongue ceased, and the dribbling of saliva stopped. The thyroid treatment was gradually increased in amount and very shortly pituitary (whole gland) was added in increasing dosage, until at the present time, the child is taking 3 grains of thyroid extract and 9 grains of pituitary extract daily. The effect of the treatment has been interesting. Almost immediately the somnolence decreased, the mental condition improved, and the child now notices objects and will reach for them. He can at this time (Dec., 1920) stand by holding on to a chair. The weight remains constant. The rudimentary penis has not

shown any evidence of growth, consequently, at some future time, testicular extract will be added to the medication.

COMMENT: The case is reported because as far as I can find it is, I believe, one of the youngest cases of Froehlich type of hypopituitarism to be noted. Though this is undoubtedly a case of poly-glandular dystrophy, particularly of pituitary and thyroid enlargement, I believe the pituitary element to predominate and feel that this theory is borne out by the x-ray photo of the sella turcica. Though the sella is only moderately small a close approximation of the clinoid processes was shown, as is typical in these cases, is particularly marked here. The value of pituitary gland feeding, *per os* has been often questioned. It appears from the course of this case, that such treatment has proven of value.

The presence of brain tumor has been considered but in the absence of outspoken "neighborhood symptoms" such a diagnosis seems doubtful. Time must decide this.

Editorials

THE ADRENALS AND THE EMOTIONS.

A recent article on the James-Lange theory of the emotions in relation to the adrenal glands* suggests that there is still current some misconception regarding the relations of these glands to sympathetic activity. The author says: "Cannon and his collaborators attempted to show that the physical concomitants of fear were produced through psychic stimulation of the adrenal glands." As a matter of fact no such attempt was made, nor was such a belief ever held by the investigator quoted. That strong emotions, pain and asphyxia do cause an augmentation of epinephrin discharge from the suprarenal glands is inherently probable and is supported by many data. Stewart and some other writers, on the other hand, have been unable to convince themselves by direct experimentation that such is the case. In any event, however, the suprarenal discharge cannot be regarded as having any other effect than to augment the action of the sympathetic impulses, the initiation of which precedes the adrenal activity. The fact that only relatively slight effects upon sympathetically innervated structures can be produced either by stimulating the nerves to the suprarenal glands or by direct massage of the glands, and the further fact that under experimental conditions the glands within an hour or two become so exhausted that massage of them is no longer capable of evoking any significant reaction, would seem to indicate that epinephrin discharge plays a relatively minor role in the reactions to emotional stress or pain.

The James-Lange theory postulates that we cannot experience an emotion unless we also experience the physical changes that habitually accompany it. "We are afraid because we run" rather than, as generally believed, "we run

*Kieley, C. E.: James' theory of the emotions in relation to the adrenal glands. J. Lab. & Clin. Med., St. Louis, 1920, 6, 193-194.

because we are afraid." Kieley attempted to put this theory and his misconception of Cannon's theory to the experimental test. To two patients with marked affect disturbances he administered apocodeine over a period of nearly two weeks, with the idea of counteracting or neutralizing the action of the hypothetical excess of circulating epinephrin, and thus doing away with the bodily reactions to which, according to the James-Lange theory, the emotions might be due. The results were negative. The affect disturbances were in no degree ameliorated. The author concludes that, "granting Cannon's contention," the two experiments reported indicate that an emotion can be experienced independent of the physical changes that habitually accompany it.

A striking antithesis of this conclusion can readily be secured by administering 0.5 milligram of epinephrin to a susceptible patient, as is done in making the well-known "Goetsch test." The patients not infrequently develop tremors, pallor, lacrymation—in short, a typical picture of acute emotional distress. But when questioned such patients may state that they are entirely free from any affect reaction, even though they are normally of a somewhat emotional trend. Such observations would seem to afford definite proof that the James-Lange theory is not tenable. —R. G. H.

THE ACTION OF HYPOPHYSEAL EXTRACTS.

It is a matter of common observation that the administration of hypophyseal extracts to one and the same individual or to different individuals not infrequently yields physiological responses of apparently opposite types. Such paradoxical phenomena are more or less disconcerting to the clinician and the investigator alike.

There are at least three possible explanations of these differences in reaction, no one of which can at present be considered as all-sufficient, though a combination of parts of each, may in the last analysis contribute to the interpretation when the data are sufficiently complete.

In a recent article by Parisot and Mathieu (1920) the idea is developed that the differences in the type of response are largely dependent upon the size of the dose employed.

The so-called "dynamogenic" effects are expressed in the results obtained by the use of doses comparable in amount to what the gland itself is supposed to produce during its normal activity, while the "antidynamic" effects appear when doses are applied in amounts which are outside the range of normal glandular productivity. Such a conception suffers from the flaw that we do not know the rate of production of the active principles by the hypophysis. Yet the inherent possibility that the nature of the response is influenced in part by the size of the dose used is entirely valid in many cases.

The second possibility is derived from the observation of Schmidt and May (1917) that by mild hydrolysis of "tethelin" [discovered by Robertson (1916)]—the alleged active principle of the anterior lobe—there is obtained a solution which exerts the oxytocic and pressor effects commonly attributed to posterior lobe extracts, while "tethelin" itself shows no such activity. This finding gives rise to the opinion that perhaps the anterior lobe produces the mother-substance from which the effective principles of the posterior lobe are formed, and that the varied reactions obtained by these latter extracts are due to the predominance of one or another of the compounds resulting in the progress of the transformation, and represent either different degrees or different types of change of the mother substance. Confirmation of this idea must await the chemical isolation, identification and testing of the active principles.

A third possibility is that the physiological status of the subject with regard to the condition of tone of the responsive mechanism at the moment of the application of the extract, is an important factor governing the type of response that will be elicited. There is no reason to expect that, for example, a given blood vessel which is in a condition of constriction will respond to a certain amount of hypophyseal extract with the same type of reaction as will the same vessel to the same dose when it is in a state of relaxation. There is ample experimental evidence supporting this view which if substantiated by further studies is capable of application in principle to the interpretation of the opposite effects produced by the administration of many other substances.

These three possibilities then, the differences in the size of the dose representing differences in the amounts of active principle; the presence in the extracts of differently acting substances in different relative amounts; and differences in the physiological condition of the subject at the time of the administration of the extract, serve as indices for the interpretation of the paradoxical effects obtained. Whether or not any one of them is sufficient to alone explain the phenomena or whether the principles of all must be used is obviously a matter that can only be determined by further exact studies, and it would seem as if the most promising field for such work lies in the determination of the chemical nature and constitution of the active principles of the extracts. —F. S. H.

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Book Reviews

THE ENDOCRINES. By Samuel Wyllis Bandler. Phila. & Lond., 1921. W. B. Saunders Co. 486 p. 8°.

The book comprises mostly a reprint of a series of articles which the author has previously published separately. In addition there are final chapters on "clinics" and illustrative cases. Most of the subject matter has been presented in abstract form in previous issues of this Journal and hence calls for no extensive review.

The book as a whole comprises an interesting exposition of the beliefs which have led the author to the practice of employing endocrine products either exclusively or in part in ninety per cent of the prescriptions he writes.

The matter is presented in a way that renders impossible an impersonal evaluation of its significance. It is, in short, an expanded testimonial based upon personal experience. As such it inevitably raises the question as to the author's competence as a diagnostician and therapeutist. To those who believe the author a master the book will appear a highly significant addition to the literature. On the other hand, there is nothing in the presentation to exclude the judgment that he is merely a deluded enthusiast. The reviewer has no definite information upon the point.

This is said with no invidious intention. The same may be said of other books on so-called practical endocrinology. So far as the reviewer is aware such books without exception are based upon inadequate physiological conceptions. This is necessarily so since endocrine physiology is still in a nebulous condition. Nothing is to be gained, however, by selecting more or less random data to bolster up preconceived theories and ignoring such as are inconvenient. Much would be gained if writers in this field would accept the obvious fact that our fundamental data are in a state of chaos and present their material on a frankly, empirical, statistical basis.

Irrespective of our ignorance of the physiology of the placenta or the mammary glands, for instance, their exhibition as therapeutic agents may or many not be valuable. Bandler insistently states that they are valuable. Most therapeutists doubt or deny this. The matter can be determined in only one

way and that the way by which all therapeutic claims must be substantiated or disproved, namely by scientific investigation. They must be administered under controlled conditions to a large number of patients and the outcome honestly considered with adequate regard to negative as well as positive results. Especially, the element of suggestion must be rigidly excluded. To carry conviction the results must finally be presented for what they are, namely, a body of statistics, with due regard to the canons of statistical science.

That this offers a difficult task is obvious. Until it is accomplished, however, endocrinology can lay no convincing claim to serious regard as a valid science. In the meanwhile the field inevitably will continue to offer a happy hunting ground for quacks and faddists. For this reason, the reviewer ventures to hope that the author of The Endocrines will soon find time to reduce his extensive experience to an impersonal body of observed facts and present it as formal evidence, the lack of which we must all deplore.—R. G. H.

NEUE BEITRÄGE ZUR KENNTNIS DER LANGERHANSSCHEN INSELN IN MENSCHLICHEN PANKREAS. Seyfarth (C.), Jena, 1920, 104 p.

This is a highly important study. First of all much valuable material on the embryology of the pancreas is given. It is stated that the islets of Langerhans develop from the primary pancreatic ducts. Not only during fetal life, but also after birth and even in adult life new islets are continually formed out of the small excretory ducts. These questions have been studied not only in normal organs, but also in the pancreas of syphilitic fetuses and children. Under normal circumstances there, capsules do not exist around the islets. When a capsule is observed it consists of the connective tissue between the acini and does not form a true capsule. The islets are not organs with a special function. They form simply a part of the secreting parenchyma. Therefore, the theory that diabetes has a special connection with the islets is rejected by the author. All diseases of the blood vessels of the pancreas, but especially arteriosclerosis, may cause diabetes. Other causes affecting the pancreas and causing diabetes are alcoholism, syphilis, tuberculosis. Also other infections may produce changes in the pancreas and consequently diabetes. These are only a very few facts taken from this book, which may be most warmly recommended to all workers in the field of diabetes. Six splendid plates increase the value of this study.—J. K.

DIAGNOSTIC UND ERNAHRUNGSBEHANDLUNG DER ZUCKERKRANKHEIT IN DER PRAXIS. (Diagnosis and dietetic treatment of diabetes in medical practice). Schall (H.), Leipzig, 1921, p. 70.

This little book is perhaps the least successful one on this subject in existence. The chemical methods given for the determination of acetone, diacetic acid and β oxy-butyric acid are simply ridiculous. If an investigator wishes to carry out this kind of work he should do it properly; otherwise, he had better not try it at all. The author seems never to have heard of treatment with alimentary rest. Allen, Joslin, Leyton, and others seem to be perfectly unknown to Schall. It is not necessary to give further evidence that this book is superficial and useless. It does not speak well for the medical profession that it is already in the second edition.—J. K.

Abstract Department

(ADRENAL) Clinical notes upon suprarenal insufficiency. Babonneix (L.), Monde méd. (Par.), 1917, **27**, 167-71; Midland, M. J. (Birmingham), 1917, **16**, 129-132.

A brief report of a patient who died suddenly following recovery from acute tonsilitis. The autopsy showed complete destruction of the adrenals. The author assigns two essential functions to these glands—angiotonic and antitoxic; the former maintains the blood pressure at a certain level by adrenine, a product of the medullary substance. The latter neutralizes toxins by the lecithin produced by the cortical layer. Adrenal insufficiency results, therefore, on the one hand in circulatory disturbances—dilatation of the ventricles, acceleration, weakening and irregularity of the heart-beat, small pulse, pallor, white line, syncopal attacks; and on the other hand by an accumulation of undestroyed toxins, with digestive disturbances, anorexia, vomiting, colic, asthenia, etc. The sudden cardiac failures following acute infections like typhoid, diphtheria and scarlet fever, are not due to bulbar intoxication, myocardial disease, neuritis of the vagus, etc., but are purely dependent on adrenal insufficiency. The author agrees with Sergent regarding adrenal encephalitis and considers many so-called neurasthenics examples of adrenal insufficiency and believes chorea due to disease of these glands. Very many cases of sudden death ascribed to aortitis or coronary artery diseases are in reality due to profound changes in the adrenals. Again, most cases of sudden post-operative death or surgical shock are due to the same cause. The "incoercible vomiting" of pregnancy has the same etiology. He is an enthusiastic advocate of prompt adrenal therapy in the above conditions.—H. L.

Blood sugar before and after reduction of the ADRENALS in epilepsy, according to Fischer (Blutzuckerspiegel vor und nach der therapeutischen Nebennieren—"Reduktion" bei Krampfkranken nach Heinr. Fischer). Bausch (W.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1353.

The author determined the blood sugar in five patients after extirpation of an adrenal for epilepsy, but found no change. The blood sugar content was always perfectly normal.—J. K.

(ADRENALS) A case of phaeochromocytoma (paraganglioma) of the suprarenals with hypertrophy of the left heart. Bergstrand (Hilding), Hygiea (Stockholm), 1920, **82**, 321-334.

Following a brief description of the types of tumors originating in the suprarenal glands, the author reports a case of paraganglioma of the right suprarenal gland that was discovered at autopsy in the body of a woman, fifty years of age, who died from pneumonia. The tumor was oblong, measuring 5 c.m. x 8 c.m., and weighed 200 grams. It was definitely encapsulated and originated in the medulla of the gland. The tumor was well supplied with atypical blood vessels and had only a small amount of stroma. The tumor cells were packed into a network made by the blood vessels. The cells were all of one type, but differed in size. They were polygonal in shape and contained chromaffine. A few giant cells with polymorphous nuclei occurred. Nerve elements could not be demonstrated. Associated with the tumor was marked hypertrophy of the left ventricle so that the heart weighed 500 grams, and since there was no other apparent cause for this, the author believes the hypertrophy to be due to chronic hyper-adrenalinemia.—D. J. G.

(ADRENAL) Spolia opima. Bland-Sutton (Sir J.), Brit. M. J. (Lond.), 1918, (ii), 593-597.

This paper, among other things, describes a malignant tumor of the adrenal in a man of 45. In 1912 the lower half of the humerus was excised, and found to be occupied by "a red and extremely vascular tumor presenting the naked-eye appearance of a myeloma." In 1918 the patient died suddenly, and post-mortem examination revealed the fact that both adrenals were converted into plum-colored masses as big as fists. The lower half of the right kidney, the abdominal lymph nodes and the heart were all involved in secondary metastases. The microscopic structure of the tumors in the adrenals and kidneys was found to be the same as that of the tumor in the humerus previously removed. Each consisted of an enormous number of thin-walled blood vessels, and resembled a cavernous naevus. The nodule in the heart had the same structure as the normal zona fasciculata of the adrenal gland. The remarkable feature of the case is its chronicity. It is pointed out that the pathological features presented by this case are similar to those that characterize the rare condition known as general thyroid malignancy in which a moderate, and apparently benign, enlargement of the thyroid gland is associated with multiple tumors, especially in the bones. The structure of such deposits is indistinguishable from that of normal thyroid tissue. The case presented is regarded as an example of "general adrenal malignancy."

—L. G. K.

ADRENAL reduction for the cure of epilepsy (Die Nebennierenreduktion als Krampfheilendes Mittel). Brüning. Deutsche med. Wchnschr. (Berlin), 1920, **46,** 1351-1353.

Technical details are given. Extirpation of an adrenal does not cure epilepsy, but is always followed by improvement and the irritability of the patients is much diminished after the operation. The patient must not be operated upon when he is too young, for then hypertrophy of the remaining adrenal may destroy the results. There exist also now and then accessory adrenals, which may influence the effect of the operation. The operation is only indicated in epilepsy with spasms. Petit-mal and epileptical somnolence are not improved by this treatment. In traumatic or Jackson's epilepsy it is necessary to remove first the primary cause in the brain. If this is not followed by improvement, reduction of the adrenal ought to be carried out.—J. K.

Treatment of spasms with extirpation of one of the ADRENALS (Zur Behandlung von Krämpfen mit Extirpation einer Nebenniere). Bumke (O.) & Kuttner (H.), Zentralbl. f. Chir. (Leipzig), 1920, **47,** 1410-1411.

Description of the technic of the operation.—J. K.

(ADRENALS) The cause of anaphylactic shock (Der Ursprung des anaphylaktischen Schockes). Forssman (J.), Biochem. Ztschr. (Berlin), 1920, **110,** 133-163.

Extirpation experiments on guinea pigs from which the adrenals were removed, and after recovery from the operation, into which acute lethal doses of sheep corpuscle hemolytic serum were intravenously injected, demonstrated that the resultant shock was neither weakened nor increased and that consequently adrenin cannot have a significant influence on its development.—F. S. H.

Changes in the chromaffin content of the ADRENALS in experimental diabetes of central origin (Über die Veränderungen des Gehaltes der Nebennieren an Chromaffiner Substanz bei einigen experimentellen Diabetesformen zentralen Ursprungs). Fujii (Ijuro), Tohoku J. Exp. Med. (Sendai), 1920, **1,** 38-72.

The methods of Negrin and Brücke, slightly modified, are used for estimating the amount of chromaffin material in rabbits killed by a blow on the head. In rabbits in which glycosuria developed following sugar puncture the chromaffin substance is decreased, but in those in which no glycosuria developed following sugar puncture there is no alteration. Eckhard's operation in three rabbits increases only very slightly the reducing substance in the medulla.

In four rabbits with splanchnics on one side cut, sugar puncture decreases the chromaffin substance on the side of the intact splanchnics. Sugar puncture in two rabbits with both splanchnics cut produces neither glycosuria nor diminution in chromaffin substance. Diuretic injection in six normal rabbits causes a temporary glycosuria and an increase in chromaffin, but diuretic injection in four animals with both splanchnics severed has no influence on glycosuria or adrenalin secretion.—E. V. C.

Similar processes of alterations, especially those of the ADRENALS (Fatti simili, descritti nella noto precedente in caso di alterazione principalmente delle capsule surrenali). Garibaldi (G.). Clin. dermosifilopat. d. r. Univ. di Roma, 1917, **35**, 61-68.

The author gives the history, characteristics, symptoms, and pigmentation disturbances of a case of acromegaly, in which hypertrophy of the adrenals is suspected. At autopsy the various organs were normal except the adrenals. These were enormously enlarged, firm in consistency, and reddish in color. Histological examination disclosed no difference between the pigment of the pathological areas and the main substance of normal organ. The entire mechanism of this hypertrophic alteration of the adrenals is considered as a vast phenomena of hemorrhagic infarction, produced by the pathological state of all the capillaries, the latter condition in turn being the result of weakness of the parenchymatous tissues. The author concludes by explaining that the phenomena, for processes that simulate tumors and the corresponding alteration of blood and vessels, is not a unique example of pathology. On the contrary, the condition can be verified by any case of leucocytosis or of syphilis. —D. P.

Relation between splanchnic nerve function and ADRENAL secretion. Gley (E.) & Quinquaud (A.), Acad. r. Belg. bull. cl. d. sc., No. 4, pp. 315-316.

The authors supplement the report of researches published in 1914 and arrive at the conclusion that there is no such thing as physiological epinephrinemia. (See previous abstracts in Endocrinology.) Physiol. Abst., **5**, 40.

(ADRENAL) Gastric superacidity. Hayes (W. V.), N. York M. J., 1920, **112**, 5-8.

Hyperacidity may result because of nervous disorders, mental states, and reflexes from parts of irritation, especially of the gastrointestinal tract. Gastric secretions may also be excited by the stimulating action of foods and hormones. Certain cases of hyperacidity are readily controlled and benefitted by the administration of adrenal nucleoproteid and adrenal extracts.—H. W.

(ADRENALS) Hypertension and arterial fibrosis. Hood (C. T.), N. York M. J., 1920, **112**, 152-156.

An increased salt concentration in the tissues results in an accumulation of fluid therein and an increased capillary tension which requires in turn an increased systolic pressure. This condition demands an extra effort on the part of the left ventricle which may in time result in hypertrophy of the left ventricle or of the entire heart. In **Addison's disease** there is a low salt concentration, hence, on the basis of the above statements, such low pressures are to be ascribed to the lack of a sufficiently high salt concentration in the body tissues.—H. W.

(ADRENAL) Changes in organ weight produced by diets deficient in antiscorbutic vitamine. LaMer (V. K.) & Campbell (H. L.), Proc. Soc. Biol. & Med. (N. Y.), 1920, **18**, 32.

Young guinea-pigs weighing 250-300 grams, fed on a diet deficient in water-soluble C (antiscorbutic vitamine), show at death a pronounced increase in weight of the adrenal glands amounting to approximately 100 per cent. when computed on basis of body weight minus alimentary canal. (Confirming McCarrison's statement.)

The increase in size is equally definite but not so pronounced when computed on basis of the beginning, or maximum, body weight attained. Starvation controls do not show an increase in adrenal weight.

The increase in adrenal weight is directly proportional to the length of time which the animal is on the scorbutic diet and is most pronounced in those animals in which life has been prolonged by affording them partial protection with small but insufficient quantities of tomato juice.

This may be interpreted as indicating a compensatory response to the decreased adrenalin production known to exist in the scorbutic animal. This point is of interest in connection with the extensive intramuscular and intestinal hemorrhages found in scurvy. —Quoted.

ADRENALS, enlargement of the—in a fatal case of DIABETES. Litchfield (W. F.) & Little (E. M.), Med. J. Australia (Sidney), 1917, **2**, 73-74.

A post-mortem report of a case of diabetes in a woman of 53 terminating fatally in coma some time after two operations from gangrene of the extremities. The **spleen** was small and hard. The **pancreas** was atrophied and hard. The adrenals were both much enlarged. The **hypophysis** appeared to be normal. Microscopically the pancreas showed a fine fibrosis and the islands of Langerhans were present in normal numbers. The adenal cortex was increased.

The authors consider that some agency produced an adrenal hyperfunction and hypertrophy, which in turn induced the diabetes and ultimately caused the pancreatic fibrosis.—F. S. H.

ADRENAL preparations and their activity on peroral administration (Versuche über die Wirksamkeit der Nebennierenpräparate bei peroraler Zufuhr.) Loewe (S.) & Simon (Marie), Ztschr. f. d. ges. Exp. Med. (Berlin), 1918, **6**, 327-334.

Using rabbits, the authors carried out a series of 23 experiments in which they studied the absorption of adrenin administered by mouth by its effect on the peripheral vessel. It was found that an active preparation failed to produce any significant narrowing of the vessels or antiphlogistic action as is observed to a marked degree when the substance is injected subcutaneously or intravenously. Consequently, massive doses must be given **per os** for effectiveness.—F. S. H.

(ADRENALS) Addison's disease (Beitrag zur Kentniss der Addisonschen Krankheit). Löffler (W.), Zeitschr. f. klin. Med. (Berlin), 1920, **90**, 265-285.

Five cases are reported. Post-mortem examinations were made on four of them with the following pathological findings: The medulla of the **adrenals** was completely changed into tuberculous caseous tissue; the cortex was largely destroyed by tuberculous granulations; in all cases normal tissue could be found in the cortex, showing signs of regeneration. It is probable that first the medulla had become affected and the cortex had been secondarily attacked. In none of these cases were cells found either in the plexas solaris or the "Grenzshang" of the sympathetic that were chrom-staining. In a fifth case with tuberculous changes in the lungs, **the liver, spleen,** kidneys, **prostate,** adrenals and peritoneum. Both adrenals contained much normal cortical and medullary tissue. Status lymphaticus or **thymolymphaticus** was found in two of the five cases. In two others there were only a few symptoms of status lymphaticus; in the fifth case no signs of a status could be detected.—J. K.

ADRENAL paraganglioma (Le paragangliome surrénal). Peyron (A.), Ann. de l'Inst. Pasteur (Paris), 1917, **31**, 313-367.

Two types of epithelial tumors are recognized as springing from the suprarenal capsule; that arising from the chromaffin tissue of the medulla is known as "paraganglioma," while the tumor originating in the cortex is called "cortico-suprarenaloma." Mixed types involving both cortex and medulla are not believed to occur. Paragangliomata are of far less frequent occurrence than are the cortical tumors, and are rarely malignant, the author describing the

first known case. Most of the work was done on tumors found in the horse, but one case of a paraganglioma in a sheep is also recorded. Histologically, the primary paraganglioma in the horse takes the form of gland-like epithelial cavities, often of considerable size and of variable form. These represent the axial cavities of the normal suprarenal in an enlarged and altered form. Another important characteristic is the presence of cellular masses or strands of dense cytoplasm with small nuclei, resembling the chromophobe cells of the **hypophysis.** These nests of multi-nuclear cells represent a form of cellular renewal and multiplication. Intravacuolar secretion of chromaffin granules occurs, accompanied by the disappearance of the nuclei of many of the cells. Whether an adrenalaemia occurs or not is left for others to settle. The histology of the one case of malignant paraganglioma on record is also fully described. The metastases seem to spread largely by the venous system. In this case they were found in the kidney, lungs and a lumbar ganglion.—L. G. K.

(ADRENAL) Suprarenal sarcoma of the Robert Hutchison type. Weber (F. P.), Brit. J. Child. Dis. (London), 1920, **17**, 133-139.

Weber reports a case of what was evidently primary malignant disease of the medullary portion of the right suprarenal gland with multiple secondary metastases in the cranium of the type collected by Robert Hutchison. The patient was a girl of five years of age with a family history which was negative in every respect. Her liver was enormously enlarged, occupying most of the front of the abdomen and palpable as far down as the pelvis on the right side. The **spleen** was not felt. The eyes were both swollen and ecchymotic. The child was nearly blind in both eyes for almost a month. Opthalmic examination showed both optic discs to be pale with blurred edges, indicating a condition of post-neuritic atrophy of the optic nerve; there were no retinal hemorrhages. Because of this involvement of the skull and orbits and the presence in some cases of decided exophthalmos, Weber states that the cases may at first sight be regarded as chloroma or some form of acute or subacute leukemia, but this error could be avoided in the majority of instances by a careful examination of the blood.

The child died. Autopsy showed a tumor the size of a big orange, but of irregular shape, attached to the upper pole of the right kidney. It showed actively growing nodules which microscopically had the appearance of round cell sarcomas. It doubtless originated in the medullary portion of the right suprarenal gland and remains of suprerenal cortical tissue could be made out by microscopical examination in the layer of compressed capsule-like tissue enclosing the neoplasm. Weber, however, changed his original diagnosis of sarcomatous origin after reading Dougias Symmer's

paper on "Recurrent neuroblastoma" and came to the conclusion that the tumor in the right suprarenal in his case was, like others of this type, really a malignant hypernephroma of the suprarenal medulla, not of sarcomatous origin but of neuroblastomatous nature. The liver showed tumor cells resembling those found in the suprarenal. The kidney, left suprarenal and spleen were normal. There were metastatic growths in the abdominal lymph glands, cranial cavity, orbits, ovaries and dura mater, all resembling the suprarenal neoplasm. There were no growths in the brain itself. Perhaps the two most valuable diagnostic signs, according to Weber, of the Robert Hutchison type during life are: first, the dark ecchymotic swellings of the eyelids on one or both sides with or without exophthalmos, and, secondly, the optic neuritis or post neuritic atrophy. In the absence of both of these signs, one ought to hesitate in regard to the diagnosis.—M. B. G.

(ADRENAL) Observations in connection with the early development of the human suprarenal gland. Wieman (H.), Anat. Rec. (Phila.), 1920, **19,** 269-279.

An embryological study based on one 9 mm. and one 12 mm. human embryo.—W. J. A.

(ADRENALS) The Diagnosis of Suprarenal Tumors, especially in regard to Blood Pressure. Weber (F. P.), Practitioner (Lond.), 1920, **105,** 181-185.

A very brief, sketchy article, but calling attention to some interesting clinical aspects. Suprarenal tumors metastasize, as do malignant thyroid neoplasms, especially in the bones. Mention is made of the "infant hercules type," the precocious child resulting from primary tumors of the suprarenal cortex. Attention is called to the "Robert Hutchinson type" of malignant suprarenal tumors in children with metastases in the cranium, frequently so located as to produce a characteristic proptosis with ecchymotic edema of the eyelids. Scurvy with intraorbital hemorrhage, and chloroma can be readily differentiated. The blood pressure in these cases, even in children, is apt to be raised.—H. L.

ADRENIN, and vitamine in the treatment of the otosclerotic syndrome (L'adrenalina et le vitamine nel trattamento della sindrome otospongiosica [otosclerosi]). Caldera (C.), Arch. ital. d. otol (Napoli), 1920, **31,** 11-15.

The author obtained very good results when giving adrenin orally in cases of otospongiosis both as regards improvement in taste and improvement in hearing. Since the disorder has a patho-

logical-anatomical analogy to rachitis the author also fed vitamines with equally good results, though unfortunately the period of observation is as yet too short to allow definite conclusions to be drawn. From: Ber. d. ges. Physiol. u. exp. Pharm. (Berlin), 1920, 3, 340. —F. S. H.

Antagonism of depressor action of small doses of ADRENALIN by tissue extracts. Collip (J. B.), Am. J. Physiol. (Balt.), 1920, **53,** 477-482.

The fall in blood pressure following small doses of adrenalin is antagonized by various tissue extracts, while the rise in pressure produced by larger doses is augmented and prolonged. Both effects are of the same order.—T. C. B.

Antagonism of inhibitory action of ADRENALIN and depression of cardiac vagus by a constituent of certain tissue extracts. Collip (J. B.), Am. J. Physiol. (Balt.), 1920, **53,** 343-354.

Of endocrine interest is the fact that "extract" of heart, **spleen, pancreas, testes, anterior and posterior lobe of the pituitary thymus, thyroid** and **parathyroid** glands, in addition to stimulating the uterus of the rat, guinea pig, virgin dog and cat, antagonized the inhibitory action of adrenalin on these organs. Intravenous injections of extract of spleen augments the pressor response to adrenalin. —T. C. B.

Effect of ADRENALIN on venous blood pressure. Connet (Helene), Am. J. Physiol. (Balt.), 1920, **54,** 96-121.

The venous pressure rises in dogs and cats after intravenous injections of adrenalin. The two factors chiefly responsible are the decreased heart rate diminishing the unit output, and a vaso-constrictor mechanism in the veins. In anesthetized dogs with good vagal tone the rise is due to the first factor. In cats the second factor predominates.—T. C. B.

Adrenalin in the Treatment of Vertigo (L'adrenalina nella cura delle vertigini). D'Arbela, Riv. Crit. di Clin. Med., (Firenze), 1920, **21,** 250-251.

Starting from the statement that vertigo is the subjective expression of a sympathetic vaso-tonic unbalance of the Labyrinth, made by Vernet in the Presse Med. of July, 1920, adrenalin should be the ideal treatment. Adrenalin is supposed to excite the sympathetic nervous ends, to regulate the blood pressure and to be antitoxic. Therefore it has been employed with result at the dose of five drops to twenty drops twice a day. The A. treated these last four years numbers of patients suffering from vertigo with very encouraging results.—G. V.

Diminished renal permeability for sugar in experimental ADRENIN diabetes (Die sogenannte Nierendichtung gegen Zucker beim experimentellen Adrenalin diabetes). Hildebrandt, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1436.

Pollack has stated that when adrenin is injected regularly into animals the kidneys lose their permeability for sugar and that therefore the injection on the second or third day no longer gives rise to glycosuria. Hildebrandt has determined the blood sugar content by Bang's micro method and cannot confirm this. The reason why no glycosuria is observed is not a loss of permeability of the kidney but simply that repeated injections often do not cause hyperglycemia. The work of Pollack is worthless as he worked with the Bertrand method, where it is necessary to tie the animal; the method of getting the blood is painful and much blood is wanted. We know, however, that all these facts (loss of much blood, tying of the animal, pain) have an important influence on the blood sugar.—J. K.

ADRENIN mydriasis in chronic nephritis (Die Adrenalin mydriasis bei Chronischer Nephritis). Kato (Toyojiro) & Watanabe (Masao), Tohoku, J. Exp. Med. (Sendai), 1920, **1**, 187-191.

A critical review of the literature on adrenin mydriasis with observations showing that this reaction becomes more marked in chronic nephritis with increase in blood pressure.—E. V. C.

ADRENIN injections as a method of treatment of hemorrhoids (Ueber die Behandlung der Hämorrhoiden mit Suprarenininjektionen). Krukenberg (H.), München. med. Wchnschr., 1918, **65**, 851-852.

The parenchymatous injection of 1:1000 adrenin in cases of hemorrhoids causes a rapid diminution of the disturbance. The single administration of a 0.5 cc. dose caused the complete disappearance of the swellings in the course of eight days.—F. S. H.

ADRENIN, Treatment of the vomiting of pregnancy (Les vomissements incoercibles de la grossesse et leur traitement par l' adrenaline). Rathery (F.) & Bordet (F.), Ann. méd. (Paris), 1920, **8**, 94-100.

The authors obtained success in the treatment of the pernicious vomiting of pregnancy by the use of adrenin. They prescribed the subcutaneous injection of one-half milligram of adrenin chlorhydrate in 250 cc. of normal saline solution, and the ingestion or rectal administration of one-half milligram of the same preparation the first day with the dose to be doubled by both methods of administration on the next two or three days, and then cut down to the original dose, depending on the results obtained. The pa-

tients usually responded well within 24 to 48 hours. Whether or not the pernicious vomiting is due to an adrenal insufficiency is a question, but in the cases presented the administration of adrenin did not have any influence whatsoever on the arterial tension.
—F. S. H.

(ADRENIN) Reactions following intravenous administration of arsphenamine. The influence of atropine sulphate and adrenalin chloride upon these reactions. Strickler (A. A.), N. York M. J., 1920, **112**, 498-499.

The injection of 0.5 cc. of adrenin or 1/75 grain atropine previous to arsphenamine injections in no way influences the occurrence of reactive phenomena.—H. W.

A clinical apparatus for measuring BASAL METABOLISM. Benedict (F. G.) & Collins (W. E.), Boston M. & S. J., 1920, **183**, 449-458.

A comparison of the results of basal metabolism determinations obtained using a simplified apparatus with those obtained with the older and more complicated types of apparatus. The results of the simplified method are as accurate and more easily obtained than those by the older methods.—H. W.

(CARBOHYDRATE METABOLISM) On the metabolism of glucose in surviving organs (Sur le métabolisme de la glycose dans les organes survivantes). Lombroso (U.) & Artom (C.), Arch. ital. de biol. (Pise), 1917, **67**, 244-272.

Data published elsewhere. See Endocrinology, 1919, **3**, 190.
—L. G. K.

(CARBOHYDRATE METABOLISM) On the metabolism of glucose in surviving organs (Sur le métabolisme de la glycose dans les organes survivantes). Lombroso (U.) & Luchetti (C.), Arch. ital. de biol. (Pise), 1918, **68**, 145-147.

Not of endocrine interest.—L. G. K.

Further observations on the functions of the CORPUS LUTEUM. Ochsner (E. H.), Surg., Gynec. & Obst. (Chicago), 1920, **31**, 496-501.

The author quotes the experience of veterinarians to show that the retention of a false corpus luteum in the cow prevents the onset of the period of heat. If this corpus luteum is manually expressed the cow invariably comes in heat within 48 to 120 hours. Similarly the rupture or excision of a false corpus luteum in woman brings on menstruation within 12 to 36 hours. A number of cases are cited in support of this view. The following conclusions are

then drawn: (1) That an unabsorbed false corpus luteum prevents ovulation and is a common cause of sterility, and that the expression or excision of such a false corpus luteum invariably brings on menstruation. (2) That the excision or rupture of a true corpus luteum invariably results in interruption of pregnancy at least during the early months of pregnancy, and that it may be looked upon as a common cause of abortion. (3) That an injury to either the true or false corpus luteum may simulate ruptured extrauterine pregnancy.—L. G. K.

The role of fat in DIABETES. Allen (F. M.), Harvey Lect. (Phila. & Lond.), 1916-17, Series **12,** 42-111.

Data published elsewhere. Contains an extensive bibliography on the subject. See Endocrinology, 1919, **3,** 365 and 554.—L. G. K.

(DIABETES) Healing of a trophic ulcer of the great toe in an aged glycosuric patient. Barlow (H. C.), Brit. M. J. (Lond)., 1920, (ii), 124-125.

The patient was 82 years of age and had suffered from diabetes for twenty years. The ulcer healed completely after about five months of thorough local treatment and a reduced carbohydrate and fat intake. Sugar was still present in the urine however.—L. G. K.

(DIABETES) The relation of the islets of Langerhans to diabetes with special reference to cases of pancreatic lithiasis. Barron (M.), Surg., Gynec. & Obst. (Chicago), 1920, **31,** 437-448.

Pancreatic lithiasis is a very rare disease, which occurs mostly in males during the fourth decade. The obstruction of the pancreatic duct leads to an advaced atrophy of the pancreas accompanied by more or less fibrosis. The islets may remain intact even when the acini disappear completely. The islets are epithelial structures which are entirely independent of the acini and have no relation or communication with the ducts. Changes in the islets —such as degeneration, necrosis and fibrosis generally occur late in the disease, probably as a result of a superimposed secondary infection, consequent to a prolonged stasis in the ducts. In complete accord with the results of animal experimentation occlusion of the ducts by calculi in man does not result in diabetes mellitus unless there be actual injury to the islets. Cases of pancreatic lithiasis presenting symptoms of hyperglycaemia and glycosuria reveal definite lesions of the islets at autopsy. The author's study thus bears out the conclusions that the islets secrete a hormone directly into the lymph or blood streams, which has a controlling power over carbohydrate metabolism. The histopathology of the islets in diabetes falls into three main types, which in order of their importance, are as follows: fibrosis, hyaline degenration, and

arteriosclerotic changes. The pathogenesis of these lesions may not be very dissimilar to that of nephritis when taken in the broad sense. The difference in intensity of the pathological changes in the kidney as compared with those in the pancreas may be explained by the marked difference in the character of the two organs. In the kidneys any glomerulitis or other changes in the glomeruli are followed or accompanied by alterations in the tubules; no such changes affect the tubules or acini in the pancreas, since the islets are entirely distinct from the latter structures.—L. G. K.

DIABETES in relation to the DUCTLESS GLANDS. Brown (W. L.), Brit. M. J. (Lond.), 1920, (ii), 191-194.

The author classifies glycosuria as (1) organic in origin, with structural changes in the endocrine glands leading to (a) overaction of the **thyroid, adrenal, pituitary** or (b) underaction of the **pancreas**; (2) sympathetic in origin, with no evidence of structural changes in any endocrine gland, but producing a functional (a) overaction of the adrenal, thyroid, pituitary, and (b) underaction of the pancreas. Ordinary diabetes shows no other signs of endocrine disease, while endocrine glycosuria betrays other evidences of that origin. The most reliable signs of organic disease of the pancreas are (1) an excess of unsplit fat in the stools; (2) a high diastase content in the urine; (3) the adrenalin eye test. Jaundice would further suggest that the head of the pancreas was involved. Graves' disease and pituitary affections are frequently associated with glycosuria but the case for a definite adrenal diabetes is not clear. Diabetes is, then, a sign of exaggerated metabolism evoked through the sympathetic and the associated endocrine glands, which first asserts itself in relation to the most abundant food material (carbohydrate), but as it advances expresses itself in relation to all. The treatment by alimentary rest is advocated, the effect of which is to slow down metabolism and to increase the production of pancreatic internal secretion by diverting the pancreatic activity from the production of external secretion.—L. G. K.

DIABETES et syphilis. Bouchard (J.). Thése de Lyon. 1920.

The author comes to following conclusions:

There exist cases of glycosuria and diabetes that begin after a syphilitic infection. This may happen in the secondary or tertiary stages. Often the symptoms of secondary or tertiary syphilis begin at the same time as the diabetes. There are cases of diabetes which are markedly improved or even cured by antisyphilitical therapy. Syphilis acts as a malignant growth and may produce diabetes by local changes in the brain or in the liver and pancreas. On the other hand, it is possible that syphilis acts on the whole organism and produces diabetes by "humoral disturbances." When

there are symptoms of syphilis in a patient with diabetes it is necessary to begin antisyphilitical treatment.—J. K.

DIABETES and pancreatic insufficiency: treatment by opotherapy: therapeutic differentiation of the external and the internal secretions of the pancreas (Diabète avec insuffisance pancréatique: traitement opothérapique: disjonction thérapeutique des sécrétions externe et interne du pancréas). Faroy (G.), Bull. et mem. Soc. méd. de hop. de Par., 1919 **43**, 234-237.

Corrected citation; see Endocrinology, **4**, 146.—F. S. H.

Treatment of DIABETES (Zur Therapie der Diabetes). Grafe. München. med. Wchnschr., 1920, **67**, 1453.

The data have been reported in an abstract from Deutsch. Arch. f. klin. Med.—J. K.

DIABETES, mortality in the different branches of trade in adult men in Danish towns. Heiberg (K. A.), Ugesk. f. Laeger (Copenhagen), 1916, **78**, 174-179.

The author has collected from the public health archives the cases of deaths from diabetes in the period 1904-14. He found the mortality rate was 2%. There was no apparent difference between the mortality in the different social classes (intellectual workers, farmers, tradesmen, etc.).—K. H. K.

DIABETES, Relation of the alkali reserve of the blood to glycosuria and hyperglycemia in pancreatic—. Hendrix (Byron M.) & Crouter (Caroline Y.), J. Biol. Chem. (Balt.), 1920, **45**, 51-55.

The authors of this report started with the idea that if the gastric juice were not completely neutralized in the intestine after the removal of the pancreas, it would react with the carbonates and phosphates of the blood in the portal system causing a reduction of the alkali reserve in the whole blood, inasmuch as the blood from the portal system is mixed with the blood from the rest of the body in the heart, lungs and to a less extent, in the liver. Since hyperglyceria and glucosuria appear very soon after the removal of the pancreas, it was thought worth while to study the alkali reserve of the blood as measured by the power of the plasma to combine with carbon dioxide, and compare this with the change in the concentration of glucose in the blood, and its excretion into the urine.

Five dogs were used in the study, two males and three females, one of which was pregnant. It was found that the alkali reserve of the blood as measured by the carbon dioxide of the plasma showed no increase until diabetes, as shown by the G:N ratio and increase in blood sugar, had been established for at least 24 hours. The earliest appearance of a decrease in the carbon dioxide ca-

pacity of the blood came about 48 hours after the removal of the pancreas, while there was always a definite increase in the blood sugar within one day after the operation. It is well known that glucose appears in the urine a few hours after removal of the pancreas.—F. S. H.

(DIABETES) Pre-operative preparation of diabetic patients and their subsequent treatment. Kahn (M.), Surg., Gynec. & Obst. (Chicago), 1920, **31**, 363-365.

The patient's degree of acidosis should be determined, and then corrected by reducing the fat intake to a minimum and by stimulating the carbohydrate oxidation, because of its anti-ketogenic powers. The diet therefore should be poor in fat and rich in vegetables and proteins, with the addition of a cereal which adds to the carbohydrate content. Sometimes alcohol may also be used to advantage. Alkalies should not be prescribed. The bowels should be kept open, preferably by enemata, in order to avoid draining the alkali salts from the body. Fluids should be administered in liberal amounts. Finally by the plan of Allen or by a modified starvation diet the glucaemia may be reduced. Nitrous oxide is the anesthetic of choice. In the after-treatment the glucose tolerance should be constantly increased. Caffeine is contra-indicated as a stimulant. Large doses of calcium chloride are advised, 10 gr. three times a day after meals.—L. G. K.

Yoghurt treatment of DIABETES (Yoghurtkuren bei diabetes). Klemperer (G.), Berl. klin. Wchnschr., 1918, **55**, 523-524.

The author describes the results obtained by treating six cases of diabetes with the daily addition to the diet of one liter of yoghurt milk. As a result of the ingestion of this substance the glucosuria disappeared or was markedly reduced. Notice is also made of the fact that eight other diabetics of more or less intensity showed an increased sugar output under the treatment instead of a diminution. Klemperer is of the opinion that the beneficial effects were due to the Yoghurt bacilli and that the deleterious action was due to the overwhelming of these by other intestinal bacterial forms.—F. S. H.

Fruit days in DIABETES mellitus (Früchtetage bei Diabetes mellitus). Lampé (E.), Therap. Monatshm. (Berl.), 1918, **32**, 337-338.

A brief article advocating the inclusion of a fruit day in the dietary regime of diabetics.—F. S. H.

DIABETES mellitus, particularly war diabetes, treated with enzymes (Zur Fermentbehandlung des Diabetes mellitus, speziell des Kriegsdiabetes). Lennè. Deutsche med. Wchnschr. (Berl. u. Leipz.), 1918, **44**, 39-40.

Lennè reports the effects of a commercial enzyme preparation "Diabetylin" in five cases of diabetes mellitus. The originators of the product state that it is a combination of trypsin with yeast, which "promotes glycolysis." The feeding of the product failed to cause any decrease in the glucosuria or amelioration of the patients.—F. S. H.

DIABETES accompanied by generalized xanthomatosis. (Generalizerte Xanthomatose bei Diabetes). Lubarsch (O.), Deutsche med. Wchnschr. (Berl. u. Leipz.), 1918, **44**, 484-486.

Data reported elsewhere.—F. S. H.

The treatment of DIABETES MELLITUS. Mason (E. H.), Canad. M. Ass. J. (Toronto), 1920, **10**, 1105-1111.

The following is an outline of the method used in treating diabetic patients in the Royal Victoria Hospital, Montreal: (1) Obsevation diet (for 3 days) containing—protein, 1.5 gm. per kilo body weight; fat, enough to make 20 or 25 calories per kilo; carbohydate, 1 gm. per kilo. (2) One-half observation diet. (3) One-quarter observation diet. (4) Fast. This period includes thrice boiled vegetables, bran cakes and chicken broth. (5) Determination of carbohydrate tolerance upon green vegetables increasing 10 gm. of carbohydrate per day until there is glycosuria 2 days in succession on the same intake of carbohydrate. (6) Fast, to free from glycosuria. (7) One-third trial maintenance diet. (8) Two-thirds trial maintenance diet. (9) Trial maintenance diet containing, protein, 1.5 gm. per kilo body weight; fat, enough to make 25 calories per kilo; carbohydrate, half that of the carbohydrate tolerance as detemined on green vegetables. (10) Increases above the trial maintenance diet depends upon the case, it often being wise to give 1.75 gm. of protein per kilo, a slightly larger amount of carbohydrate, or fat enough to make 30 to 35 calories per kilo body weight. After the determination of the carbohydrate tolerance upon green vegetables a regular weekly fast or one-half value day is instituted. This is continued after discharge, for it is believed to be an important factor in the ultimate improvement of the case. During the patient's stay in the hospital he is carefully educated in the nature of his condition, normal metabolism, the technique of figuring diets, kitchen work, and laboratory methods for detecting glucose and acetone in urine. On discharge he is furnished with the means of carrying out his instructions. It is found that the results vary directly with the thoroughness of the patient's education while in the hospital, and the carefulness with which their diets are supervised after their discharge.—L. G. K.

DIABETES, The diet in— (Le regime alimentaire des diabetiques). Nigay, J. de méd. de Paris, 1917, **36,** 172-174, 189-191, 209-212, 229-231; 1918, **37,** 8-10: 28-29, 50-52, 72-73, 95-96, 110-111, 130-131.

Nigay recommends fatty soups, and cabbage soup by virtue of its alkaline salt content. Hors d'oeuvres are allowable because of their high fat content. Milk is prohibited unless previously desaccharated in the form of kéfir, koumyss, etc. Eggs are looked on with favor. Fish in general is acceptable because of the high fat and protein content. Salt fish, however, is in disfavor. All meats save that from the horse can be eaten readily but within reason. Diabetics possessing a good digestive tube can eat fats in all their forms without limit. Vegetables are advocated as a good source of filling material, fresh peas, beans, lentils, etc., are permitted. Potatoes are forbidden fruit. Non-farinaceous gravies are allowable but condiments are frowned upon, as is pastry. Cheese is persona grata. Bread and cake, unless prepared by special formulae, are taboo. Dry wines and other alcoholic beverages, coffee, tea (mint and camomile) and mineral waters are permitted. The articles continue with descriptions of when the diabetics should eat, the proper diet for irreducible glycosuria, for diabetes complicated by dyspepsia, eczema, prurigo, gout, albuminuria, uremic nephritis, acidosis and inanition, on the diet sufficient to prevent denutrition.—F. S. H.

DIABETES MELLITUS and the war (Kreigserfahrungen über Diabetes mellitus). Richter (P. F.), Deutsche med. Wchnschr. (Berlin), 1920, **46,** 1380.

During the war the mortality in Germany from diabetes was greatly diminished, even up to 100%. In England, where there was much more food, though less than before the war, the mortality diminished 25%. Perhaps many patients with diabetes died from tuberculosis. The cases of severe acidosis have nearly disappeared; in its place cachexia has become much more frequent. The light cases have much improved. Many show a glucosuria, though nearly always hyperglycemia. It is of great importance to restrict the diet in regard to proteins. This is more important than underfeeding.—J. K.

A case of transitory hypermetropia in DIABETES. Rönne (H.), Hosp.-tid. (Copenhagen), 1916, **59,** 195-196.

A woman aged 46 years showed subjective signs of diabetes for a month; there was 8% glucose in the urine. One morning she suddenly could not see distinctly. The eye examination showed sight 6/6, hypermetropia 3.00 diopters. After a month she could not see through her glasses of 3.00 diopters, but the sight was good without these. A new examination showed sight 6/6, and hyper-

metropia 0.50 diopters. Such cases, but less acute, have been described before. The changes are probably related to changes of tension in the lenticular fibres caused by chemical reaction. In the discussion Lundsgaard remarked that most cases of hypermetropia in diabetes are not detected. It is uncertain if the changes of glucosuria cause the disease. Ask has found a certain proportion between the content of glucose in the aqueous humor and the blood-plasma.—K. H. K.

The prevention of DIABETES MELLITUS. Williamson (R. T.), Practitioner (Lond.), 1920, **105**, 233-243.

Diabetes is more apt to develop where there is a family history of the disease, in those whose brains are greatly overworked, in those who take too much sugar, sweet foods, or drinks, in those who take too little exercise, and those who are very stout, and eat too much. Diabetes is more prevalent in Maltese, Hebrews, Hindus and in the citizens of the United States. Excess of starchy carbohydrate food probably does not increase the risk of diabetes; diabetes, for instance, is not especially prevalent among Chinese. Sugar is more injurious than starch. Williamson recommends as preventive measures: 1 Avoid great excess of sugar, jam, sweets, chocolate, sweet foods, sweet drinks; 2 If there be positive family history or race tendency, no sugar should be added to any food or drink; a list is given of very sweet foods, fruits and drinks which should be avoided; 3 Obesity should be checked; 4 Sufficient physical exercise is important; 5 Excessive brain work and nervous strain should be avoided; 6 Restriction of alcoholic drinks; 7 Sufficient sleep; 8 Conservative diets should be recommended in diseases in which diabetes is not an infrequent complication such as **Graves' disease, acromegaly,** chronic gout, chronic Bright's disease and arteriosclerosis.—H. L.

The decreased resistance of patients with DIABETES towards infections (Über die verminderte Resistenz Zuckerkranker gegenüber pyogenen Infektionen). Wolfsohn (G.), Ztschr. f. ärtzl. Fortbild. (Jena), 1920, **17**, 678-679.

The phagocytic properties of the leucocytes of diabetic patients are less marked than are those leucocytes from normal individuals. —J. K.

DIABETIC XANTHOMA, demonstration of preparations (Demonstration anatomischer Präparate von Xanthoma diabeticum). Lubarsch (O.), Berl. klin. Wchnschr., 1918, **55**, 196.

Macroscopic and microscopic preparations from a young diabetic showed a generalized xanthomatosis. The pigmentation was particularly marked in the liver, spleen and lymph-nodes.—F. S. H.

Influence of the DUCTLESS GLANDS upon amphibian metamorphosis. Hogben (L. T.), Science Prog. (Lond.), 1920, **15**, 302-306.

An essay dealing with the more recent work on amphibian metamorphosis as influenced by the various endocrine glands.
—T. C. B.

On some ENDOCRINE GLANDS (Die alcune ghiandole endocrine). Anon. Morgagni (Milano), 1920, **62**, 513-518.

A general superficial review.—J. K.

(ENDOCRINE GLANDS) Endocrinopathic nanism accompanied by multiple dystrophies (osseous and visceral); Raynaud's syndrome and dementia precox in a case of hereditary syphilis (Nanismo endocrinopatico, coincidiendo con multiples distrofias [oseas y viscerales], Syndrome de Raynaud y demencia precoz, en una sifilitica hereditaria adulta). Castex (M. R.) & Waldorp (C. P.), Rev. Asoc. med. argent. (Buenos Aires), 1920, **32**, 270-273.

Report of a patient 25 years old, 1.30 m. tall and weighing 25 kgr. Anatomical examination of the hypophysis and adrenals showed them to be normal. There was genital hypotrophy and mild thyroid sclerosis. The lesions are attributed to hereditary syphilis.
—B. A. H.

(ENDOCRINE GLANDS) Diffuse Neurofibromatosis (Recklinghausen's Disease) (Neurofibromatosi diffusa [Morbo di Recklinghausen]). Castronuovo (G.), Riferma Med. (Napoli), 1920, **36**, 817-821.

The author gives a detailed description of the disease, reporting a case, which showed a precocious association of tuberculosis, whose asthenic conditions improved for a time with administration of large doses of **adrenin.** In the pathogenesis he lays a great stress on the endocrine disturbances—pluriglandular, but especially connected with adrenal, **hypophysis, ovary** and **thyroid** dysfunction —and, following Castellino's opinion, relates neurofibromatosis to acromegaly, Addison's disease and Dercum's disease, which all show, besides cutaneous and subcutaneous alterations, characteristic disturbances of the blood and of the metabolism. Their relationship is furthermore demonstrated by their frequent association, by their passing from one to another and finally by the improvement shown in them all with hormonic therapy (adrenal, hypophyseal, thyroid).
—G. V.

ENDOCRINOLOGY, general physiology and the thyro-parathyroid system. Delgado (H. F.), Crón. Méd. (Lima), 1920, **37**, 281-292.

A critical review containing no new data.—I. O.

(ENDOCRINE GLANDS) Sterility, sex stimulation and the endocrines. Edgar (T. W.), N. York M. J., 1920, **112**, 848-849.

From a limited number of observations following the administration of Edgar's pluriglandular serum, the author concludes that certain cases of sterility and sex depletion are, like **diabetes**, the result of endocrine want. Old age may also be placed in the category of endocrine want. It is possible that the pluriglandular serum of which so much has been claimed by Edgar, does relieve a great number of diabetics. However, the claim that the same serum reinstates sexual life may be explained by the fact that any general building up of the body results in an increased libido and sex life.
—H. W.

The ENDOCRINES in gynecology. Graves (W. P.), N. York M. J., 1920, **112**, 697-701.

The author considers that functional neuroses are continuous states of emotional excitement which are sensory in character induced by reciprocal activities following stimulation of the autonomic nervous system and certain of the glands of internal secretion.
—H. W.

(ENDOCRINE GLANDS) Infantilisme. Krabbé (K. H.), Nord. med. Ark. (Stockholm), 1919, **51**, 551-578.

The author describes 4 cases of infantilism in adults, a case of arrested development, without arrest of sexual development, and two cases of arrested development in children, which possibly may show infantilism after puberty. One of the cases was connected with Calvé-Perthes disease, another one with epilepsy. The three cases did not show any sign of endocrinal disease apart from infantilism. The author concludes that the basis of infantilism is a combination of arrest of sexual development with general arrested development, and not so much the psychic relations or the infantile proportions which in many cases may be modificated by several complications. As shown before, infantilism may be produced by **thyroid** or **hypophyseal insufficiency** (but not by **ovarian** or **testicular**). Besides these cases of dysendocrine infantilism many cases exist of infantilism in which no signs of endocrinal disease may be shown. Perhaps some of these cases are dysendocrine, but it is still not proved and we must temporarily acknowledge our ignorance concerning the pathogenesis of these cases. (The article is in French.)—K. H. K.

(ENDOCRINE GLANDS) Two cases of Apert's hirsutism, virilism and psychopathy (Deux cas d'hirsutism d'Apert avec virilisme et psychopathie). Laignel-Lavastine & Boutet (A.), Bull. et mém. Soc. méd. d. hôp. Par. 1920, **44**, 1303-1313.

A report of two female patients. The first presented general hypertrichosis and confusional anxiety which apparently was aligned with Basedow's syndrome, ammenorrhea and mitral regurgitation. There was mental debility, melancholy depression, mutism, etc. A hyperchloresterinemia was present, which when correlated with the arterial hypertension, a facile glucosuria and reaction to the glandular tests led to the diagnosis of a **hyperadrenalemia** probably as a reaction from **ovarian** insufficiency. The endocrine tests were made by studying the maximal and minimal tension, the pulse and the glucosuria following injections of extracts of **thyroid,** adrenal (total, cortex, and medulla), **hypophysis** (total, posterior lobe). The second patient presented hypertrichosis, obesity, mannish appearance and voice, ammenorrhea, imbecility, puerility and alternating periods of excitement and depression. She also had a hyperchlorestinemia and the endocrine tests led to the same diagnosis of an endocrine disturbance of ovarian origin accompanied by disturbances in the lipoid regulation.—F. S. H.

(ENDOCRINE GLANDS) Opothérapie et Endocrinothérapie. Laumonier (J.), Bull. gen. Therap. (Paris), 1920, **171,** 599-612, 637-650.

The author seems to feel that there is a tendency to confound internal secretions and organ extracts. In order to clarify the situation he gives an extensive dissertation on the subject, defining excretion and secretion, and repeating in some detail the well known facts about the conditions attending internal secretion. He then goes on to classify the internal secretions and follows the delineation proposed by Gley, who considers **hormones** those substances which affect function, and **harmozones** those products which affect structure. Of the former **adrenin** is given as a type, of the latter the **thyroid secretion.** To the reviewer, such a classification seems too essentially overlapping to be worth while. In the second part of the discussion organ extracts are differentiated from internal secretions by their toxicity, their similarity of action, the extemporaneous nature and the irregularity of the effect produced, and finally the hemoclasic phenomena attending their administration, all of which may be exhibited when preparations of glands of internal secretion are administered and which are not the properties of any particular tissue.—F. S. H.

(ENDOCRINE GLANDS) Case of myasthenia of thirty years' duration accompanied by bony alterations of the dental maxilla. Progressive evolution (Un cas d myasthénie datant de treize ans avec altérations osseuses maxillo-dentaries a évolution progressive). Lereboullet, Izard & Mouton, Bull. et mém. Soc. méd. d. hôp. d. Par., 1920, **44,** 1618-1623.

An interesting case report but presenting no definite endocrine material.—F. S. H.

ENDOCRINE disturbances (Endokrine Störugen). Lommel. Med. Klin. (Berl.), 1918, **14**, 848.

Report of a case of a 54-year-old man who was suddenly attacked with exhaustion, hypotonia, hyperthermia, marked bradycardia and loss of hair. The disturbances are attributed to a pluriglandular disorder.—F. S. H.

ENDOCRINE GLANDS, Contribution to the study of the dysfunctioning of the— during pregnancy (Weitere Beiträge zum Studium der Dysfunktion endokriner Drüsen in der Schwangerschaft). Mahnert (A.), Arch. f. Gynaek. (Berlin), 1920, **113**, 472-489.

A brief review of the subject and report of experiments made to test the presence or absence of enzymes in the blood of pregnant women capable of affecting **hypophysis** or **pineal** proteins. Abderhalden's micro-method using the refractometer was used. Out of the 25 pregnant women whose serum was examined for the presence of a hypophyseal protein-destructive enzyme 60 per cent gave a positive reaction, from which Mahnert concludes that in the greater number of pregnancies there is a hypophyseal dysfunction. Yet when he finds that out of 20 cases he gets 60 per cent that do **not** give a positive test for pineal protein destruction he also reasons that there is a pineal dysfunctioning in pregnancy.—F. S. H.

(ENDOCRINE ORGANS) Dietetic deficiency and endocrine activity, with special reference to deficiency oedemas. McCarrison (Robt.), Brit. M. J. (Lond.), 1920 (ii), 236-239.

Correction of abstract, Endocrinol., **4**, 641-642. Butter varies in its capacity to protect against edema. This variation is dependent on the quality of the cow's food. Butter is richer in anti-edema substance when the cows are fed on green fodder.—Author's correction.

The diagnosis and treatment of some diseases of the ENDOCRINE GLANDS. Murray (G. R.), Brit. M. J. (Lond.), 1920 (ii), 807-811.

This address deals with the diseases of the **thyroid, pituitary** and **adrenal** glands, special emphasis being placed on the early symptoms of disturbances in function. Besides inspection and palpation, percussion and auscultation very often yield valuable information in an examination of the thyroid gland. Percussion may help to determine the position of the trachea or the presence of gas in a cystic adenoma when infected by a gas-forming organism. Compression of the trachea is indicated by abnormally high pitched breath sounds on auscultation over the trachea. The sounds are

as distinctly audible during expiration as during inspiration. The early symptoms of hyperthyroidism are said to be a constant sense of fatigue, perhaps extending over a considerable period of time; gradual progressive loss of weight, in spite of an increased appetite; change in disposition, restlessness, mental depression or anxiety; fine tremor seen when the hands are extended; slight persistent acceleration of the pulse rate with tachycardia on exertion. There may be slight elevation of the upper eyelids, slight increase in moisture of the skin, disappearance of any former tendency to chilblains and diminution in any tendency to suffer from common colds. An increase in the basal metabolic rate of the patient is a very important symptom (see Endocrinology, 1920, **4**, 71). Rest in bed for several weeks, a liberal diet poor in proteins and x-ray or radium applications are the main points in the treatment of these early cases. Thyroid deficiency in children, in its early stages, is recognized by delay or arrest of growth and lack of normal activity; tendency to coldness of the extremities and dryness of the skin; slight thickening of the subcutaneous tissues, especially of the face, neck, supraclavicular fossae and backs of the hands; slight depression of the bridge of the nose and pale complexion. In the adult, thyroid deficiency is apt to occur between the ages of 40 and 50. The basal metabolic rate falls, there is loss of energy and slowness of the mental processes, and there may be slight myxoedematous swelling of the subcutaneous tissues. The skin becomes dryer and the hair thinner.

Enlargement of the pituitary may cause pressure symptoms such as temporo-frontal headache, diminished fields of vision, epistaxis, etc. The early symptoms of increased function may be drowsiness, sense of fatigue, depression, post-nasal catarrh and photophobia. Finally the well-known skeletal changes appear. X-ray treatment is worth trying; surgical intervention is justified only when the symptoms of intra-cranial pressure must be relieved, otherwise the treatment is symptomatic. Underfunctioning of the pituitary results in the rare condition of adiposo-genital dystrophy. Treatment by pituitary has proved disappointing. In connection with the diseases of the adrenal glands Addison's disease is given the usual text-book description. The remark is made that the administration of 15 minims of adrenin solution in ½ oz. water, 5 to 10 minutes before a meal is very effective in relaxing or preventing spasm of the oesophagus.—L. G. K.

(ENDOCRINE GLANDS) The influence of the spleen, the kidney and of the THYROID in producing anaphylactic crises (L'influenza della milza, del rene, delle tiroide nella produzione della crisi anafilattica). Pistocchi (G.), Pathologica (Geneva), 1920, **12**, 239-240.

Starting from the assertion that anaphylaxis has been of late connected with such morbid conditions as asthma, uremia, eclampsia, epilepsy, etc., and therefore the accessory syndrome must require a ground already prepared, Pistocchi produced experimental alterations of metabolism by removal of the spleen, the kidney or of the thyroid. The removal of the spleen or of one kidney did not appear to alter the anaphylactic reaction, although the experiment was always carried out before the organism could adapt itself to the new condition through a possible vicarious activity of other tissues. Following thyroidectomy the classical symptoms of anaphylactic shock were considerably reduced. The few cases which did not respond in this way are explained by the difficulty of complete thyroid extirpation in the guinea-pig. The author thinks that the delayed metabolism brought about by thyroidectomy probably acts by diminishing the nervous energy, as did the starvation experiments of Besredka.—G. V.

(ENDOCRINE GLANDS) Congenital absence of the vagina and uterus. A consideration of this problem in the light of the more recent endocrine studies and surgical advances, with the report of a case successfully operated upon by the Baldwin method, slightly modified. Robinson (M. R.), Surg., Gynec. & Obst. (Chicago), 1920, **31,** 51-57.

This paper which is largely surgical, emphasizes the point that operative measures tending to create a vaginal tract should be undertaken only in individuals who are physically and psychically women, in the full sense, which this definition implies. In order that the newly constructed vagina should approach the normal as closely as possible it should be lined with a soft, lubricated mucosa, and the employment of an intestinal loop for that purpose, as advocated and executed by Baldwin, is the choice operation. In the author's opinion it is safer to start the separation of the tissues between the rectum and the bladder, in order to establish the copulating channel, from above, instead of from below.—L. G. K.

(ENDOCRINE GLANDS) Vaso-motor disturbances of the nose with special reference to hay fever—with a report for the year 1919. Selfridge, (G.), Laryngoscope (St. Louis), 1920, **30,** 611-625.

The author, although recognizing that hay fever and its allied conditions are the result of protein sensitization, is forced to the conclusion that vaso-motor rhinitis is related to disturbances in the functions of the autonomic nervous system and disturbed endocrine glands. Direct proof is not given for this conclusion, however, a study of asthmatic types and the results of endocrine medication in a limited number of cases would seem to indicate that such cases are the result of disturbed endocrine metabolism. Perhaps, as the author suggests, the reason that certain individuals

become sensitized to proteins is because of an underlying endocrine dysfunction.—H. W.

(ENDOCRINE GLANDS) The heart in endocrine diseases (Herzbefunde bei endokrinen Erkrankungen). Zondek (H.), Berl. klin. Wchnschr., 1920, **57**, 908.

Data reported elsewhere.—J. K.

(GONADS) Homosexuality and hermaphroditism (Omosessualita' ed ermafroditismo). Carrara (Mario), Riforma med. (Napoli), 1920, **36**, 588-589.

This article is a short review of Steinach's studies on the subject, with a report of cases of homosexuals showing ovarian substance in the testes. The author ends by quoting the importance of the phenomena in heredity as demonstrated by Lazzeroni's statistics, according to which the larger part of the sexual inverts beget girls almost exclusively, the few boys that are produced are usually sexual perverts.—G. V.

(GENERAL) Cholesterinemia in normal and pathological conditions (La cholestérinémie a l'état normal et pathologique). Chauffard (A.), Laroche (G.) & Grigaut (A.), Ann. méd. (Paris), 1920, **8**, 60-91.

A cholesterinemia is frequently observed during the first three months of pregnancy, the values then tend to drop only to rise again towards its termination. A similar state of cholesterinemia is also found accompanying menstruation. Its occurrence in **diabetes** is made the subject of a brief comment.—F. S. H.

(GONADS) Eugene Steinach's work on regeneration. Granet (A.), N. York. M. J., 1920, **112**, 612-613.

A review of Steinach's article appearing in Arch. Entwcklungsmech. d. Organ, 1920, **46**, 12.—H. W.

(GONADS) The effects of castration of hen-feathered Campines. Morgan (T.), Biol. Bull. (Phila.), 1920, **39**, 231-247.

Morgan had shown that in the Sebright bantam castration changes the hen-feathered male into a cock-feathered bird. There are only hen-feathered males in the Sebright race. Campines are dimorphic—there being both hen-feathered and cock-feathered males. Hen-feathered males become cock-feathered after castration. The hypophysis seems to be slightly larger in the castrated bird. No change in the adrenals was observed.—W. J. A.

(GONADS) Cytological and experimental studies on sex in Dinophilus apatris (Zytologische und experimentelle Untersuchungen über die Geschlechtsbestimmung bei Dinophilus apatris [Korsch]). Nachtsheim (H.), Arch. f. mikr. Anat. (Bonn.), 1919, **93**, 17-140.

Not of endocrine interest.—W. J. A.

(GONADS) Hypoplasia und tumor. Tschirdewahn. Deutsche med. Wchnschr., (Berl. u. Leipz.), 1920, **46**, 616.

The author demonstrated a tumor of the dimensions of a duck's egg. The patient from whom it was removed had genital hypoplasia, the sex of the patient not being recorded. The tumor was probably partly testicular and partly ovarian.—J. K.

(HYPOPHYSIS) Case of pluriglandular insufficiency (Sobre un caso de insuficiencia pluriglandular). Bosch (B.) & Hernandez (J.), Arch. Conf. Medicos Hospital Ramos Mejia (Buenos Aires), 1919, **vii**, 87.

Observations on a case of dystrophia adiposo-genitalis.—B. A. H.

Action of HYPOPHYSEAL injections in certain syphilitic migraines and in the ordinary congestive headaches (La accion de las inyecciones hipofisarias sobre ciertas cefaleas sifiliticas y sobre las cefaleas congestivas banales). Bouveyron. Bull. de la Soc. Francaise de Dermat. et de Syphilograph (Paris), 1920, **vii**, 283-285.

Bouveyron used the intramuscular injection of posterior lobe extracts in amounts corresponding to 20 centigrams of the ox pituitary, in syphilitics with roseola and intense headache and found that all symptoms disappeared within five minutes. The roseola reappeared, however, within an hour, but the headache did not recur for two hours. If hypophyseal extract injections are made at the same time as the intravenous injection of arsenobenzol, not only are the exacerbations of headache produced by the arsenical, impeded but that already present is diminished. The extracts were also used with success in preventing the accidents of congestion accompanying the administration of arsenobenzol. Report is made of a case of bilateral tonsilitis, with a temperature of 39 degrees C., in which the headache was very severe. The latter was ameliorated in five minutes after the exhibition of pituitary extract; on the other hand, the temperature rose to 40 degrees C. in fifteen minutes. This case does not demonstrate whether the headache was of thermal or toxic origin, but does show that temperature and headache are dissociable phenomena.

It would appear as if the greater number of headaches is produced by an intracranial hypertension from the fact that they are alleviated by lumbar puncture and because in cerebral tumors, accompanied by intracranial hypertension, headache is a rather constant symptom.

The results of hypophyseal injections seem to favor this conception, according to the author, who concludes by stating that such injections can serve as a means of diagnosis of congestive headaches.—C. G. C.

(HYPOPHYSIS) Complete recovery from Diabetes Insipidus. Cammidge (P. J.), Practitioner (Lond.), 1920, **105**, 244-247.

A case is reported in detail of complete recovery without relapse for 6 years following lumbar puncture. Various diets had been instituted, antisyphilitic treatment had been tried, pituitary injections administered, but only with temporary improvement. About one ounce of spinal fluid was then withdrawn under considerable pressure. Cammidge suggests that para-syphilitic changes at the base of the brain interfered with the passage of the hypophysis secretion into the cerebro-spinal fluid and sudden release of pressure by lumbar puncture broke down adhesions and opened a channel for its normal passage again. Herrick reported a similar cure in Arch. Int. Med., July, 1912. —H. L.

(HYPOPHYSIS) Case of acromegaly (Sobre un caso de acromegalia). Chiappori (R.) & Gonzalez (T.), Arch. Confer. Medic. Hosp. Ramos Mejia. Semana Med. (Buenos Aires), 1919, **26**, pt. 2, 242.

Observation of a case with hemianopsia and mild glycosuria. —B. A. H.

(HYPOPHYSIS) Radiographs of the sella turcica (Radiografias de la silla turca). Donovan (C), Rev. de la Asoc. med. argent. (Buenos Aires), 1920, **32**, 234-238.

Technical considerations and descriptions of radiography of the sella turcica.—B. A. H.

(HYPOPHYSIS) Case of acromegaly. Faber (K.), Ugesk. f. Laeger (Copenhagen), 1916 **78**, 613-615.

Faber presents a patient with acromegaly in an early stage. The patient showed coarse, plump features, diastasis between the teeth, while the x-ray showed an enlargement of sella turcica. No change of the visual field and no optic atrophy or neuritis was present. The patient was subjectively improved after **thyroid** treatment. In the discussion Lauritzen mentioned two cases in which acromegaly was combined with goiter, one of which was also a severe diabetic.—K. H. K.

(HYPOPHYSIS) Case of Fröhlich's syndrome (Sobre un caso de sindrome de Fröelich). Garcia Lagos (C.), Semana méd. (Buenos Aires), 1918, **25**, pt. 2, 21.

A case report with no novel data.—F. S. H.

Influence of x-rays on the HYPOPHYSIS (Ueber Hypophysenbestrahlung). Geller (F. C.), Inaug. Disst., Breslau, 1920, Asbt. Zentralbl. f. Chir., 1920.

The hypophysis of young female rabbits was exposed to x-rays. The growth of the organ, especially of the middle and anterior lobe was retarded. The small cells which probably are the juvenile form of the large chromophil cells proved to be very sensitive to x-ray. The growth of the animals was less than the controls. No influence on the **ovaries** was observed.—J. K.

(HYPOPHYSIS) Report of a case of encephalitis lethargica in a pregnant woman with autopsy findings. Haag (M. D.), J. Mich. M. Sc. (Grand Rapids), 1920, **19**, 483-487.

The anterior lobe of the pituitary showed marked congestion, infiltration and hypertrophy of the basophilic cells.—H. W.

(HYPOPHYSIS) The therapeutics of the pituitary extract. Herman (G. J.), Kentucky M. J. (Bowling Green), 1920, **18**, 381-383.

Brief review of the subject; nothing new.—H. W.

Syphilis of the brain with changes in the HYPOPHYSIS (Hirnlues mit Hypophysenveränderung). Josephy, Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1323.

Data published elsewhere.—J. K.

(HYPOPHYSIS) Acromegaly. Kraus (E. T.), Berl, klin. Wchnschr., 1920, **57**, 908.

The autopsy of this case showed an eosinophil adenoma of the **hypophysis**; struma nodosa. The heart weighed 950 grams, the liver 3220 grams, the spleen 650 grams, the **thyroid** 150 grams, the **pancreas** 150 grams, and the **adrenals** 25 grams. The **pineal, parathyroids, thymus,** and **testicles** were of normal weight.—J. K.

Further evidence on the functional correlation of the HYPOPHYSIS and the **THYROID.** Larson (J. A.), Am. J. Physiol. (Balt.), 1920, **53**, 89-100.

A repetition of the work presented in a former paper, with a larger number of animals and with strict regard to the comparison of individuals from a single litter. (See Endocrin., 1919, **3**, 534.) The original results are confirmed.—T. C. B.

(HYPOPHYSIS) Infantilisme hypophysaire et sifilis. Léreboullet (P.) & Mouzon (J.), Rev. neurol. (Paris), 1917, **24**, 493-497.

A description of a rare case of causal association of syphilis with infantilism of hypophyseal origin presenting the classical picture of

the latter disturbance such as adiposity infantile genitalia, bilateral optic atrophy, right temporal hemianopsia, etc. The x-ray showed a large sella turcica, but with no definite pathological characters. Lumbar puncture showed a high pressure and the fluid contained 0.06 per cent albumen and 12 lmyphocytes per cc. The Wassermann was negative. There were no symptoms of **hypothyrodism.** Antisyphilitic treatment was begun but as yet no conclusion can be given of the results of such endeavor.—F. S. H.

(HYPOPHYSIS) Pituitary tumor-operation by transsphenoidal route. Lewis (F. O.), Penn. M. J. (Athens), 1917-18, **21,** 282-284.

Report of a case of hypopituitarism with a tumor of the hypophysis which was successfully removed by operation, the patient dying the next day.—F. S. H.

Comparative vascular action of HYPOPHYSIS extract and histamine associated with ADRENIN (Accion vascular comparada de la histamine y del extracto de hipofisis asociadas a la adrenaline). Llosa (J. B.), Rev. de la Asoc. med. argent. (Buenos Aires), 1920, **32,** 62-63.

While hypophyseal extract reinforces and prolongs the action of adrenin on blood-pressure, histamine has an antagonistic action in all doses.—B. A. H.

Deep x-ray therapy in tumors of the HYPOPHYSIS. Loeb (C.), Am. J. Ophth. (St. Louis), 1918, **1,** 397-403.

This is a review of previously recorded cases, with a report of a case greatly benefited by deep x-ray therapy, and a comparison with a case relieved by operative treatment. The x-rays were applied over the right and left tempie, right and left antrum, and nose. Between the skin and the tube, an aluminum plate of one millimeter thickness was interposed to cut out some of the soft rays. The applications were made until an erythema dose had been given. In the beginning this was given in four applications of five minutes each, in ten days to each area. Later the amount given was one-fifth less. The skin focus distance was eight inches. The equivalent spark gap of the tube varied from nine to fourteen inches, usually eleven inches. From 3-5 milliamperes to 1 4-5 amperes were passed for four to six minutes, producing in each treatment three seven milliampere minutes. Relief was obtained.—F. S. H.

(HYPOPHYSIS) Case of acromegaly of apparently acute onset. Loewenberg (S. A.), Internat. Clin. (Phila.), 1918, 28, **3,** 154-157.

A complete case report with good illustrations presenting no new data save the appearance of the clubbing of the finger-nails and the acute onset of the enlargements of the fingers and toes.—F. S. H.

(HYPOPHYSIS) Clinical contribution to the knowledge of the pathogenesis and therapy of diabetes insipidus (Contributo clinico alla conoscenza della patogenesi e terapia del diabete insipido). Nasso (I.), La Ped. (Napoli), 1920, **28**, 812-816.

Nasso reports a case of a girl of 7 years with a positive Pirquet and slight jaundice, who for the last 4 years was accustomed to drink from 11 to 14 quarts of water daily, passing from 12 to 15 quarts of urine each day. The appetite was apparently unimpaired. When intramuscular injections of pituitary extract were made the water ingestion was reduced to 3 or 4 quarts and the urine excretion to 4 or 5 quarts a day. The fact is worth noting that the patient was eliminating more than she was drinking, and yet there was no loss of body weight. The condition is attributed to hypopituitarism.—G. V.

(HYPOPHYSIS) Encephalitis lethargica. Schwartz (S.), N. York M. J., 1920, **112**, 182-185.

Encephalitis lethargica is the result of perivascular infiltration of the pons and medulla. The hypophysis because of its infundibular connection with the base of the brain may become involved in a like manner. That the lethargic condition, at least in part, involves the hypophysis is shown by the relief following the administration of anterior lobe extracts. The lethargy in such cases bears no relation to the amount of infection and focal symptoms (lethargy) set in only when the hypophysis becomes involved in the process of perivascular infiltration.—H. W.

(HYPOPHYSIS) Use of intravenous injections of pituitrin, especially in hemorrhage during the various periods of labor. Tofte (A.), Ugesk. f. Laeger (Copenhagen), 1916, **78**, 745-751.

Tofte has seen good results following the intravenous injection of pituitrin (Parke, Davis & Co.) in cases in which subcutaneous injection has been without effect. The intravenous injection may be used in every stage of labor but the main indications are: 1. Cases of placenta praevia partialis with the foetus in head-position. 2. A retention of the placenta, when Crede's expression is without effect. 3. In cases in which it is of advantage to produce a sudden and active labor, e. g.: after reposition of arms or legs. 4. In cases in which labor is to be helped but the subcutaneous or intramuscular injection is without effect. Heart and kidney diseases are not absolute contraindications against the employment of pituitrin.—K. H. K.

INFANTILISM: Brissaud and Fröhlich types. Griffith (J. P. C.), N. York M. J., 1918, **108**, 529-530.

Data reported in Endocrinology **2**, 507.—F. S. H.

The diagnostic use of the INTERNAL SECRETIONS in diseases of digestion and nutrition (Die diagnostische Verwertung der Lehre von der inneren Sekretion für die Klinik des Verdauungs-und Stoffwechselkrankheiten). Biedl (A.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1380.

Most cases of adiposity are of endocrine origin. Their diagnosis is only made "ex juvantibus." Abnormal leanness is generally due to hyperfunction of the endocrine organs. In these cases radium or x-ray treatment may prove useful if care is taken that no destruction is caused. Senile symptoms are not due only to the loss of function of the **sex glands.** All endocrine organs may play an important part in senescence. The author observed a child with senile symptoms which was cured by **thyroid** and **hypophysis** treatment. The thyroid treatment is of use in cases of obstipation; the **adrenals** seem to play a part in the pathogenesis of ulcers of the stomach, also the endocrine organs seem to be of great importance in the pathogenesis of malignant tumors.—J. K.

The principles of INTERNAL SECRETION. Brown (W. L.), Brit. M. J. (Lond.), 1920, **(ii)**, 687-691.

Much of the content of this address is of a speculative nature, and it is difficult to see the relation between some of the generalizations laid down in the introduction and the subsequent portion of the paper. For instance, it is stated that the more widely tissues differ the more they can make use of the end-products of each other's metabolism —as evidenced by plants and animals. Also in general terms the more similar are the tissues the less can they make use of each other's end-products of metabolism. They require specially elaborated secretions (hormones) to produce beneficial actions. The similarity of vitamines to hormones is claimed, as shown by their effectiveness in minute doses, their chemical similarity and the resemblance of the results produced when either is lacking. Thus rickets and osteomalacia, the neuritis of beri-beri and the neuritis of **diabetes,** scurvy and the form of purpura due to **adrenal** deficiency are said to be very similar diseases. Another generalization made, is that the sympathetic, since it is the most primitive part of the nervous system, is closely associated with the endocrine system, a still more elemental means of communication in the body. Also since specialized reproductive cells appeared before the nervous system the organs of reproduction also remain closely associated with the older chemical reactions now specialized in the endocrine glands. "The endocrine glands, the reproductive organs, and the sympathetic nervous system, therefore, remain as a basic tripod, and it is not likely that a disturbance will occur for long in one limb of this tripod without affecting the other two."

The disturbances of the various ductless glands are then considered in detail, with emphasis on some of the minor degrees of derange-

ment which usually escape unnoticed. Adrenin exhaustion is given as a possible reason for many war neuroses and other functional changes characterized by lack of vascular tone, vasomotor instability and myasthenia, especially when accompanied by a low blood pressure. Hertoghe's views, that minor degrees of **thyroid** insufficiency produce such symptoms as relaxation of the articular ligaments, particularly in the knee, ankle and thoracic vertebrae, causing knock-knee, painful heel, flat-foot and lordosis, are quoted. Infiltration of tendons and fascia producing rheumatoid pains; loss of hair in the outer half of the eyebrow, enuresis, diminished coagulability of the blood, and infiltration of the nerve centres causing mental slowness, loss of memory, etc., are similarly attributed to deficient thyroid secretion. Minor degrees of **hypo-pituitarism** are said to occur in which the condition of the skin and subcutaneous tissue recalls myxoedema, but the mental state remains active. The obesity is marked. Polycythemia is of frequent occurrence. These three glands are mainly catabolic. "They throw sugar into the blood stream for active consumption, they co-operate with the sympathetic in defensive activities, they divert the stream of energy outwards, they are accelerators." On the other hand, the endocrine elements of the stomach, duodenum and **pancreas** and the **parathyroid** glands are mainly anabolic in function. These co-operate with the parasympathetic, they divert the stream of energy inwards and store potential energy. They are retarders.

Finally the general principles of internal secretion are set forth as follows: Fertilization of the ovum initiates a tremendous impulse to growth. When growth is expressed as a fractional increase of body weight it will be found that its curve continuously diminishes from fertilization onwards. In other words, the impetus gradually wears out. But the organism is supplied with intrinsic regulators (the endocrine glands and their associated nervous mechanisms) acting as retarders or accelerators. In the first few years of life the original impetus is so enormous that a break is needed, which seems to act through the **thymus.** (The author has previously admitted that the thymus probably does not supply an internal secretion.) By seven years of age this break is no longer needed, and should it continue to be applied from any cause, infantile features persist. With the aid particularly of the thyroid and pituitary, active growth continues till a new equilibrium must be found with the development of a new set of glands at puberty. The climacteric gives another jolt to the mechanism and from this point on the dying down of the original velocity is marked. Finally the author points out that before we can apply organotherapy rationally we must have some clear idea of the chemistry of the hormones.

(The author shows by such a statement as "since the sympathetic nervous system depends on adrenalin for its activity," that he is not

familiar with or discards recent physiological work on this subject.)—L. G. K.

Psychosis and INTERNAL SECRETION (Psychose en inwendige afscheiding). de Hartogh (J.), Nederl. Tijdschr. v. Geneesk, (Haarlem), 1920, **64**, 2465-2471.

The author reports a case in which the good influence of **corpus luteum** on psychical complaints was observed. The theories are, however, very superficial. According to the author it is well known that **thyroid** hyperfunction produces Graves' disease, hyperfunction of the **adrenals** produces tumors, hyperfunction of the **parathyroids** myasthenia pseudo-paralytica and hypofunction of the **hypophysis** dystrophia adiposo-genitalis. The author states also that we know (?) that the **thymus** produces a hormone stimulating the vagus and the growth of the bones. However, very little is proved of all these statements. The article is an example of that sort of dilettantism with which endocrinology is especially afflicted. —J. K.

(INTERNAL SECRETIONS) Organ extracts as aids in labor (Organextrakte als Wehenmittel). Köhler (Robert), Monatschr. f. Geburtsh. u. Gynäk. (Berl.), 1920, **52**, 240-247.

This study is concerned with the effects that have been produced by the injection of **placenta** extracts at the end of pregnancy (19 cases), at premature deliveries (7 cases), and in attempts to induce abortion (4 cases). In all of these positive results were obtained, in that within an hour, usually in nine or ten minutes, after the injection of the extract the first labor pains appeared, and gradually increased till delivery occurred. In some cases a single injection was insufficient, but a second dose started the processes on their way again. In four cases operative interference was necessary. The breasts usually become full of milk the usual time after parturition and lactation was successful. These results confirm others by the same author in which he used extracts of many different tissues and he consequently comes to the conclusion that the effect produced is not specific to the placenta nor to any other tissue, but is a common property of all organ extracts when prepared as described.—F. S. H.

(INTERNAL SECRETION) Further investigations on the origin of tumors in mice. VI. Internal secretion as a factor in the origin of tumors. Loeb (J.), J. Med. Research (Boston), 1919, **40**, 477-496.

The **ovarian** hormone (not pregnancy, suckling, etc.), is considered responsible for differences in the breast cancer of male and female mice. Specific hormones are also postulated—that is, they influence cancer in organs to which they are normally related; for

example, **breast** and ovary, **uterus** and ovary, **prostate** and **testis**. In the development of cancer there are three factors—heredity, irritation and effect of hormones; heredity and internal secretion act together; heredity may be associated with irritation, but irritation by itself, if strong enough, may cause cancer. Physiol. Abst. 5, 490.

INTERNAL SECRETIONS in the organism of tubercular tendencies. Observations in the army (Las secreciones internas y el terreno organico tuberculizable. Observaciones en el Ejercito). Lopez (Julio A.), Semana méd. (Buenos Aires), 1920, **27**, 586.

Disturbances in the internal secretions are said to be the cause of the tendency to tuberculosis.—B. A. H.

INTERNAL SECRETIONS, and uremia (Urémie et sécrétions internes). Remond (A.), Bull. Acad. de Med. (Paris), 1917, **77**, 174-177.

A series of experiments on rabbits. In each series but one experimental animal and one control animal was used. A comparison was made of the amount of human serum obtained from a patient suffering from Bright's disease, that would kill a rabbit after having been treated for several days with **thyroid** extract, and the amount that would kill an untreated animal. Other experiments are reported of the length of time rabbits lived after being given sodium cantharidate in the ratio of 1 to 500 per kilo body weight with and without preliminary treatment with **thyroid** extract, 1 animal; **adrenal** extract, 2 animals; renal extract, 1 animal; renal plus adrenal extract, 1 animal; thyroid plus parathyroid, 1 animal; and 3 animals received thyroid plus parathyroid after the sodium cantharidate. Although there were uniform changes in the thyroid of a severe nature in those rabbits which died first, it is the opinion of the reviewer that the small number of animals used in each different series makes any conclusions of very doubtful value.—F. S. H.

(INTERNAL SECRETIONS) Chronic acrocyanosis (Acrocianosi cronica). Zagari (G.), Riforma med. (Napoli), 1920, **26**, 709-715.

This article is a report of a clinical lecture during which 2 different cases of acrocyanosis were demonstrated. Both of the cases belonged to Cassirer's classification. After discussing the syndromes according to the classification in, (a) vasomotor acropathies from peripheral angiospasm; (b) vasomotor acropathies connected with angioparesis; (c) angiotrophic acropathies (some cases of sclerodermia), he places his cases into the third class. In the discussion there is brought out the great part played in these disorders by the endocrine-sympathetic and the sympathetic system, though the possibility of the existence of cases independent of endocrine dysfunction is admitted. The first case, in which the disturbance was purely local, did not

belong to the group in which endocrine dysfunction is manifest. The second case, in that x-ray examination showed the phalanges to exhibit a previously existant acromegaly, was put in the class where endocrine dysfunction plays a role. Since the author is uncertain as to which gland is disturbed he intends to begin with thyroid treatment, inasmuch as all such cases seem to depend more or less on alterations in the function of this gland.—G. V.

INTERNAL SECRETIONS and the heart (Herz und innere Sekretion). Zondek (H.), Zeitschr. f. klin. Med. (Berlin), 1920, **90**, 171-197.

According to Zondek the heart shows the following symptoms in myxedema:.

A. Before treatment with **thyroidin:**

1. Dilation of the right and left heart. Often the aorta is enlarged. 2. The heart beats slowly; the blood pressure is normal. 3. An x-ray photograph shows the outlines of the heart more clearly than in the picture of a normal heart. 4. The atrial wave and the A wave in the electrocardiogram are lacking. In the phlebogram the A wave is also lacking. A detailed description of the electrocardiogram is given with illustrations.

B. After treatment with **thyroidin:**

1. The heart returns to its normal size again. Generally the aorta remains enlarged. 2. The pulse rate becomes normal; the blood pressure does not change. 3. The electrocardiogram and the phelbogram become normal in contour. When the P and Z waves become abnormally high this is a sign that the treatment must be stopped at once. Both in ordinary obesity and in thyrogenous obesity there is generally more or less cardiac dilation without changes in the blood vessels. The blood pressure is sometimes low in the latter. The changes in the skiagram and electrocardiogram as seen in myxedema are never observed in other cases of hypothyroidism (cretinism, alopecia, etc.). In infantilism there is often vascular and cardiac hypoplasia with a low pressure.—J. K.

Two cases of LIPODYSTROPHIA PROGRESSIVA. Neel (A. V.), Hosp.-tid. (Copenhagen), 1916, **59**, 1253-1265.

Two cases of this disease are described by the author. No history of inheritance is given in either case and the general health appeared to be good. The first case was a woman of 52 years. Her periods began at the age of 18 and lasted until she was 47 years old. At the age of 40-42 years a marked emaciation of the face occurred which was followed by emaciation of the chest and arms. The legs and hips had always been very large and did not change in volume along with the other changes. Some slight complaint of headache was made, but

nothing more. A tumor which was situated on the right arm and was probably a lipoma, did not decrease in size with the emaciation of the upper limbs. The x-ray examination showed nothing abnormal. The blood examination showed the presence of a lymphocytosis. Eight similar cases have been previously described. The second case was a woman of 30 years who up to the time she was 19 years old had been full-faced and stocky in the upper part of her trunk. From that time on she began to become emaciated in these parts while from the age of 14 years on a progressive adiposity of the legs and hips had taken place. The skin of the face appeared as that of a myxedematous person. The hands were large, with short, broad fingers. Pubic hair was scanty. The uterus on palpitation appeared to be small and infantile, while the ovaries could not be felt. The author is of the opinion that that lipodystrophia is of endocrine origin.—K. H. K.

MENSTRUATION and its anomalies (Der Menstruationzyklus und seine Anomalien). Schröder (R.), Monatschr. f. Geburtsh. u. Gynäk. (Berl.), 1920, **53**, 207-251.

A bibliographical review.—F. S. H.

Case of MYOTONIA. Jewesbury (R. C.), Proc. Soc. Med. Lond. 1918, **11**, Sect. Stud. Dis. Child., 58-60.

Not of explicit endocrine interest.—L. G. K.

Über OSTEOMALAZIA. Koltonski (Hermann), Monatschr. f. Geburtsh. u. Gynäk. (Berl.), 1920, **52**, 253-262.

The fundamental cause of osteomalacia is attributed to a disturbance of the endocrine system of some sort. The **ovaries** cannot be concerned inasmuch as the disorder occurs in man as well as in woman. Admitting that there is a pluriglandular disorder frequently made evident the author is inclined to the opinion that an adrenal hypofunction is at the basis of the disease.—F. S. H.

OSTEOMALAZIA. Wagner (G. A.), Berl. klin. Wchnschr., 1920, **57**, 934.

A report of a woman of 46 with typical osteomalacia and with **thyroid** atrophy who had never menstruated. The explanation that osteomalacia is due to hyperfunction of the **ovary** is not supported by this case. **Adrenin** had no effect, while phosphorus and cod liver oil produced some improvement.—J. K.

(OVARY) A case of OSTEOMALACIA treated by oöphorectomy. Hellier (J. B.), Brit. M. J. (Lond.), 1920, **(ii)**, 587-588.

The patient was a woman, 38 years of age, who had had four pregnancies. She did not regain her strength properly after the birth of her second child, five years previously. Eighteen months before she

was seen by the author she had an abortion in the second month of gestation. She had lost weight and had numerous pains all over for five years, and was able to walk only with difficulty. Both clavicles broke spontaneously during her fourth pregnancy, and in the seventh month she developed albuminuria and marked anasarca up to the level of the scapulae. There was a bed sore over the sacrum and the left leg was very painful. She had spinal curvature and marked contraction of the pelvis and rostration of the symphysis. Labor was induced, but craniotomy was necessary on account of the lateral contraction of the pelvis. About a month later, when first seen by the author, the albuminuria had disappeared, but the osseous system showed many anomalies—deformity of the pelvis, kyphosis, lordosis, and fracture of the femur. An x-ray examination showed the bones to be so little opaque that it was impossible to obtain a good skiagram. Both ovaries were then removed at operation; they were normal in appearance. Twelve months later the patient was much improved. She was able to walk some distance without crutches, and her pain had disappeared. The skiagram showed the bones to be more opaque and there seemed to be some new bone formation at the iliac crests. The remark is made that 80 per cent of osteomalacia cases recover under this treatment.—L. G. K.

The influence of the OVARIAN hormone on the growth of the pelvis (Über den Einfluss des Ovarialhormons auf das Beckenwachstum). Plaut (Rachel), Ztschr. f. physiol. Chem. (Berl. u. Leipz.), 1920, **111**, 36-42.

The question of whether or not the pelvic form is dependent on any function of the gonadal cell activity is discussed in this paper. Plaut injected into rabbits an oil suspension of an ether extract of **ovaries** containing **corpora lutea** of cattle, guinea-pigs and cats. Each dose was the equivalent of one ovary, and one dose was given daily for from ten to fourteen days. The oil was poorly absorbed. After waiting another fourteen days the animals were killed and the pelvic measurements were compared when possible with controls from the same litter; when not possible animals of the same age, sex and size were used. The results indicate that the extract as prepared from corpora lutea containing ovaries causes a transverse enlargement and a longitudinal diminution of the pelvis of both sexes.—F. S. H.

(OVARY) The physiology of ovulation. Schochet (S. S.), Surg. Gynec. & Obst. (Chicago), 1920, **31**, 148-149.

This is a preliminary report only, in which the author states that ovulation is due to a specific enzyme in the liquor folliculi, its nature being similar to the enzyme erepsin. Apparently there are other proteolytic enzymes in the liquor folliculi; also a lipase. Atresia of the follicles is due to this enzyme or enzymes. These experiments are

said to offer a rational explanation for the use of **thyroid** extract and **corpus luteum** in sterility.—L. G. K.

(OVARY) The physiological chemical action of follicular extract (Die physiologisch-chemische Wirkung des Follikelsaftes). Wintz (H.), Arch f. Gynaek. (Berlin), 1920, **113**, 457-471.

Among a great number of experiments carried out in the study of the internal secretion of the ovary a certain number were done in which the effects of the follicular extract were tried on blood-pressure, blood coagulation and local action on the genitals. Using rabbits as the experimental animals, small doses given intravenously caused a fall in blood pressure, while large doses gave the opposite reaction, though neither of the reactions were very marked. When the extract was injected in the ear vein and blood taken two minutes later and tested for coagulation time, it was found that this phenomenon was slightly but significantly lengthened. No effect on the genitalia was observed. No effect of the extract could be observed on the coagulation time of blood in man, nor was menstruation either augmented when slight or diminished when profuse, as the result of the injection of such extracts in 1.5cc. amounts. These experiments were all done when extracts from fresh tissue were used. When old tissue extracts were tried there was obtained a rise in blood pressure even with small amounts, there was a shortening of blood-coagulation which, however, was a transitory phenomenon, and no action on the genitalia was observed.

When **corpus luteum** extracts were similarly studied they were found to produce a fall in blood-pressure, a slowing of blood-coagulation and an hyperemia of the genitalia. (This, however, only occurs after some 30 days' injections.) A review is then given of the action of lipamin and luteolipoid preparations obtained from the corpus luteum. The former causes a slight drop in the blood pressure, while the latter has no effect. Lipamin retards the coagulation of blood, while luteolipoid accelerates it markedly.

Moreover, luteolipoid but slightly accelerates the growth of the genitalia of virgin rabbits, while the lipamin effect on the uterus and mammae is most marked. Luteolipoid when injected during the menstrual period is an efficient inhibitor, save in those cases due to endometrial pathology. Lipamin when injected in patients with amenorrhea yields relief, but has no effect on a normally menstruating woman.—F. S. H.

(PANCREAS) The blood and urine in pancreatic disease. Cammidge (P. J.), Forsyth (J. A. C.) & Howard (H. A. H.), Lancet (Lond.), 1920, **(ii)**, 393-401.

In a series of clinical observations supported by animal experiments on dogs and rabbits the authors show that the dextrin content of the urine and blood is considerably increased in pancreatic disease

even before glycosuria occurs. This dextrin is said to be an intermediate product between the hepatic glycogen and sugar. Special methods of estimating the dextrins in the blood and urine are described. The amylolytic ferment of the blood and urine is also increased in diseases of the pancreas, varying directly with the percentage of sugar in the blood after a meal and inversely as the dextrin content of the blood and urine. In the animal experiments it was shown that the greater the amount of pancreatic tissue removed, and consequently the more marked the hyperglycaemia and glycosuria, the less is the dextrin content of the blood. It was concluded that the internal secretion of the pancreas exerts a restraining influence on the glycolytic (glycogenolytic) ferment of the liver, since, following an injection of an extract of pancreatic tissue, the percentage of sugar and of dextrin in the blood is considerably reduced. A relative diminution in the secretion of the pancreas, with consequent greater liberty of action on the part of the glycolytic (glycogenolytic) ferment of the liver, gives rise in the early stages to an increased formation of the intermediate products of glycogen degradation without any change in the sugar, and in the later stages to an increasing sugar production with a proportional diminution in the intermediate products. The appearance in the blood and urine of these intermediate products of carbohydrate metabolism (dextrins) indicate a pre-diabetic condition which, if allowed to go unchecked, will be followed by hyperglycaemia and glycosuria. Incidentally it is shown that a considerable proportion of a well-boiled starch is absorbed into the portal circulation in the form of dextrins and maltose, whereas an uncooked starch enters the portal blood chiefly as glucose.—L. G. K.

Experimental studies of the internal secretion of the PANCREAS (Experimentelles Studium der inneren Sekretion des Pankreas). Kumagai (T.) & Osato (S.), Tohoku J. Exp. Med. (Sendai), 1920, **1**, 153-166.

The object of this study was to determine whether the internal secretion of the pancreas is discharged directly into the blood vessels or into the lymphatics and thence into the blood vessels by the thoracic duct. The evidence advanced is as follows: (1) Transitory glycosuria developed in all of four dogs with thoracic duct fistulae, but only in two of twelve dogs in which the duct has been simply ligated. (2) Subcutaneous injection of thoracic duct lymph in dogs with all pancreatic tissue removed has no effect upon sugar excretion, but a uniformly positive effect was noted in animals following partial removal of the pancreas. (3) In two dogs injected with pilocarpin the amylase in the lymph is increased above that in the blood, while in the normal condition it is less. (4) In two other dogs the authors found that the injection of lymph from pilocarpinized animals has an antiglycosuric effect. The authors accordingly conclude that the in-

ternal secretion of the pancreas is passed first into the lymphatics and thence in the blood stream.—E. V. C.

(PANCREAS) Test for the digestion of nuts and diagnosis of pancreatic insufficiency (L'epreuve de la digestion des noyaux et le diagnostic de l'insuffisance pancréatique). Labbé (M.), Ann. Méd. (Paris), 1920, **8**, 101-115.

Not of endocrine interest.—F. S. H.

Development of liver, PANCREAS and fore-gut in the duck and the mole. (Zur Entwicklungsgeschichte der Leber, des Pancreas und des Vorderdarms bei der Ente und beim Maulwurf. Ludwig (E.), Anat. Hefte (Weisb.), 1919, **56**, 513.

Of embryological interest. Not much space is given to the pancreas.—W. J. A.

PANCREAS, Accessory pancreas in the dog. Mann (F.), Anat. Rec. (Phila.), 1920, **19**, 263-268.

An accessory pancreas was observed in a dog during experimental operation. It was located below the ligament of Treitz. On histological examination it appeared normal, possessing acini, ducts and many small islets.—W. J. A.

The PLACENTAL gland and placental extract. Bandler (S. W.), N. York M. J., 1920, **112**, 745-750.

Placental extracts tend to diminish uterine bleeding and are second only to **mammary** extracts in controlling excessive menstruation, though they lack the power of the latter of diminishing the size of the uterus. Placental extract often prevents threatened miscarriage or abortion, especially if given along with **thyroid** extract. The psychic symptoms of restlessness and mental irritability which result because of an over-activity of the posterior **pituitary**, are quieted by placental extracts. The instincts of libido sexualis can be controlled or modified by the administration of placental extracts, especially in conjunction with extracts of the **thymus**. The importance of the placenta and placental extracts is the ability to influence the posterior pituitary and to stimulate the **anterior pituitary** and the **adrenal cortex**. Prior to the presentation of the above observations the author goes to some length in presenting his views concerning the interrelation of the endocrine system in the female. The gist of his theory is given in the following quotation: "The production of menstruation is initiated by the **ovary**, not forgetting the interstitial structure. Co-operation is evidenced by the **corpus luteum** and thyroid and posterior pituitary. Unless the posterior pituitary is inhibited, menstruation takes place. * * * It would seem as if all those activities suggested and started in each

premenstrual phase are then accentuated and made into a definite balance for nine months by the introduction of the placents. The balance in the autonomic nervous system which takes on the form of a crisis at menstruation is altered by placental action and is postponed to the day of labor. In pregnancy the entrance of the anterior pituitary and particularly of the adrenal cortex is assured or produced by the placenta."—H. W.

PARATHYROID transplantation; how to choose the material for transplantation (Epithelkörperverpflanzung; die Wahl des Transplantates). Borchers (E.), Zentralbl. f. Chir. (Leipzig), 1920, **47**, 1366-1368.

The question whether transplantation of the parathyroids is useful in tetany, especially in the postoperative form, is still largely discussed. The investigators, however, do not agree. Borchers tried to find the reason of the different results of different workers. One of the differences may be due to the way the surgeon treats the parathyroid. This tissue must be handled with extreme care. But there is a much more important factor. Most organs transplanted as parathyroids are not parathyroids. In 11 cases the author himself removed during an operation for goitre a parathyroid for transplantation. The organ was situated in its typical location. Before transplanting a small piece was taken for histological examination. Of these 11 organs only one proved to be a parathyroid; 8 times it was an accessory **thyroid**, once a lymph gland and once a little piece of fat. To avoid such results the author advises the following technic. During an operation for goitre in man (it is preferable that the goitre is not too large) a parathyroid (or the organ that is believed to be one) is removed and kept in sterile physiological solution at 37 deg. C.; a very small piece is taken, fixed in boiling formalin, cut with the freezing microtome, and examined in glycerine. This takes no more than 10 minutes. If the organ proves to be a parathyroid it is transplanted at once into the left musculus obliquus intermus abdominis of the tetanical patient.—J. K.

(PARATHYROIDS) Experimental studies on tetany (Experimentelle Untersuchungen über Tetanie). Farner (E.) & Klinger (R.), Mitt. a.d. Grenzgeb. d. Med. u. Chir. (Jena), 1920, **32**, 469-497.

In the cat nearly always small accessory parathyroids may be found in the thymus itself or its surrounding connective tissue. The authors removed in 40 cats the four principal parathyroids. The effect was not the same in all animals. Often an acute or sub-acute tetany developed which frequently ended fatally, but many animals remained in good health after the operation. This is probably not due to the remaining accessory glands as there was no correspon-

dence between the existence of such glands and the symptoms. When soluble calcium salts are given these have a good influence on the symptoms. Twice the authors tried transplantation of a parathyroid to cure the postoperative tetany. In both cases temporary improvement was seen. Administration of **thyroid** had no or at most an unfavorable effect. Noël Paton has shown that guanidine or methylguanidine when given to animals, produces symptoms closely resembling tetany. The authors consider tetany as an intoxication with guanidine compounds. The function of the parathyroid would be to destroy (probably to oxidize) these substances. The good result following calcium treatment would be due to the fact that calcium salts give a precipitate with guanidine compounds. The intensity of tetany would depend upon the quantity of parathyroid tissue and the quantity of guanidine compounds in the body.—J. K.

The PARATHYROID and convulsive states. Jelliffe (S. E.), N. York M. J., 1920, **112**, 877-879.

Convulsive states may be looked upon from a neurological standpoint as the result of a lowered or altered function of the synapses. The action of the normal parathyroid gland appears to control or steady synapse function, possibly because of its control over calcium metabolism. The administration of parathyroid preparations by way of the rectum seems to control convulsive states more readily than by way of oral administration.—H. W.

(PARATHYROIDS) The problem of spasmophilia (Ein Beitrag zum Spasmophilieproblem). Kleinschmidt (H.), Berl. klin. Wchnschr., 1918, **55**, 1017-1021.

Although this discussion fails to consider the possible role of the parathyroids in spasmophilia its conclusions are important as a point of view in their indirect endocrinological application. The author considers that the facialis phenomenon is of pathological significance at all ages of childhood, and indicates a congenital functional feebleness of the nervous system.—F. S. H.

(PINEAL) Epiglandol in dementia praecox. Becker (W. H.), Therapt. Halbmonat. (Berlin), 1920, **34**, 667-668.

Epiglandol is an extract prepared from the pineal. Fraenkel and Pilcz reported cases of dementia praecox with sexual irritability in whom a good effect was obtained after the injection of epiglandol. Becker tried it in 5 cases. In two of them no effect whatever was seen; in a third patient perhaps the inclination towards masturbation was decreased a little. The two other patients ceased masturbating after some injections. In none of the five patients could any other improvement be obtained.—J. K.

Contributions to the knowledge of the PINEAL gland in mammals (Bidrag til Kundskaben om corpus pineale hos pattedyrene). Krabbé (K. H.), Det kgl. Danske Videnskabernes Selskabs Biologiske Meddelelser (Copenhagen), 1920, **II, 2,** 1-111.

The author describes the embryological development and histological structure in a series of mammals: Two didelphys-embryos, talpa, erinaceus, sorex, vespertilio-embryos, vesperugo-embryos, spermophilus-embryos, guinea-pig, horse and pig-embryos, sheep, ox, dasypus, tatusia-embryo, cat, leopard, mustela, meles, halichoerus, phocaena (adult and embryos), several monkey-species (callithrix, macacus, cerecopithecus, cynocephalus, simia troglodytes). The comparative considerations showed that in most mammals the pineal gland consists of a rather uniform, non-follicular parenchyma. This consists in some mammals (phoca, rodentia, insectivora) of one species of cells (pineal cells) with a relatively large nucleus and a little protoplasm without distinct limits. In most mammals there is further a lot of glia-cells between the pineal cells. In the ungulates the glia-cells are predominating, more scarce in monkeys and carnivores. In higher monkeys and in man there are numerous nerve-cells in the parenchyma between the pineal-cells. The organ shows ordinarily a considerable vascularisation especially in halichoerus. Calcifications are found in man, in chimpanzee and the ox. Mast-cells are found in several mammals.

In dasypus the pineal gland is completely absent; in whales it is very rudimentary. The author describes further the different types of evolution in the fetal life. Concerning the function he concludes that the pineal gland evidently has a function in most mammals except the whales, edentates and perhaps the sirenia. The glandular structure, the amitoses, the high vascularisation point to a glandular function, but it must be taken into consideration more than it ordinarily is done, that this function might have a relation to the metabolism of the brain and the cerebrospinal fluid. The varying structure of the pineal gland, for instance the abundant development of nerve-cells in man and of glia-cells in ungulates could, indicates that the function is somewhat varying in the different mammals. The paper is illustrated with 71 figures.—Author's Abst.

The antidiuretic effect of PITUITARY extract in DIABETES INSIPIDUS. Davidson (M.), Lancet (Lond.), 1920, **(ii),** 401.

The patient, aged 35, complained of great thirst and polyuria, passing on the average over 300 oz. of urine per day. The urine was pale, acid in reaction, of low specific gravity (1000) and contained no sugar or albumen. A skiagram showed no abnormality of the sella turcica; his visual fields were not diminished nor was the fundus oculi abnormal. The patient was treated with daily injec-

tons of 1 cc. of pituitrin for 8 days and the quantity of urine was materially reduced and the specific gravity raised. Pituitrin given by mouth was without effect. When discharged, however, the polyuria still continued.—L. G. K.

Influence of PITUITARY extracts on the absorption of water from the small intestine. Rees (M. H.), Am. J. Physiol. (Balt.), 1920, **53**, 43-48.

The main object was to explain the antidiuretic action of pituitary extracts. The author has previously suggested that the antidiuretic effect may be due to interference with intestinal absorption of water (see Endocrin 1918, **2**, 188) and the present observations are concerned with this phase of the problem. The usual technique of cannulated loops was employed. The conclusion is, that while subcutaneous injections of pituitrin bring about delay in the absorption of water from the intestine, it is not sufficient to entirely account for the delayed excretion from the kidney. There is some constriction of the intestinal vessels, but not enough to cause variations in general blood pressure.—T. C. B.

Glycosuria during PREGNANCY. Cron (R. S.), J. Mich. M. Sc. (Grand Rapids), 1920, **19**, 399-404.

A positive reaction with Fehling's solution during pregnancy does not necessarily indicate diabetes mellitus, but usually lactosuria or alimentary glycosuria and rarely renal diabetes. Lactosuria may be looked upon as physiological during pregnancy for the reason that from 30 to 50 per cent of such females are less tolerant to glucose than non-pregnant females, although they show no hyperglycemia and are not true diabetics. Pregnancy may occur in diabetes or diabetes become manifest during pregnancy.—H. W.

(PROSTATE; GONADS) New facts on the pathology and surgery of the prostate with remarks on Steinach's experiments (Neueres aus Pathologie und Chirurgie der Prostata, zugleich Bemerkungen zur Steinachschen Verjüngungsmethode). Fischer (A. W.), Therap. Halbmonat. (Berlin), 1920, **34**, 658-661.

Prostatectomy means the removal of the submucous hypertrophical glands. Patients often become younger after the operation because they are rid of their urinary complaints. If a "catheter á dernieure" is the left in the bladder the same effect is seen. The cutting of the vas deferens produces a diminished growth of the submucous glands of th prostate. The publications of Steinach and Lichtenstein are not quite clear, since in none of the cases it is told whether the patients had urinary complaints or not. Only one case proves something. In this case fo Lichtenstein prostatectomy had not effect whatever. Ten weeks after the operation the vasa defer-

entia were ligated with success, as far as the senile symptoms were concerned.—J. K.

(PROSTATE; MAMMAE) Remarks on the article of Kondoleon: "Enlargement of the mamma after prostatectomy" (Bemerkungen zu der Arbeit Kondoleon's: Vergrösserung der Brustdrüse nach Prostatektomie). Zuckerkandl (O.), Zentralbl. f. Chir. (Leipzig), 1920, **47**, 1513-1514.

Kondoleon published in No. 36 of the same journal an article in which he maintained that he had observed two men in whom an enlargement of the breasts had occurred after prostatectomy. He concluded that the prostate has an internal secretion, the loss of which produced growth of the breasts. Zuckerkandl, however, makes the following criticisms: 1. Nothing is said of the histological processes in the enlarged breast. 2. What surgeons call prostatectomy has in reality nothing to do with it, but is only a removal of the hypertrophical submucous glands, while the prostate itself remains in the body. It is concluded then that Kondoleon's cases prove nothing. —J. K.

(SEX) Comparative anatomy of the genito-urinary organs of the lower animals. Tucker (H.), N. York M. J., 1920, **112**, 525-530.

General review of the primary and secondary sex characters in the lower animals. Nothing new.—H. W.

SEXUAL disturbances in wounded soldiers (Perturbamenti della sessualita' dei feriti di guerra. Desogus, Riforma Med. (Napoli), 1920, **36**, 583-585.

In 90 per cent of cases with cerebral lesions sexual alterations occurred, hardly ever in cases of peripheral nerve lesions and only when algias or traumatic neuroses followed the lesion. The localization of the cerebral lesion is immaterial. Desogus does not accept the endocrine theory as causative, since in experiments on adult animals not even with the removal of the **thyroid** could such a severe syndrome be obtained. The perturbations are laid to dynamic disturbance of the cerebral genetic centers.—G. V.

(SPLEEN) Splenectomy, with report of two cases. Miller (G. T.), N. York M. J., 1920, **112**, 304.

Good review of the relation of the spleen to disease.—H. W.

SPLEEN and carbohydrate metabolism (Milz und Kohlenhydratstoffwechsel). Togawa (T.), Biochem. Ztschr. (Berlin), 1920, **109**, 1-17.

Using many rabbits, frogs and guinea-pigs as experimental animals, Togawa found that after removal of the spleen the fasting

animals contained more glycogen than did the similarly treated unoperated controls although the blood sugar was the same both before and after operation. Extract of the spleen causes a decrease in the liver glycogen, and a slight hyperglucemia but no glucosuria. The injection of spleen extract tends to increase the adrenine hyperglucemia, but when the spleen is extirpated no disturbance of the adrenine hyperglucemia is produced. When fructose is injected intravenously into animals without spleens the resultant hyperglucemia is of a higher degree and lasts longer than in normal controls. When adrenine or strychnine is injected into such controls the loss of glycogen from the liver is greater than in animals from which the spleen has been removed when similarly treated. No changes were observed in the blood sugar concentration of normal animals when they were fed with desiccated spleen. It is concluded from these observations that the spleen plays a role in carbohydrate metabolism which warrants its placement with the other endocrine glands as a factor in the general system.—F. S. H.

(TESTES) Three clinical observations of primitive hypogenitalism under the type of eunuchoid feminism, gerodermia or genital dystrophic senilism of Rummo and Ferranni and telemorphism or regressive feminism (Tres observaciones clinicas de hipogenitalismo primitivo bajo el tipo de feminilismo eunuchoide, geroderma o senilismo genito-distrofico de Rummo y Ferranni y de telimorfismo o feminilismo regresivo). Castex (M. R.) & Waldorp (C. P.), Rev. de la Asoc. med. argent. (Buenos Aires), 1920, **33**, 458-476.

Three typical cases discussed from the point of view of endocrine participation. They are attributed by the authors to hereditary syphilis.—B. A. H.

The effects of ligating the TESTES of hen-feathered cocks. Morgan (T.), Biol. Bull. (Phila.), 1920, **39**, 248-256.

Ligation of the testes in adult cocks of hen-feathered races results in the atrophy of the glands. Cock-feathering follows this operation.—W. J. A.

(TESTES) Orchitis in mumps. Wesselhoeft (C.), Boston M. & S. J., 1920, **183**, 425-430; 458-460; 491-504; 520-524.

The author, after citing many interesting references concerning the relation of mumps to the sex glands, adopts the following tentative theory to explain the connection of mumps with orchitis: (1) Chemotaxis of groups of tissue cells in various parts of the body for certain poisons (Abderhalden) and, (2) Selective affinities of certain strains of a given organism for certain tissues of the body (Rosenow). The testes alone are not involved in mumps but also

the **ovaries**, and Bartholini's glands; mastitis, adenitis, dachryocystitis, and **pancreatitis** are among the complications of the disease. Involvement of the **prostate** gland (atrophy) is far more apt, than orchitis, to bring about sterility for the reason that an insufficient prostatic fluid during emission greatly decreases the chances of fertilization. Orchitis as a complication of mumps is confined to the age of puberty and adolescence. Orchitis occurred as a complication of mumps 1,468 times in a series of 8,153 cases or in 18 per cent.

Mumps may be manifest solely in the testicle. Atrophy of the testicle following orchitis occurs within from 4 to 6 weeks after the onset and is observed in 54 per cent of the cases. Orchitis and atrophy of the gland may not be associated with disturbances of any kind, however, disagreeable sensations, intense neuralgic pain, decreased sexual appetite (temporary), with diminished ability to perform coitus, or active sterility may result as sequences of orchitis. "Feminism" rarely develops and when present indicates a previous double orchitis. Mumps are so rare before the period of puberty that no eunuch has been described as the result of this disease. The author calls attention to the fact that mumps are rarely the cause of permanent sterility and that atrophy of the testicle does not usually involve all of the spermatic tissues present in the gland. The article closes with a consideration of the prophylaxis and treatment of mumps and an appendix of 77 references.—H. W.

(TETANY) Some rare consequences of influenza (Seltene Folgeerscheinungen der Influenza). Berger, Wien. klin. Wchnschr., 1920, **33**, 742.

A demonstration of a patient with tetany and ptyalism following influenza. These symptoms began three weeks after the fever had disappeared. At the same time the patient complained of pyrosis without hypersecretion of the stomach, dermographia, or urticaria-like symptoms of the skin. These symptoms are said to be proof of vagotonia. The patient had had a light post-operative tetany for the preceding seven years and which was increased by the influenza; but became latent again after subsidence of the fever.—J. K.

Contribution to the anatomical and pathological study of the THYMUS in infants (Contributo allo studio anatomico e pathologico del timo nella prima eta'). Canelli (Adolpfo F.), La Ped. (Napoli), 1920, **28**, 753-764.

Canelli reports the result of a study of the post-mortem findings in 115 cases and concludes that in order to observe the thymus at its best we must be able to see its relations to the jugular notch, therefore the sternum must not be removed at first. Topographically we may make three classifications of thymus, i.e., Thoracic, Cervico-

thoracic, and Cervical. This last can be considered ectopic. As regards the number of lobes, in order of frequency, we have the bilobatus, unilobatus, trilobatus and scutaneous types. The greatest part of hypertrophic thymus' belong to the bilobate form. The color of the thymus is related to the general conditions of nutrition, to local diseases, to general diseases and to the post-mortem condition. The relative weight (fresh gland) varies within very wide limits, as it is, especially in the first four years of life, dependent on the course and the nature of the disease. The average water content seems to be in an inverse ratio to age.—G. V.

(THYROID) Radium in goiter. Aikins (W. H. B.), Am. J. Roentgenol. (Detroit), **7**, 404-411.

After presenting the outstanding symptoms of toxic goitre the author reviews the theories of its etiology. The body of the paper, however, is devoted to a discussion of the treatment, based upon 12 years' experience. The author's technique of applying radium is given and a series of cases reported. It is his opinion that the effect of radium in toxic goitre has been in some respects similar to x-rays but that the former has many advantages. Some of these are exactness of dosage, far greater penetration and the absence of a noisy exciting apparatus.—J. F.

(THYROID) Diagnosis of myxedema. Anders (J. M.), Am. J. M. Sc. (Phila.), 1920, **160**, 801-808.

Many cases of myxedema go unrecognized even by experienced clinicians. Of 55 cases collected from the American and Canadian literature 74 per cent had failed of diagnosis by one or more physicians. The most characteristic signs of myxedema are firm, inelastic thickening of the skin and subcutaneous tissue which does not pit on pressure and mask-like immobile features. The mucous membranes are often infiltrated and the teeth may become loose. The tongue, lips and nose are thick and the voice has a peculiarly monotonous character, with frequent curious nasal explosions. Cerebration is characteristically slow, though memory may be good. Scantiness of hair is common. Albuminuria is frequently found and occasionally casts in the urine, hence the condition is often mistaken for nephritis, little as the two conditions fundamentally resemble each other. Rudimentary myxedema is frequently associated with other endocrinopathies, especially acromegaly. In such cases the addition of thyroid to other appropriate treatment may give brilliant results. Anders believes that exophthalmic goitre and hypothyroidism are frequently co-existent. In cases of suspected myxedema, and especially when evidence of other endocrinopathies is found, the administration of thyroid material as a therapeutic test is often advisable. In view of their amenability to treatment, the recognition

of incomplete types of myxedema is important. As pointing to the correct diagnosis, subnormal temperature with chilly sensations, yellowish, firm, inelastic skin, depressed perspiration, general "bulkiness," with facial stolidity, irritability, and more or less circumscribed thickening of the skin and mucous membranes are especially significant. In illustration of the chief points in the article a case is reported.—R. G. H.

THYROID dysfunctioning resulting in nanism and infantilism (Presentation d'un cas de nanisme et infantilisme d'origine dysthyroidienne). Armand-Delille (P. F.), Bull. et mém. Soc. méd. d. hôp. d. Par., 1920, **44**, 1392-1395.

The patient was a man of 22 years presenting the appearance of a boy of 12. The stature was 1 m. 32 and the weight 36 kilos. The external genitalia were infantile but normally formed. No testicular exctopy was present. There was absolutely no development of axillary, or pubic hair. Epiphyseal union had not occurred. Intelligence was about normal. The thyroid was not palpable. Thyroid medication was begun but no report of the result is given.—F. S. H.

Anatomical changes in and insufficiency of the THYROID (Anatomische Veränderungen der Schilddrüse und Schilddrüseninsuffizienz). Berlinger, München. med. Wchnschr., 1920, **67**, 1334.

Data reported elsewhere.—J. K.

(THYROID) Co-relation of results of treatment by surgical and x-ray methods. Bingham (G. H.) & Richards (G. E.), Canad. M. Ass. J. (Toronto), 1920, **10**, 988-995.

It is pointed out that since "immature cells and cells in an active state of division are more sensitive to x-rays than are cells which have acquired their fixed physiological character," the effect of x-rays upon the thyroid should take place in the following order: The hyperplasias should be influenced most, the adenomatous type next, and the cystic type should practically not respond at all. This is borne out by the authors' experience. They adopt Judd's classification of simple colloid, adenomatous and toxic goitres. Of the simple colloid goitres 90 per cent were completely cured by x-ray treatment. The adenomatous type was found to respond very poorly, and surgical treatment is advised for them. Of 300 toxic cases 50.3 per cent were completely cured, 11.3 per cent were improved and 5.3 per cent showed no improvement. The remainder were not classified. The order of disappearance of the various symptoms is as follows: Nervousness and irritability, tremor, tachycardia, loss in weight, goitre, exophthalmos. The length of time required for each case is from 6 to 8 weeks. The cases which

are not definitely cured but are improved, are made thereby much safer surgical risks. The advantages of the method are the ease with which it may be carried out, its safety to life, its painless nature, and freedom from shock. Its disadvantages are the length of time required and the possible production of fibrosis of the capsule.—L. G. K.

(THYROID) The cardinal diagnostic manifestations in exophthalmic goiter with report of cases. Butler (E. E.), Kentucky M. J. (Bowling Green), 1920, **18**, 367-369.

A general discussion of the cardinal symptoms of exophthalmic goiter and the presentation of 3 cases; nothing new.—H. W.

(THYROID) Contributions to the Biochemistry of Iodine. III. The comparative effects of thyroid and iodide feeding on growth in white rats and in rabbits. Cameron (A. T.) & Carmichael (J.), J. Biol. chem. (Baltimore), 1920, **45**, 69-100.

This paper gives a semi-critical review of the studies made of the effects of feeding thyroid and iodides to various animals. The authors report a similar study on 40 male and 16 female white rats. Of these, 31 males and 16 females were from 9 litters; and 7 controlled experiments were carried out with thyroid and 4 with sodium iodide. The initial age of feeding varied from 40 to 60 days and the periods of observation varied from 18 to 72 days. The remaining 10 animals were of different ages and from different litters and were used in the specific experiment to induce tetany by feeding large doses of thyroid. The diet used was bread and milk throughout with one exception. Three thyroid preparations were studied. In one experiment 5 rabbits from one litter were used. Extensive tabulations are made and protocols given. The effects of the feedings on the body growth, weight and length, and on the size of the liver, kidneys, heart, spleen, lungs, **testes, adrenals** and thyroid are recorded. The results indicate to the authors that continued small doses of desiccated thyroid gland fed to young white rats produce (a) a definite and invariable decrease in growth rate; (b) hypertrophy of the organs concerned with increased metabolism-heart, liver, kidneys, adrenals, etc.; (c) disappearance of fat. They also claim that the decrease in rate of growth is proportional to (a) the amount of thyroid fed and (b) the iodine content of the thyroid fed. The hypertrophy varies with the dose and length of application of dose, and appears to be proportional to the iodine content of the dose. When sodium iodide is fed in amounts varying from quantities equal in iodine content to the thyroid doses to amounts 100 times as great, no effect on growth rate or hypertrophic changes are produced. Both the thyroid and the iodide feeding increase the colloid in the thyroid and thyroid feeding inhibits the growth rate of the thyroid. Iodide does not pro-

duce this effect. The suggestion is made that since of numerous tissues tested only thyroid produces this effect, thyroid feeding can be used as a discriminatory test for preparations alleged to contain the essential thyroid secretion. (It is the opinion of the abstractor that the number of experiments described are quite insufficient for the determination of all the points discussed, particularly since the authors themselve state and their figures show that wide variations occurred.)—F. S. H.

(THYROID) Acute, Febrile, Epidemic Myxedema with Tracheal Stenosis (Mixedema acuto febbrile epidemico con stenosi tracheale). Citelli (S.), Riv. Crit. di Clin. Med. (Firenze), 1920, **21**, 262.

Citelli reports an epidemic of febrile acute myxedema characterized by swelling of head, neck and thorax, often complicated with tracheal stenosis. The patients all recovered within a few weeks.—G. V.

THYROID gland of the tuberculous (Le corps thyroide des tuberculeux). Coulaud. Bull. et mém. Soc. Méd. d. hôp. d. Par., 1920, **44**, 1551-1555.

Coulaud reports the results of an examination of 120 thyroid glands obtained from as many cases of pulmonary tuberculosis. No record was kept of the size of the glands examined. Of the 120 studied, three exhibited tuberculosis of the thyroid itself. There was one parenchymatous goiter and two of the cystic type. Frequently microscopic evidence of a cystic tendency coinciding with diffuse sclerosis was obtained. Twelve cases showed thyroids apparently entirely normal in function. Some fourteen of the glands examined gave no definite evidence of a functional diminution, although a tendency to follicular hyperplasia was present. The residual cases showed large areas of peri-vascular sclerosis embedded in a glandular parenchyma poor in connective tissue and apparently normal, or else abundant connective tissue around the vessels and prolongations into the intervesicular spaces.

Coulaud concludes from this extensive study that the thyroid gland functions well in the tuberculous, perhaps a bit too much, in spite of the sclerotic lesions that are present. He intimates that possibly the sclerosis is a sequel of the intensive functioning of the gland.—F. S. H.

(THYROID) The concentration of the serum and the viscosity of the blood in myxedema and the effect of thyreoidin on them (Serumkonzentration und Viskosität des Blutes beim Myxödem und ihre Beeinflussung durch Thyreoidin.) Deutsch (G.), Deutsches Arch. f. klin. Med. (Leipzig), 1920, **134**, 342-351.

The viscosity of the total blood remains normal in myxedema, while the viscosity of the serum is increased. Hence it is probable that the quantity of protein is high. This is confirmed when the serum is examined with the refractometer. The refractory index is high in myxedema, especially in the more serious cases. In some cases of hypofunction of the thyroid without myxedema the same is observed. The administration of thyroid was in all cases of myxedema and in most cases of hypothyroidism followed by a decrease of the protein-content and of the viscosity of the blood. Only in one case of myxedema (produced by x-ray treatment of Graves' disease) and in a few caes of hypothyroidism this effect was not observed. In these cases the administration of thyroid had likewise no influence on the other symptoms.—J. K.

(THYROID) The Diagnostic Value of the Estimations of the Basal Metabolic Rate. Else (J. E.), Northwest Med. (Seattle), 1920, **19**, 171-175.

The author devotes about half of his article to a compact historical summary of the development of basal metabolism from the purely scientific physiological investigations of Liebig, Voit, Lavoisier, Pettenkoffer and Rubner, and to the practical application of this knowledge mostly in America by Atwater and Rosa, Gephart and Du Bois, and Benedict. Else then records briefly the observations of Friedrich Müller in cases of thyrotoxicosis, the fundamental work of Magnus-Levy in first demonstrating and calculating the lowered metabolism in hypothyroidism and the opposite condition in hyperthyroidism by indirect calorinetry. Details are then given of the actual operation with a Benedict apparatus and the method of calculating the basal metabolic rate. Else does not determine the respiratory quotient, but uses 0.82 as recommended by Benedict, Emmer, Roth and Smith. Three illustrative cases are presented, one of hyperthyroidism with rate of 72 per cent above normal, one of hypothyroidism, rate 28 per cent below; and a myxosarcoma of the thyroid with normal rate of 5 per cent above theoretical normal. Twenty-four references to the literature are appended.
—H. L.

(THYROID) The technic of goiter operation (Zur Technik der Kropfoperation). Enderlen (E.) & Hotz (G.), Zentralbl. f. Chir. (Leipzig), 1920, **47**, 1365-1366.

Ligation of all four arteries of the thyroid in operation for goiter has been recommended, but Madlener, who has performed this operation, observed 24 days later a postoperative tetany, ending fatally in 6 days. According to the authors this cannot be due to the operation, since they ligated the four arteries in thousands of cases without ever observing tetany. If Madlener would be right transplantation of endocrine organs would never be possible. Mad-

lener observed suppuration in his case after the operation. It is very probable that this suppuration caused necrosis of the parathyroids.—J. K.

(THYROID) Colorimetric studies of tryptophan. II. (Colorimetrische Untersuchungen über das Tryptophan. II. etc.). Fürth (Otto) & Lieben (Fritz), Biochem. Ztschr. (Berlin), 1920, **109,** 124-152.

The thyroid gland of man is relatively rich in tryptophan by the new method of determining this substance described by the authors.—F. S. H.

(THYROID) Diagnosis and treatment of hyperthyroidism. Fussell (M. H.), N. York M. J., 1920, **112,** 205-212.

Conditions of hyperthyroidism must be differentiated from cases of neuresthenia. In the neuresthenic muscular tremors are intermittent, the mental character is introspective, there is no flushing of the skin, the heart slows while recumbent, there is a loss of appetite, the metabolic rate is not increased, the Goetsch test is negative, sugar tolerance is normal and there is no response to thyroid preparations. On the other hand the hyperthyroid patient presents continuous muscular tremors, flushing of the skin, an alert and apprehensive mental character, dilation of the heart, an increased appetite, an increased metabolic rate, a positive Goetsch test and active responses to thyroid medication. The treatment of hyperthyroid cases should consist of rest but where this is not possible the gland should be operated upon. If the individual is toxic, rest, ligation of thyroid arteries and the x-ray should be tried before surgery is resorted to.—H. W.

(THYROID) Cure of tuberculous goiter (Contributo alla cura della struma tubercolare). Giacinto (G.), Policlin. (Roma), 1918, **25,** sez. chir., 225-230.

Giacinto reports the case of a man, 42 years old, who for eight months had noticed that the right lobe of the thyroid gland was enlarging. Irregular neuralgic pains were also felt in the tumor, irradiating downward and outward or upward. These pains were variable, appearing usually in the evening, and were not modified by the ordinary sedatives. The temperature rose slightly toward evening. The hard tumor was tender, with irregular surface, and immovable except for slight movement during swallowing. There was slight emotional tachycardia, but no signs of exophthalmic goiter. The urine was normal. The weight had dropped over 15 pounds in two months. The diagnosis wavered between malignant goiter and woody thyroiditis, but an exploratory incision showed the capsule much thickened and bound down to adjacent tissues. A wedge was excised, 5 cm. long by 3 cm. wide; the inner

end seemed to be normal tissue, but a cheesy tubercle was apparent above. No tubercle bacilli could be discovered. Treatment by daily injection of alternating iodin and arsenic was successful.
—F. S. H.

(THYROID) The Heart in Graves' disease. Goodall (J. S.), Practitioner (Lond.), 1920, **105**, 37-46.

The condition of the heart is of immense importance in Graves' disease in deciding prognosis and in determining the type of treatment. The extent of cardiac pathology depends upon (a) the duration of the disease, (b) the intensity of the intoxication, (c) the pre-existing state of the heart. The systolic blood pressure, according to Goodall, is usually 10 to 20 per cent below normal, the diastolic is about normal, the pulse presure is low. Operation on the thyroid raises the blood pressure, sometimes enormously and acutely and the author believes over-action of the adrenals to be the cause of sudden death after thyroid operation. In the average case, the blood pressure is raised at first for a short period then falls below normal for a longer time, which is the "safe operation stage," then rises again, either due to adrenal activity or cardiac hypertrophy. The low pressure stage is recommended for operative intervention because of (1) only slight myocardial exhaustion; (2) less risk of postoperative acute rise with sudden death from ventricular fibillation; (3) little risk of hemorrhage. Goodall points out that his views are not in agreement with Kocher. Several types of electrocardiographic tracings are included. The tachycardia of Graves' disease is shown to be supra-ventricular, auricular in origin. As myocardial exhaustion increases, atonia sets in and gradual dilation follows. True angina in Graves' disease is said to be exceedingly rare. The electrocardiogram in moderately advanced cases will show left ventricular proponderance and lengthening of the P.R. interval showing impaired conductivity of the Bundle of His. Finally auricular fibrillation appears. Turning to treatment, Goodall apparently places no faith in medical remedies. Even x-ray is not highly recommended. Attention is called to the danger of burns, the inability to gauge the dose accurately and the rendering of operation more difficult. The author favors operation and suggests that the amount removed should depend on the severity of the symptoms. Preliminary ligation is advised in selected cases. (Many authors would disagree with Goodall's ideas about blood pressure and therapy).—H. L.

(THYROID) A contribution on blood pressure in Graves' disease. Goodall (J. S.) & Rogers (L.), Brit. M. J. (Lond.), 1920, (ii), 588-590.

The authors quote a series of 20 cases of exophthalmic goitre, 10 in women and 10 in men, to show that the systolic blood pres-

sure is generally considerably below that expected for normal individuals of the same age. The diastolic pressure is very little affected. The blood pressure is relatively lower in the women than in the men, but the occurrence of pre-existing arteriosclerosis or ventricular hypertrophy is advanced as an explanation of the higher blood pressure seen in most of the males. The authors believe that the blood pressure in Graves' disease passes through three stages: (1) a preliminary stage of hypertension associated with the onset of the disease, and of brief duration; (2) a stage of hypotension, which is relatively long, lasting for months or years; (3) a stage of secondary hypertension which appears to be associated with "a reduction of thyroid superactivity, with consequent relative increase in that of the suprarenal" and "some secondary change in the cardio-vascula system, such as cardiac hypertrophy." The second stage is regarded as a safe operative condition. Often a marked post-operative rise in blood pressure occurs. This is not infrequently associated with cardiac acceleration and irregularity of the pulse due to auricular fibrillation. In extreme cases ventricular fibrillation may cause death. "A low systolic pressure in Graves' disease, other factors being equal, indicates from an operative point of view: (i) little myocardial exhaustion, (ii) a small post-operative rise in blood pressure and consequently little liability to post-operative cardiac failure, (iii) less hemorrhage."
—L. G. K.

(THYROID) Ueber sporadischen Kretinismus. Guleke, Berl. klin. Wchnschr., 1920, **57**, 861.

Data published elsewhere. (See Endocrinology, **4**, 700).—J. K.

(THYROID) Diffuse colloid goitre (Die diffuse Kolloidstruma). Hellwig (A.), Mitt. a. d. Grenzgeb. d. Med. u. Chir. (Jena), 1920, **32**, 508-540.

A very detailed report of histological studies and review of the literature on the subject. The author considers the "struma diffusa colloides" as a thyroid with an increased function due to infection with the hypothetical "Kropftoxin." These patients show an increased irritability of the involuntary nervous system, and their endocrine system is hardly equilibrated. Administration of iodine, psychical or physical over-stimulation may produce Graves' disease in these individuals.—J. K.

(THYROID) Diagnosis of hyperthyroidism. Johnson, (C. H.), J. Mich. M. Sc. (Grand Rapids), 1920, **19**, 456-459.

A negative **adrenin** test excludes hyperthyroidism while a definite positive test means hyperthyroidism in all but a small percentage of the cases. This test is always positive in true cases of hyperthyroidism.—H. W.

The postulated antagonism between THYROID and SPLEEN (Über den angeblichen Antagonismus von Schilddrüse und Milz). Klinger (R.), Biochem. Ztschr. (Berl.), 1918, **92**, 376-384.

This paper is a report of a study of the oxygen consumption, thrombin content of the serum and bone-marrow of thyroidectomized or splenectomized rats and cats. The results of the study afford no confirmation of the idea of the existence of an antagonism between the spleen and the thyroid.—F. S. H.

(THYROID) Remarks on goiter (Based on 190 thyroid operations by the author). Lahey (F. H.), Vermont Med. (Rutland), 1918, **3**, 30-33.

A brief review with no novel data.—F. S. H.

THYROID injection in cachexia strumipriva (Injecto de tiroides en una caquexia estrumipriva.) Lenzi (L.), Semana méd. (Buenos Aires), 1918, **25**, pt. 2, 61-62.

A brief statement that the injection of thyroid extract in a case of cachexia strumipriva ameliorated the distressing symptoms. —F. S. H.

THYROID instability and neuro-arthritis with multiple swellings (Neuroarthritisme a fluxions multiples par instabilité thyroidienne). Léopold-Levi Presse méd. (Paris), 1918, **26**, 191-192.

A case report of a neuropathic case bordering on neurasthenia accompanied by arthritis. The thyroid gland gave evidence of frequent congestive attacks by its repeated swelling and subsequent reduction in size. Other tissues and parts of the body exhibited this alternating enlargement and regression. The case was diagnosed as a neuro-arthritis predominately angio-neurotic. The evidences of hyperthyroidism were plentiful and confirmed the hypothesis of a thyroid instability regulable by thyroid administration. The author considers that the angio-neurotic condition is the basis of the congestive disturbance of the thyroid leading to the appearance of hyperthyroidism.—F. S. H.

THYROID gland. Lim (R. K. S.), Sci. Progress (London), 1920, **15**, 243-249.

Hyperthyroidism, hypothyroidism, the function of the thyroid in the lower vertebrates, the nature of the thyroid secretion, and the function of the secretion of the parathyroids are discussed. The conclusion is drawn that "the function of the thyroid varies according to age. In the young it hastens development, in the adult it maintains the working of the body processes at a normal rate, and in the aged it probably ceases to function."—Chem. Abst., **15**, 257.

(THYROID) Flatulant dyspepsia of Basedowians (La dyspepsie flatulente des basedowiens). Loeper (M.), Prog. méd. (Paris), 1918, 3.s., **33**, 345-347.

Out of 40 cases of Basedow's disease, Loeper reports four with diarrhea and 13 with dyspepsia. The flatulent dyspepsia is attributed, not to thyroid hypersecretion but to compression. Nevertheless there are other dyspepsias that may be considered as taking their origin from the toxic thyroid.—F. S. H.

THYROID glands—metastasizing effects. McLean (A.), J. Mich. M. Sc. (Grand Rapids), 1920, **19**, 558-560.

A general discussion of thyroid metastases and their relation to malignant growths.—H. W.

(THYROID) Case of early myxedema. Mahon (F. F.), J. Roy. Nav. M. Serv. (Lond.), 1917, **3**, 481-482.

A brief report of a patient showing the early signs of myxedema. The disease was aborted by treatment with thyroid extract and potassium iodide. One 5 grain B. & W. thyroid tablet was taken daily; when less was ingested a relapse occurred.
—F. S. H.

(THYROID) A case of myxoedema. Mathers (A. T.), Canad. M. Ass. J. (Toronto), 1920, **10**, 859-862.

The patient was a married woman, aged 32, anemic and somewhat emaciated in appearance. There was a yellowish tinge to the skin which was dry. The hair was dry and of a very fine texture. The nails were brittle. In the region of the eyes and across the bridge of the nose some oedema was present. Physical and mental processes were slower than normal. Mental examination showed that hallucinations were very evident and that delusions of persecution were prominent. A gastro-intestinal x-ray series revealed "a remarkable degree of atony and stasis throughout the whole tract." The case was diagnosed as myxoedema and the patient was placed on thyroid extract—two grains three times a day. The dose was gradually increased, and in a short time the mental symptoms entirely disappeared, and a second x-ray series showed that the gastro-intestinal stasis and atony had completely vanished. The contention that the secretion of the thyroid has an activating influence on the abdominal vagus would seem to be borne out by the results in this case.—L. G. K.

(THYROID) Goitre. Matthews (A. A.), Northwest Med. (Seattle), 1920, **19**, 183-185.

Matthews reports 75 consecutive goitre operations with three deaths. He warns of the frequent intolerance to surgery in the

toxic goitre patient and the importance of patience and conservatism. Plummer's classification of goitre is adhered to. The cautious use of iodides in physiologic-non-surgical goitre is recommended. Matthews believes that endemic goitre is dependent on water from so-called goitrous wells that have passed through certain geologic strata. Bircher's important experiments are referred to. The theory of McCarrison that goitre is due to toxic substances of infectious origin, chiefly from the colon, is alluded to, and the interesting cures or improvement in cases of exophthalmic goitre obtained by him and Lane in short circuiting the large bowel. Matthews considers the non-hyperplastic toxic goitre more dangerous than the exophthalmic goitre. The author seems to lack confidence in the permanency of cure by medical treatment in toxic goitre, but in advocating surgery points out that success in thyroid surgery depends on wise judgment, as to when to operate and how much to operate.—H. L.

(THYROID) Pathology of the heart in myxedema (Zur Klinik des Myxödemherzens). Meissner (R.), München. med. Wchnschr., 1920, **67**, 1316-1317.

A report of three cases.

1. A man of 56 suffered since 12 years old from classical myxedema. The heart was enormously dilated on the right and on the left. The heart sounds were normal. The pulse rate was 50-52. The x-ray picture showed an enormous heart and an enlarged aorta. The volume of the heart became normal again after treatment with thyroid.

2. A woman (age not given) with hypothyroidism. The heart was dilated on the left side. The second aortal sound was accentuated. Pulse 58. The face and tongue were swollen. The urine contained leucocytes, erythrocytes and albumen, but no casts. Edema of the ankles was present. Blood pressure 180. The diagnosis as between myxedema and nephritis was very difficult. By thyroid treatment the urine became normal; the blood pressure sank temporarily, the pulse rate was raised but the heart remained unchanged. Perhaps the dilation of the heart was due to another cause (nephritis) as the other symptoms of hypothyroidism.

3. A woman of 39 became acutely ill with swelling of the face and tongue and loss of hair. Pulse rate of 54. The heart was normal. She was cured by thyroidin, though the heart did not undergo any change by this treatment. Probably the disease was too acute to produce changes in the heart.—J. K.

(THYROID, PARATHYROID) The effects of thyreo-parathyroidectomy in the guinea pig. (Sur les effets de la thyreo-parathyreodectomie chez le cobaye). Mira (M. F. de), J. de Physiol. et de Path. Gén. (Paris), 1920, **18**, 976-980.

The total removal of the thyroids and parathyroids in 12 animals was found to cause death in from 2 to 57 days. Apathy and slowness of movement and generally fibrillary twitching of the muscles occurred. Tetanic attacks preceded death. Convulsive seizures were absent in some cases of prolonged survival. Most of the cases were characterized by loss of weight. The results were independent of the ages of the animals.—L. G. K.

THYROID treatment of edema (Oedembehandlung mit Schilddrüsenpraparaten). Molnar (B.), Wien. klin. Wchnschr., 1920, **33**, 1111-1114.

The author employed thyroid therapy in 20 cases of edema. He began with 1 gram of dry gland daily; in one case he even gave 3½ grams daily without complications. In four cases of nephrosis, a good result was obtained in two. In five cases of Bright's disease no result was seen. No success was observed in five patients with cardiac myo-degeneration. In another case, however, the result of the thyroid treatment was indirect. First, digitalis and caffein had no effect; then thyroid was tried during 16 days without success. After this digitalis was once more tried with a most brilliant result. A patient with lymphogranulomatosis and acromegaly, with cardiac insufficiency, edema, ascites, hydrothorax when treated with thyroid, became markedly diuretic with loss of weight. In this case it is not quite sure that the polyuria was due to the treatment, since the patient had a tumor of the hypophysis, to which the polyuria might have been due.—J. K.

(THYROID) The medical aspects of Graves' disease. Morsman (C. F.), Northwest Med. (Seattle), 1920, **19**, 178-182.

Morsman prefers the terms Graves' disease to exophthalmic goitre because exoptthalmus is frequently absent, and to hyperthyroidism because other ductless glands are often involved. He mentions the preponderance of Graves' disease in females and the probable relations with the gonads as evidenced by physiologic hyperthyroidism in adolescence and pregnancy. The author does not agree with Leonard Williams that Graves' disease is the adult form of mongolism. The alimentary hyperglycemia of Graves' disease is discussed together with the technic of obtaining the blood sugar curve. In discussing treatment Morsman points out that treatment either by surgery, x-ray or radium of the thyroid gland is not sufficient because disturbances occur in other structures than the thyroid; dietetic and hygenic treatment must also be employed; closer relation between the trained internist surgeon and roentgenologist will serve the patient best. Various drugs and ductless gland products that have been tried in Graves' disease are briefly commented upon.—H. L.

(THYROID, ADRENIN) The differentiation of early tuberculosis and hyperthyroidism by means of the adrenalin test. Nicholson N. C.) & Goetsch (E.), Canad. M. Ass. J. (Toronto), 1919, **9**, 481-489.

There are many patients who symptomatically might be considered as suffering from either incipient tuberculosis or mild to moderate hyperthyroidism, or both. The authors use as a diagnostic aid in these conditions the constitutional hyper-sensitiveness to adrenin exhibited by all cases of hyperthyroidism, whether associated with tuberculosis or not. Tuberculosis uncomplicated by hyperthyroidism does not cause a positive reaction to adrenin. The test is carried out as follows: After a day of complete rest in bed two readings are taken at five minute intervals, of systolic and diastolic blood pressure, pulse rate, and respiration, and all signs and symptoms of hyperthyroidism are noted; 0.5 cc. of a 1:1000 adrenin solution is injected subcutaneously in the deltoid region. Records of pulse and blood pressure are then made every two and one-half minutes for ten minutes, then every five minutes up to one hour, then every ten minutes for half an hour or longer. In a positive reaction there is usually an early rise in blood pressure and pulse of from 10 to 50 points. In the course of half an hour there is a moderate fall, then a slight secondary rise, then a fall to normal in about 90 minutes. Along with these there is an exaggeration of the clinical picture of hyperthyroidism, especially the nervous manifestations such as tremor, apprehension, throbbing, asthenia, vasomotor changes. A majority of these signs and symptoms must be definitely brought out or increased before the test can be regarded as positive.—L. G. K.

(THYROID) Goiter. The indications for and the technic of the surgical treatment of goiter, illustrated by three cases. Ochsner (A. J.), Surg. Clin. Chicago (Phila.), 1917, **1**, 47-63.

The indications for surgical interference in goiter patients according to Ochsner are, the development of the growth to the point where evidences of toxemia are given, when it interferes with deglutition and respiration, and when it refuses to respond to medical treatment after a reasonable length of time. The inference is made that such operations should not be done during puberty. The three cases described are used to illustrate the preparatory and surgical technic employed. In order that as little anesthetic as possible be used, so that the danger from post-operative pneumonia be minimized, Ochsner gives ¼ grain of morphine and 1/100 grain of atropin hypodermically one-half hour before anesthesia, and when anesthesia is complete raises the head of the patient to an angle of 45 degree, thus producing cerebral anemia and making anesthetization during the operation unnecessary. Sufficient thyroid tissue is left behind in every instance to provide for about the

normal secretion. The after-treatment consists in proctoclysis with 500 cc. normal salt solution started every four hours. If the pulse tends to rise and excitement occurs a hypodermoclysis of 1000 cc. normal salt solution is given in the pectoral region. On leaving the hospital the patient is cautioned against excitement. the eating of meat, and the drinking of stimulants.—F. S. H.

(THYROID) The differential diagnosis of tuberculosis. Otis (E. A.), Boston M. & S. J., 1920, **183**, 695-702.

Hyperthyroidism is not infrequently seen in many persons who show early signs of tuberculosis, i. e., tachycardia, frequent sweating, lassitude, cough and evening temperature.—H. W.

(THYROID) Goitre and its medical treatment. Pearson (J. M.), Canad. M. Ass. J. (Toronto), 1920, **10**, 983-987.

In the treatment of those forms of goitre producing symptoms of hyperthyroidism the necessity for rest and correct feeding is emphasized. The rest must be such that the environment is as closely adapted as possible to the individual, and all channels of disturbance alike to physical and mental sides closed. An oversupply of assimilable food should be provided. Certain diets with a high iodine content seem to prevent the occurrence of goitre. The Japanese use seaweed as a food and they are practically immune to goitre. Seaweed contains a large quantity of iodine. Certain drugs are briefly mentioned since they are used to some extent in the treatment of goitre.—L. G. K.

Myxedema with complete THYROID aplasia (Ueber myxödem bei totaler Thyreoaplasia). Rössle. Berl klin. Wchnschr., 1920, **57**, 861.

A demonstration of the organs and the skeleton of a dwarf of 28 in whom thyroid tissue could not be found at autopsy. The patient died of cirrhosis of the liver with intestinal hemorrhages. There was an arteriosclerosis, and the ossification was defective. The skin showed all symptoms of myxedema. The uterus and **ovaries** had the shape of a full grown woman. There were no secondary sexual characteristics. No **parathyroids** were found on the right, but were present on the left side. The **hypophysis** was rather large (725 mg.) and contained two adenomas. No traces of thyroid was found in the tongue. The zona glomerulosa of the **adrenals** showed a marked sclerosis. The **thymus** was changed into fat. The **pineal, pancreas** and **spleen** were normal.—J. K.

(THYROID) Idiopathic Osteopsathyrosis (Osteopsatirosi idiopatica). Ruggieri (Elvino), La Ped. (Napoli), 1920, **28**, 953-974.

The article is a detailed report of a case of osteopsathyrosis in a girl 13 years old, who had to that age eleven fractures of long bones. When she recovered she could not even walk, if not held. On account of the disturbed calcium metabolism **adrenal** treatment was given for a month, but with little result. **Thymus** gland was then added to the adrenal and in seven weeks from her entrance she became able to walk by herself and her weight increased from 19 kilos to 23.5 kilos. The author believes that it was a question of prenatal endocrine disturbance.—G. V.

(THYROID) Toxic goiter in orientals. Russell (W. B.), Nat. Med. J. (Shanghai), 1920, **6**, 101-108.

After a brief review of papers dealing with the general subject of goiter in China the author describes in some detail five selected cases of toxic goiter which present no special feature not found in occidentals. He recommends the usual operative treatment if satisfactory improvement does not follow rest and improved by hygienic conditions. This article is of value in connection with the suggestions of Arthur Keith and others that the Chinese as a race present the phenomena of reduced thyroid secretion.—E. V. C.

(THYROID) The therapy of Flajani-Basedow's disease (Sulla terapia della malattia di Flajani-Basedow). Schiassi, Reforma med. (Napoli), 1920, **36**, 829.

Considerations on the article published by the Policlinico-Surgical section—in which Prof. Schiassi claims that 60 per cent of the cases are apt to recover. He considers the toxemia as also influencing the functions of the **ovaries** and **adrenals.** He claims good effects from belladonna, does not trust the x-rays on account of a possible danger to the **parathyroids,** repudiates cervical sympathectomy and advises the surgical intervention on the gland only when the medical treatment proves of no avail.—G. V.

Influence of an alcoholic extract of THYROID upon polyneuritic pigeons, and the metamorphosis of tadpoles. Seaman (Emily C.), Am. J. Physiol. (Balt.), 1920, **53**, 101-108.

A study to ascertain if the thyroid contained water-soluble vitamines. Fresh glands were extracted with 95 per cent alcohol and made 0.8 per cent acid with HCl. After various manipulations a water extract is obtained, one cubic centimeter of which contains 0.05 mg. of iodine and 0.435 per cent of nitrogen. The whole extract gave marked and rapid curative results when fed to polyneurotic pigeons. Improvement began within six hours. When the vitamine fraction was removed by the phosphotungstic acid method, the extract no longer had a curative effect. A "residue" containing the same amount of iodine was without effect, showing it was not the iodine which produced the results. The effect of the

whole extract on the metamorphosis of tadpoles is very marked. "The limb buds appeared within eight hours, and complete metamorphosis with the bulging eyes and disappearance of the tail within four days." Control experiments with the thyroid "residue" were negative.—T. C. B.

(THYROID) Syndrome de Basedow et tuberculose. Sergent (E.), Paris méd., 1920, **2**, 80-84.

The tendency of Graves' disease to simulate tuberculosis, especially in the female sex at puberty and the menopause, is emphasized by Sergent, who points out that in such cases the clinical picture of Graves' disease may be complete or only minor signs may be present. In both pulmonary tuberculosis and hyperthyroidism the following symptoms may be found either separately or in combination, viz.: an unsettled temperature, an unstable pulse usually characterized by attacks of more or less marked tachycardia, variations of the blood pressure, irregular menstruation, flushed face, sweating, loss of flesh, fatigue, attacks of abdominal pain and diarrhoea, cough, and shortness of breath. Sergent concludes that at both extremes of the sexual life of women the possibility of hyperthyroidism should be borne in mind, and that the presence of pulmonary tuberculosis should be admitted only if there are definite proofs of its existence. —Med. Sc. Abst. & Rev., **3**, 213.

Experimental treatment of dementia precox with THYROID preparation (Mededeelingen over proeven van behandeling der dementia praecox met schildklierpreparaten). Schnitzler (J. G.), Nederl. Tijdschr. v. Geneesk. (Amsterdam), 1916, **60** (I), 1179-1181.

In 1914 Lemei, a Dutch psychiatrist, reported splendid results with organotherapy (thyroid) in dementia precox. Schnitzler tried this in 22 typical cases but with no definite success.—J. K.

(THYROID) Results of operations for Graves' disease with reference to the incidental blood conditions and vascular system. Sekiguchi (Shigeki) & Ohara (Hachiro), Tohoku J. Exp. Med. (Sendai), 1920, **1**, 192-210.

This report is based upon a study of fifteen cases of which ten were operated on. The authors were unable to find any pronounced alterations in red blood cells or leucocytes before operation, though the time of coagulation of the blood is increased about two minutes as compared with the normal. After operation the neutrophile leucocytes increase for a short time and the lymphocytes decrease, but this condition is noted in other diseases. When cardiac dilation occurs it is most prominent on the left ide. The systolic and diastolic pressure varies within normal limits, but the pulse amplitude seems to be increased.—E. V. C.

(THYROID) Humoral symptoms of the Basedow's disease (I sintomi umorali del morbo di Basedow). Siciliano (L.), Riv. Crit. di Clin. Med. (Firenze), 1920, **21**, 307-311.

Siciliano reviews the several modifications of the blood (leukopenia and lymphocytosis and mononucleosis), the histological modifications of the **thyroid**, the variation in iodine content, the increase of **adrenin**, the glycosuria and hyperglycemia, the basal metabolism and Aberhalden's complement deviation, and finally the action of iodine on the thyroid function. All these researches are of help in the diagnosis of Basedow's disease, yet none of them is final, as a positive reaction can also be obtained in forms of pure hyperthyroidism (not yet pathological), so that to eliminate every doubt one has to go back to the study of the clinical symptoms and to the study of the course of the disease.—G. V.

(THYROID) Exophthalmic goiter in its hereditary and familial aspects (Goitre exopthalmique héréditaire et familial). Souques (A.) & Lermoyez (J.), Rev. neurol. (Paris), 1918, **34**, 320-321.

A presentation of four cases of hereditary and familial exophthalmic goiter. Three others of this family of 15 have Basedow's disease. The occurrence of this grouping is attributed to an hereditary predisposition rendering the thyroid more accessible to various and sundry toxic infections.—F. S. H.

(THYROID) Goitre. Starr (F. N. G.), Graham (R. R.) & Robinson (W. L.), Canad. M. Ass. J. (Toronto), 1920, **10**, 977-982d.

The following classification of goitre based on a clinical and pathological study of 300 cases, is advocated.

I. Diffuse
   (a) Colloid
   (b) Hyperplasia (exophthalmic)

II. Tumours
   (a) Adenoma
      1. Simple
      2. Colloid
      3. Hyperplastic
   (b) Malignant
      1. Carcinoma
      2. Sarcoma

Surgical treatment is advocated.—L. G. K.

(THYROID) Some remarks on subthyroidism. Stiell (W. F.), Practitioner (Lond.), 1920, **105**, 146-149.

Many minor ailments, such as constipation, neuralgia, mental apathy, menorrhagia, pseudo-asthma, chilliness and palpitations are frequently due to benign (mild) subthyroidism and are relieved

by administration of thyroid extract. Stiell attempts to explain the improvement by the relief of slight myxedematous infiltration of the cortical nerve cells, nerve fibers, meninges in the case of headache; of the frontal lobe in mental apathy; of the uterus in menorrhagia; of the bronchioles in pseudo-asthma, etc. For these same symptoms Arbuthnot-Lane have removed the colon, relieving the toxemia from colonic stasis—but thyroid frequently relieves the stasis and therefore the toxemia.—H. L.

(THYROID) Struma maligna. Streiszler, Wien. klin. Wchnschr., 1920, **33,** 763.

Demonstration of a case showing many metastases in the bones. The primary goiter did not exhibit signs of malignancy. Two years after the case was first observed the patient suffered a spontaneous fracture of the right femur, the cause of which was not detected. Two years later a soft tumor of the left knee and of the sternum developed. A piece of tissue was taken for examination and a diagnosis of struma malignum was made. The primary goiter was removed and a retrosternal lobe, showing marked symptoms of malignant degeneration, was found.—J. K.

THYROID insufficiency and hypersomnia (Hipersomnia e insuficiencia tiroidea). Udaondo (C. B.), Rev. de la. Asoc. méd. Argent. (Buenos Aires), 1920, **33,** 235-244.

A report of two cases of hypothyroidism, one a woman of 29 and the other a man of 33, giving a history of a tendency to fall asleep at all times, although they had from 10 to 12 hours' sleep each night. Thyroid therapy (0.06 grams daily, then increased) cured the complaint.—B. A. H.

(THYROID DIABETES) Goiter in Graves' disease (Basedow-struma). Urban, Wien. klin. Wchnschr., 1920, **33,** 718.

The patient was a woman of 45, with Graves' disease and diabetes. Half of the goiter was removed. After several days the diabetes had disappeared; even the administration of large doses of carbohydrate did not produce glycosuria. The symptoms of Graves' disease improved rapidly after the operation.—J. K.

(THYROID) A study of the distribution of iodine between cells and colloid in the thyroid gland. II. Results of study of dog and human thyroid glands. Van Dyke (Harry Benjamin), J. Biol. Chem. (Balt.), 1921, **45,** 325-332.

This paper is a report of the distribution of iodine in the thyroid glands of normal and iodine fed dogs as well as in human glands obtained from individuals subjected to operation for toxic goiter.

It was found that following the method of Tatum the concentration of intracellular iodine is independent of the suspending medium, whether that is pure Ringer's solution, Ringer's solution containing iodine—rich colloid material, or homologous blood serum, and that autolysis apparently did not occur to any extent during the period of extraction.

The ratio value of the distribution of iodine between cells and colloid was found to be relatively constant despite great variations in morphology and iodine content of the glands examined. The ratio value for the dog's thyroid gland seems quite constant and is much lower than that of beef or sheep, while that for man lies between the two groups.—F. S. H.

Influence of THYROID extract and of other organ extracts on the metamorphosis and reproduction of CYCLOPS VIRIDIS and CYCLOPS SERRULATUS (Influenza dell'estratto di tiroide e di altri estratti organici sulla metamorfosi e riproduzione di Cyclops viridis e Cyclops serrulatus). Vecchi (Anita), Arch. di Fisiol. (Firenze), 1920, **17,** 105-136, 14 tab.

The author shows as a result of a large number of experiments on the crustacean, Cyclops, that feeding with various (mammalian?) organ extracts leads (1) to a marked abbreviation in the duration of the larval period, and (2) to a shortening of the time interval between the successive depositions of eggs by the female. These effects are exercised in the greatest degree by the extract of thyroid, then by that of **thymus,** and to a less extent by those of the **suprarenal** and **spleen. Ovarian** extract produces no well defined effects upon development—and may be compared in its action with the effect produced by a non-glandular substance such as fibrin. The duration of larval life in Cyclops viridis is about 28 days (20 to 34). Specimens allowed to hatch and undergo development in a thyroid medium metamorphose after 7 to 14 days; in thymus, after 11 to 17 days; in suprarenal and in spleen after 12 to 19 days. The experiments in which thyroid alone was fed in water were supplemented by experiments in which additional nutriment was supplied in the form of hay infusion containing the protozoan, Glaucoma. But the accelerative effect of the thyroid was still very apparent, although the period of development was thereby shortened both in experiments and in controls. Cyclops viridis completes 5 depositions of ova in water in a 39-day period, in a thyroid medium in 28 days. Those grown in thymus require 29 days, the controls (in water) 34 days; those in suprarenal 29 days, controls 34 days; those in spleen 30 days, controls 37 days. Negative results as regards development were obtained by the use of ferric chloride in low concentrations (Cf. however, positive results of Urbinati on Cyclops macrunes, 1913; Bios, **1,** 191-275). The author concludes from the results of his experi-

ments with Cyclops that the effects observed are probably due to specific organ hormones which normally promote metabolism, since they appear to exercise their effects in diverse degrees—certain ones giving marked positive results, others being indifferent.

—F. S. H.

(THYROID) Paratuberculosis of the endocrine type (La paratuberculosis de tipo endocrino). Viton (J. J.), Rev. de la Asoc. med. argen. (Buenos Aires), 1920, **32**, 239-248.

Viton believes that patients which become better after the injection of tuberculin $1x10^{-20}$ are tuberculous and is of the opinion that many cases of hyperthyroidism are of tubercular origin.

—B. A. H.

(THYROID) The interpretation of basal metabolism with special reference to hypothyroidism and hyperthyroidism. Wade (B. N.), Northwest Med. (Seattle), 1920, **19**, 175-178.

Wade refers briefly to the work of Gephart, Dubois, Benedict and Carpenter in developing the clinical application of basal metabolism estimations. So far the value of such determinations seems to be confined to lesions of the thyroid gland.

"In the treatment of hypothyroidism the aim should be to find the minimal dose of thyroxin or thyroid extract necessary to maintain the normal or average metabolic rate, and this can be better regulated by basal metabolism determinations than by the symptoms or signs presented by the patient." "Lowered metabolism is usually present for a variable length of time before the symptoms of hypothyroidism appear, and also an increased metabolism may be present for a variable length of time before symptoms of hyperthyroidism appear. Therefore the basal metabolic rate is a far better index of the degree of severity of hypo- and hyperthyroidism than the symptoms would indicate. There is also no definite relation between the metabolic rate and the severity of the symptoms. Severe cases of thyrotoxicosis as evidenced by rates of 25 to 50 per cent above normal may show only mild signs and symptoms and vice versa. Some symptoms such as exophthalmus or tremor may persist even though the metabolic rate has been reduced to normal. Basal metabolism estimations are therefore of great value in diagnosis, prognosis and in determining when and how much to operate, and in controlling the results of operations, x-ray therapy or other purely medical measures. The author advises repeated determinations for the sake of accuracy because of the fluctuations that occur and the correlation as far as possible of these figures with the signs and symptoms exhibited by the patient.—H. L.

(THYROID) The leucocytic picture after injections of iron and thyroid preparations (Das relative weisse Blutbild nach Injectionen von Eisen und Schilddrüsenpräparaten). Waser (A.), Ztschr. f. Biol. (München), 1920, **71**, 107-116.

Subcutaneous injections of thyroid extract cause an increased formation of polymorphonuclear leucocytes. The number of lymphocytes decreases. Therefore the total number of colorless corpuscles remains the same. Phys. Abst., **5**, 365.

On the heredity of diseases conditioned by VAGOTONIA (Zur Frage der Erblickeit vagotonisch bedingter Krankheiten). Heissen (F.), Münch. med. Wchnschr., 1920, **67**, 1406-1407.

Vagotonia is often hereditary or familial. Endocrine causes, exudative diathesis, and other conditional causes are of importance.—J. K.

(VAGOTONIA) The use of atropine in the treatment of the hypertonic infant. Kaiser (A. D.), N. York M. Jour., 1920, **112**, 971-973.

The hypertonic condition (vagotonia) in children is manifest by irregular vomiting, at times by visible peristalsis, muscular irritability, constipation, malnutrition, insomnia and crying. These manifestations of hypertonicity are not the result of diet and may be controlled by the administration of atropine.—H. W.

Clinical aspects of VAGOTONIA and SYMPATHICOTONIA (Influencia de la Vagotonia y de la Sympateticotonia en la Clinic). Quimper (A. H.), Cron. méd. (Lima), 1920, **37**, 300-304.

The clear and concise exposition of the relations between sympathicotonia and vagotonia indicates the importance of its study, especially for visceral neuralgia and for the interpretation of the syndromes according to which the individual may have a constitution subject to vagotonia or sympathicotonia.—I. O.

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THE PARATHYROID GLANDS

A REVIEW OF THE LITERATURE

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I. ANATOMY AND PHYSIOLOGY

Sandström (1880) was the first to describe the (external) parathyroid glands as anatomic entities; his gross and microscopic description of these bodies as found in man and in several types of animals is excellent. He thought that they probably represented undeveloped embryonic thyroid tissue. Sandström credited both Remak (1851) and Virchow (1864) with having seen these bodies and briefly described them. Baber, in a second paper on the thyroid published in 1881, apparently without knowledge of Sandström's work, devoted a special section to describing under the name of "undeveloped portions of the thyroid" what we now recognize as the external and internal parathyroids. He found no evidence, however, of their later development into thyroid tissue. Unfortunately Baber's work remained comparatively unknown and the confusion resulting from the failure to recognize an irregular and quite extensive distribution of parathyroid tissue was not completely cleared up until the work of Kohn was published in 1895. Biedl (1913)

credits Stieda (1881) with having described under the name of carotid glands the parathyroids in sheep embryos. Horsley (1886) as a result of an extensive experimental study came to the conclusion that the "undeveloped tissue" of Baber was not embryonic thyroid tissue because after partial thyroidectomy there was hypertrophy of the remaining thyroid lobe with an increase both in the number and in the size of the cells so that there was a plication of the acinal wall, but without metamorphosis of the "embryonic" tissue into thyroid acini.

Gley (1891) reviewed about 300 reported experimental thyroidectomies and found that death occurred almost always from tetany soon after the operation. He suggested that certain "glandes thyroides surnumeriaires" (external parathyroids), which he had observed first in rabbits, played a rôle in the syndrome.

The fact that tetany might follow thyroidectomy was first recognized in Billroth's clinic by Weiss in 1881. Schiff (1884) demonstrated that after complete removal of the thyroid gland certain animals, notably cats and dogs, usually developed spastic or fibrillary contractions, tetany, followed by death. This was confirmed by Wagner (1884), Carle (1888), von Eiselsberg (1889) and others. At the time Gley presented his first paper he apparently did not know of either Sandström's or Baber's work, although later he referred frequently to Sandström's excellent paper. In a most interesting series of communications before the Société de Biologie (Paris) beginning in 1891, Gley presented his evidence that thyroidectomy does not produce fatal tetany unless the "glandules thyroidiennes" (external parathyroids), the term he preferred to Sandström's "parathyroid," likewise are removed. Because he found that removal of the "glandules thyroidiennes" without the thyroid did not cause fatal tetany in the animal on which he experimented and because he found that these glands usually develop to twice their original size after thyroidectomy, he considered, as had Sandström, the "glandules thyroidiennes" to be embryonic thyroid tissue which possessed the power of taking on the thyroid function, at least in part. Gley may, therefore, be credited with having rediscovered the external parathyroid glands and of being the first to show that they are of physiologic importance.

Cristiani (1892), by the method of serial sections, showed that in the rat the parathyroids are embedded in the thyroid and that it would be impossible in this animal to spare them when doing a thyroidectomy. In the mouse he found (1893) a similar but less perfect incorporation, while in the fieldmouse one parathyroid was usually inside and the other outside the thyroid, although there was considerable individual variation in their location. Nicolas (1893) found four parathyroids in bats. Chantemesse and Marie (1893) showed that in man the external parathyroids could readily be spared in thyroidectomy and in 1907 Getzowa described in man cells situated in the thyroid that resembled parathyroid tissue.

The experimental work of Gley was confirmed by Verstraeten and Vanderlinden (1894) and they likewise considered the external parathyroids part of the thyroid gland. Moussu (1892), however, very emphatically opposed Gley's conception of the importance of the parathyroids and showed that some animals survived even "complete" thyroidectomy and that age played an important rôle in the determination of the reaction. Hofmeister (1892) stated that those animals that survived developed nutritive disturbances of one of two types which he designated as "cretinism myxoedemateux" or "cretinism atrophique." Moussu (1893) found that although the parathyroids enlarge after thyroidectomy they do not show the slightest tendency to develop the structure of the thyroid, also shown by Horsley, nor do they prevent the postoperative myxedema noted by Hofmeister. He therefore strongly maintained that they do not take over the function of the thyroid and he doubted very much if they had any real important function; if they did he suggested that it was distinct from the function of the thyroid.

Kohn, in 1895, in a very excellent article, described in detail the two "external epithelial bodies," a name which he preferred to the term "parathyroid" of Sandström or "Glandule thyroidienne" of Gley. His main contribution, however, was emphasizing the importance (in the cat) of similar tissue situated within the thyroid gland and designated by him as the "internal epithelial bodies"; these areas had been seen by several previous observers who, however, had laid no particular stress on their importance in explaining the different reactions produced by

thyroidectomy in different species (Baber 1881, Maurer 1887, Rogowitch 1888, Cristiani 1893). Hürthle (1894) also had seen this internal parathyroid tissue, but considered it the same as the masses of interacinous cells described by Wölfler (1880) and which were supposed by the latter to develop into alveolar cells and acini and which have often been considered the nuclei of thyroid adenomas. Zerlinska (1894), on the other hand, described embryologic "Läppchen" in the thyroid which he said must not be confused with the "Zellhaufen" of Wölfler; he considered them identical with the bodies described by Gley and Cristiani. Groschuff (1896), as a result of extensive embryologic studies, believed the parathyroids to be organs separate and distinct from the thyroid. Verdun (1898) showed that the parathyroids are entodermal glands and come from the dorsal part of the third and fourth branchial pouch.

Blumreich and Jacoby (1896), working on cats, carried out quite an extensive series of thyroparathyroidectomies and partial thyroidectomies with irregular results; in many instances they did not obtain tetany as a result of what they considered a complete extirpation of all thyroid and parathyroid tissue.

Vassale and Generali, in a series of papers between 1896 and 1900, completely demonstrated, however, that the removal of all parathyroid tissue, even with the preservation of thyroid tissue, led to fatal tetany while no tetany resulted from removal of the thyroid if one of the four parathyroids remained intact and capable of functioning. Because of the constancy of parathyroids in all mammals, because they have a characteristic and stable structure even in thyroidectomized animals, and like other glands grow by karyokinesis, because if spared at thyroidectomy they do not prevent the development of cretinism and myxedema, and because their complete removal results in fatal tetany, Vassale and Generali (1896) did not accept Gley's contention that they are embryologic thyroid rests but believed that they are special organs of metabolism with a metabolic function yet to be determined but distinct from that of the thyroid. Moussu (1893) had previously but almost parenthetically suggested that the parathyroids might have a separate function; his main contention, however, had been that they are unimportant

bodies, and not until the publication of Vassale and Generali's article proving that the glands have a distinct and important function did Moussu (1897) strenuously maintain the latter view. Gley (1897) did not entirely accept the conceptions of Moussu and of Vassale and Generali, but admitted that the parathyroids might assume the function of the thyroid or complete the function of the thyroid, or finally, that they might have a separate function. As late as 1901 Gley believed that a true functional association might possibly exist between the thyroid and the parathyroids and that they played a more causative rôle in exophthalmic goiter than does the thyroid.

Jeandelize (1903) from an extensive study came to the conclusion that the parathyroids are independent organs. Erdheim (1906) reached the same conclusion as the result of a most careful series of experiments in which he found that in the animals which developed tetany no parathyroid tissue remained, its absence being proved by serial cross-sections; he also found that the individual differences in reaction after parathyroidectomy were marked and that the symptoms of tetany usually reached their height in the first twenty-four hours and then in some cases became chronic and were accompanied by nutritive changes, evidenced by an excessive growth of the lower incisors; this latter observation was apparently confirmed by Hohlbaum (1912). Erdheim also studied by serial sections three patients who died of postoperative tetany; in none of these could he find any trace of parathyroid tissue. He also established some evidence that the tetany of pregnancy likewise is due to parathyroid insufficiency.

With the exception of Vincent and Jolly (1905) and Forsyth (1908) no one has recently questioned the importance of the parathyroids or the fact that their complete extirpation usually results in tetany followed by death. Vincent, in 1920, retracted the conclusions based on his earlier work with Jolly so that we may now consider the theory completely accepted that the thyroid and parathyroids are independent organs and that the removal of the parathyroids quickly results in death from tetany in the majority of instances and in most species. In herbivora tetany does not always occur; MacCallum, Thomson and Murphy (1907) had a large preponderance of negative

results in goats and sheep; they cannot explain these results except on the ground that some parathyroid tissue may have been overlooked, although none was found in a most careful search. Iselin (1908) obtained violent tetany from parathyroidectomy (with preservation of the thyroid) in young rats, although in older rats often it did not occur and then only after a longer interval and in milder form. Simpson (1911 and 1913) also found variability in reaction apparently dependent on age. Thompson and Leighton (1908) found, following the gradual destruction of the parathyroids in the dog, a train of symptoms different from those caused by excision of the glands. After ligation of all parathyroid tissue the dog passes practically without symptoms the time limits of tetanic death that occurs after excision of the glandules; gradually, however, chronic symptoms trophic in nature arise, consisting of progressive loss of weight and strength, greatly diminished resistance to infection, and a final stuperous condition ending in death without tetany.

MacCallum (1911 and 1912) and MacCallum and Vogel (1913) by cross-circulation experiments have shown that the hyperexcitability of the nervous system is peripheral and that it is dependent on some change in the character of the blood; they believe that the blood of an animal in tetany contains something that renders the peripheral nerve ganglion and the nerve endings hypersensitive and that the spasm of the muscles comes only when the ganglion cells send out abnormally violent impulses to abnormally sensitive nerve-endings. MacCallum and Vogel (1913) showed that if the blood from an animal with tetany is perfused in a normal leg the excitability to the nerves rises to a characteristically high level and that the addition of parathyroid extract to the blood has little or no effect in lowering this excitability. Parathyroid extract when injected into the circulation of an animal in tetany, fails to reduce markedly or permanently the excitability of the nerves, although it seems to affect the more sensitive ganglion cells, thus cutting off excessive impulses to the periphery; although the nerves remain hyperexcitable, tetany is usually much diminished or entirely abolished, an action analogous to that of ether. Direct analysis of the blood shows that the blood of an animal in tetany, compared with the normal blood, is very poor in calcium; adminis-

tration of parathyroid does not increase the calcium content. However, blood transfusion was found by Jacobson (1912) to have no immediate or marked action on the course of the tetany. Mustard (1911) showed that parathyroid tetany is not affected by the removal of the cerebral mortor cortex or by rendering the limb aspastic through section of its afferent nerves and concluded that apparently the tetany depends not only on a local increase of motor excitability in the spinal cord, but also on the nervous connections with some region of the encephalon below the cerebral cortex. Carlson and Jacobson (1911) found that transsection of the cord stops parathyroid tetany, but not the tetany produced by ammonia poisoning when the latter is severe. Carlson (1912 and 1913) showed that in parathyroid tetany in cats and dogs there are no spasms, contractures, or other evidences of hyperexcitability or tetany of the neuromuscular mechanisms of the digestive tract; even in very severe tetany the movements of the stomach and intestine may be normal; the variation from normal is depression or paralysis; the gastric and pancreatic digestion appear normal but retarded and there is an absence of hunger. Keeton (1914) showed a depression of both total and free acid.

Halstead, in 1912, reported an experiment on a dog which lived fifteen months after complete thyroparathyroidectomy and transplantation of two of the parathyroids with a slice of the thyroid into the rectus muscle; the transplant was removed after a year and found to be mostly thyroid tissue with a trace of parathyroid tissue; the dog survived three months longer, finally dying of thyroparathyroid deficiency.

Morel and Rathery (1912) found in the liver following parathyroidectomy what they considered definite lesions that paralleled the intensity of the postoperative symptoms. Stoland (1914) obtained somewhat similar results. Boldyreff (1913) found that the body temperature of warm blooded animals is lowered by complete thyroparathyroidectomy and that by artificial heat it is possible to bring out typical tetanic attacks which in turn are relieved by cooling the animals.

Vassale, as early as 1898, showed that tetany after parathyroidectomy is intensified during pregnancy; this work was later confirmed from his laboratory by Massaglia (1913). In

1904 Vassale reported his results on the feeding of parathyroid extract in eclampsia. Werelius (1913) likewise showed that thyroparathyroidectomized dogs seemingly go into convulsions earlier in the later stages of pregnancy and die sooner than non-pregnant dogs and concluded therefore that probably fetal parathyroids do not compensate for the absence of the mother's glands. Carlson (1912) found in the dog but not in the cat that late pregnancy accelerates and intensifies parathyroid tetany in the majority of cases.

The experiments of Hoskins and Wheelon (1914) indicate that parathyroid destruction results in an increase of the vasomotor irritability, evidenced by reaction to nicotin, epinephrin, and pituitrin, but that there is no strict parallelism between the external symptoms of parathyroid deficiency and the degree of vasomotor irritability.

Simpson and Rasmussen (1914) at first believed that when animals are in pronounced parathyroid tetany, the coagulation time of the blood is prolonged; in their later work (1916), however, they could find no consistent effect.

From the experiments of Jackson (1916) it appears that the parathyroids continue to grow in young rats even when they are held at maintenance by underfeeding. Excessive meat diet, however, was shown by Tanberg (1916) not to cause hypertrophy of the parathyroids; he found no parathyroid hypertrophy following thyroidectomy nor any change in the structure of the former. Kojima (1917) could find no alteration in the pancreas as a result of parathyroidectomy, thus controverting the observations of Stoland (1914); Kojima likewise could produce no alterations in the islands of Langerhans by parathyroid feeding and he found no demonstrable change in the remaining parathyroid tissue as a result of partial parathyroidectomy.

Paton, Findlay and Watson (1917), as a result of their studies, conclude that the nervous symptoms following parathyroidectomy are due to the condition of the central nervous system; that the cerebral hemispheres are not directly involved in the production of spasticity, tremors, and jerkings, and that they may develop independently of the cerebellum, but its integrity is essential for a sustained spastic tone; that the integrity of the spinal cord is not essential since tetany persists after

section of the spinal neurones; that efferent neurones are the structures primarily implicated and that in advanced cases disturbed equilibrium suggests the involvement of the cerebellum. They do not believe that the increased electrical excitability can be taken as a measure of the severity of the condition and deny that the parathyroids exercise a direct controlling influence on the central nervous system. The relationship which Paton and Findlay point out between the symptoms of parathyroid tetany and guanidin poisoning will be considered later.

Honeyman (1919) controverted Uhlenhuth's (1918) hypothesis, that the thymus produces substances of a toxic nature in the blood which are normally antagonized by the parathyroids, by showing that extirpation of the thymus and of the parathyroids in the guinea pig does not modify in any way the onset of symptoms of *tetania parathyreopriva* and that it appears unlikely that the thymus secretes or contains any substance capable of producing tetany.

Houssay (1919) could find no constant reaction of voluntary muscle tissue produced by the action of blood serum from dogs in tetany different from that of normal dogs, thus confirming the observations of Wishart (1916).

In 1906 MacCallum presented an excellent anatomic description of the four parathyroid glands in man. He showed that they are located in the fatty areolar tissue, distinct from the intrinsic capsule of the thyroid. Aside from this, however, they have no very constant position and may be either high or low, internal or external, separated or more or less grouped, but usually they have a fairly close relationship to the four principal thyroid arteries; in consequence their blood supply may be decreased or cut off by ligation of these vessels. Halsted and Evans (1907) made very careful studies of the blood supply by the injection method and showed that the parathyroid glands in man are always supplied by definite parathyroid arteries which enter them at the hilus. The parathyroid arteries, superior and inferior, usually arise from the inferior thyroid, but frequently from anastomosing channels between the superior and inferior thyroid vessels. The excellent drawings represent not only the common types of vessels, but also the more infrequent types. They found little, if indeed any, direct vascular connec-

tion between the parathyroid gland and the connective tissue enveloping the thyroid. Iversen (1912) found two parathyroid glands on either side in 81 per cent of subjects studied; in 9 per cent there were three parathyroids, and in a few cases five. On an average they measure 6 by 4 by 2 mm. and are situated on the posterior border of the thyroid body at its inferior pole, in connection with the branches of the inferior thyroid artery and the recurrent laryngeal nerve.

Rhinehart (1912) has shown that both the thyroid and parathyroid glands are supplied entirely by nonmedulated nerves, apparently of the same origin.

MacCallum (1905), Erdheim (1906) and Kocher (1906) reviewed the occurrence of tetany in man after parathyroidectomy; the latter had nine patients who developed tetany out of forty who had total thyroidectomies; similar studies were made by Mayo and McGrath (1911), and by Pool (1915). von Eiselsberg (1915) reported fourteen mild cases of tetany, three severe cases, and three deaths from tetany in a series of 1300 operations for goiter. These authors recognized that tetany and *cachexia thyreopriva* are distinct and separate conditions. Halsted (1907) reviewed the subject of *parathyreopriva* together with the results of parathyroid transplantation; the reports on the results obtained proved disappointing.

II. PATHOLOGY

Vassale and Donazzio (1897) showed that degeneration occurs in certain tracts of the spinal cord following parathyroidectomy, but less frequently after thyroparathyroidectomy.

MacCallum and Fabyan (1907) reported a case of quite typical myxedema in which the thyroid was absent on postmortem examination but two apparently normal parathyroids were present and the hypophysis was hypertrophic. In consequence, they believed this case offered irrefragable proof of the complete independence of the thyroid and the parathyroid glands. Yanase (1907) found hemorrhage in the parathyroid glands in a high percentage of children who died from tetany, thus leading Escherich (1909) and others to lay great stress on the parathyroid origin of infantile tetany. Thompson and Harris (1908) in the study of the parathyroids in 250 routine

necropsies, found no definite lesions in the parathyroid. Bliss (1911) studied the parathyroids in twenty-two necropsies and found three instances of hemorrhage in the glands, one in a patient with bronchopneumonia; one in a patient with bronchopneumonia and pertussis, and one in a patient with bronchopneumonia with rachitis and syphilis. In two patients who died of infantile tetany he found no hemorrhage into the glands, although in one there was an increase in vascular and in connective tissue and he concluded therefore that there is no close connection between hemorrhagic lesions of the parathyroid glands and infantile tetany. Proescher and Diller (1912) report a case of tetany in which the necropsy showed hemorrhage into the parathyroids; in addition, however, there were an external fibrous pachymeningitis, chronic leptomeningitis, edema and hyperemia of the brain and spinal cord, as well as other pathologic lesions of the plexus, spleen, intestines, kidney and liver. As yet the evidence of a pathologic condition of the parathyroids in infantile tetany and in other types of tetany, except that following thyroidectomy, is meager and questionable and does not appear to justify the positive statements concerning the cause of infantile tetany which are frequently found in periodic literature.

Marine (1913), from his experiments on fowls, believed that their parathyroids are more susceptible to overgrowth than those of mammals. McCarrison (1914) states that of the offspring of goitrous parents a small percentage are born cretins, 63 per cent with congenital goiter, 32 per cent with congenital parathyroid disease, and 33 per cent with normal thyroid and parathyroid glands. In 1915 Harbitz reviewed the literature on parathyroid tumors and reported two new cases, the one an adenoma of the parathyroid with osteomalacia, and the other an adenoma of the parathyroid with *paralysis agitans*. The following year Wood reported several cases of parathyroid tumors of the tongue, and Schlagenhaufer two cases of tumor of the parathyroids.

Jackson (1916) found in experiments on young rats held at maintenance by underfeeding that, although growth of the parathyroids persisted, there was more or less nuclear and cytoplasmic degeneration. In confirmation of previous experiments,

Tanberg (1916) found that no structural change occurs in the parathyroids as a result of thyroidectomy. Allen (1920) noted marked hypertrophy of the parathyroids but no histologic changes following removal of the thyroid in the *Bufo larvae*.

III. CHEMISTRY

Gley (1891) and Laulanié (1891-1894) showed that the urine of completely thyroidectomized dogs is more toxic than that of normal dogs. Marfori (1893) found that intravenous injections of carbonate, lactate and tartrate of ammonia in dogs causes muscle twitchings and even tetany and opisthotonus together with irregular respiration and vomiting.

Sabbatani (1901) stimulated an interest in the relation of calcium to tetany by his observations that a solution of calcium applied to the brain diminishes its irritability to electric stimulation, but that substances that cause a precipitation of calcium such as oxalates or citrates cause an increased irritability. Stoeltzner (1906) advanced the hypothesis that tetany is due to an accumulation of calcium in the blood; his theories, however, have received no further confirmation except from the work of von Cybulski (1906) and of Schabad (1910), both of whom found slight calcium retention during active tetany and a greater retention during convalescence. Quest (1905), Cohn (1907), and Aschenheim (1910) analyzed the brains of children who died of tetany, and although there was a considerable diminution of the calcium content in some there was little regularity in the results.

Estes and Cecil (1907) reviewed the question of the iodin content of the parathyroids; they state that Gley (1897) showed the presence of iodin in the parathyroids and they point out that Mendel (1900) is widely misquoted as having found large quantities of iodin in these glands. Their own experiments confirmed the findings of Chenu and Morel (1905), that the parathyroids contain practically no iodin. Estes and Cecil maintain, therefore, that iodin as a constituent of the parathyroids may, generally speaking, be neglected and that if iodin is present it is in such minute quantities as to be of no functional significance.

In 1903 MacCallum attempted to make a specific cytolitic serum for the treatment of parathyroid tetany, but with no success. Parhon and Urechie (1907) and MacCallum and Voegtlin (1908) discovered practically simultaneously the palliative effect of calcium in parathyroid tetany. MacCallum and Voegtlin formulated the hypothesis that the parathyroids control in some way calcium metabolism and showed that a 5 per cent solution of calcium acetate or lactate either intravenously or by mouth controls parathyroid tetany; magnesium salts have a somewhat similar effect, but they are not so satisfactory on account of their toxic action; on the other hand, injections of potassium salts intensify all the symptoms which in turn can be ameliorated by the injection of calcium. In 1909 MacCallum and Voegtlin showed that there is a marked reduction in the calcium content of the tissues, especially of the blood and brain, during tetany, accompanied by an increased output of calcium and nitrogen, and that there is an increased output of ammonia with an increased ammonia ratio and an increase in the amount of ammonia in the blood. They confirmed their earlier work concerning the relief of tetany in animals and in man by the administration of calcium.

Carlson and Jacobson (1910) called attention to the striking similarity, if not identity, in the tetany symptoms of thyroparathyroidectomy, the symptoms of ammonia poisoning, and the symptoms of poisoning in Eck fistula dogs if fed on meat. They found that the ammonia-destroying power of the livers of tetanic animals was markedly depressed, leading to an increased percentage of ammonia in the blood. On further experimentation, however, they found (1911) the ammonia content of the blood to be normal and that intravenous injections of calcium did not alter the ammonia concentration, but did control the tetany; calcium salts had a less inhibitory action in ammonia poisoning than in parathyroid tetany. They found that calcium and strontium salts control equally well parathyroid tetany; that they act rapidly in the earlier and milder forms, but in the later stages there is little beneficial action; that the tetany, unless extreme, is suppressed also by an extract of hypophysis and by a hypertonic solution of sugar. Edmunds (1911) confirmed the value of calcium in controlling parathyroid tetany

but found no similar effect from pituitary extract; he obtained (1913) the best results from feeding milk to which calcium lactate had been added; and as a result of sugar tolerance tests Edmunds concluded that the thyroid gland hinders the assimilation of sugar and that the parathyroids favor it. MacCallum and Vogel (1913) confirmed, by direct analysis, that the blood of an animal in tetany, compared with that of a normal animal, is very poor in calcium; the administration of parathyroid extract did not increase the calcium. Marine (1913) believed that the parathyroids of birds are more susceptible to overgrowth than those of mammals and that calcium prevents such overgrowth. The cross-circulation experiments of MacCallum (1911) and of MacCallum and Vogel (1913) support the theory that the hyperexcitability of the nervous system is peripheral and is dependent upon some change in the character of the blood. MacCallum, Lambert and Vogel (1914), by removing calcium by dialysis from normal blood and passing this blood through an isolated extremity, produced an extreme hyperexcitability of the nerves quite like that observed in tetany; two animals with parathyroid tetany were bled and in one the blood was replaced by normal blood and in the other with dialyzed blood poor in calcium (otherwise normal); the symptoms were relieved in the first but not in the second animal. Marine (1914) also showed that calcium salts have a striking palliative effect on parathyroid tetany and suggested their use as a biologic test for the determination of the presence of accessory parathyroid tissue: in the absence of all parathyroid tissue calcium salts will not save the animal's life, while in the presence of active parathyroid tissue calcium is very effective. Howland and Marriott (1918), using their micromethod (1917), found that the calcium in the serum of normal persons varies between 9.2 mg. and 11.3 mg. or about 10 mg. for each 100 c.c. of serum. In the serum of patients with rickets they found from 7.9 mg. to 10.9 mg.; a majority showed a reduction of only 1 mg. (10 per cent) and a few were reduced by 2 mg. (20 per cent). In contrast, the calcium in the serum of patients in tetany of idiopathic origin was reduced from 3.5 mg. to 7.3 mg. or an average of 5.6 mg. for each 100 c.c.; of the eighteen patients studied all but one had less than 7 mg., more than a 40 per cent reduction.

They conclude that convulsions may be expected when the calcium content of the serum becomes less than 7.0 mg. for each 100 c.c., and they consider the results strikingly similar to those found by MacCallum and Vogel (1913) after parathyroidectomy; Binger (1917) also obtained similar results. However, Howland and Marriott do not consider the reduction of calcium as the only factor in tetany because Binger found the calcium much reduced in certain cases of nephritis and because they also observed three cases of tetany following the intravenous injection of sodium bicarbonate for the acidosis of diarrhea. They found no apparent alteration in tetany in the phosphate or magnesium content of the blood.

Greenwald (1911) made a detailed study of the urine in six dogs before and after parathyroidectomy and found that the excretion of nitrogen is increased only after the appearance of tetany; the ratio of urea nitrogen to total nitrogen is decreased; the proportion of the total urinary nitrogen excreted in the form of ammonia is increased very little if at all; the concentration of ammonia in the blood is not increased; the excretion of creatinin remains about the same or is slightly diminished; the creatin, purin nitrogen and undetermined nitrogen are increased; the excretion of sulfur, especialy inorganic sulfate and neutral sulfur, is increased, and finally phosphorus is retained in the first few days and later excreted in increased amounts. In later experiments Greenwald (1913) found a marked diminution in the excretion of phosphorus in urine after parathyroidectomy, resulting in its retention in the body, but no retention of sodium or potassium. He also showed (1916) that inosinic acid is not the toxic agent in parathyroid tetany.

Hunter (1914) found in sheep following removal first of the thyroid and later of the parathyroids that during a fast more nitrogen and more purin derivatives are excreted than normal; that the urine is alkaline and that the excretion of creatin is in excess of the excretion of creatinin and that there is a high sugar tolerance; the animals succumbed to inanition. Urechia (1914) did not find a constant increase in nitrogen in the blood and urine of animals in tetany.

Underhill and Blatherwick (1914) found that in tetany, following thyroparathyroidectomy, glycogen entirely disappears

from the liver and that the blood sugar content is markedly lowered.

Koch (1912 and 1913) reported finding methyl guanidin in the urine of dogs after parathyroidectomy; he also showed that digested proteins taken into the body have very toxic effects; he suggested that the parathyroid secretion is concerned with the anabolic process closely related to the building of nucleins. In later experiments, however, Koch (1915) isolated from the urine of parathyroidectomized animals methylcyanamid and trimethylamin and concluded that somewhere in the body methylcyanamid is generated and after parathyroidectomy accumulates to toxic quantities and causes death. Paton, Findlay and Burns (1915) showed that the injection of guanidin or methylguanidin apparently produces all of the characteristic symptoms of tetany in rats.

Wilson, Stearns and Janney (1915) showed that the intravenous injection of M/3.7 or M/7 hydrochloric acid solution relieves parathyroid tetany in dogs; the hydrochloric acid was less harmful if introduced in salt solution instead of water; the usual dose was 50 to 90 c.c. of M/3.7 hydrochloric acid in M/7 sodium chlorid solution. Sodium chlorid solution (M/7) if given without hydrochloric acid, produced no effect while some of the dogs were benefited by the oral administration of hydrochloric acid. Wilson, Stearns and Janney's conclusion that the relief of parathyroid tetany by the administration of acids suggests the possibility of a beneficial action due to a variation in the acid-base equilibrium in the body and offers a new point of view for the study of this and allied conditions.

Wilson, Stearns and Thurlow (1915) studied the values of the dissociation constant (Barcroft's K) of oxyhemoglobin, the alveolar air carbon dioxid tension, and the hydrogen-ion concentration of the blood of dogs after parathyroidectomy. They found that a condition of alkalosis may develop which is neutralized by acid products formed by muscular activity incident to tetany. A condition of acidosis may result after periods of acute tetany. Periodic variations in the "nonvolatile" acid-base equilibrium seem to accompany the periodic attacks. The condition of acidosis resulting from acute tetany or the injection of acid is associated with the relief from tetany. Calcium salts,

when injected into animals in tetany, lower the value of the dissociation constant of oxyhemoglobin and the alveolar carbon dioxid tension which is an effect similar to that brought about by the introduction of acids. The second paper by Wilson, Stearns and Janney (1915) shows that after parathyroidectomy in dogs there is usually a sudden diminution in the excretion of acids and ammonia and a decrease in the ammonia ratio and the hydrogen-ion concentration of the urine. With the development of tetany, the elimination of acids and ammonia increases and the values of the ammonia ratio and the hydrogen-ion concentration of the urine are increased. The variations may indicate that a condition of alkalosis results after parathyroidectomy but is neutralized by the tetany which develops. After acute or chronic tetany, an acidosis may occur.

Peterson, Jobling and Eggstein (1916) found that the onset of tetany following parathyroidectomy bears no constant relation to the ferment-anti-ferment balance of the serum.

Binger (1917) found that a solution of orthophosphoric acid or its sodium salts injected intravenously in dogs causes a diminution in the amount of calcium in the serum. The degree of diminution in the calcium content of the serum depends on the amount of phosphates introduced. When the phosphate solution is injected in amounts equivalent to 150 mg. phosphorus to the kilogram the serum calcium drops from its normal level of 10 mg. for each 100 c.c. to approximately 6 mg. At this level a condition of tetany supervenes, provided the neutral or alkaline salts have been injected. With the injection of acid phosphate solution, the calcium drop occurs unaccompanied by tetany. The phosphate solution becomes toxic when injected in the doses noted above in the neighborhood of pH 6.0. Therefore, Binger concluded that orthophosphates of sodium, if injected in sufficient quantity and at the right reaction, are toxic and produce tetany in dogs; that the toxicity is due to a specific action of the phosphate ions in combination with the reaction of the solution in which they exist; and that the tetanic condition caused by phosphates is intimately associated with a decrease in calcium in the serum, but it is not dependent on this alone since a drop in calcium may occur without the appearance of tetany.

McCann (1918) found that after parathyroidectomy there is a marked increase in the carbon dioxid combining power of the blood plasma, coincident with the development of tetany. Following an operation on the stomach which excludes the acid secreted from the duodenum tetany develops and is accompanied by an increase in the carbon dioxid combining power of the plasma similar to that of parathyroid tetany. Brown, MacLachlan and Simpson (1920) report constitutional reactions following the intravenous injection of 1.25 gm. calcium lactate; the reaction varies between slight drowsiness and collapse and lasts from one to seven hours.

Grant and Goldman (1920) by forced breathing for from fifteen to sixty minutes, produced tetany in themselves; the symptoms included carpopedal spasm, Chvostek's, Trousseau's and Erb's signs, and in one instance, a tetanic convulsion. As a result of the fall of alveolar carbon dioxid tension produced by over-ventilation there is a reduction in the hydrogen-ion concentration of the blood, a reduction of the carbon dioxid capacity of the plasma, a change in the reaction of the urine to the alkaline side, a decreased excretion of ammonia, and a slight increase in the calcium content of the serum. Grant and Goldman believe that the underlying factor in the tetany of forced respiration is the alkalosis.

MacCallum, Lintz, Vermilye, Leggett and Boas (1920) report a peculiar condition accompanied by convulsions occurring whenever the pylorus is obstructed so that the acid gastric juice is all removed and no chlorids are given in the food; they point out, however, that the condition is not the same as that produced by parathyroidectomy. The muscular rigidity with vibrating chronic twitchings and extreme tachypnea are lacking; the animals are apathetic until seized by violent general convulsion followed by a kind of coma; electrical excitability increases, but not as in parathyroid tetany. The introduction of the chlorin ion as hydrochloric acid has no benefit, whereas the administration of sodium chlorid continuously prevents the development of changes in the electrical excitability and disturbances of the alkali reserves. Calcium lactate, although it exerts a temporary effect, has no controlling influence as in parathyroid tetany. Symptoms similar to those caused by the removal of chlorids

are produced by the injection of sodium carbonate or sodium bicarbonate solution.

Following the finding of methyl guanidin in the urine by Koch (1912) and the discovery by Paton, Findlay and Burns (1915) that both guanidin and methyl-guandin cause characteristic symptoms of tetany in rats, Paton and Findlay with Watson, Burns, Sharpe and Wishart presented a series of papers in 1916 which aimed to show the etiology of tetany and its relationship to guanidin and methyl-guanidin intoxication. Their main conclusions were that the symptoms of tetany are due to some change in the nerve cells of the cord, and that the increased excitability of the neuro-myon is caused by an action on the nerve endings. As a result of an extensive comparison of the symptomatology of idiopathic tetany, postoperative tetany in man, *tetania parathyrcopriva*, and guanidin poisoning, they concluded that all these conditions are of the same nature and that the first three are due to the development of guanidin in the body as the result of some interference with the action of the parathyroids which normally control guanidin metabolism and by so doing probably influence the tone of muscles. They believe, therefore, that in man there is a close association between idiopathic tetany and the tetany following removal of the parathyroids and that in both the symptoms are due to an increase of guanidin in the body. Paton and Findlay found a marked increase in the amount of guanidin and methyl-guanidin in the blood and urine of dogs after the removal of the parathyroids and in the urine of children suffering from idiopathic tetany. They do not believe the symptoms of tetany to be due primarily to a decrease in any constituent of the blood such as calcium ions nor to an increase in ammonia or xanthin or B-iminazolyl-ethylamin in the blood. They do not consider that an increased electrical excitability can be taken as a measure of the severity of the condition. Although they believe their experiments show that *tetania parathyrcopriva* and idiopathic tetany are identical they admit that the histologic evidence for their implication in the latter condition is not conclusive. Burns and Watson (1918) further showed that guanidin intoxication and parathyroid tetany produce an interference with the vago-cardiac inhibition which is removed by salts of calcium.

Guanidin has first a nicotin action, poisoning the synapsis; after more extensive application it has an atropin action, causing paralysis of the terminal ganglia in the heart of the frog. Guanidin does not paralyze the sympathetic (accelerator) mechanism in the heart. Henderson (1918) found that after parathyroidectomy there is a fall in the total guanidin and in the free guanidin of muscle and a rise in the creatin both absolutely and in relation to the total nitrogen. The fall in the free guanidin-nitrogen corresponds fairly closely to the rise in the creatin nitrogen and may indicate a synthesis of part of this nitrogen. The fall in the total guanidin is far in excess of the nitrogen in free guanidin and in creatin and must indicate either a liberation of guanidin from the muscle or a failure in the power of the muscle to take up guanidin formed elsewhere, either of which conditions may be correlated with the increase in the blood and the urine already demonstrated by Burns and Sharp (1916).

Pavloff (1913) reported in the publications of the University of Cracow an article on the exchange of gases and metabolism in different diets after removal of the parathyroid glands; this publication has been inaccessible. Löffler (1919) reports no change in the basal metabolism in a case of *tetania parathyreopriva*.

IV. IDIOPATHIC TETANY

Hertz (1913) gives a case report describing symptoms which, he believes, might be attributable to idiopathic parathyroid insufficiency; marked improvement followed the administration of Armour's ox parathyroid. In view of the general experience of negative results from parathyroid medication and because of the doubtful evidence in this patient of parathyroid disease too much stress should not be laid on this isolated report. Morris (1915) reported the case of a patient in Halsted's clinic who had taken 3 gr. of powdered parathyroid extract (Armour) daily for eighteen months; when the patient was first seen he was in a deplorable mental condition, nervous and helpless, urinating and defecating in bed. A very prompt improvement occurred when use of the extract was discontinued.

Mann and Thiemich simultaneously (1900) reported cathodal hyperexcitability in infantile tetany. Wilcox (1911) studied the electrical hyperirritability in its relation to the parathyroid glands and found it increased and therefore considered it a diagnostic help in latent or developing tetany. Holmes (1916) reviewed the evidence of the reliability of the electrical diagnosis of tetany and concluded that the appearance of cathodal opening contractions under 5 ma. is pathognomic in children less than five years of age. Howland and Marriott (1918) found a low calcium content with unmistakable symptoms of tetany, thus confirming the specificity of the cathodal hyperexcitability as a diagnostic method. The anodal hyperexcitability of von Pirquet is less positive, although usually accompanied by a slight decrease of calcium, but it may occur in perfectly normal infants as shown by Holmes (1916).

Falta (1915) defines tetany as an "abnormally increased condition of excitement of the nervous system, that is demonstrable in a heightened excitability of the motor, sensible, sensory and vegetative nerves, and under certain circumstances, in paresthesias, and bilateral intermittent, for the most part painful spasms, with intact consciousness, or becomes manifest through phenomena of irritation on the part of the vegetative nerves; to the picture of tetany belong also trophic and certain metabolic disturbances; the manifestations are the result of an insufficiency of the parathyroid glands."

An excellent review is given by Falta of the symptomatology and diagnosis, especially the electrical reactions, of the various forms of tetany in infants, children, and adults, including gastro-intestinal and occupational tetany and tetany during pregnancy and lactation. All of these conditions he attributes to insufficiency of the parathyroid glands and ably presents the few facts and many arguments in favor of this view. In the preceding pages we have cited the experimental evidence, but we refer the reader to Falta for a presentation of the clinical and theoretic considerations with the literature supporting the hypothesis of an underlying parathyroid insufficiency in these various tetanic conditions.

V. CLINICAL SYMPTOMS AND TREATMENT OF PARATHYROID TETANY

Clinically parathyroid tetany may occur after operations on the thyroid gland, due either to the complete removal of all or of the greater part of the parathyroid tissue or to an injury of the parathyroids or their blood supply by the operative procedures. The onset of symptoms is usually two to three days after the operation but it may be sooner or later. There may be prodromal symptoms such as headache and general weakness, accompanied by radiating pains downs the extremities, especially the upper, and chronic twitchings. The diagnosis is usually not evident until definite spasms occur; they are almost always symmetrical and bilateral. As a rule the hand is most often affected and the patient presents a characteristic contraction spoken of as the "accouchers" hand, which consists in flexion of the fingers at the metacarpal phalangeal joint with adduction of the thumb; sometimes the thumb is completely adducted and tightly clasped by the flexed second and third fingers together with flexion of the wrist and less often flexion of the forearm. Rarely are there intercurrent contractures of the muscles of the face or trunk. Erb (1874) pointed out that in tetany (not only parathyroid tetany but other forms as well) the electric excitability of the motor nerves is increased; Trousseau (1851) showed that during intervals between spasms attacks could be brought on by compression of the main nerve trunk; Chvostek (1907) found that the facial muscles can be made to twitch by tapping along the course of the facial nerve; Pool (1907) and Schlesinger (1910) demonstrated that contractures can be elicited in the lower extremities by putting the sciatic nerve on the stretch by extreme flexion of the thigh and leg on the trunk.

The results obtained from treatment with parathyroid extract or by parathyroid transplantation have on the whole proved disappointing, and the best clinical results have been obtained from the administration of calcium. In parathyroid tetany following the modern operations on the thyroid and when in all probability the parathyroid tissue is not entirely destroyed, the spasms can usually be controlled promptly by the administration either orally or intravenously of calcium lactate. As soon as the tetany becomes evident, 40 to 60 gr. of calcium

lactate should be given every two to four hours until the tetany is controlled, when smaller doses will usually be found sufficient. With some patients the calcium may be omitted after a few days, while with others it is necessary to continue its administration either intermittently or regularly for a prolonged period.

VI. SUMMARY

Our knowledge regarding the function of the parathyroid glands may be summarized as follows:

1. In many species of animals the removal of all parathyroid tissue causes death from tetany, within a few days in most instances; the herbivora are less liable to tetany than the carnivora; age appears to have a definite influence on its frequency and severity as probably also do pregnancy and lactation. There is some evidence of late trophic changes in those animals that survive parathyroidectomy and have few or no tetanic symptoms.

2. The preservation of very small amounts of parathyroid tissue prevents or renders the tetany less intense.

3. From the evidence at hand, the function of the parathyroids appears to be distinct and separate from that of the thyroid; their only relationship seems to be anatomic and not functional; the parathyroids are not embryonic thyroid tissue.

4. There is evidence that their function is in some way concerned with calcium or guanidin metabolism or with both; they may play some part in the regulation or maintenance of the acid-base equilibrium in the body.

5. The experimental evidence pointing to the parathyroids as the primary cause of idiopathic tetany, unassociated with operative procedures on the thyroid, is very limited.

6. The only definite clinical entity which has yet been proved experimentally to be of parathyroid origin is the tetany occasionally seen after operations on the thyroid. In these conditions calcium in large doses usually ameliorates the symptoms. The reports as to the benefit obtained by parathyroid transplantation or feeding are not convincing.

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EPILEPSY SUGGESTIVE OF ENDOCRINE RELATIONSHIP*

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The idea prevails with some of the laity that epilepsy is a surgical disease, and some members of the medical profession, possibly influenced by past literature, and at times discouraged with the rather slow results in its treatment, think possibly that surgery may offer more prompt relief. It is for this reason that every surgeon is approached by this class of patients. This is my excuse, if one is necessary, for presenting the subject before this society.

Epilepsy has long been divided into the symptomatic and idiopathic types. The symptomatic group comprises those in which a definite etiological basis is apparent, and included in this group are brain tumors and certain traumatic head conditions from which surgical relief is possible. The idiopathic group has been termed more appropriately "the epilepsies." Instead of "idiopathic," probably the word "unclassified," as suggested by Munson, would be more fitting. This unclassified group has at least a metabolic subdivision, and some workers think that the group in its entirety is dependent upon disturbed metabolism. In a large number of autopsies performed by Munson the number of cases in which pathological lesions were found was almost nil. Pathological physiology seems to offer the more promising field for eventually solving the problem.

The disease manifests itself through the nervous system, and it is generally believed that it is one resulting from diverse stimuli. Munson believes that its origin is in the central nervous system, and that a reaction of the nervous system may be produced either by a chemical change in the cell itself, or by the action of the stimuli reaching the nerve cells. The reaction produced in either case is similar. I do not believe that it has its origin in the central nervous system *per se*. It is more probable that it is the result of the action of external forces which tem-

* Read before the Detroit Surgical Society, February 11th, 1921.

porarily overcome the equilibrium of the nerve cells, though acting on cells that are possibly hypersensitive to such stimuli.

The trend of recent epileptologic research has been directed in large part to the gastro-intestinal tract and the glands of internal secretion. With regard to the gastro-intestinal tract, some American surgeons have done an enormous amount of work to show that the intestinal stasis in epileptics has been due to peritoneal bands, kinks and adhesions. By the surgical correction of these conditions they have attempted to cure or secure amelioration of the disease, with results which are quite doubtful. Caro, a worker in the Munson Hospital of Massachusetts, has shown from the study of a large number of autopsies, that intestinal kinks, adhesions and peritoneal bands are no more frequent in epileptics than non-epileptics. This finding is rather important from the standpoint of surgical attack of the disease, and it seems that we shall have to look elsewhere for means of combating the cause of epilepsy. Of course, we all know that constipation is the constant complaint of the epileptic, and the recent literature shows quite plainly that the dominant factor in the pathogenesis of the convulsions is impairment of metabolism, and that the spasmogenic agent is in the blood stream. This condition may well be brought about by intestinal stastis, but it seems to have been strictly proven that the causes of intestinal stasis in the epileptic do not differ at all from the causes in the non-epileptic. Bisgard and Novig have recently adduced some experimental evidence of disturbed metabolism, in that they regularly found an increased ammonia content in the blood of epileptics before an attack or its "psychic equivalent." Low values were obtained after the attack.

As the endocrine glands preside over our metabolic processes, and as epilepsy may be due to an impairment of metabolism, may they not, in many cases, play an important role in its production? With reference to this possibility, I wish to present eleven case histories as evidence pointing to the endocrine system taking a prominent part in some cases of this disease. It is interesting to note that these were consecutive cases. All were true epilepsies. In the histories I shall give only such data as may have bearing on the subject.

GROUP I. ONSET AT PUBERTY; SEIZURES AT TIME OF PERIODS.

Case 1—(Free during pregnancy). Female, married, age 27. The menstrual history is negative except that she flows scantily. Menstruation began at fifteen. Seizures commenced soon after the first menstrual period. She has had a seizure just prior to nearly every period since. The only period she has been free from seizures for any length of time was during her first pregnancy and for six months following; and during her second pregnancy, and for fourteen months following.

Case 2—Female, single, age 39, of nervous temperament. She had a few attacks of convulsions during childhood following an illness that was diagnosed as meningitis. She had whooping cough at three years of age. From her fourteenth year (puberty) until her nineteenth year she had a few petit mal attacks. Since then she has had grand mal seizures, which have been milder and less frequent the past year. They occur just prior to or just after menstruation.

Case 3—(Free after marriage). Female, single, age 23. Menstruation was established at thirteen; it is regular, but always scanty. At eight years of age she had an indefinite seizure. (She does not know about whooping cough.) No other attack was experienced until she was fifteen, which attack just preceded the first menstrual period. Since then she has had an attack with nearly every period, usually just before, but a few midway between periods. This patient was married two years ago and has not had an attack since.

Case 4—Female, single, age 38, of nervous temperament. Her flow is scanty. Menstruation began at seventeen. She has had seizures since she was eighteen. A few attacks have been experienced between periods, but eight of ten occur at menstrual time, usually just before the onset of flow.

Case 5—Female, single, age 26, of nervous temperament. Menstruation began at fifteen. Her first seizure was experienced soon after the first menstrual period. Seizures come at two to six months' intervals, always associated with the periods, and usually on the last day.

GROUP II. ONSET AT PUBERTY—TIME OF SEIZURES NOT KNOWN.

Case 6—(Termination at menopause). Married woman, age 64. Had epileptic seizures from her fifteenth to her fortieth year. Menstruation began at fifteen and the menopause appeared at forty. Seizures occurred only during the years of activity of the sex glands.

Case 7—Female, married, age 28. She has had two children. Her first seizure occurred at fifteen. Menstruation began at fifteen. Her second seizure occurred during the second pregnancy. Third and fourth attacks have recently been experienced. The records do not state the relation of the attacks to menstruation.

GROUP III. ONSET DURING PREGNANCY.

Case 8—Female, married, age 27, of nervous temperament. Her menstrual history was normal. She has one child four years old. At the time of the first seizure the patient was four and one-half months pregnant. The second occurred six weeks later, and the third four and one-half months after delivery. She nursed the baby. Since then she has had several attacks a year, and always about the time of the periods, usually just before.

Case 9—Female, married, age 34, of nervous temperament. Epileptic seizures began four years ago when she was seven months pregnant. She had one or two more during this pregnancy. Ten months after a normal labor another seizure was experienced. She has had

them ever since, usually a week after the period, on an average of one every second month. She nursed the baby and was still nursing it at the time of the first post-natal seizure.

GROUP IV. ONSET AFTER PUBERTY—SEIZURES AT TIME OF PERIODS.

Case 10—(Free during pregnancy.) Female, age 50, of nervous temperament, widow for nine years. Convulsions occurred from the first to the ninth year. At the age of nine menstruation was established, and the seizures stopped. She had whooping cough, but does not know at what age. Seizures began at eighteen. She was married at twenty and has had two children. She was free from seizures during pregnancy, and for several months afterward. Nine out of ten attacks come on the first day of the periods at intervals of one to a few months. During the past decade attacks have been more frequent. Immediately after marriage and before pregnancy the patient increased considerably in weight.

GROUP V. MALE CASE—ONSET ABOUT THE TIME OF PUBERTY.

Case 11—Male, age 17. The first attack was experienced at fifteen. He has had several seizures at varying intervals since.

In summing up these cases we find that the seizures began about the time of the establishment of menstruation in seven out of ten female cases. Of the remaining three cases, two began during pregnancy. In seven of the ten female cases the seizures occurred quite consistently about the menstrual time, usually just before. In two, the relation is not noted in the records, and in one, the attacks occurred one week after the periods. In two cases (1 and 10) the patients were free from attacks only during pregnancy and for some time following. Five had scanty menstruation. Case 3, in which the attacks ceased with the event of marriage, might suggest the possibility of a better endocrine balance, as the result of living a normal sexual life. In this class might be placed the point mentioned in Case 10, namely, considerable increase in weight after marriage and before pregnancy. I have seen other cases in which the increase in weight could not be attributed to better living habits, the sexual factor only being different. Case 6, with seizures beginning at puberty and ending at the menopause, is most interesting and suggests very strongly the metabolic influence. I know of another similar case, but it has not come under my personal observation.

In Cases 5 and 8 the patients had convulsions during childhood, and in Case 9 there was an indefinite seizure. Of these patients 5 and 8 had whooping cough during childhood, and in Case 9 this point is not known. This is very interesting in connection with the recent study of this relationship by Morse, who reports that convulsions in childhood are not likely to

eventuate in epilepsy, with the possible exception of those beginning with whooping cough.

It would seem that these points suggest strongly a connection between the disease and puberty, menstruation and pregnancy. In other words, in the majority of these cases the onset and the attacks occurred at a time when there was some radical change (puberty), adjustment or disturbance (menstruation and pregnancy), going on in the chemical laboratory of the body. With regard to the time of puberty, we all realize that this is the time of great activity of the endocrine system, as evidenced by the development of secondary sex characteristics. Also about this time we see quite frequently an enlargement of the thyroid gland in the so-called adolescent goitre. Dana states that the epileptic age is from ten to twenty, and still more definitely, from ten to fifteen. The period then of greatest endocrine activity corresponds to the period in which we see the greatest number of epileptics develop. In three-fourths of all Dana's cases the seizures began before the age of twenty.

During pregnancy as Erdheim has shown, there are definite histological changes in the hypophysis and this organ enlarges with each succeeding pregnancy. This change coincides with the clinical signs seen during pregnancy, which resemble acromegaly, manifesting themselves with such alterations as thickening of the lips or enlargement of the hands and feet. These changes are not permanent but only passing, and, therefore, might be regarded as amounting to acute acromegaly. Also, it is often stated that we have a decreased sugar tolerance during pregnancy. According to Cron, 30 to 50 per cent of pregnant women are less tolerant to glucose than non-pregnant subjects. Again, how frequently do we see the onset of goitre occurring during pregnancy, and also how frequently the further enlargement of an already existing goitre during this period. It is interesting to note that two of the three cases which did not begin at puberty began during the period of gestation.

The mental state during menstruation is most striking. We very frequently have a much changed personality, manifesting itself in melancholia, general irritability and unreasonableness. Women who ordinarily have a very fine and even disposition are very frequently emotional and cry easily. The relation of emo-

tion to epilepsy in bringing on attacks has long since been noted. At least one emotion has, in a measure, been put upon an endocrine basis, in that Cannon has presented evidence that in fear the adrenalin content of the blood is increased. In this group of ten consecutive female cases, the seizures occurred quite universally about this emotional period in seven.

The exact relationship of the endocrine glands to epilepsy, if there be any at all, is at the present time quite hazy. However, Cushing has observed from the study of a series of cases that epilepsy is a frequent accompaniment of clinical conditions in which insufficiency of the hypophyseal gland is manifestly evident. It has never been observed in hyperpituitarism. Horsely, in experimental hypophysectomies in dogs noted that the cerebral cortex was unusually excitable, and Cushing has reported that animals kept for a long time after this operation showed a tendency to epileptiform convulsions. In some cases of epilepsy the administration of hypophyseal extract has served to modify the seizures. These observations would seem to contradict some of the clinical evidence of disturbed endocrine function noted previously in regard to pregnancy. But there is no reason to assume that in every case a disturbance, if present, is in the nature of hyperactivity.

Harrower has put forward some data to show that certain cases are associated with hypothyroidism, and Sajous states that by giving small doses of thyroid he has controlled the seizures as successfully as with bromides.

There is also some evidence that hyperactivity of the adrenals is in some way related to this disease. Benedek was able to produce typical epileptic seizures in seven of nineteen patients subject to epilepsy who were given adrenalin subcutaneously. This has never been observed in other diseases, nor in normal individuals. Also typical epileptic attacks have been produced in rabbits by repeated intravenous injections of adrenalin (Tracy). Bruning has removed the left suprarenal in nine cases of epilepsy. An improvement was effected in all cases, and in two the attacks ceased entirely. However, he wishes it distinctly understood that he does not claim this to be a cure for all cases of epilepsy.

The close relation of the gonads to the other endocrine glands, especially the pituitary and the thyroid, is well known.

After a study of one hundred and fifty thousand seizures, Clark has concluded that we must look for the principle of pathogenesis in an accumulation of waste products. Probably the regulation and restriction of diet, so important in the treatment of this disease, finds its scientific explanation in the consequent lessened catabolism, there being fewer end products to be taken care of. Very little is known as yet of the metabolism in epilepsy, but with the endocrine glands recognized as the regulators of metabolism, it would seem that there is at least a fruitful field for accurate observation and investigation along these lines. Until we have more exact methods of determining histological, gross and functional pathology of these glands and, perhaps, until experimental glandular therapy has advanced further, the exact relationship will naturally remain obscure. It would be unjustifiable to draw any conclusions from so few cases as reported here, but I can see in them hints that point quite definitely to endocrine disturbance being an important factor in the causation of some cases of this disease.

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DOES THE ADMINISTRATION OF THE ANTERIOR LOBE OF THE HYPOPHYSIS TO THE TADPOLE PRODUCE AN EFFECT SIMILAR TO THAT OBTAINED FROM THYROID FEEDING?*

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In a recent paper Hoskins and Hoskins (1920)[1] have advanced evidence showing that the feeding of the anterior lobe of the pituitary gives an effect similar to, and perhaps even identical with, that which is characteristic for the administration of thyroid gland. This is the most convincing evidence which to our knowledge has been advanced in support of the hypothesis that the pituitary can act vicariously for the thyroid. Hoskins and Hoskins, in brief, showed that a preparation of the anterior lobe[2] when fed to the tadpole gave the typical responses resulting from thyroid administration, *i. e.*, cutaneous and mouth changes, leg growth, tail absorption, and other changes leading to metamorphosis. In the normal unoperated tadpole metamorphosis was prematurely inaugurated or greatly accelerated; in the thyroidectomized tadpole similar changes were induced, though, as is well known, they would never have otherwise appeared in these thyroidless specimens.

These results furthermore might appear to be partially though not completely in harmony with the findings obtained from the opposite procedure, namely, the ablation of the hypophysis. For, in the mammal, hypophyseal deficiency causes a retention of infantile characteristics, and in the tadpole the loss of the buccal component of the hypophysis results in the retention of the larval condition for the life of the individual. The opposite picture resulted from the feeding experiments of the Hoskins, namely a hastening of development, this presum-

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1. This paper appeared subsequently to the untimely death of Dr. Hoskins, by which experimental research in this field has lost a devoted contributor.

2. Anterior lobe tablets prepared by Armour and Company.

ably being due to the presence of an excess of the pituitary secretion in the organism. It might thus appear that the results obtained by the Hoskins could logically be expected, for if the loss of the pituitary inhibits metamorphosis, should not the feeding of this substance accelerate it?

Yet it must be kept in mind that the retention of the larval condition in the hypophysectomized tadpole undoubtedly is not a pure hypophyseal effect. Rather it is polyglandular in nature, for it has been known since Adler's experiments in 1914 that the loss of the pituitary leads to a profound atrophy or underdevelopment of the thyroid, findings which have been amply confirmed in a series of papers by Allen and Smith, while one of us (Smith, 1920) has shown that both components of the adrenal, the parathyroid glands, and the neural lobe of the hypophysis are profoundly affected by hypophysectomy. Of this system of organs, because of the well known metamorphic stimulus afforded by thyroid feeding in amphibia, (Gudernatsch, 1914; Lenhart, 1915; Morse, 1914; and others) it seems reasonable to refer the immediate fault for the failure of the hypophysis-free tadpole to metamorphose more to the atrophy or underdevelopment of the thyroid than to an hypophyseal deficiency.

It thus seems that we may justly implicate the thyroid in being partially if not solely responsible for the persistence of the larval condition in the hypophysis-free larvae, and conversely to suspect that the feeding of anterior lobe substance would not give the reverse of this picture, namely, an acceleration of metamorphosis.

In feeding experiments using thyroidless and hypophysectomized larvae in which for many months the sole food of these animals, aside from a small component of lettuce, was fresh beef anterior lobe, one of us (Smith, 1918, 1920) observed no evidence of metamorphosis. Nor were the normal larvae prematurely metamorphosed in any decisive way. The hypophyseal feeding of Gudernatsch (1914) also failed to show the pronounced results reported by the Hoskins.

The question which has again been raised by the work of the Hoskins is a pertinent one. Their results would appear to be decisive, although at variance with what might logically be

expected, as well as in direct disagreement with similar work of other investigators. It thus seems justifiable to present new evidence and perhaps throw more light upon this much vexed question of the interrelationship of the thyroid and hypophysis.

In the experiments herein detailed both normal and thyroidectomized frog larvae were used. The specimens of each of the series were from a common egg mass and only those individuals were used which had obtained a certain average size. Since the various groups composing each series contained only a comparatively small number of specimens (4-5) statistical treatment is precluded. Yet the results have been so decisive that a larger number of individuals appears unnecessary.

The aquariae used were those described in a previous paper (Smith, 1920). They were supplied with a continuous but small amount of freshly aërated sterilized water. The water supply was carefully regulated so that each container received approximately the same amount, hence avoiding a variable dilution of any hormonal or other principle contained in the rearing dishes. The special substances were supplied the groups daily, the uneaten particles and casts being removed 24 hours later. These special substances furnished the entire food supply of the larvae with the exception of a weekly contribution of ground fresh lettuce.

With the exception of the groups receiving fresh pituitary, fresh muscle and fresh liver, each group of a series received an identical amount by weight of pituitary substance at each feeding. The amounts fed proved to be in excess of the nutritional demands of the larvae.

The results reported by Hoskins and Hoskins from the feeding of the anterior lobe tablets used by them were fully confirmed by our work. Not only was metamorphosis in the normal tadpole prematurely inaugurated and greatly accelerated, but also as in the experience of these investigators metamorphosis was inaugurated in the thyroid-free tadpole by the administration of these tablets.

With equal certainty we also confirmed the results from the feeding of fresh and the dried pituitary prepared in this laboratory, Smith (1918, 1920). And we must also report that both Parke Davis' powder and also Armour's powder gave in general

concordant results.[3] These substances did not decisively hasten metamorphosis in the normal tadpole, nor did they induce any indication of metamorphosis in the thyroidless larvae. These results are shown in the following protocols.

SERIES II. This series was composed of nine groups of normal tadpoles, each group being composed of six specimens. These groups received respectively: (1) Parke, Davis' anterior lobe powder; (2) Armour's anterior lobe powder; (3) Armour's anterior lobe tablets; (4) anterior lobe powder prepared in this laboratory; (5) fresh beef anterior lobe; (6) powdered dried posterior lobe; (7) powdered dried muscle; (8) powdered dried liver; (9) ground fresh liver or muscle. Each group received 0.13 gm. (2 grains) of the dried substance daily. (Each anterior lobe tablet, although weighing five grains, contained but two grains of actual pituitary substance.) The fresh substances were not weighed, but were clearly in excess of the nutritional needs, as indeed was the case also with the dried foods. Measurements were taken every three days; only the following need be given:

June 25—Series started. The average total length of the specimens of the various groups was from 25 to 28 mm. with a hind-leg length of approximately 1 mm.

July 15—The specimens of each of the groups except those of group 3 had grown very considerably, now averaging 29 to 33 mm., with a hind-leg length of 1.5 to 3 mm. The specimens of group 3 averaged 25 mm. (body 10 mm., tail 15 mm.) with a hind-leg length of 3 mm. On June 25th the average length of this group had been 28 mm. The specimens of this group were emaciated, were eating but little and cutaneous and mouth metamorphic changes were evident.

July 24—The last specimen of group 3 was dead. All these specimens showed pronounced metamorphic changes but did not develop legs of normal size nor complete the absorption of the tail. The specimens of the other groups continued to grow, averaging 32 to 36 mm.

July 27-August 23—Development continued until the series was discontinued on August 23. Exclusive of the specimens of group 3 the most rapid development took place in the specimens of groups 2 and 4, the specimens of these two groups metamorphosing somewhat, though not decisively, earlier than those of the other groups.

SERIES III. This series was composed of five groups of thyroidectomized specimens, each group containing 4 specimens. These groups were fed respectively: (1) Armour's anterior lobe tablets; (2) dried anterior lobe prepared in this laboratory; (3) fresh anterior lobe; (4) dried muscle; (5) fresh muscle or liver. The same dosage was used as in Series II. Measurements were taken every three days.

July 1—Series started. The average length of the specimens of the various groups varied from 28.5 to 31 mm. The hind-limb buds were just distinguishable, being about .1 to .2 mm. in length.

July 15—Slight growth had taken place in the specimens of all of the groups except those of group 1. The specimens of group 1 averaged 28 mm. with a hind-leg length of 1.5 mm. The specimens of the other groups averaged from 29.5 to 32 mm. with a hind-leg length of .2 to .4 mm. All specimens were typical thyroidectomized larvæ.

July 24—The specimens of group 1 averaged 26.5 mm. in total length, with a hind-leg length of 3.5 mm. They appeared somewhat

3. These tablets and powders were supplied this laboratory by Armour and Company and by Parke, Davis & Company. We wish to express our appreciation for their cooperation.

emaciated and metamorphic cutaneous, and mouth changes were plainly evident. The specimens of the other groups averaged from 30.5 to 33 mm., with a hind-leg length of .4 to .6 mm. and were typical thyroidectomized larvæ.

August 9—One specimen of group 3 died on August 4. The skin and mouth was of adult type but the absorption of the tail had not been completed. The other members of this group averaged 24 mm. in total length, with a hind-leg length of 4.6 mm. The mouth and skin was of adult type in every member of this group. The specimens of the other groups averaged 34 to 38 mm. in total length, with a hind-leg length of .4 to .7 mm. and were typical thyroidectomized larvæ.

August 19—The specimens of group 1 averaged 19.5 mm. in total length (body 10.6, tail 9), with hind-legs 6 mm. in length. Three specimens had fore-legs and all were of adult shape. The specimens of the other groups averaged from 36 to 44 mm., with hind-legs measuring from .6 to 1 mm. They were typical thyroidectomized larvæ.

August 24—The last specimen of group 1 died on August 22. It was of adult type but the tail was not completely resorbed nor were the legs of normal young adult length. The specimens of the other groups averaged from 37 to 45 mm., with hind-legs measuring from .6 to 1.4 mm. They were typical thyroidectomized larvæ.

Thus the anterior lobe preparations which we have employed are separable into two classes by their ability or lack of ability to decisively stimulate metamorphosis: (1) One substance—the only one employed by the Hoskins—afforded a pronounced metamorphic stimulus. (2) The other substances failed to alter decisively the usual developmental history of the larvae. Which effect, then, expresses most nearly the actual physiological capacity of the gland when employed in feeding experiments with the normal or thyroidless individual?

Since but one anterior lobe preparation gave a pronounced metamorphic stimulus while four preparations, including the fresh gland, failed to give this stimulus, it would appear that the substances of the last mentioned class because of their numerical majority, represent in their action the physiological capacity of the gland when fed to the tadpole.

The problem now entered its second phase. We directed our attention to the determination of any peculiarities, other than physiological, which might be enjoyed by the single substance giving this extreme metamorphic stimulus so unique in hypophyseal feeding.

Because of the known potency of iodine in organic or inorganic form to metamorphose the tadpole (Allen 1919, Swingle 1919), thyroxin iodine being also potent in this respect (Rogoff and Marine 1916), it seemed not improbable that an

analysis for the iodine content of these various preparations would prove suggestive.

Analyses made by Dr. E. C. Kendall showed the iodine content of three of the anterior lobe preparations to be as follows: [4]Sample 1 contained .0228 mg. of iodine per gram; sample 2 contained .0037 mg. of iodine per gram; sample 3 contained .1787 mg. of iodine per gram; or the iodine content of 1 was .002% that of 2, .003% and that of 3, .0178%; in other words, number 3 contained 8 times as much iodine as sample 1 and 48 times as much as sample 2. But since anterior lobe substance composed but two-fifths of sample 3, the remaining three-fifths being milk sugar, therefore, the actual pituitary substance of this sample contained approximately 120 times as much iodine as sample 2.

Using the iodine content of sample 3 as a standard we then prepared three diets (diets 4, 5, 6) each having the precise iodine content of sample 3, and one check diet (diet 7). The supply from which sample 3, above, was taken served as diet 3. These diets were as follows.

Diet 4—"Anatomy pituitary" 2 parts, milk sugar 3 parts, to which thyroxin[5] was added in sufficient amount to give an iodine content of 0.1787 mg. of iodine per gm. (See analysis of 3.)

Diet 5—"Anatomy pituitary" to which thyroxin was added in sufficient amount to give an iodine content of .4467 mg. of iodine per gm. (Diets 3, 4, and 6 were fed in 5 grain doses. Each group then received 2 grains of actual pituitary substance. Diet 5 was fed in 2 grain (0.13 gm.) doses, thus to give an amount of iodine at a feeding equivalent to the other samples it needed to contain 0.4467 mg. of iodine per gm.)

Diet 6—"Anatomy pituitary" 2 parts, milk sugar 3 parts, to which KI was added in sufficient amount to give an iodine content of 0.1787 mg. of iodine per gm.

Diet 7—"Anatomy pituitary" 2 parts, milk sugar 3 parts.

Two critical series, one composed of normal and one of thyroidectomized tadpoles, were fed with diets 3 to 7. We wish to call special attention to the fact that each of the groups in a series contained the same number of animals and that the animals composing these groups were nearly of the same size. (See protocols of Series V and VI.) Further, each group of a series

4. Sample 1 was Armour's anterior lobe powder. Sample 2 was dried anterior lobe substance prepared in this laboratory, "Anatomy pituitary." Sample 3 was Armour's anterior lobe tablets.

5. The thyroxin was kindly supplied the laboratory in crystalline form by Dr. Kendall in 1918. It contained 65% of iodine.

received the same amount of dried pituitary substance and, except for the check group, the same amount of actual iodine, though in different combinations. These two series then would appear to fulfil all the essential requirements for determining whether pituitary plus iodine in certain combinations would give the effect which the Hoskins had secured and which we had confirmed with the substance which they employed, but with no other pituitary substance.

SERIES V. This series was composed of five groups of 4 normal specimens each. These groups received respectively: (1) diet 3; (2) diet 4; (3) diet 5; (4) diet 6; (5) diet 7. Each group, except 3, received daily 0.324 gm. of its special diet; group 3 received two-fifths of this amount or 0.13 gm. daily. Thus each group received an identical amount of pituitary substance. Measurements of body, tail, and leg lengths were taken every three days.

August 27—The series was started. The specimens of the various groups averaged 38 to 40 mm. in total length, with a hind-leg length of 4.5 to 7.5 mm. They were typical larvæ in all respects.

September 7—The specimens of groups 1, 2, and 3 averaged 32 to 35 mm. in total length, with a hind-leg length of 12 to 14.5 mm. The epidermis and mouth of each were assuming the adult type, the tails in a few cases were undergoing resorption. The specimens of groups 4 and 5 averaged 40 mm. in total length, with a hind-leg length of 8.5 to 10 mm. All specimens were typical larvæ.

September 16—The specimens of groups 1, 2, and 3 averaged 23 to 27 mm. (body 13 mm., tail 11 mm.). The fore-legs were out in all specimens and the mouth and skin of each specimen was of adult type. The specimens of groups 4 and 5 averaged respectively 41 and 43 mm. in total length, their hind-legs averaging 16 mm. The fore-legs were not visible. Those of group 5 were typical larvæ; the skin and mouth of each of the specimens of group 4 showed slight metamorphic changes.

September 19—The specimens of groups 1, 2, and 3 were all adult in shape and their tails were nearly resorbed (4 to 8 mm.). Two specimens of group 1, three of group 2, and one of group 3 had completed metamorphosis. The bodies of the specimens of group 4 averaged 14 mm., their tails 21 mm. Fore-legs were out in 3 specimens. The hind-legs of all were of young adult size, the skin was of adult type, and the mouths of 2 specimens were of adult type, while 2 were of larval type. The bodies of the specimens of group 5 averaged 15 mm., the tail 27 mm. The hind-legs were of young adult size, the skin was partly of adult type. One specimen had fore-legs.

September 21—All specimens of groups 1, 2, and 3, had metamorphosed.

September 26—Two specimens of group 4 metamorphosed. The bodies of the two remaining specimens measured 15 mm., the tails 18 mm. All were of adult shape. The bodies of the specimens of group 5 averaged 15 mm., their tails 27 mm. The fore and hind-legs, mouth and skin were of adult type.

September 29—One young adult removed from group 5.

October 2—The last specimens of groups 4 and 5 metamorphosed.

SERIES VI. This series was composed of 5 groups of 4 thyroidectomized specimens each. These groups were placed under the same

dietary régime as those of Series V., namely: (1) received diet 3 (sample 3); (2) diet 4; (3) diet 5; (4) diet 6; (5) diet 7.

August 26—The series was started. The specimens of groups 1, 2, 4, and 5 averaged 36 to 40 mm. in total length, with a hind-leg length of 0.3 to 0.7 mm. (The specimens of group 3 varied greatly in size and will not be included in the following. Their history varied but little from that of the specimens of groups 1 and 2.)

September 11—The specimens of the various groups averaged from 35 mm. (group 1) to 43 mm. (group 5), those of groups 1 and 2 had hind-limb buds 2 to 2.5 mm. in length, and those of groups 4 and 5 hind-limb buds of 0.5 to 0.7 mm. All specimens were typical thyroidectomized larvæ.

September 19—The specimens of groups 1 and 2 averaged respectively 35 and 39 mm. with hind-legs 3 to 4 mm. in length. Each showed distinct metamorphic changes in its skin and mouth. The specimens of groups 4 and 5 measured respectively 40 and 45 mm. in length, with hind-limb buds 0.6 to 0.9 mm. and were typical thyroidectomized larvæ.

September 29—The specimens of groups 1 and 2 averaged respectively 19 and 34 mm. in total length, with a hind-leg length of 6 to 8 mm. The skin and mouth of each specimen were of adult type. The members of groups 4 and 5 averaged respectively 42 and 47 mm. in total length, with a hind-leg length of 1 to 1.4 mm. and were thyroidectomized typical larvæ.

October 4—Two specimens of group 1 and one specimen of group 2 were nearly transformed and died the following day.

October 7—The remaining specimens of groups 1 and 2 measured respectively: body 11 mm., tail 6 mm., and body 15 mm., tail 10 mm. All had fore-legs and were adult in shape. The specimens of groups 4 and 5 averaged respectively: body 15.5 mm., tail 27 mm., and body 17 mm., tail 32 mm. They had hind-legs 0.6 to 1.2 mm. in length, and were typical thyroidectomized larvæ.

October 13—The remaining specimens of groups 1 and 2 had transformed; they were not typical young adults, but were weak and had shorter legs than normal, especially the members of group 1. The specimens of groups 4 and 5 had a typical larval shape, showed no indications of metamorphic changes and averaged respectively 45 and 51 mm. in length, with hind-limb buds 1 to 1.3 mm.

These two series have furnished concordant and decisive testimony as to the action of these thyroid-pituitary or iodine-pituitary substances. The specimens of the groups receiving anterior lobe plus inorganic iodine paralleled very closely in development and growth their fellows supplied with a diet of anterior lobe only. And we would recall at this point that no decisive deviation resulted from the administration of our dried anterior lobe substance when carefully checked by diets of fresh anterior lobe substance and fresh and dried muscle. Very different results were obtained with the specimens of those groups receiving pituitary plus thyroxin iodine or pituitary mixed with milk sugar plus thyroxin iodine. These specimens paralleled in

development the specimens fed with the "anterior lobe" tablets, the normal tadpoles showing a greatly accelerated metamorphosis, the thyroidectomized larvae an initiation and rapid progression of the metamorphic process.

It now only remains to discuss briefly the results which we have obtained. The interesting and suggestive findings obtained by Hoskins and Hoskins, and which indeed seemed to demonstrate clearly that the thyroid and anterior lobe afforded an identical stimulus to metamorphosis, and thus were here presumably similar in function, appear to have been secured by the administration of "anterior lobe" substance displaying a unique activity. This appears clearly to be the case since the fresh gland and the dried gland secured from three sources failed to give the effects which they report.

Further, the "anterior lobe" substance which gave this thyroid effect was unusual in the amount of iodine which it contained. It will be recalled that an analysis of this substance showed an iodine content of 0.1787 mg. per gm., thus exceeding by some 120 times the amount of iodine which the dried gland prepared in this laboratory contained. However, the iodine content of our pituitary (0.0037 mg. per gm.) is as great as is usually found in anterior lobe substance, for analyses have shown no more than a trace and usually an absence of this halogen, Simpson and Hunter (1911), Denis (1911), Halliburton, Candler and Sikes (1909) and Seaman (1920).

It has repeatedly been shown that the iodine content of the thyroid gland is subject to a seasonal variation, Seidell and Fenger (1913), Fenger (1918). By analogy we might find an explanation for the high iodine content of the material used by the Hoskins if it was shown that there is likewise as great or a greater seasonal iodine variability in the anterior lobe of the pituitary.

We have attempted to ascertain whether anterior lobe substance, to which iodine in certain forms was added in amounts identical with that occurring in the "anterior lobe" tablets which gave this decisive metamorphic stimulus, would likewise give this stimulus. Inorganic iodine (KI) gave negative results, although from the conclusive work of Allen (1919) and Swingle (1918), it is certain that if used in larger amounts it would have induced

metamorphosis. Our results in this respect are somewhat similar to those of Cameron and Carmichael (1920), who found that sodium iodide failed to give any of the metabolic effects (enlargement of heart, liver, kidneys, etc.), which they obtained in the mammal by thyroid feeding even when the iodine was used in amounts 100 times as great as occurred in the thyroid substance used by them. We obtained positive results with iodine in the form of thyroxin iodine in amounts identical with that found in the tablets. The tadpoles supplied with this substance paralleled in development their tablet-fed brethren.

Evidence has been repeatedly advanced suggesting a vicarious relationship between the anterior lobe of the pituitary and the thyroid gland since the pioneer work of Rogowitch in 1888. Such evidence has not clearly established such a vicarious relationship though it cannot be questioned that an inter-relationship obtains between these two glands, as indeed is the case between all the members of the endocrine system. The early removal of the pituitary leads to a striking underdevelopment of the thyroid, Adler (1914), Smith (1916), Allen (1917). There can be thus no assumption of the function of the ablated gland by the thyroid under this condition. It has been assumed that the enlargement of the pituitary subsequent to thyroidectomy, which has been clearly demonstrated by Rogowitch (1888), Trautmann (1916), Rogers (1918), Hoskins and Hoskins (1919), and others, indicated that the pituitary was compensating for the loss of the thyroid. Yet the evidence does not prove that such is the case. From the physiological side the work of Simpson and Hunter (1911) is against this view, while the classical work of Trautmann (1916) shows that although there is a hypertrophy of the anterior lobe following thyroidectomy, yet this hypertrophy ultimately leads to degenerative changes. Ablation experiments thus do not supply evidence of a vicarious relationship between the anterior lobe and the thyroid. Likewise feeding experiments have failed to establish that anterior lobe feeding gives a thyroid effect, or conversely that thyroid feeding gives an hypophyseal effect.

In 1918 one of us, Smith, noted that anterior lobe feeding to the normal tadpole produced a slightly larger individual and a somewhat earlier average appearance of meta-

morphosis and completion of the same. These effects did not exceed the normal variation and so were not decisive. In general these results have been confirmed in the present study though again they have not transcended the normal variation and so have not been decisive. Any earlier metamorphosis was not gained, however, at the expense of the size of the individual as in thyroid feeding; the effects are very dissimilar. These results secured by the administration of anterior lobe to tadpoles appear to be similar to, but not as pronounced as, the very interesting results gained by transplanting the anterior lobe into the normal, pituitaryless or thyroidless tadpole reported by Allen (1920, 1921). This investigator reports that such grafts stimulate growth but "clearly show that the anterior lobe of the hypophysis exerts an influence upon metamorphosis only indirectly through its influence upon the thyroid gland." Clearly, evidence secured from the experimental ablation, feeding, and transplantation of the anterior lobe and of the thyroid have failed to establish that a functional similarity or vicarious relationship exists between these two glands.

SUMMARY

1. We were able to confirm the results of Hoskins and Hoskins obtained by the feeding of what they supposed to be anterior lobe tablets. Tablets of this substance obtained from the same source as their material caused an acceleration of metamorphosis in the normal tadpole and induced metamorphosis in the thyroid-free larvae.

2. Fresh anterior lobe substance, dried anterior lobe prepared in this laboratory, and the dried gland from two other sources failed, on the other hand, to alter decisively the development of the normal tadpole or to induce metamorphosis in the thyroidless specimens.

3. Analyses of these two classes of anterior lobe substances revealed the fact that the substance affording a metamorphic stimulus contained 0.1787 mg. of iodine per gm. (Each gram of this substance was composed of 0.4 gm. of anterior lobe substance and 0.6 gm. of milk sugar. Thus the actual pituitary substance would supposedly have contained 0.4467 mg. of iodine per gm.) The dried anterior lobe substances prepared in this labora-

tory contained approximately 1/120 of this amount of iodine, or 0.0037 mg. per gm.

4. Normal and thyroidectomized tadpoles fed upon the dried anterior lobe substance prepared in this laboratory, to which sufficient iodine in the form of KI to give an iodine content of 0.4467 mg. per gm. was added, nearly paralleled in development the tadpoles receiving the fresh gland and the untreated dried gland. On the other hand, normal and thyroidectomized tadpoles fed upon the dried anterior lobe substance prepared in this laboratory, to which sufficient iodine in the form of thyroxin iodine was added to give an iodine content of 0.4467 mg. per gm., exhibited a rapid rate of metamorphosis, paralleling in their development the tadpoles mentioned in paragraph 1 of the Summary.

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THE INTERNAL SECRETION OF THE SPLEEN

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A wide variety of functions has been assigned to the spleen from time to time, most of them involving the life cycle of the blood corpuscles. It has been claimed, for instance, that new red blood corpuscles are formed in the spleen, also that red corpuscles are destroyed in this organ. Others have claimed that the spleen produces white blood corpuscles and still others that it is a place where white corpuscles are destroyed. The investigations in support of these hypotheses have consisted of histological examination of the splenic tissue and comparative counts of the corpuscles in the blood entering and leaving the spleen. Large numbers of blood corpuscles of all sorts are found in the spleen, but their presence can be explained just as well on other grounds than that they are being produced there. The reports on the corpuscle content of the blood to and from the spleen are very conflicting. Malassez and Picard (25), Emelianow (12) and Morris (26) report more erythrocytes in the blood of the splenic vein than in that of the artery; Virchow (44) and Frey (13) report fewer in the venous blood; Vulpius (45), Paton, Gulland and Fowler (31) and Freyer (14) find no difference in the red corpuscle content of the blood entering and leaving the spleen. Similarly divergent reports have been made in regard to the white corpuscles. According to Funke and Hirt (16), Gibson (18), Grigorescu (19), Emelianow (12), Bulgak (6) and Morris (26) the leucocytes are increased in the blood leaving the spleen; Vulpius (45) and Paton, Gulland and Fowler (31) found the number of white corpuscles in the venous blood decreased; no noteworthy difference in the leucocytes of splenic artery and vein were detected by Tarchanoff and Swaen (43), Virchow (44) and Freyer (14). One concludes, therefore, that probably the adult spleen normally contributes no new formed elements

to the blood, and that it does not continually remove any significant number of corpuscles from the circulation.

The blood corpuscles, both red and white, are produced chiefly in the red marrow of the bones. Both are destroyed in all parts of the blood stream. According to Robertson and Rous (38) the mechanism of destruction of the old erythrocytes is a process of fragmentation with more or less dissolution of the particles in the blood stream. The fragments are removed from the circulation by the spleen, assisted possibly by the liver and red bone marrow. Such phagocytic power of the spleen for the corpuscular debris has been clearly demonstrated by these authors and by Tait and McCartney (42) for other foreign matter, Indian ink and powdered quartz. The latter also demonstrated similar ability on the part of the liver and bone marrow to remove from the circulation the foreign matter injected. They pointed to the existence of sinusoids in all three organs as a significant point of similarity. The spleen removes the fragments of the corpuscles from the blood not only because they are no longer of any use in the circulation of the organism, but probably also because the cells of the spleen in some way elaborate this material as a step in the production of body pigments and for re-utilization by the bone marrow in the manufacture of new corpuscles.

Another theory is that the spleen produces an internal secretion which regulates the number of corpuscles, particularly erythrocytes, in the circulating blood. Such an internal secretion might stimulate or depress the activity of the bone marrow; it might facilitate the fragmentation or dissolution of the old corpuscles; or, it might alter the number of corpuscles in active circulation by altering their distribution.

The existence of an internal secretion and its physiological action may be demonstrated by (1) the specific effects following congenital deficiency or experimental removal, (2) the symptoms noted in cases of hyperplasia of the organ, presumably accompanied by hypersecretion, (3) the administration of the substance of the gland or an extract, either in the absence of the gland when it might ameliorate the symptoms due to removal, or, when the organ is present, to simulate hypersecretion. One has to assume, of course, the existence in the preparations em-

ployed, gland substance or extract, of the active principle of the secretion of the living cells. In our own experiments we have employed the method of injection of splenic preparations.

Some of our experiments in this connection have been reported elsewhere (10). The technique and results are in part as follows:

Rabbits were used exclusively. Specimens of blood were taken simultaneously for counting both red and white corpuscles. After an initial corpuscle count the desired dose of splenic preparation was injected subcutaneously. Subsequent red and white corpuscle counts were made at half hour intervals during the first two or three hours after injection and a final count was made four or five hours from the beginning of the experiment.

In the first ten experiments the preparation employed was powdered dried spleen, prepared by Armour & Company. The dose of 10 mgm. per kilogram of body weight of the rabbit was dissolved in about 2 cc. of physiological saline solution, warmed to 37°C. and injected subcutaneously. In each of these experiments there occurred a slight reduction in the red corpuscle count (5.88 per cent) of short duration (69 minutes), and a prompt reduction in the number of white corpuscles followed in several hours by a considerable leucocytosis. The change in the leucocyte count was identical with the effect described by Wells (47) and others as following upon the subcutaneous injection of any foreign protein and was not a specific effect of spleen because it did not occur after the administration of a protein-free preparation.

A protein-free preparation was obtained by pouring a watery solution of the powdered dried spleen (Armour & Company) into absolute alcohol, filtering off the precipitate and evaporating the filtrate to dryness on a water bath. In a second series of ten experiments this residue was used in the dose of 10 mgm. per kilogram of body weight of the rabbit.

Again the red corpuscle count was decreased following the injection, the decrease in these experiments being much more marked (18.68 per cent) and more persistent (102 minutes) than in the first series. Instead of the characteristic effect of foreign protein injections on the white corpuscles an increased leucocyte count of brief duration was recorded in every experiment oc-

curring at or about the time of maximum decrease of the red corpuscles.

We also made fresh extracts of the spleen of dogs and cats. The fresh spleen was ground with sand and macerated overnight in the cold with twice its bulk of physiological saline solution. The preparation was then strained through muslin and filtered. The filtrate was poured in a thin stream into absolute alcohol, the precipitate filtered off and the alcoholic filtrate evaporated to dryness on the water bath. Five experiments were performed in each of which 10 mgm. of the extract of dog's spleen per kilogram of body weight were injected subcutaneously, and two experiments in each of which a similar dose of extract of cat's spleen was administered. In both groups of experiments there occurred a decrease in the red corpuscle count similar to that described following the administration of the splenic preparations (Armour & Company). Furthermore, in the experiments with extract of dog's spleen a transient increase in the leucocytes appeared at about the time the red corpuscles were decreasd to the greatest extent.

The averages of the results obtained in these experiments are shown in table 1. They establish the presence in the splenic preparations of an agent capable of reducing by some means the number of red corpuscles in the circulating blood. Using larger doses, 20 and 40 mgm. of the extract of dog's spleen per kilogram of body weight, the effect of the splenic preparation was not entirely progressive (see Table 1), but further consideration will be given to this point later.

In order to determine whether the decrease in the number of red corpuscles in the circulating blood was the result of the destructive action exerted by the splenic agent on the corpuscles, specimens of blood from an ear vessel of a rabbit were obtained simultaneously in two hemacytometer pipettes in the usual manner. The blood in one pipette was then diluted with 0.7 per cent sodium chloride solution, while the blood in the other was diluted with 0.7 per cent sodium chloride solution in which was dissolved fresh extract of dog's spleen in definite amount. Several successive drops from each pipette were counted and the counts from each averaged and compared. We made determinations using dilutions of 20, 40, 80 and 120 mgm. of fresh extract of dog's

TABLE 1

Decrease in erythrocyte count following subcutaneous injection of splenic preparations.

Number of Observations	Preparation	Dose per Kilo of Body Weight Mgm	Initial Count	Minimal Count	Amount of Decrease	Percentage Decrease	Minimum in Minutes	Duration of Effect Minutes
10	Powdered dried spleen (Armour & Company)...	10	6,877,500	6,471,200	406,300	5.88	45	69
10	Protein-free splenic preparation (Armour & Company)	10	6,635,600	5,396,000	1,239,600	18.68	66	102
5	Extract of dog's spleen....	10	6,560,000	5,145,000	1,415,000	21.47	54	144
2	Extract of cat's spleen....	10	6,284,000	5,388,000	896,000	14.20	30	75
5	Extract of dog's spleen....	20	7,545,200	5,153,600	2,391,600	31.02	90	162
5	Extract of dog's spleen....	40	6,879,200	5,236,000	1,643,200	23.88	74	134

spleen per 100 cc. of 0.7 per cent sodium chloride solution. A considerable decrease in the red corpuscle count, which can hardly be explained in any other way than as a direct hemolytic effect of the splenic extract, was obtained. Also the effect was progressive so far as these observations go.

As control further determinations were made in which other tissue extracts were dissolved in the sodium chloride solution used as diluting fluid. Fresh muscle extract (dog), prepared by exactly the same method that we used in making the fresh extract of dog's spleen, and dried acid extract of secretin, prepared by the method previously described (11), were employed. Each was dissolved in the 0.7 per cent sodium chloride solution in the proportion of 40 mgm. per 100 cc. The procedure followed was exactly the same as when we used the splenic extract. The results of these experiments, together with the results obtained with splenic extract in like dilution, are shown in Table 2.

TABLE 2

Control Observations on in vitro Hemolysis.

Blood diluted with normal saline	Blood diluted with normal saline plus tissue extract	Tissue extract employed
5,608,000	5,616,000	Muscle extract (dog).
5,120,000	5,184,000	" "
5,670,000	5,296,000	" "
6,910,000	6,960,000	" "
5,502,000	5,554,000	
6,288,000	6,096,000	Secretin preparation.
5,360,000	5,601,000	" "
5,920,000	6,200,000	" "
5,392,000	5,408,000	" "
5,470,000	5,120,000	" "
8,296,000	6,560,000	Extract of dog's spleen.
6,728,000	6,536,000	" " "
5,408,000	5,008,000	" " "
5,808,000	4,952,000	" " "
7,208,000	6,104,000	" " "

It will be seen that the variations in the counts when using muscle extract or secretin preparation are within the range of experimental error of blood counts in general and with neither was any evidence of hemolysis obtained. We conclude, therefore, that the hemolysis caused by the splenic preparation is specific and not a property of foreign tissue extracts.

A number of investigators have sought for direct hemolytic action of splenic extracts outside the body. Nolf (29), Weil (46), Banti (2) and Furno (17) obtained positive results, but Achard, Foix and Salin (1), Widal, Abrami and Brule (48)

and Krumbhaar and Musser (23) were unable to detect any direct hemolytic action of fresh extract of spleen. In these observations, all of which appear to have been macroscopic only, the splenic extract was allowed to act upon washed red corpuscles rather than whole freshly drawn blood. Washing erythrocytes with salt solution, according to Olson (30), may result in the destruction of some of them. It is probable that washing the corpuscles removes the weaker ones and retains only the more resistant, which the splenic substance is unable to destroy. If the hemolytic substance in the extract of the spleen is capable of attacking the less resistant corpuscles only we can understand how it was that in the experiments just quoted no hemolysis was observed, whereas in our experiments, in which fresh whole blood was used, a marked diminution in the number of red corpuscles took place. The authors who obtained no hemolysis with their splenic preparations argued that the hemolytic substance sometimes observed was produced on standing by bacterial action in the watery extracts. As pointed out, we used for these in vitro experiments fresh extract of dog's spleen and we believe our method of procedure would reduce to a minimum the possibility of bacterial action.

Brinchmann (4) finds that feeding normal rabbits and guinea-pigs with fresh ox spleen leads to a considerable reduction in the red and white corpuscles. These effects are not produced by feeding other raw flesh of identical iron content.

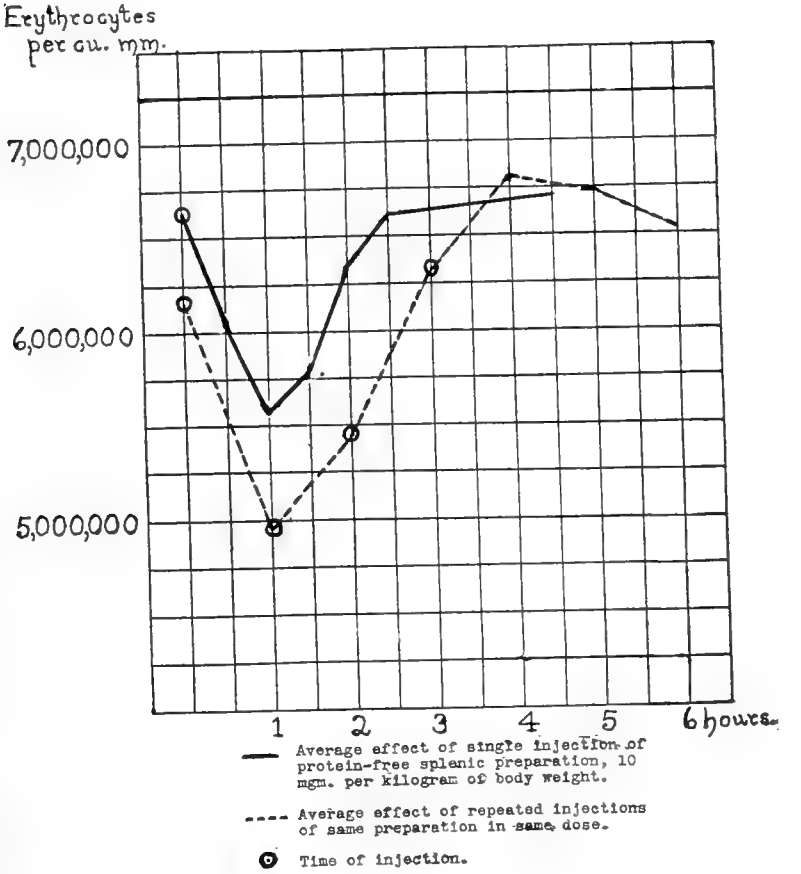
Zelenski (49) in 1891 and Danilewski (8) in 1895 were able to cause a marked increase in the number of red corpuscles in the circulating blood and also in the hemoglobin content of the blood following a single intraperitoneal injection of splenic extract. Paton, Gulland and Fowler (31) repeated their experiments without being able to detect any change in the erythrocytes. Silvestri (39) believed that he obtained an increase in the red corpuscle content of the blood in anemia by the use of injections of splenic extract. Krumbhaar and Musser (23) also were able to bring about an increase in the erythrocyte count and hemoglobin content by the injection of fresh splenic extract. This increase lasted one or two days and could be reobtained by repeating the dose.

In each of these cases a blood count was not made until the day following the injection, whereas our counts were begun immediately after the injection and continued at short intervals for several hours. It was at this time that the decrease noted by us occurred (see Table 1 for duration of effect). However, we have noted that when an animal was used for a second experiment after the lapse of a few days its initial red corpuscle count was frequently higher than it had been before any of the extract was administered.

The bone marrow usually responds to a lowering by hemorrhage or other means of the number of corpuscles in the circulating blood by increased production of new corpuscles so that, in the present instance, where the immediate effect of the splenic agent is a destruction of the erythrocytes, it is reasonable to expect subsequently increased production. This compensation might very possibly exceed the loss especially if, as has been claimed by Stradomsky (40), the product of splenic activity, in addition to acting directly to destroy red corpuscles, exerts a stimulating influence on the bone marrow. The results obtained in the group of experiments in which 40 mgm. of splenic extract per kilogram of body weight were injected subcutaneously are in accord with this idea of compensatory action on the part of the bone marrow. In this series of experiments the percentage decrease and the duration of effect were both less than when the dose was only 20 mgm. per kilogram (see Table 1). It is possible that the greater the amount of hemolytic agent present the more marked and more prompt is the compensating response. It is more probable that Stradomsky's idea is correct and that the stimulating element of the splenic extract becomes predominant in the larger doses where it is undoubtedly combined with the independent effort of the bone marrow to replace the corpuscles that are being rapidly destroyed.

This interpretation is further borne out by the results obtained when the dose of splenic extract is repeated at short intervals. In ten experiments we have given four doses of 10 mgm. of splenic extract per kilogram of body weight at hourly intervals and followed the changes in the erythrocyte count. We used the protein-free splenic preparation (Armour & Company). In the accompanying chart we have plotted the average result of the

repeated injections (dotted line) and the average change in the number of red corpuscles following a single injection of the same preparation in the same dose (solid line). In both there occurred a sharp decline in the count, but the repetition of the dose caused a prompt restoration of the number of corpuscles in circulation and a rise in the count above the original level. Three



hours after the last injection the count was still above the original.

It is worthy of note that in this series of experiments the leucocyte count increased after the first dose, as it did in the other experiments following a single injection, and frequently

remained elevated until some time after the last dose. Two explanations of the effect of the injections upon the white corpuscle count may be suggested. The increased number of white corpuscles may be evidence of the direct stimulating influence of the splenic hormone upon the bone marrow, or the leucocytes in circulation may be increased to assist by their phagocytic power the removal of the debris of the red corpuscles being destroyed by the splenic agent.

It is possible that the falling off in the erythrocyte count described may be due to a depression of the hematopoietic activity of the bone marrow by the splenic extract, or to a temporary withdrawal of red corpuscles from the circulation. Such assumptions, however, are unsupported by any evidence of which we are aware.

In 1912 Musser (27) reviewed the clinical and experimental observations which had been made to that date upon the changes in the blood following splenectomy. He says, "A general analysis shows that in the majority of cases a marked leucocytosis is present and persists for a year or more; often a pronounced secondary anemia occurs, in which the color index is normal as a rule." A little later Musser and Krumbhaar (28) followed the changes in the blood after splenectomy in seven dogs and found that anemia usually developed quickly and reached its height in from 3 to 6 weeks and then with gradual improvement the blood picture approached the normal after about 3 to 4 months. Accompanying this a marked leucocytosis was observed reaching its height in twenty-four hours but persisting to a slight degree for several months. Variations occurred, but they say, "The anemia is inevitable, as is also, later, some degree of repair." Pugliese (37) found a marked fall in the number of red corpuscles per cubic millimeter of blood followed splenectomy but says the reduction is temporary, less than two months. Hitzrot (21) reported six cases of splenectomy for traumatic rupture of the organ in patients otherwise apparently normal and in all he found a considerable decrease in the red blood corpuscles and an increase in the white corpuscles followed the operation. Tachigara and Takagi (41) compared the effects of splenectomy in young and old animals (dogs) and found that in general the results were the same. They noted a striking

increase in the number of nucleated red blood corpuscles in circulation. The total number of erythrocytes was decreased and there occurred a leucocytosis. Most investigators who have studied the blood changes after splenectomy have found that erythroblasts occur in the circulation only very exceptionally; occasionally they are seen as the animal begins to recover from the anemia.

Botazzi (3), Domenici (9), Brissaud and Bauer (5), Pel (36), Pearce and others (33, 34, 22) found that accompanying the anemia there was a very definite increase in the resistance of the erythrocytes to hemolysis, both by hypotonic salt solution and specific hemolytic immune serum. Fukushima (15) noted that the resistance of erythrocytes to hemolytic toxin produced by poisonous vipers was increased the third day after splenectomy. This increased resistance persisted four to eight weeks and then became normal or slightly subnormal. Karsner and Pearce (22) were able to show that the increased resistance is not due to the accumulation in the blood after removal of the spleen of hemolytic or anti-hemolytic bodies, but is dependent upon changes in the erythrocytes. The degree of resistance appeared to them to increase with the length of time that had elapsed after splenectomy.

Pearce and others (32, 35) examined histologically the liver, lymph nodes and bone marrow in normal and splenectomized dogs. In both the liver and lymph nodes proliferation of endothelial cells phagocytic for red corpuscles followed the removal of the spleen. This was apparently compensatory to the lost phagocytic function of the spleen. The changes in the lymph nodes suggest the idea that the leucocytosis also is a compensatory reaction to assist the removal from the circulation of the disintegrating red corpuscles. It is most marked immediately after the ablation of the spleen and gradually disappears as the changes in the liver and lymph nodes take place.

In the bone marrow there usually occurred, according to the authors quoted (35), a transformation of the fatty marrow of the long bones to a richly cellular red marrow. The change in the marrow is very gradual, not attaining completeness for six to twenty-two months. The change would seem not to be compensatory either to the post-operative anemia or to possible

hemolysis in the lymph nodes. The possibility suggests itself that it may be associated with the taking over by the bone marrow of the function of storing and elaborating the material derived from old corpuscles for purposes of re-utilization. As this function becomes developed it might constitute a stimulus to erythrogenesis and thus aid in the recovery from the anemia. The demonstration by Tait and McCartney (42) of the ability of the bone marrow to remove other foreign material from the circulation has already been mentioned. It is at least conceivable that the bone marrow might similarly remove fragmented corpuscles.

These observations on the histological changes in the bone marrow, liver and lymph glands have been confirmed by Henn (20), who also noted anemia, leucocytosis and increased resistance of erythrocytes in the animals from which the spleen had been removed.

As a control experiment Krumbhaar and others (24) diverted the venous drainage of the spleen. They ligated the splenic vein or transplanted it into the vena cava or established an Eck fistula. The result was an anemia similar to that produced by splenectomy, but on the whole of less grade and duration. An increase in the resistance of the red corpuscles, likewise less marked and less prolonged, and a leucocytosis were also noted.

Burkett (7) performed similar operations for diversion of the splenic blood from the portal circulation. The most striking change in the peripheral blood which he found to follow the operation was the leucocytosis, "Without," he says, "any special change in hemoglobin or the red blood cells which had a normal appearance in fresh blood films." However, he gives figures for two of the five dogs used and in both there was some reduction of the erythrocyte count (12.5 per cent in one of the dogs during the fourth week).

Krumbhaar (24) makes the suggestion that diversion of the splenic blood causes anemia because the internal secretion of the spleen, exerting a stimulating influence on the distant hematopoietic organs, has to be activated in the liver. It is also possible that mechanical modification of the volume of the blood

going to the liver may alter the activity of the liver so as to produce the effects described.

In conclusion, the hypothesis that the spleen produces an internal secretion is supported by (1) the changes in the erythrocytes after splenectomy, (2) the modification of the blood picture in hyperplasia of the spleen, ameliorated in some cases at least by splenectomy, and (3) the specific effects on the red blood corpuscles of injection of splenic extract.

We know nothing of the chemical nature of the supposed splenic hormone and it is difficult to formulate a consistent theory of its possible mode of action. We should like, however, to make the following suggestions: That the chief function of the spleen is the removal from the circulation of the disintegrated erythrocytes; that the splenic cells elaborate this material producing thereby an internal secretion, which was a component of the erythrocyte either stroma or pigment portion; that this internal secretion reduces the resistance of all the red blood corpuscles, the effect amounting to actual destruction of the older cells; and, finally, that this internal secretion, possibly after modification by the liver, stimulates the erythrogenic function of the bone marrow and is used up in the manufacture of new corpuscles.

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Editorials

ENDEMIC GOITER: ITS PREVENTION AND TREATMENT

That there are regions in which a high frequency of enlargement of the thyroid gland is observable in the population is a matter of common knowledge. In this country the Great Lakes goiter belt has long been known. A recent statistical study by Levin of the incidence and distribution according to sex and age of one portion of this district is of more than passing interest when correlated with the results of Marine and Kimball on the prevention of goiter in another part of the same general territory. Levin examined, without selection, 1783 persons and found thyroid enlargement in 1146 of the group coming under observation. That is to say a trifle over 64 per cent of the population showed evidence of an actual or potential pathological condition of the thyroid.

The simple goiter incidence, which Levin is inclined to attribute more to a physiological response to an unfavorable environment rather than to an immediate pathological state, though he points out that such enlargements tend to develop into actual pathological conditions, is by far the highest in the three groups into which he classifies the cases with enlarged thyroids. Some 38 per cent fall into this group, while of the residual 26 per cent, the adenomas and cystomas together contribute nearly 24 per cent and the colloid goiters the rest. In all three of the groups the incidence for the male is markedly lower than for the female. The incidence curve for age indicates that the number of persons developing goiter increases for both sexes during puberty, and drops to a lower level after the growth of the individual is attained. The curve for the female, however, remains at a high level during the child-bearing period, goes down at about 38 to 40 years and rises again at the meno-

pause. In the male the curve gradually drops till 35 or 40 years when there is a small increase in incidence.

The studies of Marine and Kimball are of immediate practical interest, in that they point the way not only for prevention of this high rate of incidence and its possible pathological sequelae, but also because statistical evidence is given that even when the enlargement is an accomplished fact adequate treatment can be instituted which in a large number of cases results in improvement or cure. These investigators made a study of the pupils in the fifth to the eighth grades of the Cleveland schools and found that goiter may be prevented simply and cheaply in normal individuals merely by the feeding of two grams of sodium iodide daily for a period of two weeks twice yearly. They observed that of 2190 pupils taking this dose, only 5 developed an enlargement of the thyroid, while of 2305 pupils not taking the salt, 495 showed an enlargement of the gland. Moreover, when 1183 pupils who showed a thyroid enlargement at the first examination were treated with the drug, 773 of them presented a decreased enlargement at the second examination, while of 1048 pupils with thyroid enlargement at the first examination who did not take the iodide, but 145 were found to have had a decrease in the size of the gland. The authors go on to state that in the practical application of the treatment there must be kept in mind the three periods when simple thyroid enlargements most commonly occur; fetal life, puberty and pregnancy, and that prevention of goiter in mother and fetus is as simple as it is for adolescence.

Such studies admirably serve to demonstrate the value of the statistical treatment of facts, since they allow the drawing of valid conclusions as to the efficacy of any particular therapy in the treatment of a given actual or potential pathological condition. They are particularly valuable in this case in that they apparently make possible the prevention and treatment of endemic goiter wherever it occurs, providing of course its etiology is the same as for the Great Lakes region.—F. S. H.

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Book Reviews

THE MUTUAL RELATIONS BETWEEN THE ENDOCRINE ORGANS (Die wechselseitigen Beziehungen der Drusen mit inneren Sekretion). Prof. Dr. Erich Leschke. Halle, 1920, Carl Marhold. Verlagsbuchhandlung. 48 p.

This nice, very readable little book gives a good review of our knowledge of the endocrine organs. The author states that nearly all endocrine diseases are polyglanular and that when the origin of a disease may be settled in one organ nearly always the others undergo more or less important changes. It is not right to distinguish between antagonistic and synergistic glands as the question is not so simple. Though no new facts are given, this book will prove useful to medical men, who do not regularly read the literature on endocrinology.—J. K.

Abstract Department

L'ACROMEGALIA. Ferranni (A.), Riforma Med. (Napoli), 1917, 857-861.

The author gives a lengthy discussion on the evolution of the conception of acromegaly, followed by historical information from the work of several pioneers on the subject. After giving the present day recognized symptoms, both physical and histological, the author, like other authorities, comes to the conclusion that the enlargement of the pituitary is associated with the affliction.—D. P.

Contribution to the study of tumors of the ADRENALS (Contributo allo studio dei tumori della ghiandola surrenale). Ausenda (C.), L'Osp. Maggiore (Milano), 1920, **6**, 264-285.

After a detailed discussion of the pathogenesis of hypernephromata the author reviews the benign tumors of the adrenal cortex. He reports having found in adenomata real glandular lumina, while in cortical hypertrophy the lumina were due to degenerative process. Pigmented adenoma is recorded, a few cases of lipomata, while angioma is very seldom found. With regard to the heteroplastic formation of bone tissue the presence of calcification as well as of real bone tissue is stressed. Medullary tumors are reported as paragangliomata, ganglioneuromata and neuroblastomata. The chief discussion concerns malignant tumors and their polymorphism. Six cases are reported of personal observation, detailed histories being given together with the autopsy findings. Chemical analyses of the several tumors failed to yield positive results. The author thinks that the atypical structure of these tumors would explain their functional aberration owing to which the neoplastic element loses its specific function to assume the proliferative (vegetative) one.

The marked polymorphism found in the tumors seems to be a peculiarity of the adrenal blastomata, as the stroma of the parenchyma. As regards the symptomatology in the several cases quoted nothing is recorded, peculiar to the adrenal, save profound asthenia, which could be referred to any other tumor which had progressed to the stages described.—G. V.

(ADRENAL) Recklinghausen's disease with evasive syndrome of adrenal insufficiency (Maladie de Recklinghausen avec syndrome fruste d'insuffisance surrénale). Chauffard (A.) & Brodin (P.), Bull. et mem. Soc. méd. d. Hôp. (Paris), 1920, **44**, 166-169.

Chauffard and Brodin report a case which apparently confirms the connection between Recklinghausen's disease and the suprarenals. Suprarenal treatment was followed by immediate and notable improvement, as in Pic's and Jullien's two cases.—F. S. H.

The ADRENALS in the pathogenesis and treatment of spasms (Die Bedeutung der Nebennieren für die Pathogenese und Therapie des Krampfes). Fischer (H.), Deutsche med. Wchnschr. (Berlin), 1920, **46**, 1437-1438.

A theoretical discussion with no report of experimental work. Stimuli producing spasms in animals only produce these spasms when the adrenals are present. When the quantity of adrenal tissue is reduced, the sensibility for spasms is also decreased. When the quantity of adrenal tissue is increased (as after castration or in chronic alcohol intoxication) even small stimuli may produce spasms. When the quantity of adrenal tissue is decreased the irritability of the voluntary muscle is diminished. Not only can spasms be obtained in such animals less easily but also consciousness is no longer lost. In epilepsy the removal of one adrenal will certainly not cure the disease but the spasms will become less intense and less frequent. As we do not know anything about the importance of the adrenals for growth one cannot recommend the operation before growth has finished. The best age is between 20 and 30.—J. K.

(ADRENALS) A note on the effect of irradiation of the SUPRARENAL region in rabbits with Roentgen rays. Grabfield (G. P.) & Squier (T. L.), Arch. Int. Med. (Chicago), 1921, **27**, 168-174.

This study reports the effect of radiating the adrenal region with the "hard type" of x-ray, both through the anterior abdominal wall and from behind. Intact rabbits were used as the experimental animals. The adrenals were examined from 1 to 46 days after the last dose. A few of the animals died, but the majority lived until killed for the purpose of the study. The 3 animals that died all showed a marked increase in the weight of the radiated glands. No reference is made to the use of controls. In general the authors are of the opinion that x-ray treatment of the adrenals induces an increase in their weight.—F. S. H.

Acute ADRENALISM during the course of a secondary syphilis and following a polymorphic erythema (Surrénalité aigue dans le cours d' une syphilis secondaire et à la suite d'un érythème polymorphe). Blum (P.), Bull. et mem. Soc. méd. d. Hôp. d. Par., 1920, 3s., **44**, 1767-1774.

A detailed clinical history presenting no new data.—F. S. H.

ADRENIN glycemia. Bornstein (A.), Biochem. Ztschr. (Berl.), 1921, **114**, 157-164.

The reaction of the respiratory exchange to adrenine administration was determined in several normal and pathological individuals. It was found in general that the drug causes an increase in lung ventilation and consequent decreased alveolar CO_2 tension with its attendant CO_2 expulsion from the lungs: the respiratory quotient rises and an increased carbohydrate oxidation ensues. When the breathing mechanism remains uniform the respiratory quotient sinks to normal or below and a marked hyperglycemia occurs. In this case the adrenine glycemia certainly does not arise from an increased carbohydrate oxidation. Adrenine also brings about a significant rise in oxygen consumptin.—F. S. H.

(ADRENIN) Bronchial asthma: response to pilocarpin and epinephrin. Alexander (H. L.) & Paddock (R.), Arch. Int. Med. (Chicago), 1921, **27**, 184-191.

In this study of 20 cases of bronchial asthma, a general examination with routine laboratory aids and drug tests revealed no constant associated condition. The most frequent finding was an abnormally increased sensitiveness to pilocarpin. These cases frequently presented constitutional defects (status lymphaticus) and abnormal reactions described as characteristic of the condition called vagotonia. The majority of the cases reacted also to the subcutaneous administration of adrenine with an abnormal rise in blood pressure and other characteristic signs—pallor, tremor, sometimes rigor—which are taken to denote an increased sensitiveness to the drug. A relation between low blood pressure and excessive adrenine reaction was apparent, while the smaller number of cases with normal or high blood pressure gave regularly normal reactions. Those cases which were found to react excessively to adrenine were found to be relieved by 0.25 cc.; a much smaller dose of the drug than is usually employed.—F. S. H.

(ADRENIN) Perfusion of the medulla of the turtle. III. Epinephrin. Bush (A. D.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 297-300.

Perfusion of the medulla, which was completely cut off from circulatory connection with the rest of the body but with intact vagus connections, showed no influence on the cardio-inhibitory center. Heinekamp's technique is questioned. (See Endocrin., **4**, 244.)—F. A. H.

(ADRENIN) The point of attack of certain drugs acting on the periphery. I. Action on the bladder. Edmonds (C. W.) & Roth (G. B.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 189-199.

Contraction of the bladder (cat) was obtained from doses of adrenalin, which raised the blood pressure as much as 35 mm. With larger doses such as those which raised the blood pressure 120 mm. relaxation only was produced. "These results were obtained whether the tracings were taken with the abdomen open, the animal being submerged in a warm saline bath, or with the abdomen closed."—F. A. H.

(ADRENIN) The point of attack of certain drugs acting on the periphery. II. Action on the retractor penis muscle of the dog. Edmonds (C. W.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 201-216.

Adrenine produced contraction in the retractor penis (exact doses not given). After ergotoxin the substance has no effect or gives only relaxation.—F. A. H.

(ADRENIN) III. A note on the action of pilocarpine, atropine and adrenalin upon the tonus of waves in the terrapin heart. Gruber (C. M.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 23-28.

Adrenine chloride decreased the increased tone set up by pilocarpin but increased the height and rate of contraction. It also antagonized the pilocarpin action in those experiments where only a slowing and decrease of the height of contraction was produced.
—F. A. H.

(ADRENIN) IV. The antagonistic actions of epinephrin and potassium chloride on the tonus waves in the excised terrapin auricles. Gruber (C. M.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 271-277.

"Epinephin in proper doses causes a disappearance of the general tone and tonus waves aroused by potassium chloride alone or in combination with calcium chloride, causes a reappearance of the contractions if they have disappeared, and increases the rate and the strength of contractions when still present."—F. A. H.

(ADRENIN) The action of epinephrin on the heart. III. The modification of the action of adrenalin by chloroform. Heinekamp (W. J. R.), J. Pharmacol. & Exper. Therap., 1920, **16**, 247-257.

Chloroform produces a toxic or paralytic dilation of the heart, ventricular fibrillation supervening. Because of this action, adrenine is contra-indicated wherever the drug might otherwise be used. The adrenine action is peripheral since it occurs after section of the vagi. The rise in blood pressure by preventing the emptying of the ventricle acts materially in causing the dilatation of the heart.
—F. A. H.

Discharge of ADRENALIN by excitation, of the splanchnic nerve (Décharges d'adrénaline par excitation du nerf splanchnique). Houssay (B. A.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1279-1281.

Adrenalin has been considered a typical hormone because, 1, it is a specific secretion of the chromaffine tissue; 2, it is thrown into the venous blood; 3, it produces definite functional effects. These facts have been disputed, and Houssay undertook to clear up the matter. The experiments were made on dogs, employing the technique of Von Anrep. The (usually) left splanchnic was cut and stimulated with a tetanizing current. The lumbo-capsular veins were dissected free so that they could be clipped or not, as desired. Arterial tension was recorded, and plethysmograms taken of the enervated hind foot. Excitation of the splanchnic with the veins free, is followed by a rise of pressure. This elevation of pressure fails or is attenuated if the veins are clipped. Stimulation of the splanchnic produces direct vaso-constriction and a discharge of adrenalin. Plethysmograms of the denervated foot show contraction of the peripheral vessels.—T. C. B.

Puncture of the bulb and discharge of ADRENALIN (Ponction du bulbe et décharges d'adrénaline). Houssay (B. A.) & Cervera (L.), Compt. rend. Soc. d biol. (Paris), 1920, **83**, 1281.

The spinal cord was sectioned below the twelfth dorsal and in some cases the pneumogastrics were also cut. With the lumbo-capsular veins free, after puncture of the bulb (fourth ventricle) there is a short dilatation of the enervated foot. With the veins clipped there is no constriction of the foot; but if the forceps are removed two or three minutes after puncture of the bulb, the foot is constricted. The experiment shows that puncture of the bulb produces an intense and prolonged discharge of adrenalin.—T. C. B.

(ADRENIN) A comparison of the prophylactic effects of atropin and epinephrin in anaphylactic shock and anaphylactoid phenomena from various colloids and arsphenamine. Hanzlik (P. J.) & Karsner (H. T.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **14**, 425-447.

"When injected together with the antigen or immediately preceding it, epinephrin in the dosage of 0.0005 cc. of 1:10,000 per gram of body weight intravenously, prevents death from true anaphylactic shock in guinea pigs. The partial protection afforded by epinephrin against the symptoms from arsphenamine disturbances is attributed to circulatory improvement. Epinephrin exerts no protection against the effects of agar sol, agar sol-gel, dextrin, peptone (small doses), starch, and when injected after or too long before the antigen in serum sensitized animals."—F. A. H .

Changes in ADRENIN action after excitation of the vagus nerve-endings (Ueber Aenderung der Adrenalinwirkung nach Erregung der vagalen Endapparate). Kolm (R.) & Pick (E. P.), Arch. f. d. ges. Physiol. (Berlin), 1920, **184**, 79-103.

Adrenine doses which have no action on normal hearts (**R. esculenta**) produce either diastolic standstill or negative inotropia and chronotropia in hearts under powerful vagus action through previous treatment with acetylcholine, **pituitrin**, muscarine, or neurine. The standstill, etc., are removed by atropine. The constrictive action on frog-vessels is removed by atropine administration, though after damage to the peripheral ganglia by nicotine it remains unaltered. After perfusion of frog-vessels with dilute acetylcholine solution adrenine is either without action or dilates. A similar reversed action is produced in the alimentary tract. There is a double antagonism between these two compounds. These "vagotropic" actions can be referred to decreased irritability of the sympathetic nerve-endings.—A. T. C.

(ADRENIN) The secretion of bile (Beiträge zur Kenntniss der Gallensekretion. I.). Neubauer (Ernst), Biochem. Ztschr. (Berlin), 1920, **109**, 82-102.

Studies of the amounts, specific gravity, surface tension, viscosity, reducing power and dry matter of bile produced under normal conditions and under the influence of pilocarpin, atropin and adrenin administration in rabbits. Under so-called normal conditions, after the operation, the amount of bile secreted generally slows down during the first hour and a half to a level, which shows periodic variations with a slight tendency to diminution. The specific gravity of this bile is around 1.01 and slowly decreases during the progress of the experiment along with the total solid content, which at the beginning ranges between 2 and 2.5 per cent. The surface tension is quite constant in the different animals, ranging from 617 to 631, and tends to increase during the period of observation. The viscosity lies around 103. Although the urine contains sugar at the end of the experiment, the bile is sugar free. When pilocarpin is injected the course of the bile secretion is as under normal conditions, though possibly to a lesser degree: the specific gravity tends to increase as does the per cent of dry matter, while the surface tension and viscosity are unchanged. No sugar is present in bile after the injection of pilocarpin. Atropin apparently causes no definite change in these factors when injected into rabbits. When adrenin, however, is administered the bile secretion sinks below that obtaining in the control animals; in fact, with large doses secretion is stopped. The specific gravity rises as does the per cent of dry matter. The surface tension falls and the viscosity is often markedly increased. Subcutaneous adrenin injec-

tions always cause the appearance of sugar in the bile; this is rarely seen after intravenous injections.—F. S. H.

On the sensitiveness of the physiological assay of ADRENALIN; constants of action (Sur la sensibilité de l'essai physiologique de l'adrénaline: constantes d'action). Launoy (L.) & Meugny (B.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1510-1511.

In estimating the therapeutic value of adrenalin, two physiological constants are established and defined: a, Toxicity constant, the smallest dose of adrenalin which will cause death in fifteen minutes; b, Cardio-vascular constant—minimum, medium and maximum. The minimum hypertensive dose is the smallest dose that will raise the pressure not less than 1 cm. Hg., nor more than 3 cm. Hg., with return to normal in the second half of the minute following the injection. The medium hypertensive dose is the smallest dose that will cause a rise of pressure not less than 4 cm. nor more than 6 cm. Hg., with return to normal in seventy-five to ninety seconds. The maximum hypertensive dose "approchée" is the smallest quantity of adrenalin that will raise the pressure not less than 7 cm. Hg., and a return to normal in one hundred fifty to one hundred eighty seconds. The toxicity constant 0.00025 to 0.00030 gm. per kilo of body weight.

The cardio-vascular constants are: Minimum, 0.0000005 to 0.000001 gm.; medium, 0.000005 gm. per kilo; maximum, 0.000015 gm. per kilo.

The absolute maximum is 0.00005 gm. per kilo. Its toxicity does not permit a repetition on the same animal.—T. C. B.

(ADRENIN) The part played by the liver in the regulation of blood volume and red corpuscle concentration in acute physiological conditions. Lamson (P. D.), J. Pharmacol. & Exper. Therap., 1920, **16**, 125-134.

The sudden increase in erythrocytes following the intravenous injection of adrenine is caused by an obstruction in the venous outflow from the liver, an increase in the portal pressure and a constant passage of fluid into the liver lymphatics, thus concentrating the blood. It is shown, by removal, that the liver is responsible for this increase.—F. A. H.

(ADRENIN; PITUITRIN) The restoration of the frog's heart in chloroform poisoning. Ransom (F.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **14**, 367-377.

Perfused frogs' hearts depressed by chloroform were restored to normal or nearly normal activity by adding 1:1,000,000 adrenine. Under the influence of adrenine the hearts continued to beat for

some hours in the presence of toxic amounts of chloroform. Pituitrin failed to have any effect as a restorative.—F. A. H.

(ADRENIN) The action of drugs on the output of epinephrin from the adrenals. VI. Atropine; pilocarpine. Stewart (G. N.) & Rogoff (J. M.), J. Pharmacol. & Exper. Therap., 1920, **16**, 71-107.

The adrenal vein blood was collected in a "cava pocket" made by tying the renal arteries and veins, the lumbar veins before they cross the adrenal, the abdominal aorta just above the bifurcation and the tributaries entering the segment of the cava which constitutes the pocket. A cannula was inserted into the lower end of the pocket. Blood was trapped by clipping the cava just below the liver. Epinephrin was assayed on rabbit's intestine and uterus segments. No significant alteration in the rate of output of epinephrin from the adrenals is caused by either of these drugs. A moderate increase may be produced by atropine. In one experiment a moderate depletion of the epinephrin store by pilocarpine was indicated.—F. A. H.

(ADRENIN) Epinephrine content of the suprarenal glands in anaphylaxis. Smith (M. I.) & Ravitz (S.), J. Exper. Med. (Balt.), 1920, **32**, 595-600.

Guinea pigs were used in these experiments, as were rabbits. Although controls were used no note is made of whether or not they were litter controls. The animals were sensitized by a subcutaneous or intraperitoneal injection of ox serum, and after an incubation period of at least two weeks they were reinjected with the antigen intravenously. Immediately after death or at the height of the shock the adrenals were removed, weighed and their adrenine content determined. The results of the experiments were uniformly negative in that the adrenine store of the adrenals was found to remain unaltered under the conditions described.—F. S. H.

(ADRENIN) The blood picture before and after the Goetsch epinephrin test. Trott (Rose M.), Arch. Int. Med. (Chicago), 1920, **26**, 352-356.

Observations were made of 13 cases in which the Goetsch adrenine test was applied. The morphology of the blood was studied. It was found that the subcutaneous administration of from 4 to 8 minims of adrenine will quickly produce a rise in the leucocyte count and cause an absolute lymphocytosis in hyperthyroid individuals. From these experiments it is concluded that in toxic goiter an increase in the lymphocytes is not always present, especially in the borderline cases. A normal differential count is often found and in some cases a polymorphonuclear leucocytosis exists.—F. S. H.

Are the active principles of CORPUS LUTEUM and the PLACENTA specific for the sex (Ist die aus Corpus luteum bzw. Placenta hergestellte wirksame Substanz geschlechtsspezifisch)? Herrmann (E.) & Stein (M.), Zentralbl. f. Gyn. (Leipzig), 1920, **44**, 1449-1451.

When the active principle of corpus luteum or placenta is injected into female animals the sexual organs become enlarged. In male animals, however, the gonads are reduced in size.—J. K.

Cholelithiasis and involuntary nervous system (Cholelithiasis und vegetatives Nervensystem). Lehmann (G.), Berl. Klin. Wchnschr., 1921, **58**, 30-31.

The author injected pilocarpin, atropin and adrenine into 40 patients with cholelithiasis. He found just the same reactions as in persons without this disease. The antagonism vagotonia-sympathicotonia as described by Eppinger and Hess does not exist. Many patients have vagotonia and sympathicotonia at the same time.—J. K.

Experimental studies on DIABETES. Series I. Production and control of diabetes in the dog. 3. Effect of protein diets. Allen (F. M.), J. Exper Med. (Balt.), 1920, **31**, 555-574, ibid. **4. Control of experimental diabetes by fasting and total dietary restriction.** 574-586, ibid. **5. Various failures of dietetic treatment and their causes.** 587-608, pls. 65-66.

Continuing the studies previously reported (cf. Endocrin., **4**, 446), Allen found that no specific differences were observed between the glycosuric effect of different kinds of protein when fed to his experimental animals. The second paper gives in some detail the effects of dietary restriction on the partially depancreatized dogs, the main point of which was to determine whether downward progress is inevitable in an animal with potentially severe diabetes, so that symptoms must occur ultimately in spite of dietary restriction. The report indicates that there was a gain in tolerance resulting from the treatment. In the third paper the following conclusions are drawn: Practically every detail of clinical diabetes can be produced in partially depancreatized animals. The resemblance is made still more exact by the susceptibility of such dogs to acidosis and coma. The animals at first show considerable tendency to regain assimilation, comparable to that in the early stages of most human cases of diabetes; and in some instances they recover so as to be able to endure any degree or duration of carbohydrate feeding, and can be made diabetic only by further removal of pancreatic tissue. This recuperative tendency can be negatived by overfeeding. With duration of diabetes the power of recuperation diminishes. In the absence of a progressive pancreatitis these dogs

show no downward tendency that is inherent. The conclusions rest upon observations as long as six years from the first pancreas operation and three years of known diabetes. Every detail of the downward progress of human patients on various diets is reproduced in such animals. The important point is that, granting the absence of spontaneous downward tendencies as stated, all the different kinds and degrees of downward progress in the records of animals in this and the preceding paper are purely the results of overstrain of the internal pancreatic function by excess of food. Varying degrees of success and failure in the dietetic control of diabetes are illustrated. The benefit of the classical treatment by exclusion of carbohydrate and limitation of protein is confirmed: though such a result is not permanent.—F. S. H.

A case of hereditary DIABETES. Allen (F. M.) & Mitchell (J. W.), Arch. Int. Med. (Chicago), 1920, **25**, 648-660.

A case report of a patient who came of a family in which 7 out of 14 children of one father (1 by 1 woman, 13 by another) were diabetic. Clinical examination of the patient and his family for general and focal infections, including clinical and serological examinations for syphilis, were negative. In general, the diabetic heredity, which apparently came through the father, was manifest in the children who most resembled him in coloring or complexion, eyes and hair, but the rule was not absolute. As far as the glucose tolerance tests could decide, the diabetic tendency was inherited as a unit character and the tolerance of the remaining children was apparently normal.—F. S. H.

Experimental studies in DIABETES. Series II. The internal pancreatic function in relation to body mass and metabolism. 5. The influence of fever and intoxication. Allen (F. M.), Am. J. Physiol. (Balt.), 1920-21, **54**, 375-381.

The first four papers of this series are published in the American Journal of the Medical Sciences. In the present research it was desired to compare several forms of infectious and non-infectious fevers in their influence on partially depancreatized dogs. Protocols of observations on distemper, pneumonia, pleurisy, subcutaneous abscesses, infected glands, ratus, peritonitis, etc., are given. The conclusion is reached that the aggravation of diabetes which occurs in human cases in the form of an increased tendency to glycosuria and acidoses does not occur in dogs. Infection and fever have no specific influence in diminishing the diabetic tendency in dogs. The aggravation of human diabetes is a reaction to intoxication rather than to fever.—T. C. B.

Experimental studies in DIABETES. Series II. The internal pancreatic function in relation to body mass and metabolism. 7.

The influence of cold. 8. The influence of extremes of age upon the production of diabetes. 9. The influence of pregnancy upon experimental diabetes. Allen (F. M.), Am. J. Physiol. (Balt.), 1920-21, **54**, 425-459.

These three papers deal with the problems indicated in the subtitles. In the majority of cases cold environment caused hyperglycemia and sometimes glycosuria. These were produced more easily as the diabetes was more severe. In some instances the plasma sugar was unaffected or lowered. "The impression that diabetic patients do worse in cold weather is probably explainable by the discomfort of chilliness when undernourished, the tendency to take more food, and sometimes by the limitations of exercise. These may be important sometimes from a practical standpoint, but any direct influence of climate upon diabetes must be very slight if it exists." "The power to produce glycosuria must be distinguished from the power to produce diabetes."

It is conceivable that senility may influence carbohydrate assimilation by quantitative alterations of metabolism, or functional or anatomic changes in the pancreas. Observations upon senile dogs failed to show any changes from the normal in tolerance, microscopic structure or ratio of pancreas to body weight.

Previous work indicates that glucose tolerance of puppies is less than that of adult dogs. No exact studies of the richness in islands, but no striking departure from the adult average was noticed in the pancreas. The ratio of pancreas weight to body weight was irregular. The general average in puppies did not differ from that in adults. The remnant left after pancreatectomy generally grows considerably in puppies. The tendency to diabetes is distinctly less in puppies.

As pregnancy involves an increased assimilation of food, and the formation of new tissue, it is possible this condition may aggravate diabetes. On the other hand Carlson suggests that diabetes may be prevented by the internal secretion of the fetal pancreas. Partially depancreatized dogs were used, and controls described. The possible effect of changes in the sex organs was studied. No positive influence of the sex glands upon diabetes was demonstrable, and there were no changes in the pancreas with pregnancy or lactation. "Observations on a partially depancreatized dog during pregnancy are opposed to the view that any appreciable quantity of internal pancreatic secretion passes from the fetus to the mother." A distinct lowering of the carbohydrate assimilation was shown during pregnancy. It is suggested that Carlson's results on totally depancreatized dogs are to be interpreted as cachexia. "The slight tendency to aggravation of the diabetes and the ready control by diet support Joslin's experience of the

feasibility of completion of pregnancy by diabetic women under suitable condition of treatment.—T. C. B.

(DIABETES) The relations between glycosuria and glycemia. Faber (K.) & Norgaard, Acta med. Scand. (Stockholm), 1921, **53**, 666-672.

The authors determined the glycemia threshold of 52 diabetics at the cessation of glycosuria following Allen's treatment. In 11 it was found to be 0.09 to 0.13%; in 28 it was 0.14 to 0.18%; in 12 of the remaining 14 the glycosuria was diagnosed as of the alimentary type and gave a glycemia of 0.09 to 0.13%, the remaining two a higher value of 0.16% was found. The glycemia seems to be constant in amount in the same individual for long periods of time, and does not seem to be any different from the normal, particularly in the cases of alimentary glycosuria. There is apparently no connection of the degree of glycemia with the age or sex of the patient or the duration of the disease. A brief discussion is made of the method of testing for the urinary and blood sugar and the time of taking the sample for analysis.—F. S. H.

(DIABETES) On the threshold value for glycosuria. Hagedorn (H. C.), Acta med. Scand. (Stockholm), 1921, **53**, 672-679.

Not of endocrine interest.—F. S. H.

Cases of mild DIABETES. Jacobson (Th. B.), Acta med. Scand. (Stockholm), 1921, **53**, 679-683.

No new data.—F. S. H.

DIABETES The relations between creatinuria and acidosis in—. Lauritzen (M.), Acta med. Scand. (Stockholm), 1921, **53**, 688-700.

Using a method of doubtful exactness for the determination of creatine, the author presents six curves purporting to show the relation between urinary creatine, acetone-bodies and sugar. The results are interpreted as showing that the cause of diabetic creatinuria is like that of acidosis, a deficient metabolism of carbohydrates.—F. S. H.

Pernicious anemia and DIABETIC cases. Slaymaker (S. R.), Med. Rec. (N. Y.), 1916, **38**, 191-194.

The author records symptoms in a case of pernicious anemia and an improved condition due to Fowler's solution and Blaud's pills. To safeguard from remissions splenectomy is contemplated. Three patients exhibiting marked glycosuria together with gangrene or cellulitis were serious cases. An effort is made by diet to reduce the sugar and at the same time avoid acidosis.—F. S. C.

Experimental studies in DIABETES. Series II. The internal PANCREATIC function in relation to body mass and metabolism. 6. Gas bacillus infections in diabetic dogs. Wishart (Mary B.) & Pritchell (Ida W.), Am. J. Physiol. (Balt.), 1920-21, **54**, 382-387.

Four dogs had died of gas bacillus. As gas bacillus is rare in dogs it was decided to follow up these accidental observations by experiments on diabetic dogs, to determine whether the animals are abnormally susceptible to such infection either by reason of excess of circulating sugar, or a lowering of resistance; also if there is an aggravation of diabetes by such infections.

It is concluded from the observations that there is no lowering of resistance in these animals due either to the diabetes or to an excess of sugar. The lowering of tolerance by infection was demonstrable both by feeding and by intravenous glucose tests.

—T. C. B.

DIABETES insipidus. van der Heide (C. C.), Ned. Maandschrift v. Geneesk. (Leiden), 1920, **1**, 618-624.

A report of two cases with normal sella turcica on x-ray examination. In one case **pituitrine** had a temporary good influence, in the other case it was not tried. The article is not of much interest as the patients were not examined in an exhaustive way.

—J. K.

Fat metabolism in DIABETES mellitus. Blau (N. F.) & Nicholson (S. T.), Arch. Int. Med. (Chicago), 1920, **26**, 738-750.

The authors made a study of 26 cases of diabetes with regard to the relation between the blood fat and the blood sugar. The results of the observations lead to a classification of the individuals studied into three groups, on the basis of the effects of the Allen-Joslin method of treatment. About 42 per cent of the cases showed at the beginning of the treatment a marked increase of the blood lipoids accompanied by a drop in the blood sugar. In about 27 per cent of the cases the blood fat seemed to rise and fall with the blood sugar. In about 31 per cent of the cases there was a continued high blood fat content while the blood sugar was decreasing.—F. S. H.

Case of hirsutism with DIABETES mellitus (Un cas d' hirsutisme avec diabète sucré). Emile-Weil (P.) & Plichet, Bull. et mem. Soc. méd. d. hop. de Par., 1921, **45**, 312-320.

A rather complete clinical case report of this condition followed by a detailed autopsy record of a woman of 38 years of age. The hirsutism had appeared at the age of 26 years after a normal pregnancy, and was complicated by obesity and diabetes mellitus, which finally terminated in a galloping febrile tuberculosis. The

only abnormal organ found at autopsy was a fibrous ovary in which no interstitial cells could be found. Since no adrenal changes were found this case must be attributed to the functional and anatomical suppression of the ovary. The author does not think that the simultaneous occurrence of the diabetes and the hirsutism is a coincidence and feels that it is somehow associated with the adrenals, though the connection is hard to see.—F. S. H.

The relation of hypoTHYROIDism to DIABETES MELLITUS. Fitz (R.), Arch. Int. Med. (Chicago), 1921, **27**, 305-314.

A review of the literature and discussion of the earlier findings precedes the report of the findings in 5 cases of diabetes associated with nontoxic thyroid enlargement, in 4 cases associated with toxic thyroid disease, in 3 cases of exophthalmic goiter complicated by diabetes, and 9 cases of exophthalmic goiter and toxic adenoma in which operation was performed. Attention is drawn to certain features that are marked in regard to the results of these studies. It appears that hyperthyroidism and diabetes occur together in the same person in a small number of cases. There is, however, no established evidence that such coincidence is more than chance. The diabetes usually follows the thyroid disturbance, but may precede it, and tends to parallel in severity the severity of the thyroid intoxication. There is no reason for assuming that partial thyroidectomy alone has any curative effect on diabetes, as the patients in this series with nontoxic goiter who were operated on showed no improvement of the diabetes. On the other hand, certain patients with toxic thyroid disease and diabetes, improve to a considerable degree after the thyroid symptoms are checked. This probably occurs because of a change in the rate of metabolism and not because a portion of the thyroid gland has been made functionless.—F. S. H.

DIABETES mellitus, On determination of carbohydrate tolerance in patients with—. Lundsgaard (C.), Acta med. Scand. (Stockholm), 1921, **53**, 685-688.

This article starts off with the statement that no exact definition exists of the expression: individual tolerance for carbohydrate. The author is apparently unfamiliar with the mass of material in the American literature. He goes on to describe results obtained from 40 patients who had been starved till sugar-free and then put on a high carbohydrate diet, increasing every day by 100 calories. His conclusions are too indeterminate to be of wide practical importance.—F. S. H.

DIABETES mellitus. Milber (H. H.), Wisconsin M. J. (Milwaukee), 1918, **17**, 48-51.

A brief discussion of pancreatic diabetes and the Allen treatment. Nothing new offered.—C. W.

The D. N. ratio in DIABETES MELLITUS. Mosenthal (H. O.) & Lewis (D. S.), Johns Hopkins Hosp. Bull. (Balt), 1917, **28**, 187-191.

The authors present the data of one case of diabetes mellitus demonstrating a maximal dextrose-nitrogen ratio of 3.65:1. This maximal ratio has been demonstrated in a few rare cases previously by other observers. Over a period of 12 days this high ratio was shown to exist almost constantly, indicating that the tissues were entirely incapable of utilizing the glucose from either protein or carbohydrates. Calories from fats were partially made use of, but only those from alcohol were entirely metabolized. The islands of Langerhans in the pancreas showed advanced hyaline degeneration. The Allen treatment did not prove efficient in this case, due perhaps to the existence of an infected bunion which complicated the maximal diabetes.—J. M.

The use of a high fat diet in the treatment of DIABETES mellitus. Newburgh (L. H.) & Marsh (P. L.), Arch. Int. Med. (Chicago), 1920, **26**, 647-662.

This paper gives in some detail the various high fat diets used in 10 cases of diabetes mellitus. Three diets are described and tabulated with variations within each group allowing for change of fuel supply. The authors claim that the diets outlined will tend to keep the patients sugar free, will tend to prevent the occurrence of a serious acidosis, will maintain nitrogen balance and will make possible the return to the ordinary activities of everyday life.—F. S. H.

DUCTLESS GLANDS, Studies on the minute innervation of—. White (H. O.), Anat. Rec. (Phila.), 1920, **18**, 265.

Speculative only.—W. J. A.

DWARFISM (Zwergwuchs). Sternberg (K.), Wien, med. Wchnschr., 1919, **69**, 2533.

See Endocrin., **4**, 267.

Combined DYSTROPHY with loss of vesical control. McKendree (C. A.), Neurol. Bull., N. Y., 1918, **1**, 61-63.

A case report not of endocrine interest.—H. W.

(ENDOCRINE ORGANS) A study of unusual endocrine disturbances; their associated myopathies, endocrine balance and metabolism findings. Brock (S.) & Kay (W. E.), Arch. Int. Med. (Chicago), 1921, **27**, 1-37.

An interesting and detailed clinical description and discussion of three unusual cases in which remarkable endocrinopathies are associated with unusual manifestations of the muscular system. The length of the article and the intensive treatment accorded each patient make a satisfactory abstract out of the question, and the article should be consulted in the original by those interested in the phases covered. The first case is one of the dystrophia adiposogenitalis in which it was difficult to differentiate between the hypophyseal and the pure or primary genital forms of the disorder. Although there were no changes in the sella turcica, no signs of intracranial pressure, no polyuria, no subnormal temperature and no blood changes, yet the lowering of the basal metabolism is considered as favoring a pituitary participation as against the **gonadal** determinant. Muscle dystrophy was present. The second case is considered as one in which there was a hyperactive adrenal system because of hirsutism, increased blood pressure, increased muscular strength and cardiac hypertrophy. The definite **thymus** shadow indicates participation of this gland, while the peculiar adiposity, the shallow sella turcica, the increased sugar tolerance bespeak a definite **hypopituitarism.** The increased muscle strength is all out of proportion to the size of the individual. The third case is described as having a cretin facies, a **thyroid** enlargement, a subnormal temperature, an increased sugar tolerance, a thick skin and a hypotonic vegetative nervous system. Testicular atrophy was present. **Parathyroid** involvement is suggested by the myotonia. The three cases studied were examined by almost all of the well known laboratory methods.—F. S. H.

(ENDOCRINE ORGANS) Blood-sugar regulation and the origin of the hyperglycemias. I. Glycogen formation and glycogenolysis. Langfeldt (E.), J. Biol. Chem. (Balt.), 1921, **46**, 381-390.

The first paper in this series deals with a review of the literature and the expression of the views of the author with regard to the mechanism of blood-sugar regulation, as based on the experimental work from the historical point of view. Ibid. II. **Conditions of action of liver diastases.** 391-402. This paper gives the report of the experimental work carried on which leads to the theory developed by the author and which is presented in the 3rd and last part. The experiments consisted in incubating glycogen with liver diastase at different hydrogen-ion concentrations by which the optimum for the reaction was found to be at pH 6,2 in the presence of phosphate ions, and for the chloride diastase at 6,8. When **adrenine** was added to the ferment mixture the reaction optimum is shifted to the alkaline side with the pH of 7,73. When **thyroiodine** is added no change is observed; but when both adrenine and thyroiodine are added a very marked effect is observed in the form of an accelerating action on

glycogenolysis. Extracts of the posterior and anterior lobes of the **hypophysis** have no influence on this process. Ibid. III. **Theory.** 403-409. On the basis of the experimental results and of the exposition of the facts observed by others, an attempt is made to explain the blood-sugar regulation and the mechanism of the origin of the hyperglycemias. In the first place the author is of the opinion that it is not necessary to suppose any cause at a distance serving as a regulating mechanism for liver glycogenolysis and that the theory of the requirement of the organs for sugar may be disregarded. We do not know of nor have we proved the existence of any glycogenolytic agency in the liver other than diastase. As this enzyme action is dependent on the precise regulation of the hydrogen-ion concentration we may suppose that glycogenolysis is regulated by the hydrogen-ion concentration in the liver tissue. According to this opinion sugar formation should be constant. Under normal conditions the liver always discharges the same quantity of glucose, i. e., with a constant blood flow and at a constant temperature. A part of the glucose is burned, a part is stored in the muscles and tissues as glycogen, and the remainder returns to the liver and is reformed into glycogen. Here glycogen formation depends upon the **pancreas** hormone, and the material for this formation is chiefly the carbohydrates and the proteins of the food. This theory also explains why the blood-sugar concentration is constant when the liver is exhausted of glycogen, and in starvation. The conclusion is reached that glycogen formation and glycogenolysis are consecutive processes. Now hyperglycemia may arise in three ways. By a change in the hydrogen-ion concentration of the liver tissue, by a displacement of the curve of action of the liver diastase such as may be produced by adrenine or by adrenine and thyroiodine combined, and by a lack of formation of glycogen on account of the insufficient functioning of the pancreas hormone.—F. S. H.

A note on the brown granules formed in some ENDOCRINE ORGANS. Lim (R. K. S.), J. Physiol. (Lond.), 1920, **54**, xxx.

"These granules have been noticed in the **suprarenal** cortex of the cat, the **corpus luteum** of the rabbit, and the pars nervosum of the human **hypophysis.**" Their staining properties are described. —T. C. B.

The process of growth during hypofunction of one or more ENDOCRINE ORGANS, induced experimentally in young cats and dogs (Le processus de la croissance dans l'hypofunction d'une ou plusieurs glandes endocrines, provoquée expérimentalement chez les chats et les chiens tout jeunes). Pugliese (A.), Arch. ital. de Biol. (Torino), 1920, **70**, 1-34.

The simultaneous extirpation of one **adrenal** and one **thyroid** lobe with or without splenectomy produces no apparent effect in adult or nearly adult cats and dogs. They remain in good condition, can procreate and raise offspring. Unilateral **thyro-parathyroidectomy** favors increase of body-weight in very young animals; removal of one adrenal slows it. Kittens below the age of 4 months do not as a rule survive the removal of one adrenal and one thyroid lobe. After an initial lowering of body-weight following the operation, succeeds a period of feeble and difficult development, at the end of which the body-weight is about one-fifth more than that preceding operation. The succeeding decline is more or less rapid, the animals dying between 80 and 104 days after the operation. Body fat is greatly reduced. The bones are smaller, thinner, contain much less nitrogenous material and fat, while their ash, calcium, and phosphorus content are increased. At death the remaining adrenal and thyroid lobe, and the **pituitary** appear to be hypertrophied. Splenectomy has no effect on these results. The effects on pups are less. They survive the operation, grow at a slower rate than the controls, fatigue more easily, present less resistance to disease, but the body temperature remains unaltered, and though the bones are smaller and thinner, their composition is not greatly altered. Fat is somewhat diminished, both in bones, blood, and liver, and the fat depôts are diminished. The remaining adrenals of these animals do not appear to hypertrophy, the thyroid may or may not do so. To a hypertrophied thyroid corresponds a reduced **thymus**; to a thyroid appearing normal corresponds a thymus greatly enlarged. The pituitary is only one-fourth to one-fifth of normal size. Of the other organs only the liver and heart show decreases greater in proportion than that of body-weight.—A. T. C.

(GENERAL) Review of symptoms of osteomalacia as a pluriglandular endocrine disorder (Uebersicht über die Symptomatik der Osteomalazie als innersekretorischer pluriglandulärer Erkrankung. Nach 11 eigenen und nach Literaturbeobachtungen). Naegeli (O.), München med. Wchnschr., 1918, **65**, 585-586.

A general consideration of the pathology of the muscular, skeletal, nervous and endocrine system as associated with osteomalacia. Osteomalacia may be looked upon as the result of an unbalanced endocrine system.—C. W.

(GENERAL) Beta-imidazolylethylamine as a powerful stimulant of the gastric glands (Beta-imidazolyläthylamin als mächtiger Erreger der Magendrüsen). Popielski (L.), Arch. f. d. ges. Physiol. (Berlin), 1920, **178**, 214-236.

Histamine has been shown to be produced by the action of bacteria on histidine. Injected intravenously into dogs it rapidly pro-

duces a fall of blood pressure, with excitement, then depression, secretion of saliva, tears, and pancreatic juice, urination and defaecation. Introduced into the intestine it is without action. Injected subcutaneously, it only induces acid gastric secretion. Injection of 0.00021 gm. per kilo body-weight produces 3.75 cc. per kilo. This secretion takes place after section of the vagi and injection of atropine, and is probably directly on the cells. This substance is probably produced when tissue extracts are subcutaneously injected.
—A. T. C.

(GENERAL) Influence of acids on the stimulative action of tissue extracts on gastric secretion. (Einflus der Saüren auf die Magensaftsekretion erregende Wirkung der Organextrakte). Popielski (L.), Arch. f. d. ges. Physiol. (Berlin), 1920, **178,** 237-259.

Tissue extracts introduced subcutaneously induce, like histamine, marked gastric secretion; acids such as citric, acetic, mono- and di-chloracetic, lessen the action. Trichloracetic acid increases it. The active substance (probably histamine) probably unites with the first series of acids. Giddiness and apathy, which follow subcutaneous injections of histamine, result from the abstraction of fluid from nerve cells consequent on the marked gastric secretion. Therapeutically this substance should not be used intravenously, since it can lead to dangerous results.—A. T. C.

(GONADS) Hermaphroditism in China. (Author's name omitted.) China M. J. (Shanghai), 1920, **34,** 608-611.

A useful review of literature, special attention being devoted to an article by Berthold Laufer entitled "Sex Transformation and Hermaphrodites in China" (A. J. Phys. Anthrop., 1920, iii, 259-262). One case of pseudo-hermaphroditism is reported.—E. V. C.

(GONADS) Hermaphroditism in fundulus heteroclitus. Chidister (F. E.), Anat. Rec. (Phila.), 1917, **12,** 389-396.

The author describes the only known case of hermaphroditism in this species. The discovery is of particular importance because this species is much used in experimental embryology. It was a conspicuously well marked male in external appearance. The gonads which gave the secondary sex characters were entirely male and were in no way attached to the diffuse egg masses. The latter were found in close association with the organs of digestion and in some cases occupied positions under the serous coats of the organs. Apparently well developed eggs were present and were found to be incapable of fertilization. The testes were entirely normal. The striking feature was that the diffuse egg masses exerted no influence on the secondary sex characters as do normal condensed ovaries.—J. M.

(GONADS) A case of Chinese hermaphrodite and a case of a dicephalous monster. Lin (C. S.), Nat. M. J. China (Shanghai), 1920, **6**, 208-211.

A description of one case of pseudo-hermaphroditism.—E. V. C.

(GONADS) True hermaphroditism in man (Ueber wahre Zwitterbildung beim Menschen). Polano (O.), Ztschr. f. geburtsh. u. gynäk. (Stuttgart), 1920, **83**, 114-150.

This is an extended report of a case of true hermaphroditism in an individual of 24 years of age in whom there were present the external and internal genitalia of both sexes. The **ovaries** gave every evidence of functional activity, though the **testicles** were not yet at the adult stage. The male and female hormonal activities due to the gonads were apparently in full operation.—F. S. H.

(GONADS) The metabolism of the eunuch. Read (B. E.), J. Biol. Chem. (Balt.), 1921, **46**, 281-283.

Report of the amounts of total nitrogen, urea, ammonia, creatinine and creatine in the 24 hour urine of a eunuch. Creatine was found to be present in some quantity as well as was ammonia. The abnormal creatine content in castrated males was confirmed in 5 other cases. There appear to be differences in the effect on metabolism that are related to the different ages at which the individuals are castrated. From the fact that creatine is found in the urine of these individuals the conclusion is made that the removal of the male organs at a suitable age tends to develop chemical as well as secondary sexual female characteristics in the individual.—F. S. H.

(GONADS) Atypical male sex-ensemble in the domestic goat. Stone (Robert S.), China M. J. (Shanghai), 1920, **34**, 611-623.

The author's abstract is as follows: "A case of atypical male sex-ensemble occurring in a goat is reported. The abnormality consisted essentially of persistence and growth in this male individual of certain of the female genital ducts and of inhibition of development of the male external genitalia. The abnormality was seen to be the result of unusual embryological development. The cause probably depended upon some temporary derangement of the endocrine system during embryonic life, which gave rise to a physiological state favoring the development of female characters."—E. V. C.

(GONADS) Ovulation, corpus luteum and menstruation (Ueber Ovulation, Corpus luteum und Menstruation). Tschirdewahn (F.), Ztschr. f. geburtsh. u. gynäk. (Stuttgart), 1920, **83**, 80-111.

This is another of those lengthy papers on the factors of the menstrual cycle, in which all the previous studies are reviewed.

Extensive tables are given of the type and time of menstruation in various patients, but no statistical study is attempted. The opinion is expressed that one, rarely two, follicles periodically ripen in the healthy woman. The follicles rupture individually and in the same person between the 10th and the 26th day after menstruation. While the ovum is passing through the tube the transformation of the follicle to luteum is taking place. The hormone formed by this, which perhaps is already performed by the theca lutein cells, acts on the uterine nucosa to prepare it for implantation or menstruation.

—F. S. H.

Epilepsy and HYPOPHYSEAL adiposity (Epilepsie combiniert mit endogener [hypophysärer] Fettschut). Ibrahim, Kor. Bl. d. allg. ärztl. Ver. v. Thüringen (Jena), 1919, **48**, 119.

See Endocrin., **4**, 128.

Tumor of HYPOPHYSIS (Hypophysisgezwel). Klinkert (H.), Ned. Tijdschr. v. Geneesk (Haarlem), 1921, **65**, 466-467.

The patient reported in this study was 40 years old. His illness began with atrophy of both optic nerves and hemianopsia. No headache was present. The pressure of the cerebrospinal fluid was found increased by the lumbar puncture test. In the cerebro spinal fluid albumin was found. The x-ray showed changes in the sella turcica. No symptoms of acromegaly were present.—J. K.

(HYPOPHYSIS) Adiposo-genital dystrophy accompanied by epileptic attacks (Distrofia adiposo-genital frusta con ataques epilepticos). Malamud (T.), Prensa med. Argent. (Buenos Aires), 1920, **7**, No. 3, June 30th.

Case report of an epileptic of 14 years with adiposity and menstrual difficulties. Improvement by subcutaneous hypophyseal opotherapy.—B. A. H.

(HYPOPHYSIS) Cure of dystrophia adiposo-genitalis on basis of hereditary lues (Heilung von Dystrophia adiposogenitalis auf der Basis von Lues hereditaria). Nonne (M.), Deutsche med. Wchnschr. (Leipz. u. Berl.), 1918, **44**, 536.

A report of a case of adiposo-genitalis showing adiposity, infantile genitals, absence of secondary sexual characters, polyuria and infantile psyche. The patient gave a three plus Wasserman reaction. The mother and three of her sisters also gave positive Wasserman reactions and demonstrated signs of hypophyseal disturbances.—C. W.

Muscular INFANTILISM. Gibson (A.), Arch. Int. Med. (Chicago), 1921, **27**, 339-350.

This is a case report of a patient complaining of muscular weakness. There was a creatine excretion which suggested infantilism, a marked adiposity, a normal blood sugar and a normal sugar utilization. **Adrenine, pituitrine,** and **thyroid** substance were administered at one time or another and the metabolism was studied in the two latter attempts at medication. Pituitary administration had no effect, while during the thyroid administration excessive carbohydrate was used without obviously modifying the thyroid effect. There was initially a slight increase in creatine, which lasted two or three weeks, which later was not obtained. The diagnosis is tentatively given as muscular infantilism.—F. S. H.

(INTERNAL SECRETIONS) Tissue extracts with specific action (Studien über die von einzelnen Organen hervorgebrachten Stoffen mit spezifischer Wirkung. III.). Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berlin), 1920, **182,** 28-49.

The "optones" (completely hydrolysed products) of the **corpus luteum** and **testes** produce a mydriatic action on the enucleated frog's eye, and diastolic standstill on Straub's heart-preparation, and seem to belong to the group of parasympathetic inhibitory substances. Pituitary and thyroid optones produce miosis, and either no heart action or a powerful pulse increase. The **thymus** optone produces mydriasis, but only slight pulse slowing. The **ovarian** and **anterior pituitary** optones promote **adrenin** mydriasis. When miotic and mydriatic optones are used together, mydriasis is usually pronounced. Only a **thyroid-testis** optone combination leads to miosis. —A. T. C.

The INTERNAL SECRETIONS. Friedman (E. D.), New York, 1919, Wm. Wood & Co., 36 p., 8°.

See Endocrin., **4,** 470.

The influence of glands with INTERNAL SECRETIONS on the respiratory exchange. 1. The effect of the subcutaneous injection of adrenalin on normal and thyroidectomized rabbits. Marine (D.) & Lenhart (C. H.), Am. J. Physiol. (Balt.), 1920-21, **54,** 248-260.

Asher and Flack gave the first concrete evidence that there was a relation between **thyroid** and **adrenals.** They showed that stimulation of the laryngeal nerves in rabbits prolongs the rise of blood pressure following injections of adrenalin. The authors have compared the effect of subcutaneous injections of adrenalin in normal and thyroidectomized rabbits. The dose of adrenalin was arbitrarily fixed at 0.5 cc. per kilo. The rabbits were deprived of food for 15 hours before the experiment. The results on rabbits confirm those of Sandiford on man. Adrenalin causes a rise in oxygen con-

sumption in both normal and thyroidectomized rabbits. The O_2 consumption following adrenalin is delayed in thyroidectomized rabbits, and does not last so long. The decrease in the metabolic rate following thyroidectomy is gradual, and requires several days for its demonstration.—T. C. B.

LYMPHATISM with disturbed INTERNAL SECRETIONS (Lymphatismus mit innersekretorischen Störnngen). Moose (M.), Berl. klin. Wchnschr., 1920, **57**, 971-974.

In a girl of 19, 5 weeks after an attack of influenza, there developed a general weakness with rheumatic pains, local edema of face and legs, dryness of skin, enlarged **thyroid**, large tonsils and enlarged follicles of the tongue. A persistent **thymus** could be detected by percussion. Tuberculosis of both lungs was present.—J. K.

(INTERNAL SECRETIONS) Experimental studies of the properties of surviving vessels tested by chemical methods of stimulation (Experimentelle Studien über die Eigenschaften überlebender Gefässe unter Anwendung der chemischen Reizmethode). Rothlin (E.), Biochem. Z. (Berl.), 1920, **111**, 219-256.

This first paper is mainly concerned with a description of the conditions regulating the proper conduction of experiments for the study of vaso-active compounds on isolated blood-vessels, which leads to the conclusion that such material is quite suitable for qualitative work where high sensitivity is required. II. The action of some chemical vaso-tonic substances of organic nature (II). Experimentelle Untersuchungen über der Wirkungsweise einigen chemischer, vasotonisierender Substanzen organischer Natur auf überlebende Gefässe), idem. 257-98. Using the isolated blood-vessel as the test organ R. was unable to demonstrate the presence in norm. blood of any vaso-tonic substance besides **adrenin** with any safe regularity, although in blood serum there is found a vaso-constrictor substance which is not adrenin. Adrenin action is then tried out on various blood-vessels from different organs and different animals. The irritability of the renal vessels towards adrenin is the same as is that of the others studied: they can be constricted or dilated at will by the drug, depending on the dose employed, and both the proximal and the distal portions react in the same way. However, on the coronary vessels a qualitative and quantitative difference is obtained. The coronary vessels from the equine type are contracted. In the bovine type weak concentrations cause a weak contraction, while stronger doses, after a latent period, bring about a dilation. The vessels from swine and sheep act similarly. On the isolated lung vessels of both equine and bovine type adrenin in normal doses produces contraction. III. idem. 299-335. This third and last paper of the series first takes up the effect of Beta-imidazolylethylamine

in the same manner **adrenin** was studied. Apparently there exists a qualitative difference in the action of histamine on different surviving blood-vessels. Arterial strips from various sources from various kinds of animals, as well as the vessels of the rabbit ear, are regularly contracted by the compound in concentrations in which adrenin has a similar action. All the vessels of the frog, however, are inconstant in their response and the effective doses are from 10 to 100 times as weak. **Pituglandol** is also inconstant in the type of its reaction on the frog, though it constricts the vessels of the rabbit ear. **Lienin,** a preparation from the **spleen,** acts as a vaso-constrictor on the isolated segment, the vessels of the rabbit ear and those of the frog's vessels that are capable of being so influenced. These effects on the isolated blood-vessel strips are in general quite comparable with those obtained **in vivo,** and serve to demonstrate that the latter are largely the results of the response of the tissue itself and not due to mediation through extraneous sources.—F. S. H.

The effect of MENSTRUATION and OVARIOTOMY on the cutaneous reaction to tuberculin (La cuti-réaction a la tuberculine pendant les règles et après ovariotomie). Coulaud (E.), Bull. et mem. Soc. Méd. d. hop. de Par., 1921, **45,** 155-159.

C. observed that the skin-test with tuberclin was negative in 2 cases during the first day of menstruation, becoming positive 8 days later. In a third case the reaction was negative on the day the periods were expected but did not appear, and was positive 15 days later, although menstruation had not occurred. In 2 out of 5 goitrous cases the reaction was very weak on the first 2 or 3 days of the periods and later became strongly positive. Tests were also made on 60 apyretic tubercular patients -and it was noticed that the reaction is weaker at the beginning of the menstrual period. This was very marked in 12 of the cases and was substantiated by suitable dilution tests. When patients were tested after ovariotomie some 44% of the unilateral operated gave negative reaction, while over 50% of the bilateral cases were negative. Since this diminution of sensitivity to tuberculin is apparently coterminous with a diminution in immunity, the author goes on to discuss in general terms the part possibly played by the **thyroid,** the **ovaries** and the other endocrine glands in the reaction of the organism to the tuberculin skin-test.

F. S. H.

MENSTRUAL blood (Das Menstrualblut). Stickel (M.) & Zondek (B.), Ztschr. f. Geburtsch. u. gynäk. (Stuttgart), 1920, **83,** 1-26.

The authors have undertaken an intensive study of the properties of menstrual blood, the results of which are serviceable in differentiating this excretion from possible pathological conditions. They hold that for an accurate examination to be made the blood

must be collected from the uterine cavity since the passage through the cervix produces certain morphological changes. In addition the sample to be examined must be thoroughly shaken before study. No changes can be detected in the hemoglobin content and morphological blood-picture of whole blood during menstruation. In menstrual blood an oligocythemia is present, the erythrocytes range between 2,600,000 and 3,270,000. Leucopenia is also evident. The hemoglobin of menstrual blood is always less than that of whole blood, but the diminution is not proportional to the decrease in erythrocytes. On account of this fact the hemoglobin content is relatively too high and is usually over 1. This phenomena is attributed to a local partial hemolysis. The lymphocytes tend to increase at the expense of the neutrophils. The specific gravity of menstrual blood is relatively low, the water content is high and the coagulation property is lost.—F. S. H.

Formation of the definitive cortical layer and origin of definitive ova in the OVARY of the cat (Formation de la couch corticale définitive et origine des oeufs définitives dans l'ovaire de chatte). De Winiwater (H.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1403-1405.

Histological matter only—T. C. B.

Definitive cortical layer at the hilus of the OVARY and pseudo-néoformation (Couche corticale définitive au hile de l'ovarie et pseudo-néoformation ovulaire). De Winiwater (H.), Compt, rend. Soc. de biol. (Paris), 1920, **83**, 1406-1408.

Histological matter only—T. C. B.

Autotransplantation of the OVARY in the omentum (Autotransplantation von Ovarien uns Netz). Köhler, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 91.

In serious disease of the adnexae in young women the author implants some slices of ovary into the omentum. The slices must be thick to prevent resorption. In 5 of the 6 cases the effect was good and no symptoms of castration were seen. In one case menstruation reappeared regularly.—J. K.

(OVARY, TESTIS) An analysis of the behavior of organs after transplantation in the rat; and of the power of resistance of the constituents of the various organs. Loeb (L.), J. Med. Research (Boston), 1918, **39**, 189-216.

Experiments are reported in which various tissues were transplanted from one rat to another or to itself. The factor governing their growth or failure to grow under various conditions are studied in considerable detail. Among the tissues so studied were the ovaries

and testes. It was found in the case of the ovaries that the Graffian follicles matured and from them normal corpora leutea developed whether the ovaries were transplanted to the male or into another female. A corpus luteum existing in the ovary at the time of transplantation, however, was found to undergo rapid degeneration. In the case of testicle transplantation it was found that the interstitial tissue perishes while the elements of the tubules soon degenerate.
—J. M.

(OVARY) Circumscribed edemas. Diseases of the lymphatic system. Pathogeny and treatment (Les oèdemes circonscrits, maladies du système lymphatique, pathogénie et traitement). Mauriac (P.), Ann. Méd. (Paris), 1920, **8**, 271-279.

This paper contains a brief review of the general subject of circumscribed edemas and takes up in particular a case of a woman 48 years old complaining of localized edema of the hands and digits. Thyroid treatment was inefficacious. A turpentine injection produced favorable results, subsidence of the edema and return of the menses which had been lacking for 10 years. The cause of the disturbance is attributed to a relative ovarian insufficiency.—F. S. H.

The tendency of carcinoma of the PANCREAS to spread by blood-vascular invasion. Adams (F. D.), Arch. Int. Med. (Chicago), 1921, **27**, 175-183.

In the group of cases here reported, the carcinoma of the pancreas showed a definite tendency to invade the local blood vessels and to disseminate metastases to the liver and lungs, and in some instances to other parts of the body. The type of tumor in which this occurs is the adeno-carcinoma.—F. S. H.

(PANCREAS) Experimental studies in diabetes: Series II. The internal pancreatic function in relation to body mass and metabolism. Allen (F. M.), Am. J. M. Sc. (Phila.), 1920, **160**, 781-801.

Removal of as little as a fourth or a third of the pancreas causes dogs to show an increased tendency to glycosuria. Successive removal of portions of the pancreas shows that the point at which diabetes begins is sharp and definite. Removal of about seven-eighths of the gland is necessary to produce diabetes in the dog. Since a relatively small mass of normal tissue can prevent diabetes, it is suggested that any positive means of augmenting the endocrine pancreatic function even by a little would give therapeutic results far surpassing those of the negative plan of sparing the function by diet.—W. J. A.

(PANCREAS) The concomitance between the appearance of the functional islands of Langerhans in the embryo and the establish-

ment of the glycogenic function of the liver (De la concomitance entre l'apparition des îlots de Langerhans fonctionnels chez l'embryon et l'établissement de la fonction glycogénique du foie). Aron (M.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1448-1450.

A histological study. The conclusion is reached that the glycogenic function of the liver is established at the time when the islands of Langerhans change from the embryonic to the functional type.—T. C. B.

On the development of the functional islands of Langerhans in the embryonic PANCREAS (Sur le développement des îlots de Langerhans fonctionnels dans le pancréas embryonnaire). Aron (M.), Compt. rend. Soc. de biol. (Paris), 1921, **83**, 1445-1448.

Histological material only.—T. C. B.

(PANCREAS: SUPRARENALS) Relation between the pancreas and the suprarenal capsules, from the point of view of diabetes (Relation entre le pancréas et les capsules surrénales ou point de vue du diabétes). Hedon (E.) & Giraud (G.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1310-1312.

In a preceding note (C. R. Soc. de Biol., 1920, **83**, 330) the authors have given the curve of glycemia during the first hours following pancreatectomy. In this paper they discuss the question whether there exists a functional relation between pancreas and suprarenals in relation to the metabolism of sugar. The experiments were made on dogs. Pancreatectomy associated with extirpation of the capsules gave rise after some hours to hypoglycemia. In one dog the removal of a pancreatic graft and the left suprarenal (the pancreas and right suprarenal had been previously removed) was followed by hypoglycemia. In order to eliminate the possibility of surgical shock causing the effect, the glands were crushed below the suprarenal veins and the inferior poles resected. Immediately after, total pancreatectomy, the blood-sugar fell during the first fifteen minutes and then rose markedly. Another dog survived 12 days with an intense diabetes. The conclusion is that the result of extirpation of the pancreas with total capsulectomy cannot be attributed simply to traumatism. The effect of capsulectomy on a dog previously depancreatized and in full diabetes is negative for 24 hours. The amount of blood-sugar then begins to fall. The experiments are favorable to the hypothesis of a functional relation between the pancreas and suprarenals, but the problem is still obscure.
—T. C. B.

(PANCREAS) Giant islands of Langerhans in a new-born child of a glycosuric mother (Ilots de Langerhans géants chez un nouveau-né,

issu de mère glycosurique). Dubreuil (G.) & Auderodias, Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1490-1493.

A history of a case of glycosuria in a pregnant woman in whom delivery was induced at the beginning of the ninth month. The child weighed 5050 gm. and lived but a few minutes. Examination of the foetal pancreas showed the islands of Langerhans to be enormously increased in size, appearing as large masses of compact epithelium. As the blood of the mother contained a large amount of sugar the fetal blood must have been hyperglycemic by reason of the placental exchange. The excess of nutritive material accounts for the exaggerated weight of the fetus. But the fetus was required to continually destroy this excess of sugar in the blood and consequently the pancreas had developed the islands of Langerhans to meet the emergency. The authors think this is positive experimental proof of the function of the islands in the regulation of the blood sugar. In the presence of exaggerated need, the organ hypertrophies.—T. C. B.

(PANCREAS) A research on blood-sugar in depancreatized dogs. Delatour (B. J.), Arch. Int. Med. (Chicago), 1920, **25**, 105-110.

The effect of the administration of adrenin on the blood-sugar of completely depancreatized dogs was studied some days after the operation. It was found that the complete removal of the pancreas produced a permanent hyperglycemia which was but little if any increased by the intravenous injection of epinephrin. The author is of the opinion that in such animals the sugar is passing freely into the blood unburnt and that, therefore, adrenin can have very little further effect in inhibiting sugar metabolism. He concludes that it is reasonable to believe that the pancreas produces some substance which favors the metabolism of sugar in the tissues since sugar injected intravenously is not handled as readily in the depancreatized dog as in the normal animal.—F. S. H.

The rôle of the PANCREAS in hyperglycemia from ether. Ross (E. L.) & Davis (L. H.), Am. J. Physiol. (Balt.), 1920, **54**, 391-397.

There has been a tendency to forget the pancreas when dealing with glycosurias and hyperglycemias not directly associated with diabetes. In the present paper the hyperglycemia induced by ether was investigated. Dogs were used. One group was partially depancreatized, and another group completely depancreatized. The effect of ether anesthesia on the urine dextrose was measured. In both groups the hyperglycemia induced by ether was practically the same as that of normal dogs. There is a marked decrease in the dextrose output in the half hour urine during anesthesia, compared

with that of a half hour before anesthesia. Ether markedly decreases the rate of mobilization of dextrose. The results lead to the conclusion that in normal animals ether causes hyperglycemia by reducing the influence of the pancreatic secretion on glycolysis. —T. C. B.

Carcinoma of the PANCREAS. Speed (K.), Am. J. M. Sc. (Phila.), 1920, **160**, 1-10.

Not of immediate interest.—W. J. A.

The PARATHYROID bodies and Bright's disease. Bergstrand (H.), Acta med. Scand. (Stockholm), 1921, **53**, 644-651.

The author found that in ten cases out of fifty where the parathyroids showed pathological conditions there was an accompanying marked renal disorder. This finding, taken together with the fact that the literature also reveals the occasional concurrence of parathyroid and renal disorders, leads Bergstrand to the opinion of a possible correlative pathogeny. He states that the rabbit is the best animal for use in such studies because it is the only animal in which the measures of the weight of the endocrine glands is established. Apparently he is ignorant of the work of Donaldson and Hatai on the albino rat.—F. S. H.

(PARATHYROIDS) Observations on parathyroidectomized dogs. Hastings (A. B.) & Murray, Jr. (H. A.), J. Biol. Chem. (Balt.), 1921, **46**, 233-255.

The study reported in this paper was limited to an investigation of the blood-serum calcium, the alkaline reserve of the blood plasma, the hydrogen-ion concentration of the blood plasma, the blood-sugar and the symptomatology of parathyroidectomized dogs. It was found that the hydrogen-ion concentration of the plasma remained within normal limits, though the carbon dioxide combining capacity of the blood was slightly diminished. The calcium content of the serum was cut in half within a few days and was hardly diminished subsequently. When the concentration reached approximately 7 mg., tetany developed. Phosphorus and sulfur were increased in the blood. No significant changes were found in the blood-sugar. Hence the previously observed calcium deficiency in parathyroidectomized dogs is verified, but no support is found for the theories based on a disturbed acid-base equilibrium.—F. S. H.

Mammalian morphology of the PINEAL (Bidrag Til Kundskaben om Corpus Pineale). Krabbe (K. H.), Det. Kgl. Danske Videnskabernes Selskab., Biol. Meddelelser (Copenhagen), 1920, II, 2.

This is a monograph dealing with the morphology of the pineal body in mammals. The author reviews the literature and reports

his own findings of the embryology, anatomy, and histology of the following classes of mammals: Monotremata, Marsupialia, Insectivora, Chiroptera, Rodentia, Proboscidea, Ungulata, Sirenia, Edentata, Carnivora, Pinnipedia, Cetacea, Primates. The conclusions are that great variation occurs within the different species of mammals, yet the glands have certain characteristics which are common to all, viz., the organ is cellular and there is no division into a cortical and medullary portion. The parenchyma consists of pineal cells, nervous elements, and neuroglia. The pineal cells form the main bulk of the organ. These have a bullet-shaped nucleus containing one to two nucleoli. In man and some of the higher mammals there sometimes occur cells having irregular nuclei. Numerous mitotic figures are present in these classes. Nuclear excretions may be seen. The cytoplasm of the cells is scant and cellular processes are absent. Such cells are distinctly different from any other cells found in the nervous system. They may be related to neuroglia. The nerve fibers and neuroglia form a network around the pineal cells. Nerve elements, in the form of nerve cells and fibers, are not conspicuous in the pineal body except in man and some of the higher monkeys. The amount of neuroglia present differs greatly in different species. The blood supply was abundant in all the glands examined. Pigment was also present in all the mammals examined, especially marked in horses. Concretions were found in glands from man, ox, and chimpanzee.

Embryologically the pineal body develops from an outgrowth of the roof of the diencephalon. The organ is not a rudimentary type, nor is there any reduction of it at puberty. The organ may not have the same function in all mammals; however, the structure suggests a glandular function. It may also serve as an outlet for the spinal fluid.—D. J. G.

Effect of feeding the PINEAL body upon the development of the albino rat. Sisson (W. R.) & Finney (J. M. T. Jr.), J. Exper. Med. (Balt.), 1920, **31**, 335-346, 1pl.

The method employed in the experiments was to feed desiccated pineal body to rats and compare the resultant growth as measured by weight changes with controls from the same litter. Observations were also made of the changes in the appearance and texture of the coat, descent of the testes, state of nutrition, skeletal changes and activities. At autopsy measurements were made of the body and tail lengths and tissue was obtained from the endocrine organs and studied histologically. It is the opinion of the reviewer that this is a most carefully carried out series of experiments. During the entire series of experiments the animals all remained in an excellent state of nutrition. Although the pineal powder was given in large doses, it in no way affected their general health. The

activities of the test animals equalled and corresponded to those of the controls. In no instance was any sexual precocity noted. The testes of both the test and the controls descended almost simultaneously; furthermore, no differences were noted in the appearance, size, or consistency of the testes of the test and control animals of the same litters. There was essentially no variation between the weight of the pineal-fed animals and their controls, either during the course of the period of study or at its termination. Microscopic studies of the endocrine organs of both control and pineal-fed rats revealed normal conditions. As far as these observations go, then, they present no evidence of the presence of an active substance in the pineal body that influences growth of the characters studied.—F. S. H.

On the presence of histamine in extracts of the posterior lobe of the PITUITARY gland and on preliminary experiments with the pressor constituent. Abel (J. J.) & Nagayama (T.). J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 347-399.

Extracts made from fresh pituitary glands in which long boiling and long exposure to acids is avoided, contain a small amount of histamine.

Extracts which are employed in therapeutics contain more of this amine. It was estimated from one experiment that a 1 c.c. phial of such a preparation contained about 0.025 mgm. of histamine. The method of preparation determines to some extent the amount of histamine present. Continued boiling of a fresh extract of the pituitary with dilute acid increased the amount of free histamine and abolished the pressor substance. Extracts treated in this way produce a marked fall in blood pressure which is due to histamine and a histamine-like substance, about four-fifths of the effect being due to the latter. The latter substance gives the Pauly reaction but not the biuret reaction, is soluble in alcohol but insoluble in chloroform. There is a residual oxytocic activity after the treatment of pituitary extract with acid, this being due to histamine and the histamine-like substance.

Histamine and the histamine-like substance are apparently not specific constituents of the infundibulum as they occur in animal extracts of all kinds, being formed from the hydrolysis of proteoses. The observations of these authors point to the conclusion that there is but one hormone in the infundibulum.—F. A. H.

A pressor compound from the PITUITARY gland. Crawford (A. C.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15**, 81-94.

Extraction by absolute ethyl alcohol was used to remove the depressor substance and the substance which gives the Pauly reaction from desiccated posterior lobes. The residue was extracted

repeatedly by water containing carbon dioxide. A ppt. was thrown down from this aqueous solution by $HgCl_2$. The colloidal solution produced by decomposition of the washed Hg precipitate hydrogen sulfide was evaporated to dryness and taken up with methyl alcohol, precipitated by ether and extracted by absolute ethyl alcohol. Further purification gave a white amorphous precipitate which possessed a marked pressor reaction and gave no Pauly reaction.
—F. A. H.

Administration of a pituitary extract and histamine in a case of diabetes insipidus. Gibson (R. B.) & Martin (F. T.), Arch. Int. Med. (Chicago), 1921, **27**, 351-360.

This paper reports the study of a severe case of diabetes insipidus with chronic syphilis in which the symptoms were not relieved by lumbar puncture, but when 1 cc. doses of pituitary extract (obstetrical) were administered subcutaneously temporary relief was obtained, in that the volume of the urine was reduced and the concentration increased. A normal 24-hour concentration and volume, however, was not obtained at any time. Histamine (one injection of 0.2 mg.) gave a similar but less effective result. When desiccated whole pituitary substance was given by mouth, a slight immediate effect was observed. As a result of the pituitary extract injections there was a lower nitrogen elimination with considerable retention, diminished ammonia and undetermined nitrogen, and a somewhat increased uric acid output; the nitrogen partition was nearly normal. Glycogenesis was not reduced. There was hypoglycemia. Blood urea, creatinine, plasma chlorides, and total plasma proteins were normal. There was a high blood uric acid.—F. S. H.

(SEX) Sexual differentiation in Rana Temporaria. I. The acting mechanism in over-ripe eggs (Experimentelle Untersuchungen über die sexuelle Differenzierumg bei Rana temporaria. I. Die Wirkungsmechanismus überreifer Eier). Adler (L.), Arch. f. d. ges. Physiol. (Berlin), 1920, **183**, 23-39.

An attempt to connect sex differentiation with thyroid structure. Thyroid change resembling that in Graves' disease is usually present in metamorphosed frogs from over-ripe eggs; most of such frogs are males.—A. T. C.

(SEX) Experimental Hermaphroditism (Experimenteller Hermaphroditismus). Sand (K.), Arch. f. d. ges. Physiol. (Berlin), 1918, **173**, 1-7.

Transplantation experiments on guinea-pigs and rats, if preceded by castration, lead successfully to hermaphroditic conditions S.'s results in general are in agreement with those of Steinach.
—A. T. C.

(SEX) Experimental Hermaphroditism (Bemerkung zur Arbeit von Knud Sand über experimentellen Hermaphroditism). Schultz (W.), Arch. f. d. ges. Physiol. (Berlin), 1920, **179**, 217-218.

A claim for priority over Steinach, especially as regards methods.—A. T. C.

Note on the SPERMATOGENESIS of the blind worm. (Study of the atypical seminal cells.) (Note sur la spermatogénese de l'orvet.) (Etude des cellules séminales atypiques.) Dalcq (A.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1302-1304.

Histological material only.—T. C. B.

(SPLEEN) Contribution to the study of anemias accompanying splenomegaly in the nursling (Contribution à l'ètude des anémies avec splénomégalie chez le nourriseon). Hallez (G. L.), Nourrisson (Paris), 1921, **9**, 24-39.

This paper gives a description of the pathological anatomy in cases of anemia accompanying splenomegaly in infants. In the **bone-marrow** the connective tissue is found to be thinned in certain places and apparently a hypergenesis of nucleated erythroblasts is present. The **thymus** is generally increased in volume, though the structure is normal.

The etiology seems largely to lie in the field of syphilitic disturbances. Treatment consists of anti-syphilitic medication when necessary and opotherapy with fresh bone-marrow substance. Splenectomy at this age is not indicated.—F. S. H.

Homeotransplantation and autotransplantation of the SPLEEN in rabbits. III. Further data on growth, permanence, effect of age and partial or complete removal of the spleen. Marine (D.), & Manley (O. T.), J. Exper. Med. (Balt.), 1920, **31**, 113-133.

The results of these experiments on rabbits show that the spleen homeografts do not differ from most other homeografts in that they do not persist beyond the usual 1 to 2 weeks common to such attempts, although the possible advantages of consanguinity, age and splenectomy were fully utilized. This is, however, in sharp contrast to **thyroid, sex gland** and **adrenal** cortex homeografts and suggests that spleen is stronger antigen and excites a greater degree of immunity more quickly. With autografts survival and growth are the rule, and failures are due to technical errors. Age is an important factor; the younger the rabbit the more growth is aided. This beneficial effect decreases gradually and becomes negligible after sexual maturity. Removal of the spleen is a powerful stimulus to the growth of transplants. The effect varies inversely with the age, and is unusually negligible after sexual maturity. This

suggests that the spleen is most important in early life and after sexual maturity is either unimportant or its functions may readily be assumed by other tissues. There is some indication that subcutaneous grafts react to infections in the same way as the intact spleen.—F. S. H.

(SYMPATHETIC GANGLIA) Are the superior cervical ganglia indispensable to the maintenance of life? Meltzer (I. J.), Proc. Nat. Acad. Sc. (Balt.), 1920, **6**, 532-539.

In studying certain phases of the "paradoxical" pupillary reaction at various times it was noticed that the animals died soon after the operation, if both superior cervical ganglia were removed, and that autopsy revealed the presence of pulmonary lesions—bronchopneumonia in the upper and middle lobes, and edema of the lower lobes. Experiments were, therefore, made to test the question which is the title of the paper. Of 28 rabbits in which the superior cervical ganglia were removed from both sides, 6 died in less than 24 hours, 9 died in less than 2 days, 5 in less than 3 days, 1 each in 4, 5, 6, 8 and 10 days. All had pulmonary lesions. Two cats died in less than 2 days. Experiments were made to eliminate the possible effects of injury to the vagus.

An hypothesis as to the mechanism by which the ganglia may control life is offered. Fibers from the ganglia reach the respiratory center, and the tonus of the central laryngeal control is maintained by continuous impulses from the superior cervical ganglia. After removal of the ganglia the laryngeal center loses its tonus and coordinating activity upon the laryngeal muscles during respiration. The loss of coordination gives rise to results similar to those following cutting of the vagi. The origin of the impulse is explained by comparing the ganglia to glands of internal secretion. In four rabbits the ganglia on both sides were torn away from their upper connections, but were left connected with the sympathetic nerve. Two ganglia from another rabbit were placed deeply in the wound before closing it. All four animals survived many weeks, and were killed by chloroform; the lungs were normal. These findings are considered suggestive.—T. C. B.

Some facts concerning the histology of the ectopic TESTICLE (Quelques faits concernant l'histologie du testicule ectopique). Michon (L.) & Porte (P.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1438-1439.

Histological material only.—T. C. B.

Note on simple hypertrophy of the THYMUS (Correlated from radiographic tables and clinical case descriptions) (Note sull' ipertrofia semplice del timo corredate da tavole radiografiche e de-

scrizione di casi clinici). Gatti (O.), Folia med. (Napoli), 1917, **3,** 436; 459; 473-479.

The author discusses the normal occurrence of the thymus in childhood and in the adult. This is followed by an extensive consideration of the results of compressions produced by hypertrophy of this gland, and concludes that the condition, as an etiological agent, is associated with the more common infectious inflamatory processes. After a brief historical survey of thymus compressions, the author takes up several related forms of respiratory disturbances, with special reference to a clinical case. A child, one month of age, made a peculiar rattling sound upon heavy breathing. The condition gradually became more and more severe, until it was permanent and continuous, giving rise to suffocation and cyanosis. The x-ray showed hypertrophy of the thymus. Treatment by radiotherapy resulted in complete recovery and the child when observed a year later was in perfect health with no signs of relapse.—D. P.

Status THYMOLYMPHATICUS. Hart (C.), Ztschr. f. ärztl. Fortbild. (Jena), 1920, **17,** 673-676; 697-700.

A general review without new data.—J. K.

Enlarged THYMUS gland in infancy and its treatment by radium. Brayton (H. W.) & Heublein (A. C.), Boston M. & S. J., 1919, **181,** 740-743.

A report of several cases where infantile thymic enlargement has been successfully treated with radium applications.—H. W.

The genesis of amphibian-neoteny. The physiology of the amphibian THYROID (Untersuchungen über die Entstehung der Amphibienneotenie. Zugleich, ein Beitrag zur Physiologie der Amphibienschilddrüse). Adler (L.), Arch. f. d. ges. Physiol (Bonn), 1916, **164,** 1-101.

Histological examination shows that the thyroids of frog larvae and metamorphosed frogs correspond to the climatic conditions of their surroundings. Frogs from the Alps have relatively large thyroids with many small vesicles, those from the Adriatic coast usually small thyroids with a few large vesicles, and those from middle Germany with an intermediate climate show an intermediate condition. With cultures kept at a temperature above optimum-growth is delayed, and metamorphosis still more delayed so that the metamorphosed frog is larger than normal; its thyroid is usually smaller, but of normal structure. With cultures kept at first at a low temperature (8° to 10°) and then changed to a high temperature (30° C.), metamorphosis is delayed and growth more so. The young frog is smaller than usual and in extreme cases dwarf frogs

are produced (which soon die). The thyroids show marked atrophy, in a large number of cases indicating a complete disorganization. In the reverse culture (hot-cold) metamorphosis is more greatly delayed, leading to larger animals. The thyroids are larger than normal; their structure resembles the initial stage of goiter. The colloid becomes more fluid. Since the thyroid shows such specific morphological changes under the influence of extreme temperature changes it is probable that slight temperature changes also produce a functional effect so that the amphibian thyroid can act as a regulatory mechanism.—A. T. C.

(THYROID) Contributions to the biochemistry of iodine. IV. The effect of thyroxin on growth in white rats and in rabbits. Cameron (A. T.) & Carmichael (J.), J. Biol. Chem. (Balt.), 1921, **46**, 35-56.

Using rat and rabbits as the experimental animals, the authors added to the diet of bread and milk certain amounts of thyroxin depending upon the daily body weight. Extensive tables are given of the growth of the animals as a whole and of the relative size of the various organs an autopsy of the treated subjects and the controls. The thyroxin-fed rats showed distinctly less fat than the control animals, but not so markedly as did rats that had received thyroid gland in the ratio of 1:5,000 of body weight. The thyroids of the treated rats were always paler in color than those of the controls. The results show conclusively that thyroxin produces a distinct decrease in growth-rate, and a hypertrophy of the liver, kidneys, heart, **spleen** and **adrenals.** The effect on the **testes** was uncertain, thus demonstrating that qualitatively thyroxin and thyroid produce the same results. It is evident, then, that thyroxin answers satisfactorily to all the tests to which it can be subjected, as to whether or not it is the essential chemical compound (autocoid, hormone) secreted by the thyroid gland.—F. S. H.

(THYROID) Delayed hereditary lues (Lues hereditaria tardia: Endocrinopatias. II. Tiroides). Castex (M. R.) & Waldorp (C. P.), Prensa med. Argent. (Buenos Aires), 1920, **7**, No. 5, July.

The stigmata of hereditary syphilis are in large part due to a thyroid dystrophy. The nasal hydrorrhea often has as its cause a hypo- or dysthyroidism. Mongolism is a dystrophy of endocrine origin produced by syphilis.—B. A. H.

(THYROID) Tuberculosis in a region of endemic goiter (La tuberculose dans une région à goitres endemiques). Coulaud, Bull. et mem. Soc. méd. d. hôp. d. Par., 1921, **45**, 5-8.

In the departments of the North, the Adrennes and l'Aisne goiters appeared more numerous after the German invasion than

formerly. Amenorrhea also was frequent which, due to the under nourishment of the individual, gave rise to a compensatory hyperthyroidism. One hundred families were examined and out of this number 220 individuals were goitrous, while some 230 persons in these families were tubercular. Coulaud summarizes by stating that both hypo- and hyperthyroid conditions were found in the goitrous families and that it is more a question of thyroidal families rather than goitrous families. Tuberculosis did not appear in the goitrous until the menopause, while the hypothyroid cases are, so to speak, never afflicted, if they are it is with latent types. The number of cases of tuberculosis observed were by and large in the non-goitrous or non-hypothyroid persons.—F. S. H.

Case of THYREOAPLASIA (Ein Fall von Thyreoaplasie). Falta, Wien. klin. Rundschau., 1919, **35**, 91.

See Endocrin., **4**, 166.

(THYROID) Graves' disease with unilateral exophthalmos (Ein Fall von Morbus Basedowii mit einseitigem Exophthalmus). Falta, Wien. klin. Rundschau, 1919, **33**, 90; Klin-therap. Wchnschr. (Berl.), 1919, **26**, 295.

See Endocrin., **4**, 165.

Concerning the diagnosis and treatment of HYPOTHYROIDISM. Janney (N. W.) & Henderson (H. E.), Arch. Int. Med. (Chicago), 1920, **26**, 297-318.

Studies are reported of 17 cases of latent and obvious hypothyroidism. The usual clinical history was written: physical examination, differential blood count, glucose tolerance test, and basal metabolism determinations were made. The authors consider that latent hypothyroidism is more frequent than generally supposed, since among 18 consecutive cases it was present in 12, four cases being dysthyroidism and only one presenting classical myxedematous symptoms. The analysis of the clinical data show that in over 50 per cent of the cases the following stigmata are present; history of obesity, particularly in early life; mental symptoms; marked liability to contract infections; hair anomalies; dry harsh skin with pigmentation and atrophy; cold extremities and cold skin generally; obesity; decreased size of thyroid; subnormal temperature, pulse and respiration. Of all the data, the lowered temperature, pulse and respiration occur most frequently. The basal metabolism rate is of great value in diagnosis and treatment, but cannot be considered as an absolute criterion. Usually the blood glucose tolerance test is abnormal in respect to the height of the curve and the delayed return to the normal level in cases of thyroid disease, but is only diagnostic of endocrine disease in general. There is no constant

relation demonstrable between the blood sugar curve and the metabolic rate in thyroid disease. Treatment of hypothyroidism is best carried out with thyroxin and controlled by basal metabolic rate determinations.—F. S. H.

The action of THYROID on tadpoles (Ueber die Wirkung der Schilddrüse auf Kaulquappen). Jarisch (A.), Arch. f. d. ges. Physiol. (Berlin), 1920, **179**, 159-176.

The larval organs of tadpoles disappear in shortest time when they are fed single large doses of thyroid. The retrogression affects the gills, with fatal results. By administration of oxygen the tadpoles can be kept alive. Retrogression and metamorphosis can be checked by different diets, the action of which is parallel to their protein-sparing properties. Corresponding food protects the tadpole from resorption of larval parts. Thyroid acts through its influence on metabolism. It increases catabolism and hence accelerates the resorption of larval organs. No direct action of thyroid on metamorphosis has been demonstrated.—A. T. C.

(THYROID) Symptoms of hyperthyroidism observed in exhausted soldiers. Johnson (W.), Arch. Diagn. (N. Y.), 1918-19, **11**, 260-268.

See Endocrin., **4**, 169.

(THYROID) Prophylaxis of Endemic Goiter (Zur prophylaxie des endemischen Kropfes). Klinger (R.), Corr. Bl. Schweiz. Aertz. (Basel), 1918, **48**, 546-548.

The plea is advanced for the use of sodium iodide as a prophylactic agent against endemic goiter. See later publication: abstracted in Endocrin., 1919, **3**, 585.—H. W.

(THYROID) The prevention of simple goiter (Die Prophylaxe des endemischen Kropfes). Klinger (R.), Schweiz. med. Wchnschr. (Basel), 1921, **51**, 12-15.

Klinger reports the results of the administration of small doses of iodine on the prevention of simple or endemic goiter in children in seven Swiss schools in the region around Zürich. His observations cover a period of 15 months. He used both sodium iodide and a proprietary organic preparation, "Iodostarin," preferring the latter because of the bitter taste of sodium iodide. He began the treatment with 30 mgm. (approx. ½ gr.) iodide at weekly intervals, and after three months reduced it to 10 mgm. weekly. Before beginning the prophylactic treatment he conducted a careful survey of the incidence of goiter among the children, classifying the condition of the thyroids in the following groups: (1) not or scarcely palpable;

(2) palpable but not enlarged; (3) slightly enlarged; (4) moderately enlarged; (5) large goiters. In some school districts as high as 95% of the children between the ages of 6-10 years had enlarged thyroids and in other districts as low as 82% at the time of the initial survey. The age group 10-14 years, as would be expected, showed still higher incidences of goiter even 100%. These percentages indicate a highly goiterous district. With such a high natural incidence of goiter his observations were confined largely to the **curative** rather than to the **prophylactic** effects of iodine. The curative effects are striking: Thus of 760 children 90% were goiterous at the first examination. After 15 months' treatment with 10 to 30 mgm. iodine as "iodostarin" weekly, only 28.3% were goiterous out of a total of 643 children examined. As striking results were obtained with sodium iodide in another school where a total of 60 mgm. of iodine per pupil was administered in six months. Thus of 179 pupils, of whom 90% were goiterous at the beginning of the feeding, only 41% were goiterous after six months. The point the author wishes to drive is that exceedingly small amounts of iodine (comparatively) are needed to produce these remarkable thyroid changes.

As to the form of iodine used, cheapness and convenience of administration should rule. Tablets are most convenient. In over 1000 cases observed for sixteen months, no untoward effects were noted—not even a single case of iodism, although carefully looked for. Attention of physicians is called to the fact that fears of untoward effects (iodism or iodin—Basedow) even from the use of excessive physiological amounts of iodine (3-5 mgms. weekly) are without foundation.

He concludes that endemic goiter in children may be completely controlled at a nominal cost by the simple expedient of giving 3 to 5 mgm. iodine once or twice weekly over a period of a month and repeated each Spring and Autumn. The carrying out of the prophylaxis should be placed in the hands of physicians, preferably the school and district physicians. With the state-wide use of prophylaxis, goiter could be eliminated, the general health standards improved and those mental and physical defects (cretinism, mutism, idiocy) so intimately associated with a deficiency of the internal secretion of the thyroid could be greatly reduced.—D. M.

(THYROID) Myxedema. Klinkert (H.), Ned. Tijdschr. v. Geneesk. (Haarlem), 1921, **65**, 467.

A report of a patient with deafness and noises in the ears. The lips were thick, she lost her hair, showed a swollen tongue and a dry skin. After thyroid treatment, the myxedema, the deafness and the noises in the ears disappeared, but a tremor appeared, which may perhaps be considered as a symptom of Graves' disease.—J. K.

(THYROID) One thousand one hundred and forty-six goiters in one thousand seven hundred eighty-three persons. Levin (S.), Arch. Int. Med. (Chicago), 1921, **27**, 421-433.

"Obscurity and darkness in the field of medicine excite the profession to research." With this introductory remark Levin proceeds to tabulate and discuss the goiter incidence observed by him in the Great Lakes region. No selection was made of the subjects coming under examination. He divides his individuals into 3 groups. The first consists of those having simple goiter, giving no symptoms save an homogeneous enlargement of both lobes and isthmus that may be small, moderate or large. In this group he could place 682 cases or 38.2 per cent, of which 29.1 per cent were males and 45.5 per cent females. Group 2 consisted of cases where adenoma was present, whether small, large or moderate in size. Cystomas were included. In this class 420 goiters were found or 23.5 per cent of the total incidence, of which 15.0 per cent were males and 30.3 females. In group 3 were placed all those cases designated as colloid goiter. The state was determined by the firmer, doughy consistency of the gland. In the group 44 individuals were placed. That is to say, the class represented 2.5 per cent of the examined individuals. Of these 0.76 per cent were males and 3.8 per cent females. Levin concludes by stating that in a zone in which thyroid enlargements occur, as in the one he studied, there is a normal physiological hypertrophy of the gland and that this should not be called goiter, though it must be remembered that long continued enlargement means permanent enlargement. The incidence curves show that goiters increase in both sexes during puberty, and drop to a small degree after the growth of the individual is attained. The curve remains in the female for the child-bearing period, going down at about 38-40 years, when it rises again for the menopause. In the male the curve gradually drops till 35 or 40 years, when there is a small rise due to growths in the glands. The simple goiters maintain the high percentage till 35 years is attained and the adenoma and cystoma sustain the height of incidence curve after that age. The various water supplies—spring water or Lake Superior water—influence the enlargements of the thyroids the same.

—F. S. H.

Studies on compensatory hypertrophy of the THYROID gland. V. The effect of the administration of thyroid, THYMUS gland and tethelin and of a meat diet on the hypertrophy of the thyroid gland in guinea-pigs. Loeb (L.), J. Med. Research (Boston), 1920, **42**, 77-89.

L. found that the feeding of desiccated thyroid to guinea-pigs following extirpation of most of their thyroid glands markedly inhibited compensatory hypertrophy of the remaining fragment—an

additional confirmation of a long known fact. He fed large amounts of thyroid (8-12 grains over a period of 10-15 days) and examined the thyroid remnants after intervals of 17-29 days. Most of the animals lost weight. Thymus gland had no effect. Previous work by the author had suggested that potassium iodide might counteract the effect of thyroid feeding, but no experimental proof of this was obtained. The author thought he observed less compensatory hypertrophy in the warmer months (May to October) than in winter, thus tending to confirm in guinea-pigs the well established fact of seasonal variations in thyroid activity.

Tethelin, administered in 50 to 60 mgm. doses subcutaneously every three or four days to four guinea-pigs was without effect on the thyroid hypertrophy. Studies on the effect of a diet consisting principally of meat given during a period of three and one-half weeks was without effect on the compensatory hypertrophy of the thyroid gland.—D. M.

Heterotransplantation of the THYROID gland. Loeb (L.), J. Exper. Med. (Balt.), 1920, **31**, 765-784.

This paper deals with the heterotransplantation of the thyroid gland free from bacterial contamination in mammals. Thyroids were removed from guinea-pigs and transplanted into rats. In this series it was found that as late as 9 days after the transplantation a number of acini are preserved and mitoses occur. This is the latest term at which mitoses and living tissue are found. The conclusion is made that there is a general incompatability between the body fluids and the transplant. The destructive action of lymphocytes and connective tissue play only a minor part. In the second series thyroid glands from rabbits were transplanted into rats. Here living acini were found as late as 11 days, though mitoses were not observed after the ninth day, even at that time their presence was exceptional. Capillaries may grow actively in the tissue surrounding the transplant, but usually do not invade the implanted tissue. The third series consists of studies of the effects of the transplantation of thyroids from rabbits into guinea-pigs. The results were not as satisfactory as the previous attempts. Otherwise, the conditions are similar to those generally seen in heterotransplants. In a fourth series thyroids were removed from cats and then transplanted into rats. Here the results appear to be indicative of a better resistance of the transplants towards the destructive agencies of the host. Apparently the primary factor in the destruction of the heterotransplants is the injurious effects of the heterotoxins; these change the metabolism of the transplanted cells which now exert an effect upon the blood-vessels, connective tissue cells, and lymphocytes.—F. S. H.

(THYROID) Some points on the surgical treatment of goiter. Mackenty (J. E.), Laryngoscope (St. Louis), 1918, **27**, 912-914.

A discussion of operative procedures in the treatment of goiter in which is urged the work of goiter surgery be taken up by laryngologists.—H. W.

(THYROID) The nature of chemical heat-regulation. II. Physiological heat regulation (Ueber das Wesen der chemischen Wärmeregulation. II. Die physiologische Wärmeregulation). Mansfeld (G.) & v. Pap (L.), Arch f. d. ges. Physiol. (Berlin), 1920, **184**, 281-293.

Isolated hearts from cooled animals (rabbits) use 2 to 3 times as much sugar as those from animals kept at a summer temperature, while those from animals kept for some hours at 34° to 35° C. use scarcely any. The blood-serum of cooled animals raises the sugar-consumption of isolated hearts from warmed animals, and vice versa. Cooling of **thyroidectomized** animals does not increase the sugar-consumption of the exsected heart, and the serum of warmed thyroidectomized animals does not lower the sugar-consumption of isolated hearts from cooled normal animals. It is hence concluded that chemical regulation against heat and cold is brought about by two chemical substances, which control oxygen consumption of the organs; both hormones are probably thyroid products.—A. T. C.

The physiology of the THYROID. IX. A defense (Beiträge zur Physiologie der Schilddrüse. IX. Zur Abwehr). Mansfeld (G.), Arch. f. d. ges. Physiol. (Berlin), 1920, **181**, 249-270.

Controversial, defending previous conclusions against Hári (the same journal, vol. 176).—A. T. C.

(THYROID) Prevention of simple goiter in man. IV. Marine (D.) & Kimball (O. P.), Arch. Int. Med. (Chicago), 1920, **25**, 661-672.

Observations on the prevention of goiter in man on a large scale have extended over a period of thirty months. The results show that it may be prevented very simply and cheaply in normal individuals. While thyroid enlargements of adolescence are more common, they are not more important than those occurring in mother and fetus. Prevention of adolescent goiter is properly a public health problem, while the prevention of fetal and maternal thyroid enlargements is largely a responsibility of individual physicians. The presence of pathologic conditions may modify the result of the prophylactic treatment in individual cases. While such instances are rare, they are important and merit detailed reports. The treatment consists in the administration of iodine, by mouth, by inhalation, or by external application. The former is preferred for reasons of con-

venience, economy and dose regulation. An ounce of syrup of ferrous iodide or hydriodic acid given over a period of from 2 to 3 weeks repeated twice yearly is apparently ample. As a public health measure 2 grams of sodium iodide spread over a period of 2 weeks and repeated twice yearly has been successful. This dosage prevented enlargement of the thyroid in more than 99 per cent of the children in the mildly goitrous district studied.—F. S. H.

(THYROID) Exophthalmic goiter. Nye (H. W.), Med. Herald (Kansas City), 1920, **39**, 299-300.

A report of a case of exophthalmic goiter in a woman 32 years old with a pulse of 140 to 160, extreme nervousness, exophthalmus, severe headaches, glucosuria, etc. Removal of the thyroid was considered unadvisable because of the severe degree of toxicity. The superior thyroid arteries were ligated and the gland was injected with boiling water without beneficial results. Finally it was decided to try the effects of high frequency currents applied to the neck and also precussion of the seventh cervical vertebra, the rationale being "that the disease is an angio-paralytic affection and that stimulation of the vasomoter center in the cord by concussion of spinal processes of seventh cervical is beneficial." In addition the patient was given capsules of pancreatin. These treatments were continued for three months with the result that the menses returned, the pulse dropped to 80 or 90 and the patient declared herself well.

—C. W.

(THYROID) Substernal goiter, with pressure symptoms. Rachford (B.), Am. J. M. Sc. (Phila.), 1920, **160**, 410-414.

A clinical case of hyperthyroidism complicated by pressure paralysis of the right side of the diaphragm and right vocal cord and by displacement of the heart, showed fairly satisfactory recovery following treatment consisting of Roentgen ray, rest and medication.

—W. J. A.

Further experiments on the influence of fat- and lipoid-substances and of protein-free extracts of THYROID on metamorphosis and growth (Weitere Versuche über den Einfluss von Fett- und Lipoidsubstanzen sowie von enteiweissten Extrakten der Schilddrüse auf Entwicklung und Wachstum). Romeis (B.), Arch. f. d. ges. Physiol. (Berlin), 1918-19, **173**, 422-497.

Experiments with horse-thyroid extracts on **R. temporaria** tadpoles are reported in this paper. Various fractionations were made with acetone, alcohol, and ether, and the effects of the fractions on growth and metamorphosis are detailed. The fraction soluble in boiling alcohol and separating on cooling consists chiefly of fats and fatty acids and markedly inhibits both growth and metamorphosis.

After removal of substances soluble in ether, acetone, and absolute alcohol, alcohol-water extracts hasten metamorphosis and inhibit growth, producing the same effect as a 96 per cent alcoholic extract of fresh gland. Aqueous thyroid extract from which proteins have been completely precipitated strongly inhibits growth and metamorphosis. Thyreoglandol only accelerates metamorphosis when given in large doses over a long period, and then only slightly; growth is increased. The more completely protein is removed from aqueous thyroid extract the weaker is the metamorphosis acceleration; sometimes growth is increased. Since the action of solutions similarly treated, but in which proteins have been previously hydrolysed, markedly inhibits growth and promotes metamorphosis, it is suggested that similar hydrolytic cleavages take place in the production of the thyroid secretion.—A. T. C.

Syphilis of the THYROID (Syphilis van de Schildklier). Roorda Smit (J. H.), Ned. Tijdschr. v. Geneesk, (Haarlem), 1921, **65**, 156-159.

The author observed two cases of Graves' disease of syphilitic origin which were cured by anti-syphilitical treatment. Both patients had a psychosis which also disappeared after treatment.—J. K.

(THYROID) Improvement in Graves' disease subsequent to severe focal infection. Squier (T.), Am. J. M. Sc. (Phila.), 1920, **160**, 358-366.

Two cases of hyperthyroidism are cited in which complicating infections first caused a marked increase in the severity of the thyroid symptoms. This was followed, after the acute infection had subsided, by a striking improvement if not a cure. The author believes it is not improbable that the improvement seen is due to actual loss of secretory tissue through post-infectious sclerosis of the gland. —W. J. A.

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Internal Secretions

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THE SIGNIFICANCE OF THE INTERNAL SECRETIONS IN DISTURBANCES OF METABOLISM AND DIGESTION

Report given to the Homburg Meeting for Diseases of Metabolism and Digestion, September 26, 1920.

PROF. DR. ARTHUR BIEDL
PRAG

Metabolism, this continuous exchange of material and energy in the organism takes its origin in chemical processes, and must, therefore, naturally represent the chief field of activity of chemical regulations. One can well say that in all departments of biology the tenets of the internal secretions have extended themselves during the last thirty years to an unexpected expansion and depth. They have taught us that the chemical messengers of all tissues, but before all the endocrine glands, are concerned with development, formation, and growth in its progressive and regressive phases, in the somatic and psychic constitution of the individual, and that the degree of activity of all the tissues, organs and systems is also more or less influenced. It has also taught us that all hormonal correlations in spite of their phenomenal multiplicity are in the last analysis a matter of a direct or indirect alteration of the biochemistry, in its widest sense, the metabolism. In order to represent correctly the relation of the internal secretions to metabolism, it would be actually necessary to consider the whole realm of endocrinology *in extenso*. We will, therefore, confine ourselves to the discussion of the diagnostic significance of the internal secretions in disturbances of metabolism and the digestive organs. Thus the study can be

taken up on the basis of the relations that have so far been ascertained between endocrine organ activity and metabolism, and calling attention to those phases where in individual cases the metabolic participation, particularly its first preparatory phase, digestion, in healthy and diseased conditions can be charged up to the endocrine glands. It is my intention to treat not only of the role of the science of the internal secretions in the diagnosis of disorders of metabolism and digestion, but much more will the questions be answered regarding *the influence of the endocrine glands* individually and as a whole *on the magnitude and course of metabolism*. We will also consider their influence on the variations in disease and the kind, intensity and course of these variations, and finally that which is most important for the physician how and what kind of a point of attachment can be gained for a workable therapeutic treatment of the diseases from the extensive information at hand.

From the experimental and clinical analytical studies on the physiological role of the endocrine glands, the general conclusion presents itself before all others that the range and course of metabolism, in its total exchange with its two parts, basal metabolism and production efficiency, just as in its individual components; protein, fat, carbohydrate, mineral and water exchange, to a much greater degree than has previously been recognized, is directed and regulated by the endocrine glands. From this it follows further that in our critical examination of metabolism, we must utilize all those points of attachment more than we have before which will put us in a position to obtain more intimate data concerning the individual endocrine glands, or more exactly in regard to the endocrine formula of the individual. The way is known to us. In countless individual cases the important influence on morphogenesis during embryonic and post-embryonic development of the glands of internal secretion is thoroughly established, and has been proven in growth and adult life. It shows itself in the constitution of the individual, the outer appearance of the bodily constitution, the habitus, has with its related single components served as a measure of the critical judgment of physicians from earliest times. Even today we can only judge of the constitution when we can study the unit components of the organic makeup by measuring, weighing and other comparative evaluations. They are as follows: the body weight;

the body length as an index of the growth of the long bones; the breadth of the chest as an indication of the skeletal development of the trunk; the mass and tonus of the musculature; the firmness of the fat deposits; the condition of the skin, and its appendices, the hair and nails. I may indeed suppose that the facts concerning the role of the growth-influencing glands on the habitus and constitution are well known. It accordingly seems superfluous to me to analyze more closely those variations which can be attributed to abnormal conditions, and particularly to the quantitatively varying function of one or more of the glands on the proportionality of the body structure, on the integument, and the sexual landmarks, on the irritability and activity of the neuro-muscular apparatus and the vegetative organs, and on the temperament and the psychic idiosyncrasy of the individual. Having gathered together the individual findings we can say: when we have grasped the bodily organization of an individual *in toto* and when we have correctly analyzed its single component factors on the basis of the previous and increasingly extensive information—we are still unfortunately very far from an exact and measured constitution analysis, the first weary steps of which have now been taken by Hammar in Upsala—then the internal secretory constellation, the endocrine formula is so far made clear that we now have obtained a new standpoint for the critical examination of the metabolism of the individual. We will first of all oppose the so-called *standard values* for the magnitude of the energy consumption and for the nature of the dietary needs and consumption, which have been obtained from many studies, with the acknowledgment that these can scarcely help us in our practical experience. For it is clear that actually *different standard values* must serve for normal function, for the over-function and the under-function of the individual endocrine glands. Hence the terminology, hypo- and hyper-thyroidism, hypo- and hyper-pituitarism, hypo- and hyper-genitalism are in reality only schematic, separating concisely conditions which are not determinable quantitatively and which cannot be separated from each other by sharp boundaries. Therefore, we are compelled to prepare *individual standard values*. The average values extremely important for statistics and political economy have lost their significance in the clinic. In the individual we see far-reaching differences not only in the amount but also in the kind

of the food ingested, we find differences in the nutritive condition, in which no parallelism can be found between the amount of food intake and the body weight, used as an index of the condition of nutrition; in fact quite often a marked discrepancy exists. I will call attention to a well known example, a problem which confronts us in the light of the theory of internal secretions. That is obesity. It is incontestable that adiposity can only arise when the food ingestion exceeds the energy needs of the body for a prolonged period. In other words, no other form is conceivable than the *adiposity of overfeeding*. The experience, that there are individuals who for the most part come from families with hereditary adiposity without detectable overfeeding and without marked diminution of muscular activity, who become fat and who even remain fat with an adequate restriction of food intake leads to the origin of the term "constitutional adipesity." It is obvious that countless studies have been undertaken to show that the cause of this condition is a metabolic anomaly, and to discover whether it is due primarily to a lessened energy output and further whether the condition arises from a lower catabolism or from a lowered efficiency of production, be it through a diminution of the specific dynamic action of the foodstuffs, or be it because of a greater utilization of the energy derived from the food during work. A closer exposition of these studies is superfluous. We know that the sum total of the previous researches have afforded no decisive proof either for a lowering of the catabolism, or for a lowering of the decomposition energy of protoplasm in obesity. The lower values, particularly those found in the prolonged experiments of v. Bergmann could indeed, in this sense, be quoted. I might recall to your minds the much more important demonstrations of the observations, first made by v. Noorden, and since then by other clinicians, that in many cases of obesity there is no loss of body weight even when extraordinarily small amounts of calories are ingested.

The principal objection which we raise against the respiration studies is that they cannot answer the questions that have been put to them. For apart from the fact that the short-period methods are complicated by errors, which are large enough to explain the genesis of adiposity by a diminution of catabolism, the very marked variations in basal metabolism shown in v. Berg-

mann's tables afford no valid conclusions if the figures obtained are compared with the average values. We have no right to draw conclusions from this comparison. Neither the average energy need, while resting, nor the average production efficiency during muscular work can serve as a basis for the comparison. We must *a priori* expect far-reaching differences in different individuals if we but recognize the different original size and the still more marked variability of the function magnitude of the endocrine organs. This contention is confirmed by the results of the metabolism experiments. The values obtained from different individuals, even when reckoned on the basis of body weight or body surface, vary within such wide boundaries that one indeed cannot use the average values obtained in the fasting condition for the individual for the calculations. Let us pass along. The basal metabolism as a measure for the work, which in the resting, fasting organism is represented by the vegetative organs and the maintenance of the normal muscle tone, must change with a change in the operative factors. The endocrine glands stand in the first rank as directive agents of these phenomena. In a similar manner the influence of the endocrine glands on the efficiency of production is also availing in that appetite, nutrition and impulses to movements are dependent upon them in part as are the strength and duration of muscular activity. Now the small unmeasurable muscular movements of the daily life whose number and magnitude are dependent upon the agility and the temperament of the individual, or more acurately his endocrine glands, yield in their totality undoubtedly an energy consumption that is not to be discounted. That production efficiency differs strongly at different ages according to the magnitude of the muscular activity is self-evident. That metabolism differs at different ages is a matter of record. But too little attention has been paid to the fact that primary differential endogenous factors are determinative for the differences in muscle tonus and for the different stimuli to muscular activity as is commonly demonstrated by the impetuosity of youth, the restraint of the movements of the adult, and in the increased comfort-seeking of the middle-aged and in the high degree of rest needed by the aged.

Although the individual energy need is defined in its two components by endogenous factors, and since these show indi-

vidual variations of the widest degree, so we are no longer able to make constitutional adiposity dependent on the proof of a slowing of nutrition but must in consequence consider *every adiposity as constitutional* as endogenously conditioned. We can, of course, formulate the conception in another way and say: every adiposity is a dietary adiposity which does not arise absolutely through over-feeding, but only through an *individual call* for excessive food intake. Of prime importance are the endogenous factors of the endocrine glands.

However obvious this point of view may appear, or however little it contains of what is new or surprising, it is a matter of great interest that when individual cases are subjected to other methods of investigation we thereupon acquire definite directions for an efficient therapy. We are no longer concerned in the analysis of the respiratory gases with the comparison with standard values, but turn to the more exact method of experimentation. After a careful weighing of the points of control given by the clinical signs and after the establishment of the individual standards which also undergo variations, experimentally active amounts of one or the other or several glands of internal secretion are administered and whether or not a change in the catabolism can readily be obtained is determined. A constant detectable marked increase in the metabolism which is caused by a certain hormone or a definite hormone combination and *by this only* proves indeed that the individual in question has a lower exchange as a personal standard than is stipulated in hormonal equilibrium. At the same time we have also ascertained the cause of the equilibrium disturbance.

The practical clinical continuation of this method of research shapes itself up rather simply; its results are none the less striking. We use the body weight as the measure of metabolism, and can easily find a normal diet on which the body remains constant. Now the administration in small quantity of a definite hormone, one day's administration is sufficient, occasions a distinct alteration of the body weight safely over that imposed by the probable error of the determination: *Ceteris paribus* such an alteration is not to be expected from any other hormone or any other hormone combination. We have determined in this manner the endogenous factors of the disordered metabolism, and the prompt, often overwhelming, effect of the organo-therapy

which has been carried on strengthens the justness of our conclusion. In many cases no difficulties are encountered in foreseeing with great probability from the clinical character of the adiposity the pathogenetic determinative endocrine gland. I can well omit the description of the differential landmarks of the thyreogenous, hypophyseal, genital and other types of endogenous adiposity, but I must call attention to the fact that in the more exact clinical analysis one runs across a not inconsiderable number of combination types. It is important that the hormone study and consequent hormone therapy should make genetically clear not only the simple but also the combination cases, and thus make possible an effective therapy. I can cite many cases from my experience in which, on the basis of the clinically determined endocrine formula in hormone research, the disturbing endocrine glands were recognized as it were at the first attempt at hormone investigation, and the further study with other hormones, by their negative results, confirmed the exclusive significance of the single organ. For example, when a case of adiposity that had already been clinically recognized as certainly of thyreogenous origin was treated with a tenth of a gram of desiccated thyroid substance three times a day, while ingesting a standard diet and while at a constant weight, the weight dropped half a kilo in 24 hours, and in six days 2.5 kilos were lost. The same case remained at a constant weight when any other hormone was given even in large amounts, and when thyroid preparation was again given the same prompt action was obtained. On the other hand, a case of obstinate obesity which occurred during the lactation period did not react at all to thyroid administration, but responded promptly to ovarian tablets. For the combination types one must first ascertain the suitable mixture of glandular preparations to be used: the last year I have used in my researches an American preparation in which several endocrine glands are contained in variable mixtures.

Of particular interest are just those cases in which the clinical signs are indeterminate, even under certain conditions misleading. An example of this is a nineteen year-old young man with heavy fat deposits, particularly on the breast, in the mammae, the lack of any trace of hair on the face, on the trunk lower abdomen, on the hips and nates. The markedly developed

and on the thighs, the lack of axillary hair and the especially sparse pubic hair taken together with infantile external genitals and hypoplastic testicles, with a plainly effeminate expression, suggest an outspoken Fröhlich type. No definite indication could be found either of an hypophyseal disturbance or of an intracranial tumor. We were confined to the hypothesis of a primary hypogenitalism. But neither testicular nor ovarian substance had the slightest ability to cause an increase in metabolism. Before testing out other hormone substances, the short stature or rather the markedly short body length of 156 cm. accompanied by only a few suggestive signs of hypothyroidism, such as the hair and nails, led to a test with thyroid substance, which was strongly positive. The administered thyroid substance effected promptly the desired decrease in body weight from $2\frac{1}{2}$ to 3 kilos a week. The thyroid therapy was reduced to half the quantity after the diminution in weight had reached 18 kilos. After five months' treatment there was presented to me the now $19\frac{1}{2}$-year-old youth as a slim 160 cm. tall man with a perceptible growth of beard, so that he must shave, and with the distinct astonishing habitus of a grown man. On the anterior side of the trunk the abnormal fat deposit was lacking, which now was only to be found on the buttocks. Axillary hair had grown in, profuse pubendal hair of the male type reaching to the navel, hairy thighs, and almost completely developed external genitalia corresponding to the age and with correspondingly large testicles. The voice and psyche were completely male; the total loss of weight was 26 kilos.

This case impressively teaches us the correlative tying up of metabolism and the whole body organization with a dependence on the endocrine apparatus, but it shows us, also, the prevalence of a link of the endocrine chain, which indeed occurs in many cases, which, however, is not always schematically demonstrated, and must first be proven by experimental tests. The dominating significance of any one endocrine gland can scarcely be exhibited in the combination types of treatment. One should be particularly warned against this because it is a tendency of modern times "to cure all from one point." If we consider old age as a problem of metabolism—and this opinion undoubtedly everyone will agree with—so then one will recognize my right at this opportunity to say some words concerning old age and revert

to the recent question of averting senescence, or rather rejuvenation, which from the time of Brown-Sèquard has been of great dramatic interest. The "father of the internal secretions" placed the gonads as the axis of the problem of old age, and it is perhaps not superfluous to call to mind that the communications of this old man on his studies with the "liquide testiculaire," which he consistently administered to himself, had such scintillating confirmatory results, and similarly the evident attention which was directed to him for thirty years, which still survives to us today.

But if today one should make the gonads answerable for senescence, or more exactly those tissue elements designated by Steinach as the pubertal glands, and if one should abolish completely or avert the whole complex of old age or even one portion of the phenomenon by the reanimation of these cells, then one would overlook the important development which the teaching of Brown-Sèquard has accomplished and the results afforded by the earlier workers would be forgotten, namely, the recognition of the significance and the effect of the other endocrine glands and their co-operation.

Just as all bodily conditions and their fundamental chemical reactions are under the influence of the entire *hormone apparatus*, so is old age. This condition is regulated and directed in the degree and course of its development, not only by the testicles or ovaries, particularly the interstitial cells, but just as well by the thyroid and thymus glands, by the hypophysis and the pineal, by the inter-renal and the adrenal system, and perhaps even by other organs and tissues, in short by the whole endocrine apparatus, by its single parts, but before all by the harmonious co-operation of these parts. It seems to me quite superfluous to direct attention to the fact that in cases of premature old age on the ground of certain indications, that are perhaps striking only to him who recognizes them, that in the one case the thyroid, in the other the hypophysis or the adrenals, and even other endocrine glands can be considered as the pathogenetic centers. At times the opinion made at the time of observation is verified at autopsy. When tissue transplantation or hormone administration is used as a method of substitution therapy, rejuvenation effects can doubtless be obtained. Or how else can one interpret the fact that there is produced a surprising alteration of the entire individual by feeding thyroid to a cretin, to choose a

familiar example, whose appearance and vegetative and somatic functions are those of an old person.

In a case of ateleiosis (defective development)—the ten-year-old girl had the appearance, the metabolic, the somatic and psychic condition of an old woman—by a combined hypophyseal ovarian treatment I unexpectedly obtained the result that, together with a gradual transformation of the skin, the hair, the teeth and the nails, the increased muscle tonus and the fat pads of adolescence, there began a growth in body length and after about a six months a real child stood before me, who, however, still carried several characteristics of her earlier condition.

I will not be prolix, it is not my intention and indeed here is not the place to speak critically of Steinach's work. From my point of view, if the physiological role of a specific endocrine gland can be determined by safe proof and exact experimentation, so that we may be able to actually seize hold of the organic machinery on the basis of such determination, such a finding must be greeted with pleasure. Whether and how far Steinach's studies meet this postulate will be considered by me in another place. Here I can only touch on the fact that old age and youth are not entirely dependent on the pubertal glands, but that they bring up *questions of endocrine harmony,* a solution for which can only be obtained by bringing into use all methods of research on the internal secretions.

After this deviation we will now return to the main theme and, however needlessly, remark that all those viewpoints which are valid for the *plus deviation of metabolism* (adiposity) are also valid for the *minus deviation* (emaciation). As previously mentioned, this is endogenous and rests largely on an increased activity of glands that accelerate metabolism. The opposite case, the suppression or the decreased action of retardent endocrine glands, practically plays a much smaller rôle. Unfortunately, we do not possess any similarly acting substitution-therapy or easily applicable methods suitable for causing a retardation of an hormone over-function when it exists. The Roentgen and radium-rays act almost only in a destructive manner—definitely in their effects as function diminishers; perhaps it is only a question of technique to evolve methods for the attainment of temporary effects. By the attainment of this preliminary condition we can effectively attack idiopathic, constitutional and even

other forms of emaciation, such as today is done in the diet cures. I will briefly relate a striking case in which organo-therapy was effective. *Hofstätter*, as is well known, used pineal extracts with good result in combatting pathologically increased *libido sexualis*. And *Pilcz*, on his recommendation, tried the same treatment in a case of *dementia præcox* with favorable results. In a second case of this type Hofstätter's proposal of pineal medication was carried out and I had the opportunity of observing the case myself. Direct points of attachment for a diagnosis of hypergenitalism or a hyperactivity in a sexual sphere were lacking, the only marked symptom was the *high degree of emaciation of the patient* in spite of his *abnormally great ingestion of food*. The constant activity and increased muscle tonus made the increased caloric consumption understandable. The oral administration of a commercial preparation of alleged pineal substance was completely ineffective. The subcutaneous administration of a laboratory pineal preparation produced even after a short time a reduction of the activity and a noticeable increase of the body weight—the total increase amounting to 16 kilos—notwithstanding a decreased food intake. On the basis of these results I would use organo-therapy with pineal substance in certain cases of constitutional emaciation, but unfortunately we are today contending with the difficulty of procuring a dependable material. It might be said in passing that this applies equally well to all other spheres of endocrine preparations. Standard tests for such preparations and their physiological assay are urgently needed.

If we now direct our attention to the single factors of metabolism instead of the general, it is clear that these are under the control of the glands of internal secretion, that the need and consumption of the single foodstuffs and the manner of their decomposition in the organism are influenced by the endocrine glands as individuals and as a whole. The functional state of the individual endocrine gland must be thought of when considering the magnitude of the protein minimum, which, according to earlier studies, is likewise a matter of individuality, just as are the external factors which previously almost exclusively have been alone considered. That many of the latter are ultimately dependent on the temperament of the endocrine glands sounds at present like a snap judgment. It is entirely unneces-

sary to make further remarks upon the influence of every single gland on protein, fat, carbohydrate and salt metabolism. The diseased conditions of the endocrine glands as such and their consequence on metabolism will not be spoken of further here. The place of the endocrine glands in the pathogenesis of any individual metabolic disease demands a report by itself.

A brief consideration of the significance of the internal secretions in digestion is now in order. In diagnosis the influence of the new ideas are especially noticeable in two directions: first, the great field of the size, form, anomalies of position and changed conditions are no longer, as formerly, only handled exclusively as descriptive anatomy, or are the best cases considered embryologically and teratologically, but they are rather more looked upon as dovetailing into the total body makeup as partial constitutional components in a casual genetic analysis, in which proven morphogenic influence of the hormone glands serves as a basis. Secondly, the nervous system is not made exclusively responsible from the functional point of view for their physiological variations and pathological alterations, but the fact is being brought into increasing prominence that the chemical messengers of the endocrine glands in their activity, direct or indirect, play a regulating part, through mediation of the sympathetic and para-sympathetic nervous system, and that a hormone action deviating from the normal can play a disturbing rôle in functional disturbances.

This progress illustrates very prettily the angles of view from which we today consider those helpers of the digestive apparatus, the teeth. We know today that the regulation and properties of many endocrine glands are responsible for the observed anomalies of teeth formation and structure. That by all means rare persistence of the milk teeth and the frequent single milk teeth can no longer be considered as curios, but as expressions of a partial infantilism, for whose origin the branchiogenous organs, the thyroid and hypophysis, as was to be expected, come into play. The enamel defects of the incisors are the long expected document of a parathyroid insufficiency occurring in the earliest years of childhood, and as such point to the utilization of this organ. From the studies of Kranz, Josefson, and others, we have obtained information as to the influence which the thyroid exerts on the growth of the maxilla and dentition,

and on the spacing and peculiarities of the teeth. We must consider from an altered point of view the question of dental caries and alveolar pyorrhea, since the experimental results are always forcibly impressive with respect to endocrine and metabolic factors. The morphological anomalies in the digestive tract itself have assumed a new aspect, since the various forms of stenoses, dilatations and diverticular formation in the oesophagus, the place and structural anomalies of the stomach and intestine are none other than infantilisms and can be considered as signs of further developed constitutional variation conditioned by the glands of internal secretion, occurring in fetal life and during the growth period. The necessary individual observations and experiences in this field are indeed still few. To a certain extent these apparent anatomical alterations and the functional disturbances following them fall in the broad terrain of the muscle tonus of the vegetative organs. It would naturally lead very far if one were to treat the tonus problem in its entirety. Only one thing is to be noted, and that is that even if today the nature of tonus is by no means sufficiently clear and even if the question of the part of the sympathetic, parasympathetic and central nervous systems figure in the discussion of tonus, the dependency of tonus on and its influencing by the endocrine glands is undoubted and is directly proven in many cases. Diagnostically and therapeutically we can deduce important conclusions, under certain circumstances, from this state of affairs. I call to mind —to give one example only—the action of the hormone of the thyroid or the pars intermedia of the hypophysis on the tonus of smooth musculature and to the generally known striking consequences of thyroid medication in certain forms of habitual constipation apparently of thyreogenous origin. Many times we have to do with the common effect of several endocrine glands in pathological changes and diminution of tone. Here pluriglandular therapy comes into its own on the basis of the clinical point of attack.

The principles for the secretion disturbances of the digestive tract are the same as those for the anomalies of tonus and motility. I can, therefore, consider them briefly. The progress of the studies of constitutional makeup are putting us in a position, to an increasing degree, to appraise the magnitude of the endocrine components in the origin and shaping up of the ground, on

which a pathological impetus can give rise not only to abortive functions in increasing intensity, but also to an anatomical destruction.

It is only necessary here to call attention to the relation of the adrenal system to the origin of gastric ulcer, which indeed is not yet definitely proven, and particularly the most recent study reported from Russia in which the important rôle of the different endocrine organs for the origin, growth and the retrogression of malignant tumors in animals is discussed.

That the magnitude of the functions of the secretory apparatus of the digestive tract is intimately related to the endocrine system needs no particular exposition, if we call to mind the fundamental researches that have been made in just this field. Many digestive organs, such as the liver and the pancreas, produce simultaneously an external and internal secretion, they are of the greatest significance for the preparatory phase of digestion and also for total metabolism. They are, however, at the same time links in the chain of the endocrine glands and are connected with all the other links in a most intimate interchange of effectiveness. It would be very enticing to expand more extensively on this very attractive theme.

In the conclusion of this discussion may I especially point out that I have been able to handle this extensive sphere only in programmatic brevity and, as it were, as a sketch planned to touch the high points in a penetrating presentation. I may well hope, however, that I have perhaps succeeded in directing notice to a province of biological study that still needs many active workers, and is indeed worthy of them.

ENDOCRINE PROBLEMS IN PELVIC SURGERY WITH SPECIAL REFERENCE TO VICARIOUS MENSTRUATION.*

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The study of endocrine function is perhaps at its most perilous stage. So marvelous have been the results of the earnest and scientific work of pioneers in the field that the medical profession is in danger of imitating the attitude now assumed by the general public, accepting any and every oracular dictum concerning the application of internal secretion therapy to practice, demanding only the authority of the printed word, and forthwith making the innocent patient material for research. Medicaments are being exploited which we know on sober reflection to be too highly potent for indiscriminate use. It is fortunate that we are beginning to see in the literature a note of caution, and that *conservative* summaries of present limitations, and careful experimental studies offset to some degree the flood of impulsive conclusions often stated as positive facts, with which we are all familiar. Because, for instance, we should all like to see systems of antagonists found for over-active secretions, it would be gratifying, but perhaps premature to consider the problem solved by the mere announcement of a "postulate of control or inhibition" with insufficient foundation of research or careful study.

Yet there is every prospect that by constant process of sifting the grain from the chaff, the endocrine concept will eventually furnish us an effective and definite armour for combatting the inroads of constitutional inferiority, of disease, of age, itself.

The importance of the study is accentuated by our increasing realization of the widespread scope of endocrine control over body development and activity, including physical growth, mentality, muscular energy and response to stimuli, sex function and metabolism.

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*Abbreviated from a paper read before the Texas State Medical Association, May, 1921.

With the primitive vegetative functions, as Novak pointed out, the mechanism is essentially of the endocrine type, with some degree of contributory regulating influence on the part of the sympathetic nervous system. Under this classification we may group genetic functions, and the prompt, convincing results of hormone therapy in gynecology has accentuated interest here.

While in pelvic disorders there will always be a place for the surgical correction of mechanical, inflammatory, or neoplastic defects, by discriminating appeal to hormone therapy, needless surgery can be avoided and necessary surgery supplemented.

Three cases are herewith reported, all presenting pelvic symptoms, selected because each is a fairly typical example of the syndrome produced by predominant disorder of one gland of internal secretion, because each gave a positive "therapeutic test" and because in each case a routine "gynecological procedure" would perhaps have been followed a few years back, without the possibility of correcting fundamental causes. The first is presented as an example of thyroid deficiency; the second as a case of deficiency of the anterior lobe of the pituitary body; and the third, a definite case of vicarious menstruation, was treated on the basis of modification of excess of the ovarian secretion.

Case I. Thyroid Deficiency with Obesity. Mrs. J. R., a housewife of 42, was referred to our service for surgical correction of uterine displacement, believed to be causing her presenting symptoms —pelvic and lumbar pain. Her menstruation appeared at twelve, had been fairly regular, profuse, free from cramping, and the menopause had not occurred. She had three children. Obesity had always been present, more marked during the past four years, and her present complaint, severe, continuous pelvic and lumbar pain, had developed during the latter period.

The patient is a short, stocky woman, her lower measurement equally the upper, very obese (weight 300 lbs.), with smooth, puffy non-pitting skin. The head is large, with oval contour. There was a slight laceration of the cervix and perineum, and a slightly retroflexed uterus; the genitalia and secondary sex characteristics were well developed. The urine and blood examinations were both negative upon extrance. Blood pressure was 130-85. A diagnosis of thyroid deficiency, with myxedema and obesity, was made and surgical interference not advised, as the symptoms were believed referable to the obesity with resultant sacro-iliac sub-luxation.

Thyroid extract, gr. 2½, three times daily (later twice daily) was administered under careful observation for ten days in the hospital, and a decreased amount given under observation of her local physician later. The weight was reduced eleven pounds in five days; a remarkable total reduction of fifty-eight pounds occurred in ten days, without any hyperthyroid symptoms. Our information is that the

resultant weight of 242 pounds has been maintained since (12 months) under very small doses of thyroid extract. The pelvic pain promptly disappeared, and a well fitting sacro-iliac support relieved the lumbar symptoms. A specimen urine analysis during treatment will be of significance: specific gravity, 1025; urea, 15.0 gm. per liter; ammonia, 0.4 gm. per liter; clorine, 1.2 gm. per liter; large amount of indican; no sugar, albumen or casts; in other words, the kidneys were rapidly eliminating the cellular waste, principally as urea.

Case II. Anterior Pituitary Deficiency. Miss E. U., a spinster of 32, whose predominant symptoms were *amenorrhea* and *pelvic* pain, gave the following history: The onset of menstruation was at 14 years; it was of the thirty-day type, with dysmenorrhea. At sixteen, irregularity appeared with decrease in amount, these symptoms being aggravated until two years ago, when the periods at that time appearing at intervals of from four to six months, ceased. For the past two years there has been marked general pelvic pain increased at monthly intervals. The patient upon examination was seen to be of masculine type, with dark coarse skin, hypertrichosis, heavy voice, slight obesity, underdeveloped secondary sex characteristics and genitalia, no stenosis of the cervix uteri. Her configuration was significant; small head, a normal torso with abnormally short, large boned limbs. Pelvic examination revealed a cystic tumor on the left side, presumably ovarian. Blood and urine were normal. The weight was 150 pounds. Blood pressure was 120-75.

Exploratory operation revealed a medium sized simple cyst of the ovary, with clear fluid, which was removed. The patient was given thyroid and ovarian extract with whole pituitary gland in small doses, and, after two months, regular (though scanty) menstruation returned. There was no decrease in weight.

Case III. Vicarious Menstruation-Hypergonadism. Mrs. B. F. S. a housewife of 32, entered Baylor Hospital with the following story: Her parents and near relatives were all living and in good health. Up to five years ago her personal history was uneventful except for dysmenorrhea. Her menses began at 15 years, and have always been irregular and accompanied by pain. She had two children. Five years ago she noted slight nausea, cramping in the pelvis and occipital headaches, all marked before and during menstruation. A year later she was operated upon for appendicitis and retroversion without relief. Her chief complaints at this time are headaches, nausea, dysmenorrhea with constant vomiting of blood, bleeding from the left conjunctiva and, rarely, bleeding from the left ear. These symptoms for two years have been present three weeks out of every four, during which time the patient is bedridden, and has been given large doses of morphia. In the intervals she is completely well, and requires no medication. Dilatation of the os had at times induced an increase in the usually very scanty menstrual flow with temporary alleviation of symptoms.

The patient was a tall, emaciated woman. Physical examination disclosed practically nothing significant. There was a slight retroversion still present, and no stenosis of the os. The blood and urine reports were normal. The coagulation time was 2½ minutes. Blood pressure was 140-90. The patient was kept under close hospital observation for three weeks to verify the symptoms and exclude hysteria and drug addiction. The symptoms, including vomiting of blood and bleeding from left ear continued. It was found possible to reduce greatly the amount of morphia and eliminate it during free intervals. Lutein was given intramuscularly for several days to observe the effect. The symptoms were aggravated until the treatment was discontinued. On the evidence that the symptoms complex was caused by increased or modified ovarian secretion, a double ovarectomy was performed.

There was no ovarian or broad ligament congestion noted, the uterus was slightly retroverted and the round ligaments pale and attentuated. The pathological report of Prof. Geo. T. Caldwell was as follows: "One of the ovaries contains a cyst 2 cm. in diameter and other small serous cysts; the other ovary is quite small, measuring 3.5x1.8x0.7 cm. This small ovary is more fibrous than normal. Microscopically the ovaries contain small corpus luteal cysts, with some increase in surrounding fibrous tissue. One area is edematous and contains diffuse hemorrhages, elsewhere the ovarian tissue appears entirely normal."

Convalescence was stormy, all the previous symptoms being tremendously aggravated for three days, after which the patient had a free interval followed by three menstrual periods at the regular intervals with the usual complex present. Menstruation then ceased *abruptly* as did *all* the attendant symptoms.

DISCUSSION

The first case is presented as a rather typical example of hypothyroidism with myxedema and obesity. The menstrual history is suggestive—early onset, increase in duration and amount, freedom from dysmenorrhea, late menopause as contrasted with the late onset, and amenorrhea of the pituitary case.

The physical appearance, obesity, subdermal infiltration, pasty skin, generally stunted stature, well developed sex characteristics, may also be contrasted with the pituitary type. Concerning the treatment it was noted that no tachycardia or other evidence of excess thyroid medication developed in spite of the prompt weight reduction of sixty pounds in ten days.

The second case presents a syndrome which has been generally accepted as pointing to insufficiency of the secretion of the anterior lobe of the pituitary body. This case presents a picture of arrested development of long bones, attested by the squat stature, the disproportion between the normal torso and the short limb, the microcephalic head. This was associated with amenorrhea and partial absence of genital function, without the adiposity associated with cases in which the posterior lobe is seriously deficient. The menstrual history is also significant: late onset, cessation of periods for months at a time and finally complete amenorrhea, differing markedly from the early onset with free, painless periods in thyroid dyscrasias. This suggests the syndrome described by Levi and Loraine, and amplified by Englebach, as pointing to one predominant endocrine dystrophy, deficiency of the anterior lobe. There was sufficient evidence, however, of pluriglandular involvement to warrant combined therapy.

Case III. Vicarious menstruation has been regarded as due to a constitutional anomaly of the sex organs and the explanation sought in physiological or pathological prevention of normal menstruation, as during pregnancy or lactation, the post-climacteric period, or after hysterectomy. Predisposing physical defects—hypoplastic uteri, hematokolpos or stenosis of the os, have all been suspected as accessories. In a number of cases collected by Roth, the place of hemorrhage was: nose, 30%; fistulas, 18%; skin, 10%; lungs, 8%; mammae, 5%; stomach, 4%; bladder, 3.5%; ear, 2.5%; eye, 1.3%. In Roth's collection of cases the treatment consisted of suggestion, hot applications, excision of fistulae or ulcers, bleeding, purges, corpus luteum, ovarian or thyroid substance, intrauterine dilatation, surgical correction of defects, or intravenous coagulants. The outcome is stated as: better through treatment, 22%; self cured, 18%; unchanged, 58%; died, 2%.

It is essential of course to rule out, in consideration of these cases, conditions also diagnosed by hemorrhages, as acute bronchitis, pulmonary tuberculosis, pulmonary embolus, ulcer, carcinoma, hemorrhoids, renal stone. Here, of course, the periodic course and attendant general complex is invaluable in diagnosis.

While unquestionably organic, constitutional, or genital defects, environment, psychic shock, and any number of other factors may increase or decrease the syndrome, we are fairly safe from the evidence in looking for the fundamental cause in an unbalanced endocrine system dependent upon a perversion or excess of ovarian secretion.

In ordinary menstruation, the congestion of uterine mucosa caused by the ovarian (corpus luteal) secretion, is preceded or accompanied by changes in other localities. We are familiar with the rise in vascular tension and blood pressure, the hyperemia of the various mucous membranes and glandular structures, the hypertrophy of the thyroid, the cerebral congestion, together with muscular hyperemia and cramping, and in many individuals dermal disorders such as urticarias or cloasma. The same symptoms, more aggravated, are seen at puberty, during pregnancy, and at the climacteric.

Zondek's tests confirmed the instability of the vascular innervation at the menopause.

Dysovarianism may act both directly and through stimulation of the posterior pituitary, the thyroid, and possibly adrenals, so that the resultant complex becomes a general pluriglandular disturbance. There are two factors present, the primary amount of modification in ovarian secretion and the degree of instability of the individual's sympathetic system and remaining endocrine organs. Upon these factors rest the severity of the disturbance.

It is not difficult to carry a step further these signposts of the menstrual crisis—the various hyperemias and congestions, the increased vascular tensions to produce the symptomatology seen in vicarious menstruation.

The cause of this ovarian dysfunction is of speculative interest; among other causes, local fibrosis, thickening of the tunica albuginia and focal infections could be suggested.

The therapy in such cases is confessedly radical and doubtless less drastic measures combining the same effectiveness and permanency will eventually be evolved, since we are probably dealing with a perversion rather than a mere increase in ovarian secretion. Radium and roentgen therapy are in the indeterminate state. Dederer, in a somewhat similar case, had an apparently successful result through resection of the nerve supply of the ovaries. Kuntz and others report, however, that the evidence indicates that the sympathetic innervation (derived from the ramus ascending from the inferior mesenteric ganglia to the renal plexus), does not supply the ovarian follicles or the interstitial secretory tissue, and concludes that degenerative changes after resection are due to paralysis of the blood vessels. Hence, if we may draw an analogy from thyroid ligation, the effect of the denervation should be temporary.

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THE NEW VIEWS AS TO THE MORPHOLOGY OF THE THYMUS GLAND AND THEIR BEARING ON THE PROBLEM OF THE FUNCTION OF THE THYMUS

By J. Aug. Hammar

UPSALA

It has almost become an established expression in discussing the thymus gland to call it an "enigmatic organ." This may still have been justified a couple of decades ago, when our knowledge of this organ was restricted to certain not very clear data; but nowadays the expression is scarcely more justified for this than for a large number of other organs in the body. It can even with justice be said that in certain not unessential respects our knowledge of the thymus is more thorough than that of the majority of the organs closely related to it functionally. If, nevertheless, the expression in question or the view that it represents reappears not infrequently even in publications of recent date, this is certainly connected with the fact that the knowledge of the results of more recent investigations is still but slightly spread; one often comes across, at least in clinical literature, expositions that start out from older and notoriously incorrect views.

It was accordingly with pleasure that I carried out the wish expressed by the editor of Endocrinology to give a brief exposition of the more recent observations regarding the thymus, especially with respect to its normal morphology. And in doing so one can certainly not altogether exclude certain aspects of the organ during disease nor the question of its function.

Merely from considerations of space, however, it is impossible to give here more than an exposition of certain main features of the subject. Ten years ago I gave a more detailed account of the question (Fünfzig Jahre Thymusforschung, Ergebn. d. Anat. u. Entwicklungsgesch. Jg., 1910) and I can all the more readily refer the reader to this for details because, as far as I can see, no reason to alter in any essential point the view there put forward has arisen since that time. On the contrary this view has of late gained a broader basis in many points, and in several aspects it has become more clearly elucidated

than it was then. Due attention will be paid here to certain of these advances.

As it seemed to me desirable to try here especially to elucidate such points as are important for human physiology and pathology and in which the new results contain some new principles, I have given my account chiefly the form of certain leading theses, each of which is developed and illustrated.

1. THE THYMUS IS AN EPITHELIAL ORGAN, INFILTRATED WITH LYMPHOCYTES.

Ever since Kölliker (1879) drew attention to the fact that in an early embryonal stage the thymus has an epithelial anlage and is probably a derivative of a branchial cleft, there came the problem of explaining how from this epithelial germ had arisen the finished structure of the organ, with its combination, resembling the lymphoid tissue, of a reticulum and free lymphoid cells stored in its meshes. It is well known that earlier two different ways of answering this question were attempted.

The "*pseudomorphosis theory*" inaugurated by His (1880) and Stieda (1881) was that the epithelial anlage had elements of connective tissue growing through it, which caused its decomposition and substituted it so that only scattered epithelial remains in the form of Hassall's concentric corpuscles were left, while the rest of the parenchyma was differentiated, like a genuine lymphoid tissue, in the ingrown mesodermal elements. The term "epitheloid" cells introduced by Watney (1881, 1882) in his excellent works on the histology of the thymus and not infrequently used afterwards up to the present day for the hypertrophied medullary cells, arises from a view of that sort, as also does the term "endothelial" or "endotheloid" cells, used by Klein (1880) for the same formations. That these terms do not agree with our present views of the structure of the organ the following will show.

With the "pseudomorphosis" theory there competed from the very first another one, called the "*transformation theory*," which had already been outlined in its most general features by Kölliker himself. According to this view there was no such regression of the original anlage as the former theory assumed, but the organ as a whole was supposed to appear by a direct transformation of the epithelial anlage. The more detailed con-

sequence of this view was brought out by Stöhr (1905, 1906), who pointed out that, according to this idea, which he himself adopted, the small thymus cells were not lymphocytes, but small epithelial cells.

Both these views had originally been put forward without any detailed investigations as to the histogenesis of the thymus. Neither of them was able to stand this test. In different vertebrate classes it was established that the thymus reticulum appears through a transformation of the epithelial cells of the anlage to a ramified form, while the lymphocytes enter from outside and at first diffusely infiltrate the whole epithelium. The hypertrophy of the central epithelial cells of the organ is only secondary, and the central part, rich in protoplasm, that thus arises, forms the medulla of the organ and the region around the edge, richer in nuclei, its cortex. Within the medulla, on the other hand, there appears later on an increase in the size of separate epithelial cells or groups of cells, giving rise to the medullar differations known under the name of Hassall's corpuscles or their homologues, which are rather different in separate species ("uni-cellular Hassallian corpuscles," "myoid cells," "irregular cell complexes," etc.).

Nowhere does the thymus appear more clearly in its quality of epithelium infiltered by lymphocytes than in certain Teleostei and Ganoids (Hammar, 1908; Ankarsvärd and Hammar, 1913), where at the moment of infiltration the organ still has the character of a thickened surface epithelium—a thymus placode—and in the majority of species investigated the organ also retains this character throughout life, while in other species it is separated secondarily from the surface by ingrowing layer of connective tissue.

In the case of mammals the occurrence of a lymphocytic infiltration of the epithelial anlage during embryonal life was first convincingly shown by Maximow (1909), for birds and reptiles by Vera Dantschakoff (1908, 1910, 1916:1), for Amphibia by Maximow (1912), for Selachia by Hammar (1911), and Maximow (1912). In all cases there are present at first large lymphocytic forms, which secondarily assume the small dimensions characteristic of the thymus lymphocytes only after their entrance into the organ and repeated divisions there.

The proof of the immigration of the lymphocytes into the

thymus anlage during development and, in connection with this, the transformation of the latter into an epithelial reticulum; the far-reaching morphological resemblance between the small thymus cells and typical lymphocytes (Laurell;* Pappenheimer, 1913; Pinner, 1920, etc.); the great resemblances between the two kinds of cells from a biological point of view: amoeboid movement (Hammar, 1905; Jolly, 1914:2, 3); great sensibility to Röntgen rays (Heineke, 1905; Rudberg, 1907, 1909; Regaud and Crémieu, 1911, 1912, etc.); the identity of the two kinds of cells from a serological point of view (Ritchie, 1908; Felländer, 1912, etc.) and, finally, the analogous conditions of the lymphocytes in the thymus on the one hand, in the real lymphoid tissue and the blood on the other, during involution and other conditions—about which more will be found below—all these factors form so strong a chain of evidence in favor of the "small thymus cells" having the very much discussed nature of real lymphocytes that even in the latest posthumous editions of Stöhr's own text book his view of them as epithelial cells has now been abandoned.

It ought, however, to be mentioned that this view of Stöhr's is taken up by different investigators (among others Schridde, Dustin, Fulci).

With regard to the details of the histogenesis in man it may be mentioned that the infiltration of the epithelial anlage by lymphocytes begins as early as towards the end of the second month of prenatal life, at an embryonal length of about 30 mm., that the formation of the medulla begins at about the length of 40 mm., and that the first Hassallian corpuscles appear towards the end of the same month at about a length of 50 mm. At the end of the second month the organ already consists of two conical lobes, situated close together in the anterior mediastinum, each with a longer or shorter pointed upper end, the thymus horn, and a basal end usually bent round backwards in the shape of a hook, *the cardiac bends.* Towards the middle of each lobe septa of connective tissue penetrate, especially its thickest parts from all sides, dividing the cortex into so-called cortical follicles. The medulla remains undivided. At the same time

* The myoid cells with cross-striated fibrillae in their interior are regularly found only in inferior vertebrates. In exceptional cases a similar structure has been seen also in individual medullary cells of the human thymus (Pappenheimer 1910, Salkind 1915, Wassjutotschkin 1918).

as the organ continues to increase rapidly in size by mitotic division both of the lymphocytes and the reticulum cells, the formation of medulla—the result of the enlargement of the reticulum cells—encroaches upon the inner parts of the cortical follicles, which consequently assume the character of lobuli, consisting of both medulla and cortex. As, owing to ingrowing connective tissue, these in their turn are undergoing a similar development, and this process is continually repeated, there issues from the originally simple central medullary region of the lobe a central medullary cord, ramified and often exceedingly sinuous; around this are grouped all the thymus lobuli in each lobe, and with it they also subsequently remain connected. Sometimes this central cord also shows at its surface a thin layer of cortex, and it is therefore best to call it *the central parenchymal cord*. In exceptional cases the growing in of the connective tissue causes, especially in the neighborhood of the thin thymus horns, a splitting-off of one or more parts of the parenchyma as an entirely independent division, an accessory lobe, but otherwise the whole parenchymal mass is coherent in each lobe; lobuli bounded on all sides by connective tissue, as described in earlier accounts, do not exist (Hammar, 1911:1).

While in this way a more and more abundant lobulation is developed, the organ grows rapidly during prenatal life. Postponing to another occasion a more detailed account of the results of a numerical analysis that I have carried out on about 80 normal human thymus glands from embryonal life, I shall give here only a few preliminary details.

The analysis that was carried out thus shows how the number of Hassall's corpuscles quickly increases. They are started as small formations of 10-25 μ in diameter, often in the neighborhood of some small vessel. One or two adjacent reticulum cells increase in size and assume a spherical shape. When on this enlargement they reach neighboring cells in the medullary reticulum, the latter cells are thrust to the side owing to the pressure of growth and take up a position close to the central cell or cells, which they concentrically enclose like the scales of an onion. Even the peripheral cells often fairly soon become hypertrophied, so that the formation grows farther and fresh cells are joined to its periphery. When the growth proceeds in this manner two or more corpuscles may reach each other, join

together, and continue to grow as a unit. In this way there arise the so-called compound Hassallian corpuscles, which are formed, however, mostly in the later embryonal or postembryonal stages. The lymphocytic and leucocytic forms found in a great number of the Hassall's corpuscles do not take part in the formation, but are as a rule in a more or less advanced state of disintegration. Their number is sometimes so great in a Hassallian corpuscle that it is expanded by them like a little cyst. These Hassall's corpuscles richly invaded by lymphocytes seem to be more than usually numerous in congenital lues.

The majority of Hassall's corpuscles do not normally attain, even in postnatal life, a greater diameter than 25-50 μ. With increasing diameter the larger forms are as a rule more and more rare. It is very rare for any Hassallian corpuscles to attain a greater diameter than 200 μ during embryonal life. Postfoetally, on the other hand, the maximum limit is, as a rule, about 500 μ, i. e., 0.5 mm.; only in some exceptional cases have I found still larger forms postfoetally, up to a diameter of 1 mm. and more.

At the time of birth the thymus in man has a shape that is exceedingly drawn out, transversely. It may occupy a considerable portion of the available space in the thorax. Its lateral surfaces may, with their decidedly convex shape, bend into their respective pleural cavities. With the beginning of pulmonary breathing a change takes place in the shape of the organ; it becomes more elongated, its extension in a sagittal direction increases, while at the same time the sagittal diameter of the thorax increases, its lateral surfaces become planer, even concave and grooved (Hammar, 1916:2; Gräper, 1920).

It forms no part of the plan of this account to enter more closely into the comparative morphogenesis of the thymus. It may be mentioned, however, quite incidentally, that our knowledge of the process of the development of the definitive total form of the thymus, differing in different species, has increased considerably of late year, among others in case of Ammocoetes (Castellaneta 1913, Salkind 1915, Wallin 1917), Elasmobranchii (Fritsche 1910, Hammar 1911, Maximow 1912), Ganoids (Ankarsvärd and Hammar 1913, Castellaneta 1917), Teleostei Hammar 1908), sparrow (Helgeson 1913), duck (B. Hamilton

1913), Marsupialia (Fraser and Hill 1915, Fraser 1915), pig (Zotterman 1911), cattle (Hagström 1921), rabbit (Hanson 1911), guinea-pig (Maximow 1909, Ruben 1911, H. Rabl 1913), mole (H. Rabl 1909), Prosimii (Nierstrasz 1912), and man (Hammar 1911:1).

It may be said that these investigations afford additional confirmation of the ideas as to the originally branchiogene metameric nature of the organ. Thus circumstances have arisen which make it probable that even in the cases in which a metamerism of this sort does not appear in ontogenesis, the organ has issued from a cell material coming from the entoderm of branchial clefts and thus originally metameric (Ankarsvärd and Hammar).

In addition it has been shown how different are the factors, apparently partly of a mechanical nature, that become active in different species and produce the important differences in position and shape that may characterize the organ even in closely related species (Hagström).

Finally, in the case of mammals it has also been shown that the epithelial thymus anlage itself is by no means equivalent in all cases, as it is certainly, in the majority of known cases, purely entodermal, issuing from the third branchial pocket, but in some species (mole, guinea-pig) it is purely ectodermal, in others, on the other hand, such as the pig, of mixed ecto-entodermal origin. Especially illuminating in this respect is Frasers and Hill's discovery in Trichosurus, where not only together with thymus III, a similarly entodermal thymus IV was shown for the first time in a mammal as a *normal* occurrence, but also, still further, certain parts of the ectoderm of the cervical sinus, about the same as in the pig, are used for the formation of an ectodermal (or ecto-entodermal?) "thymus superficialis."

2. THE THYMUS IS NOT A TRANSITORY ORGAN, BUT PERSISTS AND FUNCTIONS EVEN UNTIL OLD AGE. AT PUBERTY ITS PARENCHYMA BEGINS TO BE REDUCED: "AGE INVOLUTION."

No idea about the thymus gland has perhaps been more widespread and more generally adopted than that the organ is of a transitory nature, that at a certain early age it begins to decline and soon disappears, or at least ceases to function.

It is true that the views as to the time both for the beginning of the regression and the disappearance of the organ have varied to a very great extent. The opinion already upheld by Galenus, that the turning-point in the existence of the organ is at birth, has still found followers in this century (Collin and Lucien, 1905, 1906). Sometimes writers have even wished to assign the entire activity of the organ to embryonal life and assumed that it was spent soon after birth. The most general view during the latter part of last century held, however, that the highest point of the development of the organ was during earliest childhood, 1 to 2 years; opinions were very much divided as to how soon and to what extent the organ atrophied after this time. When in exceptional cases a large thymus was found after the time when it was considered that the thymus would normally have been involved, it was called a "persistence" of the organ, or, later on in such cases, when it was considered that the organ had already been atrophied and had again grown and begun to function once more, a "revivescence."

In the form indicated here the old theory of an "age involution" of the thymus was certainly incorrect.

Although a few earlier anatomists (Cowper, Krause) had already expressed a similar opinion it was Waldeyer (1890, 1891) who drew more general attention to the fact that even in older people (60 to 80 years old) there exists a thymic fat body with considerable parenchymous remains. It may seem strange that this state of affairs could have been neglected so long by the majority of anatomists and that, quite generally, opinions could have been so long divided on an anatomical question of such a kind that one could have supposed the scales should easily have given the decision. The chief reason for this is, however, that it was overlooked how, under the influence of disease or other disturbances in the general economy of the organism, considerable alterations in the conditions of size and structure of the organ regularly occur rather independent of the stage of age involution that was present before the disturbance in question.

Sometimes it is a case of pathological increase of the thymus parenchyma, a hyperplasia of the thymus, but much more often, and as a rule, it is a reduction—not infrequently intense—of the parenchyma, an accidental involution. The greater fre-

quency of the latter is the reason why the average values obtained by a statistical revision of human dissecting material, leaving the conditions mentioned out of consideration, have, almost without exception, given sub-normal values. In the next paragraph I shall deal more in detail with thymus hyperplasia and accidental involution.

If we wish to eliminate this source of error, we may take as the basis of our view as to the normal conditions of the organ in man only organs from persons who have met with a sudden death by external violence, etc., while in good health and in a good state of nutrition. A statistical determination based on these principles and published by the author in 1906 showed that the turning point in the existence of the organ is at the age of puberty (11 to 15 years). Up to this time not only does the size of the organ itself increase, but, what is the essential point, the parenchyma remains undiminished in total volume. After this time, on the other hand, there occurs a rapid reduction of the bulk of parenchyma in the organ, while at the same time the interstitial connective tissue usually assumes the character of adipose tissue and forms a greater and greater part of the organ. With its typical structure retained in principle, the division into cortex and medulla retained, mitotic division of leucocytes and reticular cells proceeding, and with greater and smaller Hassallian corpuscles, the parenchyma remains as a system of parenchymous cords, growing more and more sparse and more and more narrow, quite up to old age. It is only after the age of 55 that among healthy persons who have met with a sudden death we find occasional cases in which a division into cortex and medulla can no longer be established, while, on the other hand, in other individuals it can be demonstrated under similar conditions quite up to 70 years of age.

The circumstances just mentioned, especially the occurrence of mitoses and of small incipient forms of Hassall's corpuscles, and, above all, the retention by the organ of the power to react, as in earlier ages, against disease, etc., by accidental involution of different types, indicate that even at this great age the parenchyma is still functioning.

The old theory of the age involution has thus undergone revision to the effect that the involution does not appear until puberty and that it certainly causes a gradual reduction of the

parenchyma, but in such a way, however, that a functioning parenchyma remains as a rule, even in old age. In other words, the organ is a factor to be reckoned with throughout life, and not only during childhood. Under such circumstances there can no longer, of course, be any question of a "persistence of the thymus" in the usual meaning of that term. It was obviously in the main just the normal cases that, owing to confusion as to what was normal in this respect and what was abnormal, were put under this heading. Where there is an increase of the parenchyma beyond the normal limits for the age it cannot be termed "revivescence," but here as elsewhere in similar cases, the term hyperplasia is the proper one.

It is not only in man that the involution of the thymus due to age begins at sexual maturity. In various animals it has been possible to establish the existence of similar conditions; thus in the guinea-pig (Goodall, 1905), the rabbit (Söderlund and Backman, 1909), in Raja clavata and Raja radiata (Hammar, 1911:2), in certain Teleostei (Hammar, 1908), in the rat (Jackson 1913, Hatai 1914*). Only in the case of birds are the conditions uncertain. According to Jolly and Levin (1913) involution does not occur in this case until a far later period than sexual maturity. Whether this circumstance may be correlated with the importance that the thymus has, according to Soli (1911) for the normal percentage of calcium in the egg shells of the birds is for the present impossible to determine.

That the sexual glands really play a decisive part in the age involution of the thymus is best shown by the condition of the organ after castration (Calzolari 1898, Henderson 1904, Goodall 1905, etc.). This matter has been examined with special care by Gellin (1910). He found that prepubertal castration does not affect the thymus before the age of puberty, when it allows the amount of the parenchyma in the organ to remain at a higher level than the normal. It is remarkable, however, that this level does not seem to be constant, but with increasing age a reduction of the parenchyma takes place even in the castrated subject, though more slowly and to a less extent than is normal. This circumstance must be considered as indicating that by the side of the predominant influence that the sexual

* Hatai finds the maximum weight of the thymus of the rat at the age of 85 days, but he does not make any statement as to the period of puberty in his material.

glands exert on the process of age involution, other factors, at present unknown to us, are, though to a less extent, also operative. Interesting in this connection is Gellin's experience that the transmission of Röntgen rays through the sexual glands, which does not cause complete destruction of their endocrine elements, delays, but does not altogether stop, the occurrence of involution.

Of great interest, too, in this respect are the results of Fiore and Franchetti (1911). These authors found a reduction of the thymus of young rabbits and rats before sexual maturity after subcutaneous injections of the blood of full-grown animals of the same species. If a premature age involution and not merely an accidental involution were present, which is not yet certain, this would very likely mean that thymus depressory substances continually occur in the circulating blood of the adult.

During the last 15 years my attention has been directed to an attempt to collect material—normal in the sense previously mentioned—of human thymus glands, and I have analyzed this material according to a specially worked out numerical method, published in 1914. The new material, consisting of about 120 postfoetal cases, has confirmed the fact that age involution in man occurs between the age of 11 and 15 years, but it has also shown that at all ages there normally occur such great individual variations that a very large material is undoubtedly needed if we are to determine with certainty, statistically, when in the prepubertal age the gland, on an average, attains its greatest development.

As the collecting of material is still proceeding I shall put off, even now to another, I hope not very distant occasion, the communication of the absolute and relative values obtained. Among the relative values the relation between cortex and medulla ($\frac{\text{cortex}}{\text{medulla}}$), which is of especially great importance for determining the character of the image of structure, has been separately calculated and is called the *index* of the organ.

The figures show that at the appearance of age involution it is first of all the cortex that diminishes in extent, whereby the index, too, is lowered. It is only later on that the medulla, too, undergoes, on an average, a reduction, which results in an

increase in the index value.* The absolute number of Hassall's corpuscles appears often to be somewhat reduced even in the periods 6 to 10, 11 to 15 years; it then decreases with the beginning of the age involution simultaneously with the reduction of the parenchyma. The large forms of Hassall's corpuscles with a diameter of 301 to 400 and 401 to 500 μ do not occur regularly at any age; the earliest age at which they were found was in a two-year-old child; they seem to disappear again as soon as the age of manhood is reached, so that the oldest individual in whom the size of 401 to 500 μ was found among the normal material was 35 and the oldest in whom a size of 301 to 400 μ was present was 38.

In this way the structure of the normal human thymus presents quite a different appearance at different ages, and the following types of structure can be established for the postfoetal period; there are, of course, no fixed limits of age for these, and through numerous individual variations they pass over into one another: (1.) *The type in childhood* (from birth to 10 years of age) with sparse interstitial connective tissue, abundant parenchyma, in which the cortex, consisting of closely united follicles, is predominant; (2.) *The puberal type* (about 11 to 15 years) with broad interlobular septa of connective tissue, but without reduction of the parenchyma. (3.) *The type in youth* (16 to 20 years) with broad interlobular septa of connective tissue, in which the formation of adipose tissue is generally going on to a striking extent, and with reduction of the parenchyma, in which the cortical follicles are now decreased and are separated from each other by wider interfollicular septa of connective tissue; (4.) *The type in the age of manhood* (21 to 45 years) with an interstitial tissue, usually consisting of adipose tissue, parenchymous strands—more or less thrust apart and generally rather narrow—and cortical follicles which are sparse and small, but dis-

*What has been mentioned above is true of age involution of the human thymus. It is now of no slight interest to find that in an animal such as the rabbit, in which the normal percentage of the blood lymphocytes, even postpuberally, is about twice as great as in man, the thymus cortex forms a far greater percentage in the parenchyma than is the case in man. As Gedda (1921) points out, and as is also shown by the figures arrived at by Söderlund and Backman (1909), the medulla and the cortex in the rabbit show a parallelism with regard to the conditions of quantity during age involution, so that even during this period there is a high index in the thymus of the rabbit. It is perhaps superfluous to point out that this difference between species with blood rich and poor in lymphocytes agrees well with what is stated below with regard to the general constitutional character of the variations in the lymphocyte component of the body.

tinct and generally forming rounded prominences on the strand of marrow; (5.) *The type in old age*, with narrow parenchymous strands, atrophied or quite broken off at various places, in which the cortex still is to be seen, not, however, as distinct prominent follicles, but only as patches with more abundant cells here and there in the strands.

By the side of these changes and apparently even before the age involution there occurs, as Strandberg (1917) has shown, even from birth, a growing-in of elements of connective tissue into the parenchyma. This process starts especially from the adventitia of the vessels situated at the boundary of the medulla and cortex and has a progredient character, so that with increasing age a more and more abundant system of fine *circummedullary connective-tissue* bundles arises, connected also with the deepest ends of the interfollicular tissue. This circummedullary connective tissue acquires a certain importance in certain morbid processes, especially in the development of luetic sequestral cysts (the "Dubois abscesses"—see Hammar, 1920).

Microscopical investigation affords us more exact information as to the details of the process of age involution. It appears that in man, as in other species investigated, we are here concerned in the first place with a rarefaction of the lymphocytes in the organ; only in the second place are the reticulum cells and the Hassallian corpuscles involved in the course of the involution in any striking way.

It is the decrease in the number of lymphocytes that is the chief cause of the diminution in the volume of the cortex. They are not situated so close together as before, either, the result of which is that the reticulum cells of the cortex appear with increased distinctness; especially in the periphery of the cortical follicles the elements of the cortical reticulum often join closely, forming a cylindro-epithelial *margin layer* facing the surrounding connective tissue. In the medulla, too, after the beginning of the involution it is easier than before for a joining of the reticulum cells into irregular epithelial cell complexes to take place, a circumstance that need not be of any significance at all pathologically, though it has been interpreted as being so more than once.

It is an obvious assumption to suppose that this rarefication of the lymphocytes in the thymus at the involution of age

is connected with the fact that the emigration of lymphocytes from the parenchyma out into the surrounding connective tissue, with its blood vessels and lymphatics, which is a normal occurrence at all ages, is not compensated to the same extent as before by the mitotic division of the lymphocytes in the parenchyma. But this is not yet proved. The countings of mitoses carried out by Syk (1909) for another purpose in the thymus of the rabbit did not include the period of involution.

It is of great importance for our view as to this reduction in the number of the thymus lymphocytes at puberty to know that a similar process goes on at the same time in the real lymphoid tissue (Hellman, 1914) and in the blood (Lindberg, 1910).

With regard to the reduction in the elements of the thymus reticulum, and especially of the medulla, in the age involution it is obvious that it takes place under rather different forms in different species. In certain kinds of animals (dogs, certain Elasmobranchii and Teleostei) in large regions of the medulla the elements revert all at the same time to degeneration and disintegration and then at the places where these "*sequestra*" were situated intraparenchymatous cystic spaces, "*sequestral cysts*," are developed. In an analogous way there arise in foetuses and children, under the influence of the luetic virus, the often extensive sequestral cysts that are known in the literature under the name of "Dubois's abscesses." In other species, including man, this reduction is usually accomplished cell by cell, and so proceeds under less striking forms. The way in which degeneration takes place in the individual cells also varies; in a number of lower vertebrates a mucous degeneration seems to prevail; in man the cells swell and are filled often with gross granules the nature of which it is difficult to determine.

Normally the regression of the Hassall's corpuscles seems on the whole to take place, both before and after the occurrence of the age involution, in the way that is described in more detail in the next paragraph in connection with a discussion of accidental involution.

In more advanced stages of age involution we find almost regularly atretic changes in the blood vessels of the thymus, culminating in a more or less complete obliterating of certain sections of them. The changes, which are generally found in the thymus veins of middle size, seem to be secondary, produced

by the decrease in the supply of blood to the organ that accompanies involution of age.

3. THE THYMUS IS NEVER FOUND IN NORMAL CONDITION IN SUBJECTS WHO HAVE DIED FROM DISEASE; IN THIS CASE THE PARENCHYMA IS GENERALLY REDUCED: ACCIDENTAL INVOLUTION; FAR MORE INFREQUENTLY IT IS INCREASED: HYPERPLASIA OF THE THYMUS.

I have above already touched to some extent on the intimate connection, so very characteristic of the thymus, between its size and structure and the general condition of the organism. This circumstance, which was pointed out by Wharton as early as 1659, has been verified repeatedly by many investigators and never been denied, but it is only lately that its real importance was grasped. As a rule this involution, produced by accidental causes, has been confused with age involution.

Changes in the general condition now occur even within the compass of what is "normal," but to a far greater extent during illness. Everything indicates that in both conditions the changes in the thymus are in many respects similar and often differ only quantitatively. Thus the study of the conditions of the thymus during illness and certain other abnormal influences is an important way of obtaining knowledge about the normal reactions of the organ as well. And it is chiefly from this point of view that I touch on this study here; I shall accordingly deal with the conditions of the organ during various kinds of diseases only so far as it is required for the purpose mentioned.

An accidental reduction of the size and amount of parenchyma in the thymus, i. e., an *accidental involution*, is produced not only by the majority of diseases but also by other sorts of influences—inanition, Röntgen treatment, pregnancy.

None of the different forms of accidental involution is more accurately known than *involution caused by inanition*. Already previously experimentally proved by Friedleben (1859) and the writer (1905), still more light was thrown upon it by Jonson's (1909) detailed experiments on rabbits; his results have been generally confirmed, among others, by Jolly's and Levin's (1911 and 1912) subsequent investigations on birds as well. As this form of involution may be said to be the prototype of the

accidental involution, I shall deal with it first here. The account refers to the course at complete, acute inanition or extensive chronic underfeeding; its applicability to man, as well, is substantiated by an analyzed case of congenital pyloric stenosis (Hammar, 1918), and a case of pylorospasm with death soon after the difficulties of nutrition had been overcome; both subjects were children 2½ months old, and there was a great reduction of the amount of parenchyma (1/20 of the average amount at this age). Hart (1917) recently reported a case of acute death from starvation in a 3-year-old child, in which the weight of the thymus was 5 gm. (about 1/5 of the average weight). Here, too, the microscopical report agrees entirely with what is stated below.

In animals as in man the thymus appears to be exceedingly sensitive to the influence of inanition. The changes in the size of the organ are so considerable that the adipose tissue alone is able to compete with it in the extent of the changes of volume. Here, as in other cases, the cortex appears to be the most labile part of the thymus parenchyma. During a state of starvation it is rapidly reduced, while the medulla at first retains its size, the result of which is a lower and lower index in the numerical analysis of the organ. The reduction of the cortex is chiefly brought about by a wholesale emigration of lymphocytes from it. Normally it is principally the septa between the cortical follicles that appear to be infiltrated by leucocytic forms; and among these there are certainly always lymphocytes, but these are mixed with, and often exceeded in number, by larger forms —among others, eosinophile myelocytes and plasma cells (Schaffer). Now under the influence of hunger all the part of the interstitium adjacent to the parenchyma is flooded with lymphocytes; the larger forms of leucocytes withdraw, sometimes apparently almost disappearing altogether. At the same time lymphocytes are found in large quantities in the lymph-vessels and veins situated here. The medulla, too, becomes richer in lymphocytes. Everything points to an extensive mobilization and considerable export of the lymphocytes of the organ.

At the same time the number of mitoses in the parenchyma decreases to a very great extent. Jonson found that after four weeks' underfeeding the number of mitoses had sunk from 10,500,000 in the control thymus to about 3,100; after complete

acute inanition for 4 days the numbers were 28,500,000 and 6,500,000, respectively. In no case was the mitotic process in the organ quite extinct. As long as a difference was to be seen between the cortex and the medulla a predominance of the cortex mitoses was found. In extreme stages of involution the remaining mitoses seemed to belong especially to the reticulum cells.

The consequence of this wholesale emigration of lymphocytes is not limited to a reduction of the size of the cortex. It is generally only in the earliest stages of the process that the contrast between cortex and medulla still appears to about the normal degree; subsequently it becomes more and more indistinct and finally disappears entirely. Then the parenchyma has a uniform appearance on an ordinary nucleus-colored preparation, and from an image of this sort one easily gets the impression that the cortex has quite disappeared.

If, however, one follows the process in a section of fresh thymus tissue or tissue treated only with formalin, cut with the freezing method and colored with scarlet-red or sudan, one finds that this is not the case. As has been shown by the investigations of Holmström (1911) and Hart (1912), the cortex of the normal organ is either quite free from fat, or if fat is present, it is only as a few quite fine granules in the immediate neighborhood of the nuclei of the cortical reticulum. This fat is now considerably increased during the course of the accidental involution and at the same time the cortical reticular cell itself swells. In this way small spots, poor in nuclei and recognizable even in ordinary nucleus-stained sections, arise in the cortex; these are sometimes referred to in descriptions by the name of "vacuoles." The mottled appearance that these fat-containing cells, usually occurring in the cortex with a certain regularity, produce in the fat-stained section is seen even after the cortex is not recognizable owing to any predominance in the number of lymphocytes, and shows that the cortical follicle remains far longer than the nucleus-stained specimens suggest. Where the fat droplets are abundant in the cells of the cortical reticulum, there arise, when they are extracted during the processes of preparation, a multitude of pseudovacuoles which may give the cortical region a strikingly transparent appearance. If, at the same time, the medulla is relatively rich in nuclei,

we may get the picture of a gland with dark medulla and lighter cortex, described by French investigators as a "glande invertée." This picture appears, however, more often in illness than in starvation.

In involution due to inanition the medulla is undisturbed longer than the cortex; it decreases, however, in the later stages of involution merely because the cell hypertrophy recedes and the size of the individual medullary cells is diminished. To this is added degenerative alterations of separate medullary cells, alterations that are less striking and rather little investigated in detail.

The conditions of the Hassall's corpuscles are the most striking features in the medulla. They are more resistent than the rest of the parenchyma and accordingly collect, as the latter decreases, in a smaller and smaller region, thus becoming *relatively* more numerous. This has led various investigators to assume that an absolute, or real, increase also took place, but, as Jonson showed, this is by no means the case. On the contrary, with the progress of the involution they decrease more and more in number, although, as has been mentioned, far more slowly than the reduction of the parenchyma takes place. As long as it is principally the amount of the cortex that is being reduced, but not that of the medulla, of course countings per mgm. parenchyma, but not per mgm. medulla, give increased values. When, later on, the reduction of the medulla also becomes perceptible, the value per mgm. medulla likewise becomes higher than normally. *Increased relative, and decreased absolute, values of the number of Hassall's corpuscles thus become a characteristic feature of the accidental involution proceeding according to the inanition type,* in its somewhat more advanced stages. In extreme stages of this involution, when the parenchyma has decreased to 1/50 or 1/100 of the normal amount and is represented in the microscopical picture only by narrow stripes poor in lymphocytes, the Hassallian corpuscles may have entirely disappeared.

Even in such extreme stages of involution the process is reversible, as Jonson first showed. The organ is not destroyed, but its parenchyma is reconstituted quickly and completely under the influence of an abundant supply of nutriment to the animal. Jonson's results as to this have been confirmed

by Salkind (1915), Jackson and Stewart (1919, 1920), and others. The stages in this reconstruction process are on the whole the same as in the embryological development, first a diffuse lymphocyte infiltration, followed closely by a central medullary differentiation, and finally a reappearance of Hassall's corpuscles in the medulla. The reversible character of involution due to starvation is also shown by seasonal involution that occurs in hibernating animals, which has been investigated in, among other animals, the frog (Hammar, 1905), the chelonian (Aimé, 1921:1), and the mole (Schaffer, 1909).

The *involution caused by Röntgen radiation* is of a different nature. First observed by Heineke (1905), it has been carefully studied by Rudberg (1907, 1909) and, later on, among others, by Regaud and Crémieu (1911, 1912) and Eggers (1913). Instead of an emigration of lymphocytes there occurs in this case, even during the first 2 or 3 hours after the radiation, a wholesale disintegration of lymphocytes, while the reticular cells show themselves to be capable of resistance to a far greater extent. The disintegrating lymphocytes, and especially their nuclei, are to a great extent taken up phagocytically by the reticulum cells and seem there to be digested and dissolved. In a short time the thymus is changed in this way to practically a purely epithelial organ.

Here, too, a reconstitution of the organ is brought about in the course of time, and here it is easier to follow the conditions of the reappearing lymphocytes than after inanition involutions; they seem to appear first in the medulla, probably from its vessels, and from there they spread over the whole parenchyma. In other respects the process of reconstitution seems on the whole to proceed in the same way as after involution due to inanition.

Knowledge of the course of Röntgen involution is of importance, not only because treatment of the thymus with Röntgen rays has of late become a comparatively frequent therapeutic measure, when it has been desired to reduce the size of the organ without surgical interference, but also because our experience of Röntgen involution throws light on certain pictures that are also found in other cases and sometimes even in the normal organ. One finds not quite infrequently without any Röntgen radiation a smaller or greater number of remains,

nuclei or parts of these, gathered round the nucleus in the reticular cells of the cortex. Everything indicates that here, too, phagocytosis and disintegration of the lymphocytes has taken place in the same way as in Röntgen involution, although on an incomparably smaller scale than in this case. The correctness of this explanation is shown by the fact that a corresponding phagocytosis has been directly observed in cultures of thymus tissue (Pappenheimer 1913, Wassén 1915).

Certain older anatomists had already observed that an *involution* of the thymus takes place *in pregnancy*. In later times similar observations have been made, among others, by Henderson (1904), Schaffer (1909), Ronconi (1909), Squadrini (1910) and Utterström (1910). The course of the process in certain animals was first studied in detail by Fulci (1913), who also showed its transitory nature. Bompiani (1914), while confirming Fulci's results, has also shown that lactation delays the occurrence of this restitution process.

This involution seems in certain respects to proceed in an analogous manner to inanition involution in its earlier stages; in other respects it differs from this. In two investigated cases of pregnancy in women in which death occurred by poison without any preceding illness, there was found, not only absolutely but also relatively, a marked reduction in the number of newly-formed Hassall's corpuscles and an unusually large number of extensively calcified corpuscles. It is impossible at present to state with certainty whether these findings can be considered characteristic of involution in pregnancy.

From certain cases in which pregnant women have died from disease, it has seemed as if the thymus did not always react during pregnancy in the same way as when pregnancy was not present. This leads one to think of the possibility of a change in the disposition, a "retuning" of the organ in connection with the alteration in the activity of the whole endocrine system, which apparently takes place during pregnancy. This matter is not yet ready for even a brief exposition.

Finally with regard to *the accidental involution* occurring *in disease*, it shows in many cases a course that closely resembles that of the involution due to starvation; here, too, the numerical values are then characterized by a decrease of the thymus index until finally the difference between cortex and medulla

is effaced, and by an increase in the relative number of Hassall's corpuscles and a decrease in the absolute number. If an involution of this sort keeps equal pace with the disturbance of the general nutrition that is seldom absent during illness, it is tempting to assume that here, too, as in starvation, the involution is caused merely by the disturbance in the general nutrition, though it is certain that in both cases the possibility of its influence making itself felt in a roundabout way through other, possibly endocrine, organs is at present not excluded. There is not always, however, a parallelism of this sort between the disturbance in the general nutrition and the degree of involution of the thymus. In certain diseases a marked reduction of the gland already occurs even at a time when the general condition, as indicated by the intactness of the adipose tissue and the musculature, is but little affected. This is, for instance, the case in the so-called "Spanish influenze." Such cases suggest the idea that the illness in question has also a more direct depressing effect on the thymus.

In another group of diseases, on the other hand, the accidental involution has a character differing from that of inanition involution, inasmuch as in its course, otherwise fairly similar, it is not connected with a reduction but with an increase of the Hassallian corpuscles and principally the absolute number of small, newly-formed corpuscles. It is especially in acute infections of different kinds that this type is found. It may, therefore, for the sake of brevity, be denoted as *the infection type*. Similar conditions were also found in an analyzed case of snake-bite with death on the third day (Hammar and Lagergren 1918, Hammar 1918). In cases where death has occurred before the thymus involution has obtained any intensive character this increase in the number of the small Hassallian corpuscles is beyond all doubt. Thus the number of these corpuscles in certain investigated cases of death from diphtheria amounts to almost 10 times the *highest* normal value found at a corresponding age. The involution seems as a rule to be accompanied by a relatively small tendency of growth in the individual newly-formed corpuscle, if we are to judge from the fact that in such cases the number of corpuscles in the group of lowest magnitude (Group I, 10 to 25 μ diameter) is the dominating one, and not, as is normal, the number in the next low-

est (Group II, 26 to 50 μ); this is not only the case in the beginning, but even after longer duration, of the illness. In other words, in infection involution the quotient II/I is decreased and is usually less than 1.0, while normally it is almost always greater than 1.0.

Now we have the remarkable state of affairs that even in infection involution, the more the general condition is disturbed, the more this increase of the Hassall's corpuscles is lessened, so that finally the course of the involution shows, in this case, too, the same character as in inanition involution, i. e., it is accompanied by a reduction in the absolute number of the Hassall's corpuscles. Even in such cases, however, the slight tendency to growth in the corpuscles remains almost to the last, and in this way the quotient II/I is an expression of the effect of the infection for a longer period than the increase of the Hassall's corpuscles itself. This state of affairs is of no little interest as indicating that the excitatory influence of the infection that stimulates the new formation of Hassall's corpuscles, "the eH-excitation," has not ceased, but that it has only been suppressed to a less or greater extent by an antagonistic "eH-depressor" influence, probably caused merely by the disturbance of the general nutrition. I shall return to this question later on.

Even in details much of what has already been mentioned above as regards inanition involution is also true of involution in disease. Here, too, the lymphocytes are rarefied principally by emigration, only in more exceptional cases and to a slight extent by disintegration in loco. Here, too, an increased fat granulation in the reticulum cells of the cortex is a regularly occurring phenomenon. These cells then swell into a more rounded and voluminous shape; at first they retain their processes, but later on they seem to lose them and then they have quite a free position in the parenchyma. If, then, the number of the interjacent lymphocytes is small, the fat-granule reticulum cells may come so near each other that the whole parenchyma at such a place—usually the interior of a cortical follicle—may seem to be in dissociation. Such "*dissociation foci*" are the rule in certain diseases, e. g., Spanish influenza; in others, on the contrary, they do not occur, in spite of the reticulum cells being abundantly filled with fat granules; the retic-

ulum cells are then undergoing the changes just mentioned more separately without any aggregation into foci.

Whether a formation of foci of this sort takes place or not, it is remarkable that these fat-granule cells undoubtedly decrease in number during the progress of the involution, but nevertheless no real signs of degeneration can be detected in them. The nucleus of the cell does not, as a rule, show any such signs; still less can any detritus denoting disintegration of cells be found. On the other hand, in the cases in which there is some more abundant fat granulation in the cells of the cortical reticulum, there also occur rounded fat-granule cells, of much the same aspect, in the surrounding interstitial tissue. The pictures seem directly to suggest that the fat-granule cells are able to release themselves from the cortical reticulum and to pass out from the parenchyma. That this sort of emigration of reticulum cells containing fat granules is a usual phenomenon in cultures of thymus tissue has at any rate been shown by Wassén (1915), by direct continuous observation of the living material. Pappenheimer, too, (1913) seems to have met with similar phenomena in his thymus cultures. As the assumption of the existence of this state of affairs *within* the organism as well is of considerable fundamental importance, caution demands more positive proof than can be given by a fixed material before a view of this sort can be definitely maintained. The question as to whether similar pictures occur in other forms of accidental involution has not been investigated, but at least in the case of inanition involution it seems fairly probable.

In more exceptional cases fat granules are also found in reticulum cells of the medulla, and, in a way that scarcely seems to follow any law, fat can usually be shown to be present in a number of larger Hassallian corpuscles. Whether in these places the fat is autochthonous or whether we possibly have a phenomenon of immigration as well, is at present undecided. In the fibroblasts of the interstitial tissue fat granules are usual in accidental involution; in the thymus lymphocytes, on the other hand, they are found comparatively seldom (e. g. in diphtheria), and even then only in minimum sizes and amounts.

What has been said above will show how a *regression of Hassall's corpuscles* takes place to a great extent in many cases

of accidental involution. Such cases are consequently well fitted for the study of the way in which these formations undergo regression, all the more so as corresponding pictures can also be found in normal organs and thus there is a basis for the assumption that the normal regression of these formations proceeds on the whole in a similar manner.

With regard to this I shall at first discuss the so-called "*degenerate Hassall's corpuscles*," which, usually varying in size between 200 and 500 μ, occur even normally in the human thymus. They consist, as a rule, of a few peripheral layers of flat nucleated cells, and within them a very large number of flattened or shrunken elements without nuclei, often with a more or less distinct concentric stratification around one or several centres, fill up the space in loose arrangement. They often contain calcified parts of a spherical or flake-like shape. Sometimes the contents consist of elements, containing nuclei, resembling swollen leucocytes. These "degenerate Hassall's corpuscles" are as a matter of fact by no means to be looked upon as regressive forms, inasmuch as they are the structural type that human Hassallian corpuscles regularly assume when in their growth they have reached about the degree of magnitude alluded to above. Their disappearance sometimes seems to be preceded by a breaking-up of the peripheral cell-layers and a passing-out of a part of the contents of the corpuscle. This portion seems to be then taken up by the reticulum cells of the surrounding parenchyma and under their influence to be absorbed, while the peripheral cells may remain for a time in the parenchyma, recognizable by their characteristic grouping and their flattened form. Corpuscles of this sort are not infrequently invaded by the surrounding parenchyma, which at its proliferation penetrates the peripheral layers so that the centre of the corpuscle seems more or less filled up with lymphocytes and reticulum cells (Chiari, 1894; Hammar, 1905). The presence of the latter cells shows that the process in these *parenchyma invaded corpuscles* is of a different kind from the leucocytic invasion which has been described above and which as a rule is present in smaller forms of corpuscles.

More often, however, the regression of the large forms seems to take place without any such breaking, by liquifaction of the contents. The fact that, according to the investigations

of Kutscher (1901), Jones (1903), Hedin (1906), Rhodin (1911) and others, the organ contains a proteolytic enzyme may perhaps help us to understand these and simular regressive phenomena in the thymus. The corpuscles in question are changed in this way to *cystic forms* with a flat epithelial wall; according as the contents are absorbed the cyst passes from a spherical to a more irregular shape and is finally changed into a narrow cleft with its walls close to each other. Even smaller corpuscles (50 to 200 μ in diameter) not infrequently give rise to cystic forms during their regression. These smaller cystic corpuscles are especially common in the central parenchymal cord, where they are not unfrequently found even in the newly born child.

The *calcified corpuscles,* too, are not to be looked upon as regressive from a morphological point of view, even if, when the calcification affects the whole corpuscle, they are probably of no significance functionally and can then be found not very infrequently partly or quite imbedded in the interstitial tissue as relics of a parenchyma that has already disappeared. Sometimes it seems as if only the lime is absorbed during the regression of a calcified corpuscle, leaving an organic substratum of rather characteristic "mucus-like" staining, while sometimes the corpuscle as a whole may shrink, showing uneven resorption surfaces looking as if they were corroded and resembling those which, in bone resorption, characterize the so-called Howship's lacunae.

The smaller forms of Hassall's corpuscles, almost always preponderating in number, at least as far as they consist of still nucleated living cells, seem chiefly to disappear by a reduction in size of their cells and the resumption by the cells of their character of typical medullary reticulum cells. The process may be called a disaggregation and the loosened corpuscles, engaged in regression, may be called *disaggregation forms.*

THYMUS HYPERPLASIA

The cases in which *hyperplasia* of the thymus is found are relatively rare. Such findings have been made chiefly after castration, in Graves' disease, Addison's disease, myasthenia, acromegaly and the so-called thymus death. Bergstrand (1919) has published two cases of parathyroid enlargement combined

with thymus hyperplasia. It is at present impossible to decide whether in these cases the thymus hyperplasia has been produced by changes in the parathyroids. I shall discuss the "thymus death" in the next paragraph. Of the others it is only the hyperplasia after castration and in Graves' disease that have been sufficiently investigated for it to be possible to give some indication of their character here.

With regard to *hyperplasia after castration* I have already mentioned Gellin's results as far as they bear upon prepuberal spaying. It should be added that the same investigator has shown that castration causes hyperplasia of the thymus even when carried out after puberty. It seems from this as if the effect of the castration is less that of checking the process of age involution than that of transferring the regular metabolic processes in the organ, perhaps its production and elimination of lymphocytes especially, to another and higher plane than in the case of intact subjects of the same age. That even in man and even when carried out relatively late postpuberal castration may have an effect of this sort, is shown by a case published by the writer (1918). In a woman, 51 years old, whose ovaries had been removed at 39 and 49 years of age, respectively, there was a distinctly supranormal quantity both of parenchyma and Hassall's corpuscles. At present, however, it is impossible to say whether hyperplasia after castration in man is always of the same type as in the case mentioned.

Best known is *hyperplasia in Graves' disease,* of which I have analyzed numerically 32 cases, 25 of which were already published in 1917. We are here concerned with a hyperplasia that is not infrequently considerable, in which the cortex is to a very great extent, sometimes even exclusively, the region of the parenchyma that is increased and in which the Hassallian corpuscles are increased in number, sometimes to a greater, sometimes to a smaller, extent than the parenchyma, but in typical cases always in a way that is beyond all doubt. The energy of growth in the Hassallian corpuscles newly formed in this way seems to agree more with the normal, so that the quotient II/I is here, as a rule, greater than 1.0 and sometimes is even supranormal.

In uncomplicated cases there is very little fat in the parenchyma of the hyperplastic thymus in Graves' disease, and not infrequently there is none at all. Even the hyperplastic thymus may, however, be affected by accidental involution, often recognizable by the appearance of a somewhat greater amount of fat in the reticulum cells of the cortex. In this involution it is the cortex, as usual, that first reacts by being reduced. Then in certain cases it may turn out that only the medulla, and not the cortex, remains in an increased condition and the quantitative relation between cortex and medulla is obviously altered in favor of the medulla; in other words, a low index appears. It may be assumed that such pictures partly formed the basis of the view maintained in certain quarters (Schridde 1909, 1911; Koch 1911, Klose 1912, etc.) that a hyperplasia of the medulla is, above all, the distinguishing feature of the alterations in the thymus in Graves' disease.

The results obtained by Utterström (1910) by feeding rabbits with thyroid gland indicate that it is noxae issuing from the thyroid gland that are at the root of this hyperplasia. It is true that this investigator never succeeded in his experiments in producing a real hyperplasia of the thymus, but the size of the organ was as a rule so considerable in relation to the animal's greatly reduced state of nutrition and contrasted so decidedly with that of the animals which had been brought to the same degree of emaciation by starvation that we must assume with Utterström that the supply of the thyroid substance had been an item of great importance in the excitation of the thymus. Courrier (1921) has obtained results closely agreeing with these. The thymus reacts differently on thyroid ingestion according to whether the metabolic balance is positive or negative. If it is negative, atrophy of the thymus arises because of the general denutrition. If positive, we generally get thymus hyperplasia, due, as it seems, to specific influence of the thyroid.

Lampé, Liesegang and Klose (1912) consider, however, that this thymus excitation may be caused in an indirect manner by a lesion of the "interstitial gland" in the gonads.

As in the case of age involution, so with the more temporary changes of the thymus discussed here, accidental in-

volution and hyperplasia, it seems also to be true that, as far as they are caused by the conditions of the lymphocytes, they are not peculiar to the thymus but have their analogies in the changed conditions of these cells in other parts of the organism as well. Thus the occurrence of an accidental involution even in the real lymphoid tissue has been shown by Jolly and Levin (1912, 1914:1) and Hellman (1914) and Källmark's investigations (1911) as to the total of leucocytes of different forms in the blood during starvation have thrown further light on the mobilization process of the lymphocytes that takes place under such circumstances. We have less information as to the corresponding conditions in thymus hyperplasia, but still we know that it is often combined with an increase of lymph glands and other lymphoid organs (Hellman*), a fact that has led to the wide-spread conception of a status thymo-lymphaticus—or, perhaps with a more non-committal expression, a lymphocytism (Hammar, 1913)—as existing in these diseases. The occurrence of a lymphocytosis in Graves' disease is likewise a fact well established of late years.

If we are thus justified in assuming that the changes in the number of the thymus lymphocytes in accidental involution and in hyperplasia are, generally speaking, only manifestations of processes that really involve the lymphocytes in the whole organism, then it is an obvious assumption that the same is true on the whole for changes of the same sort lying within the boundary of what is normal.

At any rate it is certain that changes of this sort occur even normally in the thymus. Even in organs from subjects who have died suddenly, for instance from external violence, while in good health and nutrition, on the one hand mitoses are never absent in the lymphocytes of the cortex before old age, and on the other hand there are always lymphocytes present in the interstitial tissue of the organ, especially, as has already been pointed out, in the interfollicular septa. It is also under these circumstances not unusual to find lymph vessels more or less filled with lymphocytes. Everything thus supports the idea of the production and export of lymphocytes even under

normal conditions. It seems to be of less importance in this connection whether all the lymphocytes leave the organ unaltered or whether a number of them are already changed interlobularly into the larger leucocyte forms present there (possibly also into erythroblasts), as is maintained by certain investigators (among others Weidenreich 1912, and Weill 1913), though the pictures certainly in many cases encourage a view of this sort. Vera Dantschakoff (1916) has also paid special attention to this process of differentiation, putting it forward as a criterion of the small thymus cells having the character of genuine lymphocytes.

With regard to the epithelial elements of the organ, too, a certain normal lability can be established. Thus even in the reticulum cells mitoses are found long after the general growth of the body has stopped. Normally, too, fat granulation may be found in the reticulum cells of the cortex, though it is far from being a constant character. And all sorts of regressive forms of Hassall's corpuscles also occur normally side by side with those that show themselves by their small size and their close structure to be new formations.

All this serves to form a basis for the conception of the thymus as an organ that not only undergoes great variations in its structure during disease and other extreme states in the organism, but even under normal conditions sensitively reflects all sorts of variations in the organism to an extent which, as far as our present knowledge extends, is not exceeded by any other organ. The losses of substance thereby incurred by the organ through the emigration and degeneration of cells* are more or less completely made good by the processes of mitotic regeneration that normally occur, both in the lymphocytes and the reticulum cells during the whole time the organ is functioning.

* From this point of view Helene Deutsch's statements (1913) as to the "normal" occurrence of a thymolytic ("thymus-abbauende") ferment in human blood are of interest. They are contradicted, however, by the negative results of Bauer (1913), Kolb (1913). Lampé and Papazolu (1913). If the difference in results is not due to technical errors, it is conceivable that the different degree of the processes of reduction in the thymus on different occasions has been of importance (Hammar, 1914 :2). In the case of thyroid disease there are, on the other hand, fairly unanimous positive results with regard to the occurrence of blood ferments of this sort (see Bauer, Kolb, Lampé and Papazolu, Lampé and Fuchs, 1913).

One must admit that it is not in the first place in an organ of this labile nature that one would expect to find traces remaining of an innate abnormal constitution in the cases where this may be looked for. In thus wishing to make a "persistence" or a "revivescence" of the thymus into a specially pregnant expression for such a constitutional anomaly—lymphatism—too little attention has, to my opinion, been paid to what is perhaps the most striking quality of the thymus—its capacity for rapid and powerful reaction.† On the other hand the organ is, just because of this, suited to give valuable indications as to the state of the organism on the special occasion of its investigation. In this respect the trained eye can even now learn from the organ, and it is to be expected that, with extended experience as to the correlative conditions of the organ, these possibilities will be very essentially increased. In the present state of our knowledge there is, on the whole, no other organ in the body that is more fitted than the thymus to illustrate the phenomenon of the correlation of organs.

† I cannot enter here into a discussion on the problem of lymphatism; for this I refer to my earlier statements (Hammar, 1913, 1914:2, 1916, 1917).

EDITORIAL SUMMARY

The thymus gland is fundamentally an epithelial organ infiltrated with lymphocytes. The epithelial components in various mammals are of diverse origin—entodermal in some, ectodermal in some, and combined ecto-entodermal in others. In man the lymphocytic infiltration begins in the second month of intrauterine life.

Contrary to frequent statements the thymus persists as a functioning organ throughout life, although at puberty "age involution," i. e., reduction of parenchyma begins. Five types depending upon age can be differentiated: (1) Type of childhood; (2) Puberal types; (3) Type of youth; (4) Adult type; (5) Senescent type. These types are described.

Descriptions of the thymus gland based upon material from diseased subjects are misleading. Such glands are never normal.

Usually the parenchyma is reduced; occasionally it is hyperplastic. The normal ratio between corpuscles and lymphoid elements is disturbed. Even in healthy subjects the thymus is a very labile gland.

This paper will be concluded in the November issue.—Publishers.

A CLINICAL STUDY OF UNUSUAL DISTURBANCES OF THE ENDOCRINE GLANDS

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The following case is one of unique interest from the standpoint of curable disturbances of the endocrine glands.

The patient is a young woman, 24 years of age, whom I first saw in September, 1920. She had been married two years, and had never been pregnant. Her present complaint was that for three or four months she could not lie on her left side on account of pain and distress in the region of the heart; that on waking in the morning her face was swollen more or less all over, but worse under the eyes. Sometimes the swelling was excessive. This swelling would not disappear until the afternoon of each day, unless she used hot applications. She said there was no swelling of the legs, but she had had that condition three or four years ago. Her bowels could not be moved without an enema, and she had taken an injection of a quart of soap and water every day for four years. Lately she has been sleeping very poorly, and for the last three weeks has been getting up five or six times at night to urinate; during the daytime the frequency was not far from normal. Up to two years ago she says her cheeks were always red, but since that time she has been very pale. She suffers from profuse perspiration; sometimes she fairly drips with it, especially on the arms and down the legs, and she even has to change her clothing. She is depressed and cries frequently. She craves sweets, and can eat half a pound of candy at a sitting.

Past History. From childhood up she was a very large girl, had a large abdomen, and during her girlhood developed enormous breasts. Although menstruation began at ten years of age, it was never regular, recurring at intervals of anywhere from two to six weeks. Lately, the menstrual blood has been very black. She has no pain with menstruation, and has no indication as to when the flow is to begin.

At the time of her marriage, two years ago, she weighed 165 pounds. Her height is 5 ft. 4 in. One year ago her weight had fallen to 103 pounds. At the present time it is 142. She states that her waist line has diminished six inches, i. e., from 42 to 36 in., in two years. She formerly wore a 28 corset, and now wears a 22. She states that she never had any hair on her body of any kind or description, except the eye brows and on the scalp, until one and a half years ago. The hair began to grow at the time she began to lose the extra flesh. She says that up to eight or nine years of age she was a blond; now

her hair is medium brown. She has never until recently been able to smell anything, even when held close to her nose. She has always been normal mentally, a good student, full of life, and enjoyed fairly good health up to the present time; she has been very active, able to work, and enjoyed walking, dancing, and other exercises.

Family History. Her father, she states, is very tall and slim. Her mother is but 4 ft. 6 in. in height and weighs 251 pounds. She has two brothers and two sisters living; the two brothers are large and normal; the two sisters are very large women. Six brothers and sisters died very young; she does not know the cause. Neither her father nor her mother has any gray hair, while one sister, age thirty-one, has white hair.

Present Condition. Mentality is, and apparently always has been, perfect. The contour of the face is perfect; the eye-brows are perfect. The teeth are fine and properly spaced. The throat is normal; the skin soft and normal. Hair on the body is normal. Reflexes are normal. Blood-pressure, heart, lungs, and urine are normal. The abdomen is negative. She breathes somewhat rapidly, at this time—32 to the minute, but she says she always has breathed rapidly.

The condition apparently shows a previous history of subpituitary secretion, and at the present time an increased thyroid secretion, with what seems to be a disturbance of the suprarenal glands. A diagnosis of a disturbance of the suprarenal glands was based on the bladder irritability, profuse perspiration, the almost anaphylactic puffings and swellings, and the sluggishness of the peristalsis of the bowels; and an increased thyroid secretion was based on the sleeplessness, rather rapid heart action (108), the craving for sweets, and also on the increased perspiration.

Treatment consisted of suprarenal substance, whole gland, a 1-grain tablet twice a day. In a week the face puffing had disappeared, the heart had improved, the bowels moved without an enema, the night urination had stopped, she was sleeping finely, and the perspiration was less. The treatment was continued for another week, with continued improvement in every respect. Medication was then stopped for a week, and at the end of that time constipation had developed and she had again to take enemas; the profuse perspiration had again begun; and she also again had to rise at night to urinate. She was then given one suprarenal tablet a day, and in a few days again the bowels moved without an enema and the perspiration became normal. During this week she began to note odors, and the least unpleasant odor was intensely disagreeable to her. It was the first time she had ever been able to smell.

In November, 1920, still continuing the one suprarenal tablet a day, she lost entirely her taste for sweets and even disliked

anything sweet, while before she had craved sweets. Medication was stopped in December, and she has been a perfectly normal, well woman since (June, 1921).

This case history is remarkable not only for the great improvement from so little medication, but on account of the marked change in the secretions of the endocrine glands which occurred after marriage. As she so naïvely states, she is not at all the girl that her husband married.

REPORT OF CASE OF HYPOPHYSEAL TUMOR, WITH RADIOGRAPH

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December 22, 1919. G. V., Serbian miner (Endocrine No. 24), referred by Dr. J. E. Bacon of Miami. *Complaint:* Headache, vomiting, failing vision.

Personal and family history negative. Patient's habits good. (Examination of patient was rendered difficult by the necessity of employing an interpreter.)

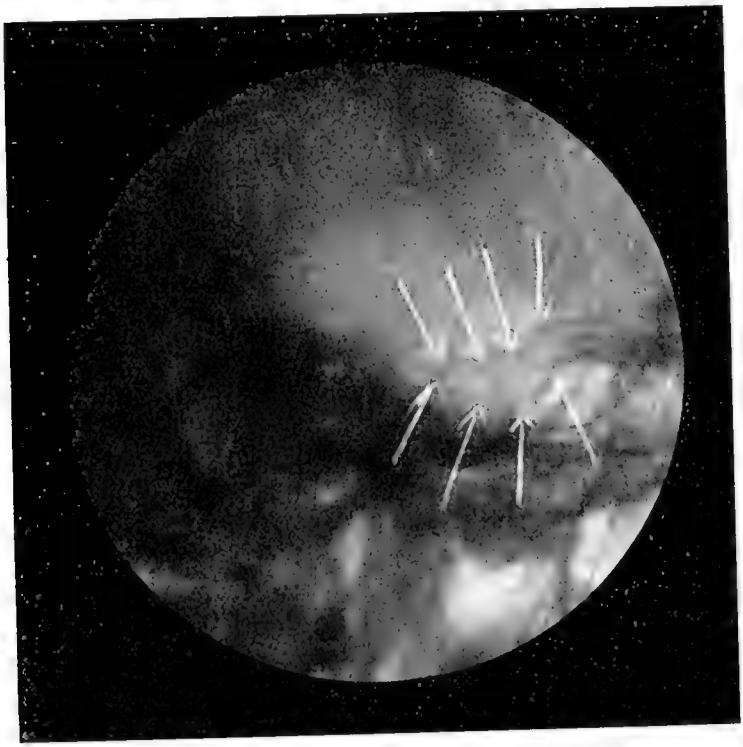
Present Malady: For three months patient has complained of severe headache, not well localized. This lasted for several days at a time at first, but was later continuous. Says appetite and sleep are "fair." Complains of muscular weakness. Has had occasional attacks of vomiting. On automobile trip to Phoenix of 120 miles vomited several times. Has been more or less dizzy for some time. Complains of failing vision, which he says has been rapid for the last two weeks. Became very constipated about six months ago. Previous to that time he had been regular in habits. Complains of shivering "easily." (Interpreter.)

Physical Examination: Fairly well nourished man of medium height. No stigmata. Muscular tonus poor. Visceral and cardio-vascular examination negative. Blood pressure 122. Pulse 72. Temperature 98.2 (4 P. M.). Sugar tolerance not ascertained. Urine highly acid, total quantity 500 cc., otherwise normal. Wassermann for blood and spinal fluid negative. Cell count of spinal fluid negative. No thyroid enlargement. No pigmentation.

Neurological Examination: Motor findings negative, except that on clasping fingers tightly a marked fine tremor developed in right hand. Patient showed surprise, and said he had not noticed this before. Sensory findings negative objectively. Patient complains of sensation of twitching of face accompanying headache. Mental dullness noticeable. No history or evidence of elation, depression, or irritability.

Analysis of Symptoms: Pronounced neighborhood, but relatively inconspicuous glandular symptoms. X-ray (taken by Dr.

W. W. Watkins, Phoenix) shows presence of hypophyseal tumor. Eyes (Examination by Dr. Ancil Martin, Phoenix): No oculomotor palsies, diplopia, or nystagmus. Pupils 4 mm. in diameter. Reaction to light and accommodation prompt. Fundi: marked choked disc, right measuring 1½ mm., left 1 mm. In the swollen nerveheads are seen small hemorrhages, and white streak-like



exudates. Vision greatly impaired, and fields for form and color reduced. Nares and sinuses negative by physical findings and x-ray. Hearing impaired. Watch tick 1/36. Whisper 3/20. Speaking voice 12 20. Labyrinthine reflexes exaggerated but normal qualitatively. Smell diminished or absent. Says "Taste is not quite right."

Operation advised, but refused.

Patient died in Gila County Hospital in November, 1920, completely blind, and with power of speech gone. Could say only the word "eat" before death. No autopsy obtained.

THE HEART IN THE EXPERIMENTAL HYPERTHYROIDISM WITH SPECIAL REFERENCE TO ITS HISTOLOGY

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INTRODUCTION

It is generally known that cardiac disturbances occur in patients suffering from goitre, in not only the exophthalmic type, but also apparently simple goitre, and that cardiac weakness is one of the most frequent causes of sudden death. The subject is, therefore, one of great interest to clinical and experimental investigators.

These cardiac disturbances may occasionally be caused by pressure of the tumor upon neighboring structures—venous or respiratory obstruction, or mechanical affection of the smypathetic or vagus nerves ("mechanical goitre heart"—A. Kocher). In the majority of the cases, however, they may be attributed to a certain kind of intoxication, concerning the etiology of which there is a diversity of opinion. Bircher has claimed that the cardiac disturbances associated with endemic goitre are due, not to the goitre itself, but to the general intoxication which is responsible for the changes in the thyroid glands. Most observers believe, however, that the cardiac manifestations associated with goitre arise for the most part from thyroid intoxication (especially in Graves' disease) and chiefly from an excessive stimulation of the cardiac accelerator nerves.

Concerning the histology of goitre hearts, fatty degeneration of muscle-fibers appeared to be the only lesion ever found by the observers previous to Fahr (1916), who recently found evidence of chronic interstitial inflammation occurring in the heart muscle. In his case of Graves' disease, as well as of simple goitre, there were collections of round cells, chiefly lymphocytes, among the muscle-fibers and in the neighborhood of the blood vessels. In the large myocarditic areas the muscle-fibers were separated from one another and showed various degenerative changes, i. e., fragmentation, dissolution, etc. Scattered among

the lymphocytes in these areas were a number of fibroblasts, while in the smaller areas there were lymphocytes only. Fatty degeneration of muscle-fibers was observable only to a limited extent.

Upon the basis of the evidence above cited, Fahr considered that the toxin circulating in the body of a goitre patient may cause not only an excessive stimulation of the cardiac nerves, but further have a direct effect upon the heart muscle itself.

Recently I had an opportunity to examine the hearts of two exophthalmic goitre patients, and was able to confirm the findings of Fahr, lymphocytic infiltration between the muscle-fibers or around the blood vessels being observed.

For solving the question of the etiology of the goitre heart, it is of the utmost importance to investigate the cardiac manifestations in artificial hyperthyroidism, usually produced experimentally by thyroid administration, and to compare them with those in human subjects sufferng from goitre.

Tachycardia was produced in various animals by means of thyroid administration by Ballet and Enriquez, Canter, Georgiewski, Hellin, Lanz, Angiolella, Ludke, Lepine, Peiser, Edmunds, Pfeiffer, v. Fürth and Schwartz, while Paessler and Schulze, Marine and Lenhart, Cunningham, and Carlson and his pupils failed to demonstrate its occurrence in thyroid-treated animals. Farrant (1913), by his careful investigations (recording accurately the pulse rate of thyroid-fed cats by the aid of a polygraph), later confirmed the fact that thyroid feeding induces a steady increase in the heart beat, which subsides gradually after the cessation of the feeding.

With regard to the anatomical changes in the heart resulting from thyroid administration there are a number of observations. Iscovesco (1913) found that repeated injections of thyroid extract (an ether-soluble substance, isolated from thyroid tissue) produced in rabbits hypertrophy of the heart associated with enlargement of many other internal organs (suprarenals, ovaries, uterus, spleen, and kidneys). E. R. Hoskins (1916) fed small amounts of thyroid tissue to young albino rats for a long while and observed a decided hypertrophy of heart, liver, spleen, kidneys and suprarenals. Herring (1917) obtained results which were in general agreement with those of Hoskins, differing only in the degree of the hypertrophy, which in the heart, suprarenals and kidneys was larger by far. Hoskins

ascribed the hypertrophy of the organs to the increased rate of metabolism promoted by thyroid feeding, while Herring regarded an increased production of adrenalin in the body as an additional factor. The results of the recent research by Hewitt (1920) tend to show that the hypertrophy of the internal organs produced by thyroid administration is temporary, and that a return to normal proportions is indicated after the cessation of thyroid feeding.

Concerning the histology of the heart in artificial hyperthyroidism, only a few observations are recorded. Farrant (1913) found in the hearts of thyroid-fed cats and rabbits morphological changes varying from a condition of general wasting of muscle-fibers to what may be described as a condition of hyaline degeneration. Finding that the muscle-fibers were swollen, with few nuclei and no transverse striations, and that both the fibers and the nuclei stained poorly, he termed these changes "myocarditis without evidence of inflammation." Herring (1917) stated that the enlarged hearts of thyroid-fed rats showed upon microscopic examination an increase of muscle-fibers and many of them an apparent increase in size.

In view of the results of the investigations briefly cited above, it would appear that the cardiac changes resulting from thyroid administration are similar to those known as the changes in "goitre heart" in human subjects, but by no means form the complete picture of the latter, as is shown in the histology of the heart—in experimental hyperthyroidism and in goitre. According to the foregoing investigators, it is at most a hyaline degeneration that has been produced experimentally in the heart muscle of animals by thyroid administration, whereas in human goitre heart even marked myocarditic lesions have been observed (Fahr). As long as we fail to identify the cardiac disturbances resulting from an experimental hyperthyroidism with those of human goitre hearts, we are not justified in assuming that the cardiac disturbances associated with goitre arise from thyroid intoxication or from an excess of thyroid secretion in the body.

I have long been aware that, in the course of the experimental hyperthyroidism produced by thyroid feeding in albino rats, sudden death is by no means infrequent, and that there are occasionally findings which enable us to ascribe such death

to a cardiac insufficiency. Because of a suspicion that more severe changes than a hyaline degeneration might be detected microscopically in these hearts, I undertook to investigate the histology of the hearts of a large number of albino rats, either killed or dying during the course of thyroid administration.

EXPERIMENTAL DATA

(1) The effect of feeding with toxic doses of thyroid upon the structure of the heart.

In this series of investigations the material examined was obtained from 38 thyroid-fed albino rats, 28 of which were killed and 10 found dead during the course of the experiment. The experiment was begun with 53 animals chosen for thyroid administration. Of these, 25 died, but 15 had been dead so long when discovered that the visceral organs were unfit for histological use. Each animal was kept in a separate wire-net cage, in a large cement-floored animal room, light, dry, warm, well-ventilated, and clean. The food was bread and milk mixed fresh each day, and green vegetables on alternate days. The thyroid administered was exclusively desiccated powder which had been prepared by the writer himself from fresh thyroid glands by the aid of Faust's apparatus, at a low temperature of 35-40° C. Various amounts of this desiccated thyroid, containing 0.488 per cent. of iodine, were added to the food daily—to 14 males, 0.5 grms.; to 9 males and 9 females, 0.3 grms; to 10 males, 0.2 grms.; to 11 males, 0.1 grm. As controls a number of healthy rats were kept in cages in the neighborhood of the experimental animals, and were fed on similar food, with the addition of corresponding amounts of desiccated beef in place of the thyroid.

Under the influence of 0.1-0.5 grms. of desiccated thyroid per day most of the animals lost appetite for food after three or four days and became inactive and weak, lying flat on the floor. Some of them, being exceedingly susceptible to the toxic effect of the thyroid, died during this period. Most of the animals, however, survived the period of depression and became apparently vigorous in the second week, some of them appearing to be rather nervous and excited. A large number died about this time, the moribund condition (dyspnoea, hypersalivation, etc.) setting in very suddenly. A few survived longer than two weeks. Such animals were liable to become abnormally irritable and voracious. Despite an increased consumption of food, however, they became emaciated and died eventually, sometimes very suddenly. In one case a sudden death was evidently evoked by over-exertion. This was a male rat that had been receiving 0.5 grms. desiccated thyroid daily for three weeks, but which had been apparently in a vigorous condition; it died very suddenly after being chased by another excited male rat. On dissection there was no trace of wound or bleeding to which the sudden death might be attributed. The cause was probably cardiac insufficiency.

As to changes in the body weights of the thyroid-fed animals, an actual diminution was observable in only a few, whereas the gain in weight was noticeably less in the thyroid-fed animals than in the controls, kept for the same length of time under similar dietetic and environmental conditions; the differences varied from 16 to 34 per cent. per ten days. The rats receiving buccal administration of the above doses of thyroid, if not killed before that time, all died within three weeks. The average duration of life under the influence of such thyroid administration was eleven days.

At various intervals during the course of the thyroid feeding twenty-eight animals were killed by chloroform and completely bled. The hearts were cut off from the blood-vascular trunks, cleansed of blood and the auricles and ventricles slit up. The other internal organs were also dissected out. After being weighed these were preserved in 10 per cent. formol solution. For microscopic examination sections 5μ thick were made from the heart muscle and other organ tissues and stained with haematoxylin—eosin, haematoxylin—Sudan III, in some cases Giema's stain (used according to Schridde) or methylgreen—pyronin stain (Pappenheim-Unna).

The heart weights of the thyroid-fed animals were compared with those of the controls in terms of weight per 100 mm. body length, i. e., distance from the tip of the nose to the center of the anus. The measurement was made immediately after death, before rigor mortis set in. The average weight of the hearts per 100 mm. body length in the several series of thyroid-fed males varied from 0.536 to 0.677 grms., that of the controls averaged 0.510 grms. Percentage differences are, therefore, from 5 to 33 per cent. In the females the average weights of the hearts per 100 mm. body length were 0.549 grms. and 0.408 grms. in thyroid-fed and control animals respectively, the percentage difference being 34 per cent. If the heart weights of my control rats be compared with those given by Donaldson for the Wistar rats of equal body length, the hearts of my normal males average 32 per cent. and those of my females 6 per cent. heavier than those given by Donaldson. According to the latter's method, the increase in weight of the hearts ranges from 17-77 per cent. in thyroid-fed males, and 43 per cent. in thyroid-fed females.

Microscopically the hearts of thyroid-fed rats that were killed differed little from those of the control normal animals except in size, which had increased more or less markedly in the thyroid-fed animals. The hearts of the experimental animals that were found dead were conspicuously dilated, especially in the right ventricle, and a marked degree of passive congestion was noted. The coronary vessels and their branches were distended with blood. Much fluid blood with little clot was present in the cavities. Dropsy in the pericardial cavity was, however, rarely found. On macroscopic examination the myocardium and valvular apparatus showed no apparent change. Rigor mortis of the heart muscle obviously set in earlier in the thyroid-fed animals than in the normal controls. This was also true of the muscular tissue in general, and an acidosis in the experimental hyperthyroidism, noted first by Kuriyama, might bear a certain relation to the early occurrence of rigor mortis.

Upon histological examination of the hearts of these thyroid-fed rats the muscle-fibers were found in most cases to be swollen and separated. The cross-striations appeared less clear than normal. Vacuolization occurred rarely, but there was no fatty degeneration, which fact was determined by staining with Sudan III. Many nuclei were larger than normal, and the occurrence of double nuclei more frequent than normal. On the other hand, a number of nuclei showed an accumulation of chromatin particles along the axis, impaired staining, pycnosis, etc. Not only the muscle fibres but also the cells of the interstitial connective tissue were seen to be swollen, and appeared also to be increased in number.

Besides such vague and diffuse changes, the heart muscle of the thyroid-fed rats showed other very obvious changes within certain circumscribed scattered areas. Under the low power they appeared as dense patches consisting chiefly of round cells. These formations were elongated, spindle-shaped or pyramidal, as the cells were collected in the narrow spaces between the muscle-fibers. They were

found to be situated frequently in the neighborhood of the blood vessels. Under the high power it was seen that the accumulation consisted chiefly of large peculiar cells, most of which were about three or four times the size of a red blood cell. Their protoplasm was slightly basophilic and outlined faintly and irregularly. The nuclei were situated eccentrically, were quite large in size, round, oval, indented, occasionally bent or twisted in shape, and pale in color, showing few chromatin particles. In their morphology, therefore, these cells simulate the large mononuclear or transitional cells present in circulating blood. They were accompanied by some smaller cells with dark nuclei containing a dense, thick chromatin network, and correspond both in size and appearance to lymphocytes present in the circulating blood. Among these cells, especially in comparatively large areas of changes, a number of fibroblasts were found scattered or accumulated These had large, pale, oval or elongated nuclei with little chromatin and one or two distinct nucleoli; the similarly elongated protoplasm was faintly outlined and furnished with irregular processes. Some of the fibroblasts were swollen and in appearance resembled the large cells described above as the main constituents of the cell-collections. Some of the elongated cells were conspicuous for the chromatin structure, the chromatin particles accumulating along the axis of an oval or elongated and sharply outlined nucleus. These cells are no more or less than the "Myocyten" of Anitschkow. Not infrequently there were cells showing mitotic figures. A few polymorphonuclear leucocytes were occasionally found. The muscle fibres adjacent to the cell-formations above described were pushed aside by these. In the neighborhood of the smaller areas of myocarditic changes they appeared usually to remain practically intact, whereas the fibers present around or taken within the larger areas were severely disturbed, being vacuolated or dissolved. The nuclei of such degenerated muscle-fibers showed various stages of disintegration, such as pycnosis, karyolysis, etc. In places, however, some of the nuclei were seen to be less severely injured, and thin rings of muscle substance were left surrounding them.

The histological appearance of the cell collections varied considerably, owing to the number and proportions of the number of the cellular elements. In some small areas of myocardial changes there were mainly lymphoid cells, whereas in some of larger areas, usually at a later period of thyroid feeding, fibroblasts, and occasionally myocytes, prevailed over other cell types. It is interesting to note that at later periods of thyroid feeding the histological structure of the myocardial changes tended to vary considerably in the different areas, the cells of large mononuclear type or of lymphoid type accumulating in some areas and fibroblasts in others.

As to the seat of the myocardial changes it is common knowledge that these are most likely to occur in the neighborhood of the blood vessels, or beneath the pericardium. Occasionally, however, in my experiments, especially in later stages of thyroid feeding, they were to be found in any part of the myocardium. The posterior wall of the left ventricle near the base was frequently affected, though not always. The present investigation did not enable me to decide definitely whether or not the bundle of His may be involved in the lesion.

The severity of the myocarditic lesions, judged by the size and number of their areas, varied considerably according to the factors involved. They tended to become more marked according to the length of time covered by the thyroid administration. Although small cell-collections were observable in the heart muscle of animals killed as early as three or four days after thyroid administration had begun, the areas of marked myocarditic lesion, large in size and number, were

usually found in animals that had been killed or found dead about the end of the second week or later. The size of the thyroid dosage also may determine the severity of the myocarditic lesion. The animals fed with larger doses exhibited more marked changes and in a larger number of cases than those fed with smaller doses for similar lengths of time and under similar environmental and dietetic conditions. Myocarditic lesions were found in 90 per cent. of the rats killed in the course of administration of 0.5 grm. desiccated thyroid per day, while they occurred in only 50 per cent. of the animals killed in the course of administration of 0.3 grm. per day. The third and most important factor is the individual susceptibility of animals to the effects of thyroid administration. Owing to this factor, an animal fed with a smaller dose for a shorter period may exhibit a more marked lesion of the myocardium than one fed with a larger dose over a longer period. The more severe lesions were noted more frequently in the animals that were found dead than in those that were killed. Such a difference might be attributed chiefly to the fact that the material for the microscopic examination was obtained from the animals that were killed at comparatively early stages of thyroid administration—from the second to the fifteenth day, and from those that had died at comparatively later stages of thyroid feeding—from the twelfth to the twentieth day.

(2) The Effect of Feeding With a Non-toxic Dosage of Thyroid Upon the Structure of the Heart.

In this series of experiments eleven adult albino rats, six males and five non-pregnant females, were given non-toxic doses of desiccated thyroid, 0.03 grm. on alternate days. All the animals but one remained in an apparently healthy condition for a long period under the feeding, and were killed at intervals ranging from 37 to 170 days. One of the males died after 109 days, but the organs were not examined microscopically. The details of technic are as already described, and need not be repeated.

The hearts of these thyroid-fed animals, as compared with those of the normal control animals, were markedly enlarged in size and weight. The heart weight of the males averaged 0.600 grm., and that of the females 0.496 grm., an estimated increase of 18 to 22 per cent. respectively, based upon the average weights of the controls, which were 0.510 grm. for the males and 0.408 grm. for the females. If the average weights of the hearts be compared according to Donaldson's method, the increase resulting from thyroid feeding is 26 per cent. in the males and 27 per cent. in the females.

The gross appearance of the hearts of these thyroid-fed rats was quite similar to that of the controls, except for the increase in size and weight. On microscopic examination, however, one of five males and three of five females exhibited small areas of myocarditic changes. Compared with the lesions observed in the animals receiving toxic doses of thyroid, those seen in the animals in this series were conspicuous for the smaller size of the affected areas and the greater variation in the proportion of the constituent elements in different areas. Some of these areas were composed chiefly of round wandering cells, while in others fibroblasts prevailed. In one of the males showing no inflammatory change in the myocardium there was a slight proliferation of the connective tissue without any inflammatory reaction in the neighborhood of the blood vessels.

(3) The Histology of Normal Hearts. The Histology of the Hearts of Animals Dying from Other Causes Than Thyroid Intoxication.

In order to decide whether or not the occurrence of the myocarditic lesions above described was due to the toxic effect exerted by

the thyroid substance itself, I made a series of control investigations.

The hearts of 22 normal and healthy adult albino rats were examined post mortem; five of these animals were non-pregnant females and the remainder males. Most of them had been receiving desiccated beef in varying amounts.

The microscopic appearance of the heart muscle of the normal albino rats agreed in general with that of rabbits, a detailed description of which has been given by Anitschkow and also by Kiyono. The myocarditic lesions described above were not observed in a single instance.

Since the most marked myocarditic lesion had been found in the animals dying during the course of thyroid feeding, it was thought desirable to investigate the condition of the heart in the animals dying from other causes than thyroid intoxication. One of these rats, in which death was due to diarrhea, showed no myocarditic changes.

A histological examination was next made of the heart muscle from nine male adult rats in which death followed thyro-parathyroidectomy, one immediately after the operation, four within 18 hours, and the other four after two or three days. The hearts of these animals exhibited neither cell infiltration nor fibrosis, although congestion and edema of the myocardium was quite marked in five of them.

The research was next directed to an investigation into the histology of the hearts of rats dying after repeated overexertion at a high temperature, for there is a certain similarity between the condition of severe thyroid intoxication and that of overexertion at high temperature, especially when there is great excitation of heart action. Zwaschkewitsh found that the hearts of animals exposed to high temperatures for a considerable period of time showed a cloudy swelling of the muscle-fibers. Litten, Naunyn, Nasaroff, Werhovsky, and Welch found fatty degeneration of the heart muscle instead of a cloudy swelling.

As to the histology of the hypertrophied hearts, in which hypertrophy is the result of experimental valvular lesions, there are a number of studies on record. Stadler and many others found a diffuse increase of connective tissue but no inflammatory changes in the heart muscle.

Through the courtesy of Doctor S. Sugahara, I had an opportunity to examine the hearts of five albino rats (four males and one female) which had died after having been exposed to temperatures of from 30° to 40° C, and at the same time forced to overexertion for two or three hours in a warm revolving box, the procedure being repeated several times at intervals of a few days.

On histological examination myocarditic lesions such as were shown after thyroid administration were not found in any of these animals. A pregnant female rat showed a slight proliferation of the interstitial connective tissue around the blood vessels, but this was not accompanied by infiltration of any of the wandering cells.

(4) Thyroid Administration Combined With Vital Staining With Carmine.

In order to establish the nature of the various cells constituting the myocarditic lesions above described, I carried out another series of experiments, employing the method of vital staining with carmine, as Kiyono did in his investigations of the cellular elements of granulation tissue produced experimentally in the hearts of rabbits.

Six young adult male albino rats, weighing from 75 to 85 grms., which had been receiving 0.1 grm. desiccated thyroid daily in food, were injected intravenously with 0.05-0.15 cc. of a 4 per cent. solu-

tion of carmine in saturated lithium carbonate on five successive days. The animals exhibited various symptoms referable to the thyroid intoxication (anoroxia, hyperexcitability, emaciation, etc.) and were killed after having received five or six doses of thyroid and 12 to 18 hours after the last injection of carmine. The efficiency of the aforementioned dose of thyroid had been estimated by a preliminary experiment in which six rats of the same sex and similar size, receiving this dosage daily, had died after six or seven days.

In a second experiment four male rats, weighing 140 to 150 grms., and having received non-toxic doses of desiccated thyroid (0.003-0.03 grms. on alternate days) for three months, were injected with 0.1-0.2 cc. of the carmine solution per day, for five successive days and then killed. Thyroid feeding was commenced when the animals weighed only 40 to 50 grms., and the dosage was increased gradually as the body weight increased. The animals thrived and growth was neither retarded nor accelerated, as compared with the control animals. The hearts and other organs, however, were found to be somewhat enlarged.

In a third series, six healthy male rats, fed on milk and bread with or without the addition of desiccated beef, received the injection of carmine by a similar technic.

The histology of the hearts of these normal albino rats, examined after vital staining with carmine, was in general much the same as that of normal rabbits, described in detail by Kiyono, except as concerned the myocytes of Anitschkow. In the interstitial connective tissue of the heart muscle are a number of cells containing a greater or lesser number of cytoplasmic granules which stain with carmine. It has been proved by Kiyono that these cells correspond to the "clasmocytes" of Ranvier. Besides the clasmocytes, the myocytes of Anitschkow are found scattered in the interstitial connective tissues of the myocardium. According to Kiyono these cells possess no cytoplasmic granules which stain vitally with carmine. So far as I am aware, however, it is evident that the majority of the myocytes present in normal as well as in pathological heart-muscle contains these granules, varying in size from fine dust-like particles to globular bodies large enough to be easily seen by a moderately high power microscope. There is an apparent tendency for the granules to be small in size and few in number in cells with more basophilic cytoplasm, while on the other hand they appear to be large and more numerous in cells with clear, swollen cytoplasm. The fibroblasts and the endothelial cells of the capillaries contain no vitally staining granules. The cells of the muscle-fibers likewise do not stain vitally with carmine nor do they exhibit any carmine granules.

By the aid of a vital staining with carmine the nature of the cell elements in the regions of myocarditic changes, resulting from thyroid administration, was made more obvious. In the rats receiving toxic doses of thyroid there appeared an increase in the number of the vitally staining cells—"Histiocytäre Zellen" of Kiyono—throughout the interstitial tissue of myocardium. A large number of these cells were swollen and had relatively shorter processes than normal cells, and some had even rounded up. The cytoplasm was densely packed with carmine granules and often vacuolated. Not infrequently one or two of the carmine granules present in the cytoplasm were of enormous size, sometimes half the size of the nucleus. The nucleus was usually situated eccentrically and exceedingly irregular in shape, especially in the swollen polyhedral or round cells, where it was round, oval, polyhedral, indented, or even bent. The network of chromatin was for the most part quite thin, and its nodal thickenings stood out distinctly as chromatin clumps scattered in the clear karyoplasm, whereas the nuclei of the "histiocytäre" cells present in the normal

myocardium tend to show a thick and dense chromatin network. Mitotic figures are shown by some of them. The evidence of karyokinesis argues the rapid proliferation of these "histiocytäre" cells. These cells show a tendency to cluster between the muscle-fibers, or frequently in the neighborhood of the blood vessels, and to form patches of cell-collections. Judging from their morphological characters, we may easily identify the "histiocytäre cells," derived from clasmocytes, with the large peculiar cells which have been previously described as the chief constituents of the cell-collections found scattered in the myocardium of thyroid-fed rats. Among these cells is a fair number of myocytes conspicuous for the chromatin structure of their nuclei, some of which are much swollen.

The cell patches also contain other cells in varying numbers which do not stain vitally with carmine. Some of these are entirely indistinguishable from the lymphocytes present in the circulating blood, while other are quite similar in their morphological characteristics to the "histiocytäre" wandering cells, except that they contain no carmine granules. It is very difficult to decide whether the cells of the latter type are derived from lymphocytes, or whether they are "histiocytäre" cells which fail to exhibit carmine granules, owing to pathological changes in their cytoplasm. In certain cases such cells lacking carmine granules constituted the greater part of the cell-collections, together with a smaller number of clasmocytes containing fair deposits of carmine granules. Some of these cells are probably derived from the connective tissue, for they show one or two distinct nucleoli in a pale oval nucleus.

As mentioned above, the muscle-fibers in the normal hearts do not stain vitally with carmine, neither diffusely nor by granular formations, especially when the animals are killed later than half a day after the injection of the dye. In the hearts showing severe myocarditic changes, however, some of the muscle-fibers may stain diffusely pink with carmine. In such areas the cross-striations usually fade out. The nuclei therein may show various stages of disintegration, but this is not always the case. Though such a tinctorial change of muscle-fibers is seen in the hearts showing severe interstitial inflammatory changes, the two conditions appear to occur quite independently of each other. The muscle-fibers adjoining the interstitial cell-collections are not always stained pink. Red staining of heart muscle-fibers of animals injected intra vitam with carmine has been observed by Fari, by Masuda and by Kiyono, and interpreted by them as evidence of disintegration of the muscle-fibers.

Of four rats receiving non toxic doses of thyroid over long periods, only one showed the myocarditic lesion described above. It is of interest to note that in the myocardium of this animal there were some myocarditic areas composed mainly of fibroblasts. Within such areas the "histiocytäre" cells containing carmine granules were not swollen, but flattened and elongated, with dark nuclei and a thick network of chromatin. The carmine granules were small and few in number. These observations suggest that these "histiocytäre" cells were no longer in an irritated, but in a stable condition, taking part in the formation of a fixed tissue. Nowhere were muscle fibers stained pink.

(5) The Effect of Inorganic Iodine Upon the Heart Muscle

In order to decide whether the myocarditic lesions produced as the result of thyroid feeding were due to the effect of an abnormal increase in the thyroid secretion, or were simply due to the toxic action of iodine contained in the thyroid substance given, I administered an inorganic iodine salt (sodium iodid) to three albino rats that had survived a thyroidectomy.

A thyroidectomized female rat, which died after having received a buccal administration of 1 mg. sodium iodid per day for a week, showed no myocarditic lesions.

A male rat, weighing 78 grms., was injected subcutaneously with 10 mg. sodium iodid in a water solution ten days after a thyroidectomy and was killed four days later. There had occurred a fair degree of diuresis following the injection of the iodide. On microscopic examination the heart muscle showed a condition of edema, the muscle fibers being separated and the interstitial cells swollen.

Another male, weighing 69 grms., received a subcutaneous injection of 3 mg. sodium iodid in a water solution 10 days after thyroidectomy. In this case diuresis did not occur, but the amount of urine excreted tended rather to diminish. The animal became inactive and weak, and died two days after the injection. Gross and microscopic examination of the internal organs gave evidence of acute pneumonia, acute nephritis, a stasis of general blood circulation, and degeneration of the liver cells. The heart muscle showed marked myocarditic lesions in the wall of the left ventricle near the base. Fresh granulation tissue had formed beneath the pericardium, showing a tendency to grow toward the center of the wall along the interstitial tissue. In the area adjoining the pericardium the granulation tissue consisted chiefly of fibroblasts, whereas between the muscle-fibers it was composed mainly of large pale cells of mononuclear type and a few cells of lymphoid type. Muscle-fibers adjacent to the granulation tissue were vacuolated or dissolved, and the nuclei were scattered out showing various stages of disintegration. Histologically the myocarditic lesions found herein resembled so closely those resulting from thyroid feeding that one could scarcely distinguish the one from the other. The number of observations is too small, however, to warrant the drawing of final conclusions as to whether or not the myocarditic lesions, occurring as the result of thyroid administration, may be produced by the action of the iodine, which is not in the chemical combination proper to thyroid secretion.

A young female rat, not thyroidectomized, died after having received a buccal administration of 1 mg. potassium iodid 4 times a week. The myocardium showed no myocarditic lesion.

(6) The Effect of Adrenalin Injection Upon the Histology of Heart Muscle

K. Ziegler, in his experiments regarding the effect of repeated injections of small doses of adrenalin in producing arterial lesions, found cardiac lesions in a large percentage of his animals (rabbits) at an early stage of the experiment, edema and hemorrhage of heart muscle, round cell infiltration at various places, vacuolation of muscle fibers, and proliferation of connective tissue originating from the blood vessels and endocardium; at a later period an appearance of anemic infarcts or areas of induration; at the last cardiac hypertrophy supervened. Pearce examined the hearts of a number of rabbits killed immediately after an injection of adrenalin or at various intervals in the course of repeated injections of adrenalin. In the former cases he noted an edema of the heart muscle, while the latter

showed early degenerative changes of muscle fibers, followed by an increase of interstitial connective tissue. Fleischer and Loeb later repeated the experiments of Pearce. They noted that the action of adrenalin in producing myocarditic lesions is greatly increased by a previous injection of spartein, caffein or other heart tonics; the injection of a single dose of spartein or caffein (0.012 grms. of spartein sulphate or 0.025 grms. caffein sodium benzonate per kilogram) with adrenalin (0.2 cc. of a 1:1000 solution) was strong enough to cause the appearance of gross myocarditic lesions in 60 per cent. of the rabbits injected, and the appearance of microscopic lesions in almost all of the animals. Strickler and Fleischer have made a similar experiment upon dogs and observed that the injection of adrenalin plus spartein did not cause any myocarditic lesions, although it sometimes induced clinical symptoms quite similar to those occurring in rabbits as the result of the same treatment. Pisani also investigated the myocarditic lesions caused by adrenalin, and noted an early occurrence of degenerative changes of muscle-fibre (vacuolation, granular dissolution, etc.) and the later appearance of localized fibrosis originating in the interstitial tissue, which change was preceded by the infiltration of inflammatory cells. Anitschkow repeated the work of Fleischer and Loeb in an attempt to investigate more thoroughly the histogenesis of these myocarditic lesions. He observed that the myocarditic changes resulting from the injection of adrenalin plus spartein are of two types: (1) diffuse edema and its result, fibrosis; (2) inflammatory proliferation of interstitial tissue occurring in scattered circumscribed areas; fibroblasts present in the interstitial tissue polyblastic cells, derived partly from lymphocytes present in the circulating blood and partly from fixed wandering-cells in the interstitial connective tissue, and the "myocytes" of Anitschkow (of muscular origin) taking part in causing such inflammatory changes.

As a consequence of the work briefly cited above, it has been made clear that the injection of adrenalin into rabbits can cause in the heart muscle certain myocarditic lesions. From the statement of Anitschkow we are aware that such lesions histologically simulate those produced in the albino rats by thyroid administration. But since Strickler and Fleischer have failed to find the myocarditic lesions in the dogs injected with adrenalin plus

spartein, it is still an open question whether or not albino rats would respond as do rabbits to the same treatment.

I deem a decision on this point important for the solution of the problems concerning the pathogenesis of my myocarditic lesions, resulting from thyroid administration, inasmuch as it has long been an accepted theory that hyperthyroidism elicits an excess of adrenalin in the body presumably inducing an increased production of adrenalin in the suprarenal glands, as observed by Herring.

Spartein and adrenalin were intravenously injected into a number of albino rats, weighing 90 to 120 grms. First 0.001 grm. spartein sulphate per 100 grms. body weight in the solution of 1:100 was injected intravenously and 3 to 5 minutes thereafter 0.1 cc. of a 1:20,000 adrenalin solution per 100 grms. body weight. These proved to be the maximal sublethal doses that could be employed, inasmuch as four out of ten rats died immediately after the last injection, showing symptoms referable to an acute edema of lungs, i. e., dyspnea and flow of frothy, bloody fluid from the nostrils. Of seven males that survived the injection of adrenalin plus spartein five were killed by chloroform eight days and two eighteen days after the injection. For the purpose of vital staining six of them received intravenous injections of carmine (0.15 cc. of a 4 per cent. solution) daily for four days before death. Three female rats were killed without vital staining sixteen days after the injection of adrenalin and spartein.

On microscopic examination only one of the five males killed eight days after the injection of adrenalin-spartein exhibited in the heart muscle small perivascular areas of lymphocytic infiltration and proliferation of the "histiocytäre" cells. Another animal showed a slight proliferation of connective tissue in the neighborhood of the blood vessels of the heart muscle. The heart muscle of the others appeared normal. Two males killed as late as eighteen days after the injection of adrenalin-spartein showed normal heart muscle. Such was the case also in the three females killed sixteen days after the injection.

From this experiment it is evident that the injection of adrenalin plus spartein may cause certain myocarditic changes in the hearts of albino rats, but that these are far less severe than those occurring in rabbits; furthermore, that they are considerably less marked than those occurring in albino rats as the result of thyroid feeding.

(7) Anatomical Changes Observed in Other Visceral Organs of Thyroid-fed Albino Rats

In order to estimate the functional value of a heart showing the myocarditic lesions described, it was thought desirable to examine all of the other internal organs and all parts of the body, especially those which respond promptly to the impaired action of a diseased heart by certain marked anatomical changes referable to a retarded circulation of blood. Furthermore, it was thought possible that such an investigation might furnish us data that would help toward a satisfactory explanation of the mechanism through which the myocarditic lesions described are evolved.

Cyanosis of marked degree and wide extent was seen in almost all of the animals that died under the influence of thyroid feeding. On dissection many of the visceral organs, especially the lungs, liver, and kidneys, were found to be much congested and swollen, while dropsy in the pericardial, thoracic, or abdominal cavity was rarely found. Except in the lungs, there was no hemorrhagic condition in any of the visceral organs.

Liver, spleen, lungs, kidneys, suprarenal glands, and pancreas were examined microscopically. The material was obtained from fourteen normal albino rats, used as controls (ten males and four females), twelve that had been killed after having received toxic doses of thyroid, nine that were found dead in the course of thyroid administration, and ten that were killed after having received prolonged administration of non-toxic doses of thyroid. The findings in this examination will be briefly described.

Lungs:—The lungs of albino rats, even the apparently healthy controls, were frequently found infected (85 per cent.), and showing evidences of a chronic bronchopneumonia. In the majority of cases, however, the inflammatory change was not in the progressive stage, but rather in a condition of incomplete healing. The walls of the bronchi or bronchioli and those of the air-cells were thickened by the formation of large quantities of edematous young connective tissue with little inflammatory exudate. Some of such bronchi or bronchioli were found obstructed with connective tissue, often causing a secondary localized atelectasis of the related lobuli, or occasionally bronchiectasis. The lymphoid tissue present in the neighborhood of the bronchi occasionally showed a slight tendency to spread out into the adjacent parts of lung substance, and contained, besides ordinary lymphocytes, epithelioid cells, eosinophil leucocytes, plasma cells, or fibroblasts. On vital staining with carmine some of these epithelioid cells were conspicuous from the deposit of carmine granules. In a few cases there occurred a distintegration of cell elements present in the lymphoid tissue. Evidences of acute inflammation, such as the appearance of numerous polymorphonuclear leucocytes with fluid exudate in the alveoli, were not observed in any of the control animals.

In a large percentage of the rats dying at about the end of the second week or later in the course of administration of toxic doses of thyroid, the lungs were found to be extremely congested. The capillaries in the alveolar walls were greatly dilated. Many of the alveolar epithelial cells were swollen and desquamated. Fluid matter was exuded into the air-cells, often with red blood cells.

In the rats killed at comparatively earlier periods congestion of the lungs was rarely found. In the lungs of two out of ten animals killed at an early stage of thyroid feeding, there were numerous polymorphonuclear leucocytes as well as erythrocytes which had wandered out into the alveoli in rather wide areas. It is interesting to note that in these two cases the myocarditic lesion was decidedly less severe than that found in the animals that died at later periods of thyroid feeding and which showed marked congestion in the lungs but no acute pneumonia.

It is evident, therefore, that an acute pneumonia appearing in the thyroid-fed animals has little or no part in causing the myocarditic lesions above mentioned. The same is true of chronic pneumonia inasmuch as no myocarditic lesion was found in the control animals, although 85 per cent. of them showed a chronic bronchopneumonia.

In the rats receiving non-toxic doses of thyroid the lungs appeared little different from those of the controls.

Liver:—Frequently parasitic cysts were found in the liver of albino rats employed for these experiments. It is evident, however,

that the presence of these cysts for the most part has nothing to do with the function of the liver, for there is usually no histological change in the areas adjoining the cysts, except the rare occurrence of a slight proliferation of connective tissue. It is quite possible that the infiltration of a few small round cells about the gall ducts or blood vessels in the capsules of Glisson, found in some 36 per cent. of the normal controls, are not due to the parasitic cysts, inasmuch as such infiltrated areas were situated anywhere in the liver, quite independent of these cysts. Furthermore, there appeared to be no correlation between either the occurrence or the severity of such changes and the number of the parasitic cysts.

Marked histological changes resulting from thyroid feeding are shown in the parenchymatous degeneration, which was observed in quite a large number of animals receiving toxic doses of thyroid, whether killed at early stages in the experiment (50 per cent.) or found dead at later periods (73 per cent.). The liver cells encircling the efferent veins showed various stages of disintegration varying from simple fatty degeneration to necrosis. Occasionally such changes were present throughout the lobules, but were never entirely confined to the zone adjoining the portal veins, as observed in eclampsia gravidarum.

In addition to the parenchymatous degeneration, evidences of chronic passive congestion and its results were seen in the livers of the animals dying later in the course of the thyroid administration (71 per cent.). The efferent veins in the center of the lobules and the adjacent capillaries were greatly distended with blood. The liver cells were collapsed and occasionally even destroyed, the framework alone remaining. It was frequently seen that this framework was hypertrophied, and accompanied by marked proliferation of Kupffer's stellate cells.

On the other hand, in the peripheral zone of the lobules showing degenerative changes in the center there frequently occurred hyperplasia of the liver cells, presumably the repairing process. There appeared a large number of mitiotic figures or double nuclei in the cells, and many young cells with pale and clear protoplasm and large nuclei. The occurrence of hyperplasia of liver cells without previous disintegration of the same cells was, however, very rare.

With regard to the relation existing between the various histological changes above described and the myocarditic lesions, it is of interest to note that the evidences of severe chronic passive congestion of the liver were found in the animals that showed severe myocarditic lesions; whereas in the animals showing only slight or no myocarditic lesion the liver was not congested, even when a fair degree of degenerative change was evident in the liver cells.

Spleen:—Frequently the spleen in the thyroid-fed rats was more or less congested, but not as markedly as were the lungs or the liver. There was no proliferation of reticulo-endothelial cells containing granules that stained vitally with carmine. The spleen was conspicuous for hyperplasia of the lymphoid tissue. The outlines of the Malpighian bodies became indistinct, the pulp tissue being filled with numerous lymphoid cells. Such changes were observed chiefly in the spleens examined at a comparatively late stage of thyroid feeding; i. e., in six out of nine animals, treated with non-toxic doses for a long period, four out of six animals examined in the later stage of treatment with toxic doses of thyroid, but in only one out of ten animals killed at an early stage of similar thyroid administration.

Kidneys:—In 55 per cent. of the rats found dead after having received toxic doses of thyroid for some time, the kidneys were congested, the boundary zone especially being macroscopically a dark

red. Microscopically the blood vessels were found to be distended with blood.

The parenchyma of the kidneys also was more or less affected by thyroid intoxication. In the animals receiving toxic doses of thyroid it was not infrequent that fat had lodged in the renal cells, especially in the cells of the convoluted tubules near their base in the form of small globules which stained well with Sudan III. Some of the renal cells were swollen and contained poorly staining or pycnotic nuclei. On the other hand, the regeneration of the renal cells seemed occasionally to be accelerated under the influence of thyroid administration. In the kidneys of thyroid-fed rats there was often an increase in the number of mitotic figures or double nuclei in the cells, mainly in the renal cells of the convoluted tubules. The increased deposit in the renal cells of vitally staining granules was often evident in the animals examined at an early period of thyroid feeding. Such a change may be interpreted as indicative of an increased activity of renal cells, according to Dibbelt, Arnold and others.

Suprarenal glands: In the suprarenal glands of thyroid-fed rats I have often found more or less marked congestion, but failed to observe a hemorrhagic condition. In the specimens examined for severe thyroid intoxication many nuclei of the gland cells present in the medulla appeared pycnotic.

The results of these experiments indicate that severe myocarditic lesions are associated with a chronic passive congestion of other internal organs, especially of the lungs and liver. Secondly, it is shown that as the result of thyroid feeding various internal organs other than the heart may undergo certain pathological changes, but these changes are far less marked than those of the heart; they consist chiefly in parenchymatous degeneration or proliferation and not in inflammatory proliferation of the interstitial tissue of the organs. Proliferation of "histiocytäre" cells, as seen in the heart, does not occur in any other organ except the liver, in which Kupffer cells are increased in number presumably to replace the destroyed liver cells, the change being by no means distinguishable from what may be attributed to a chronic passive congestion.

DISCUSSION

The buccal administration of thyroid, either in non-toxic doses over a long period or in toxic doses over a short period, produced a more or less marked enlargement of the heart in albino rats, the results confirming those of Hoskins (1916) and Herring (1917). I failed, however, to obtain such a large increase in size as that observed by Herring, although thyroid had been administered in widely varying doses. In this respect my results are in close agreement with those of Hoskins. The greater enlargement of the organs obtained by Herring cannot, therefore,

be attributed to the larger doses of thyroid but must have been due to some other factor.

Besides enlargement of the heart, the administration of thyroid, especially in toxic doses, produced myocarditic lesions of a chronic non-suppurative nature. Although the animals were examined at various intervals in the course of the thyroid administration, it has been quite difficult to study the sequence of the myocarditic changes step by step, inasmuch as different animals, treated with the same doses of thyroid for the same length of time, may exhibit myocarditic lesions varying not a little from one another in their histological appearance, presumably owing to a difference in the individual's susceptibility to the effect of thyroid. Nevertheless, judging from the findings in a considerable number of animals examined at various periods in the course of thyroid feeding, it seems reasonable to assume some such sequence of changes as the following.

At an early period one observes a more or less marked proliferation of clasmocytes in the interstitial connective tissue of the myocardium. These cells, conspicuous by reason of the deposit of vitally stained granules in the cytoplasm ("histiocytäre Zellen" of Kiyono), tend to accumulate densely in the small areas between the muscle-fibers or in the neighborhood of blood vessels. An irritative proliferation of these cells is suggested by the fact that some of them show mitotic figures, while others appear in the form of wandering cells with rounded-up cytoplasm. A few lymphocytes usually accompany these cells, and occasionally cell masses of comparatively small size may consist chiefly of lymphocytes. It is difficult to decide, however, whether or not lymphocytic infiltration always precedes the proliferation of the histiocytäre cells. Muscle-fibers adjoining the areas of interstitial changes may apparently be pushed aside by the pressure of the cell masses, but for a while they are kept nearly intact in their morphological appearance.

At a later period the "histiocytäre" cells increase enormously in number. Some of these cells, presumably old ones, show various changes referable to a distintegration. Fibroblasts begin to appear in greater or less numbers within the areas. Some of these exhibit the mitotic figures indicative of a rapid cell division. When the inflammatory proliferation of the interstitial tissue has advanced so far as to occupy quite wide areas, the

adjacent muscle-fibers undergo disintegration or destruction, such as vacuolization, dissolution, etc.

At the last period fibroblasts or young connective-tissue cells appear to be prevalent in the myocarditic areas, and the "histiocytäre" cells are no longer wandering, but resting fixed cells. Eventually, fibrous scars may be formed there, though unfortunately none of the specimens examined showed such.

The myocarditic areas may increase in size to such an extent as to be seen easily under the low power microscope, but never become visible to the unaided eye.

In the course of continued thyroid feeding new areas of myocarditic lesions, showing a sequence of changes such as that described above, seem to set in. Therefore, in the later stages of thyroid feeding the histological appearance of inflammatory changes varies widely in different myocarditic areas, even in the same heart.

Notwithstanding a marked inflammatory reaction of the interstitial tissue, changes of the parenchyma are in general seemingly less severe, at least in the morphological appearance observable under the microscope. The muscle-fibers may appear diffusely swollen, their cross-striations less marked than normal; on vital staining with carmine they stain diffusely pink. Occasionally, their nuclei may show various stages of disintegration, i. e., an accumulation of chromatin along the axis of the nucleus, impaired tingibility, pyenosis, etc. Such changes all are in general accord with those earlier described by Farrant in thyroid-fed rabbits. Severe parenchymatous degeneration, such as dissolution of muscle-fibers, occurs to only a limited extent in the neighborhood of quite large areas of interstitial changes.

It is interesting to note that the inflammatory proliferation of the interstitial tissue develops quite independently of the diffuse parenchymatous degeneration just described. The muscle-fibers adjacent to the small areas of interstitial changes may be pushed aside, presumably by the pressure of growing granulation tissue, but do not always show degenerative changes, although they may be severely affected later, when the granulation tissue increases to such an extent as to occupy quite wide areas. We cannot assume, therefore, that the inflammatory proliferation of interstitial tissue occurs simply to replace the degenerated muscle-fibers, as has been noted both by Mollard and Regaud,

and by Anitschkow in studying the histogenesis of myocarditic lesions produced by the injection of diphtheria toxin. The inflammatory changes in the interstitial tissue appear to be evoked primarily by the inflammatory stimulation exerted directly upon the interstitium by some toxic agent, which may also be responsible for the occurrence of diffuse parenchymatous degeneration.

There has been an accepted theory that hyperthyroidism elicits an excess of adrenalin in the body, presumably inducing an increased production of adrenalin in the suprarenal glands (Herring); and, as cited before, Anitschkow has observed in rabbits, after the injection of adrenalin plus spartein, an inflammatory proliferation of the interstitial tissue of the myocardium, not always associated with degenerative changes in the muscle-fibers, and he ascribed such changes to the effect directly exerted by these chemical substances upon the interstitial tissue. It is worth while to discuss whether or not the myocarditic lesions in hyperthyroidism are due to the excess of adrenalin in the body. It is evident, however, that this probability is not of importance, for I am aware, from chemical examination, that the production of adrenalin in the suprarenals is liable to be interfered with by the administration of thyroid in such doses as to cause marked myocarditic lesions (0.5 grms. desiccated thyroid per day), and, from histological examination, that evidence of disintegration of gland-cells in the medulla of the suprarenals may occasionally accompany the myocarditic lesions. Furthermore, I have ascertained that the heart of the albino rat does not respond to injected adrenalin with so marked inflammatory changes as have been observed in rabbits by K. Ziegler (1905), Fleischer and Loeb (1909-10), Anitschkow (1913), etc.

It is generally known that various acute infections—thyroid bacillus (Romberg), meningococcus and streptococcus (Gruber)—may cause myocarditic lesions with an acute inflammatory proliferation of the interstitial tissue. In my thyroid-fed animals the marked myocarditic lesions were not associated with evidences of acute infection observable microscopically in the other parts of the body. As noted already, it has been proved that the presence of a pneumonic affection in the lungs or of parasitic cysts in the liver is of little significance in causing myocarditic lesions.

As is generally known, hyperthyroidism necessitates an overexertion of the heart, a rapid pulse being evident. Nevertheless, the myocarditic lesions herein described may not be due solely to an excessive mechanical strain, inasmuch as the animals forced to overexertion in a high temperature did not exhibit the same myocarditic lesions as those occurring as the result of thyroid feeding.

Considering all the evidence, I am inclined to believe that the stimulative or toxic agent responsible for the various degenerative and inflammatory changes in the myocardium might be found in the thyroid substance itself, introduced into the body in excessive amounts by thyroid administration.

We find it difficult, however, to explain the fact that the heart usually is affected far more severely than other visceral organs. There is the possibility that mechanical strain or overexertion of the heart may render the myocardium less tolerant to thyroid intoxication (*locus minoris resistentiae*), and thus facilitate the occurrence of myocarditic lesions, though a mechanical strain is not of itself sufficient to produce such lesions.

It is likewise difficult to explain the fact that the inflammatory changes occurring in the myocardium as the result of thyroid administration seem to be remarkable for an irritative proliferation of the "histiocytäre" cells present in the interstitial connective tissue. We are not justified in at once assuming that the inflammatory stimulus exerted by the thyroid substance is conspicuous from a histiotactic character. If the stimulus eliciting the proliferation of the "histiocytäre" elements were characteristic of the effect exerted by thyroid substance, the other visceral organs should show a similar proliferation. So far as I am aware, however, such is not the case. There is a hyperplasia of Kupffer's cells in the liver around the efferent veins, where the gland cells are annihilated, but this is by no means distinguishable from what occurs as the result of a chronic passive congestion. On the other hand, in the spleen there appears to be a proliferation of the lymphoid tissue, whereas the reticulo-endothelial cells, "histiocytäre" cells, are apparently not increased in number.

As to the functioning power of a heart showing the myocarditic lesions described, it is quite certain that it is distinctly inferior to that of the normal heart. It is of interest to note here

that the most severe myocarditic lesion was found in a thyroid-fed rat that died suddenly after overexertion, presumably as a result of an acute cardiac insufficiency. On histological examination of the other internal organs of a large number of thyroid-fed animals, it has been further ascertained that the severe myocarditic lesions are for the most part associated with changes referable to a generally retarded circulation of blood—a chronic passive congestion of various organs and its results. It is highly probable, however, that an inflammatory proliferation of the interstitial tissue may be of little significance in causing the cardiac insufficiency, inasmuch as the muscle-fibers are apparently not directly destroyed to any great extent by such changes. It seems likely that the cardiac insufficiency is due rather to the diffuse degenerative changes occurring at the same time in the muscle-fibers. Since a large number of muscle-fibers are injured, even though slightly, it is a matter of course that such hearts are not able to meet successfully a demand for extra work.

In comparing the myocarditic lesions resulting from thyroid intoxication with those occurring in the myocardium of human subjects suffering from an acute articular rheumatism, as Aschoff (1904) and Tawara, Geipel (1905), Bracht and Wächter (1909), Fraenkel (1912) and many others have described, we are struck by the similarity of the changes in these two sets of the conditions, especially in the fact that they both appear as periarterial nodules composed of large, pale, peculiar cells.

Concerning the etiology of the rheumatic myocarditis, nothing certain is known. Bracht and Wächter produced in rabbits by the inoculation of the diplostreptococus obtained from two patients suffering from an acute articular rheumatism, not only swelling of the arterioles and valvular affection of the heart, but also myocarditic lesions with degenerative changes of muscle-fibers, lymphoid cell infiltration and fibroblast proliferation, the changes corresponding in general to those in rheumatic patients, except that they did not appear as periarterial nodules. As to the cause of the nodular changes appearing in the heart of patients suffering from rheumatism, these investigators presumed that the causative bacteria might be accumulated in the neighborhood of blood vessels or between the muscle-fibres and elicit a periarterial infiltration of lymphocytes, by the action of which cells the bacteria are annihilated; and that the toxic sub-

stances produced by bacterial disintegration might evoke the formation of the nodules, which are composed of cells derived from connective tissue cells,—the changes being regarded as referable to the healing process. De Vecchi (1912), however, successfully produced myocarditic lesions localized in periarterial areas, by the injection of sterile blood obtained from a patient suffering from articular rheumatism. Aschoff contended that the nodular formations consisting of large pale cells are specific for rheumatic myocarditis, and many other investigators have confirmed his opinion. Geipel alone observed similar lesions in the heart of a patient with the contracted kidneys, and he assumed that other toxins or infective agents also may cause myocarditic changes similar to those of the articular rheumatism. It is significant that such changes can also be produced in the myocardium of animals by the buccal administration of thyroid.

In regard to the origin of the large peculiar cells composing the nodular formations of the rheumatic myocarditis, there is a considerable divergence of opinion. Aschoff and Tawara at first termed these cells "abnormally large leucocytoid elements," whereas Geipel regarded them as being derived from the connective tissue cells. Saigo was inclined to assume that some of them are of muscular origin. Bracht and Wächter agreed with Geipel in considering these cells as derived from the connective tissue cells, the fibroblasts. Aschoff (1919) stated briefly in his text-book of pathology, published later, that these cells take their origin from the connective tissue. In my observations on myocarditic changes resulting from thyroid intoxication I have ascertained, by the aid of a vital staining with carmine, that the large peculiar cells composing the myocarditic patches are derived from clasmocytes present in the interstitial connective tissue, the "histiocytäre" cells of Kiyono.

The question now arises, How do the nodular formations develop in these cases in which no bacteria take part, as supposed by Bracht and Wächter? So far as I know, in the myocarditic process resulting from thyroid feeding there is an irritative hyperplasia of the clasmatocytes in the interstitial connective tissue. The clasmatocytes primarily are not distributed uniformly throughout the interstitial tissue of the myocardium, even in normal hearts, but show a tendency to cluster in the sheaths of the blood vessels and in the areolar tissue beneath the

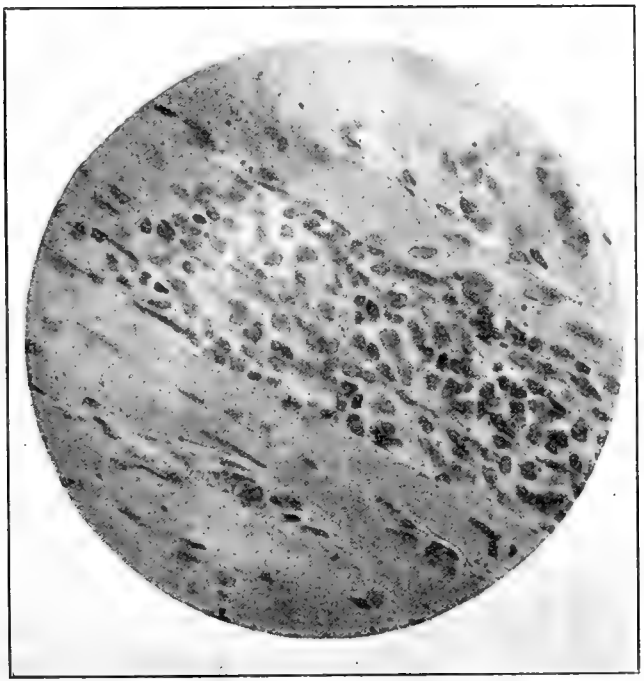
pericardium or beneath the endocardium. If there may set in an inflammatory proliferation of these cells, the histiocytäre cells derived from them would, as a matter of course, tend to accumulate in periarterial or sub-pericardial circumscribed areas, inasmuch as their mother-cells exist in these sites in larger numbers than elsewhere. In view of such an explanation we might assume that any inflammatory process in which the "histiocytäre" cells are caused to proliferate should be able to give rise the nodular formations consisting chiefly of large, pale, peculiar cells, and showing a tendency to form in the neighborhood of the blood vessels,—the microscopic appearance of these corresponding nearly with what has been described by Aschoff as specific and unique for the rheumatic myocarditis.

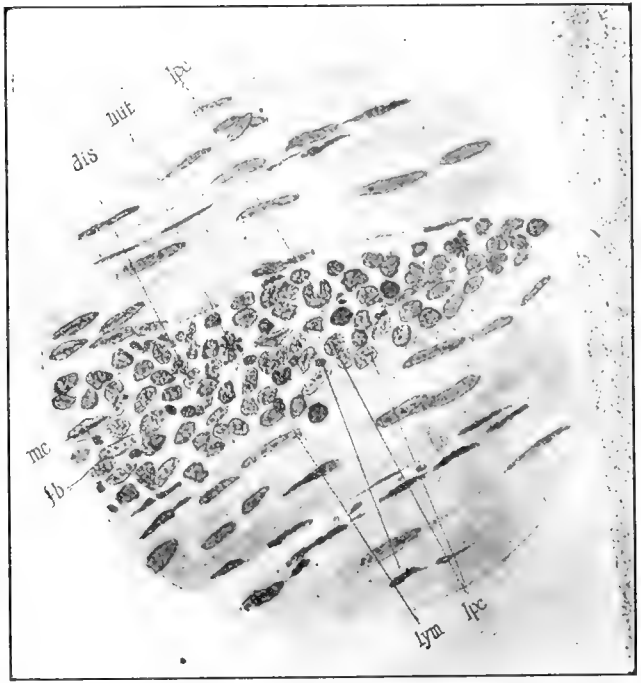
Bircher has produced goitrous changes in the thyroid glands of rats and rabbits by giving the animals water from certain wells alleged to produce goitres. According to his statement, tachycardia and hypertrophy of the heart were evident in these goitrous animals, and furthermore the heart-muscle showed a cloudy swelling or fatty degeneration which was associated with leucocytic infiltration and later scar formation. Comparing such myocarditic changes with those resulting from thyroid administration we find difficulty in discussing them in detail, as Bircher's statement concerning the histology of the affected heart-muscle is quite brief. What types of cells did the leucocytic infiltration consist of? This is a point to be established before discussing the relation of the changes.

In conclusion I will compare the myocarditic lesions resulting from thyroid administration with those found by Fahr in human goitre hearts. My findings are in general agreement with those of Fahr in the following points. (1) The inflammatory processes are chiefly localized in the interstitial tissue, the parenchymatous changes being less marked; (2) the inflammatory change is of a non-suppurative nature; polymorphonuclear leucocytes are present but sparsely in the inflammatory areas; (3) a tendency is shown to form cell collections between the muscle-fibres or in the neighborhood of the blood vessels. Concerning the constituents of the cell masses, Fahr stated that they consisted chiefly of lymphocytes, occasionally accompanied by fibroblasts. I myself have observed microscopically in the heart muscle of an exophthalmic goitre patient (a woman of 25 years.

who died immediately after a partial thyroidectomy without any further complications), in small periarterial areas, a number of small cells of lymphoid type but no cells of large mononuclear type. The muscle-fibres show in addition great quantities of a yellowish brown, granular pigment, slightly stainable with Sudan III. In another case (a woman aged 48 years, who died immediately after a subcutaneous injection of a small dose of adrenalin, without other complications) there were similar lymphocytic infiltrations between the heart-muscle fibres in the neighborhood of blood vessels or beneath the pericardium. In this case the small round cells of lymphoid type were accompanied by a quite large number of large pale cells—simulating the large mononuclear or transitional cells present in the circulating blood —and also a number of fibroblasts or myocytes. Myocytes were increased in number and diffused throughout the interstitial tissue of heart muscle. As has been repeatedly stated above, the myocarditic changes resulting from thyroid intoxication show large pale cells as their chief constituents, though in some cases small round cells of lymphoid type may compose mainly the myocarditic formations. And it has been further ascertained that most of the large pale cells correspond with the "histiocytäre" cells of Kiyono, the cells derived from clasmatocytes or fixed wandering cells present in the connective tissue. No vital staining being possible in human subjects, it is hardly possible to determine how large a proportion of the cells present in the myocarditic areas of human goitre hearts are of the "histiocytäre" type, derived from the fixed wandering cells. According to Maximow, however, lymphocytes as well as "histiocytäre" cells, might be included among the polyblastic wandering cells. If we employ Maximow's terms, *polyblastic* cells, instead of *lymphoid* or *histiocytäre* cells, as Anitschkow has done in describing the myocarditic changes, we may identify such changes resulting from thyroid intoxication with those of human goitre hearts in this respect.

Upon the basis of the anatomical findings Fahr concluded that the toxic agent circulating in the body of the goitre patient acts directly upon the heart muscle. Judging from the fact, observed in my experiments, that a mechanical strain or overexertion of the heart of itself cannot cause myocarditic lesions, as does thyroid administration, we might be justified in assum-





One of the myocarditic areas, found in the heart-muscle of a rat, which died suddenly on the twentieth experimental day in the course of the daily administration of 0.5 grms. desiccated thyroid per day. The collection of cells, situated between the muscle-fibres, consist chiefly of large pale cells (lpc)—mainly histiocytic cells derived from clasmocytes—, associated with smaller numbers of small round cells—microlymphocytes (lym)—, fibroblasts (fb) or myocytes (mc). Two mitotic figures (mit) and some more or less disintegrated nuclei (dis) are seen.

ing that the thyroid substance, introduced in large amounts into the animal organism, or an excess of thyroid secretion, produces not only an excessive stimulation of the sympathetic nerves, thus causing an increased rate and force of the heart beat, but also a toxic effect upon the heart muscle itself, causing various degenerative and inflammatory changes associated with the functional insufficiency.

The results of my experimental investigations do not furnish us with the data which would enable us to state with certainty that the cardiac disturbances associated with endemic goitres have nothing to do with general intoxication, presumed by Bircher to be responsible for the changes in the thyroid glands as well as those in the heart, or to decide positively, whether or not there are any qualitative alterations in the thyroid secretion which take part in causing the cardiac changes associated with Graves' disease. I believe, however, that my results have thrown further light upon the etiology of goitre heart, and establish evidence that cardiac disturbances, almost identical in every respect to those observable in goitrous patients, can be produced by thyroid intoxication or by an excess of thyroid secretion circulating in the body.

SUMMARY AND CONCLUSION

1. The buccal administration of toxic doses of thyroid caused, in addition to enlargement of the heart, the appearance of myocarditic lesions in a large percentage of albino rats: in 90 per cent. of the animals killed during the first and second week and almost all of those dying in the second or third week of a daily administration of 0.5 grms. desiccated thyroid.

2. The myocarditic lesions consisted chiefly in dense accumulations of large "histiocytäre" cells (Kiyono), derived from the clasmocytes present in the interstitial connective tissue, in small circumscribed areas between muscle-fibres or not infrequently in the neighborhood of the blood vessels. These cells may be accompanied by a small or occasionally rather large number of cells of lymphoid type, at earlier periods in the sequence of the myocarditic changes; in the later stages they may be associated with fibroblasts, increasing gradually in number, and eventually prevailing over the other types of cells. The muscle-fibres may be destroyed in confined areas adjoining larger areas

of myocarditic changes. The muscle-fibres may show, moreover, slight but diffuse degenerative changes, apparently occurring independent of the interstitial changes described above, such as indistinctness of cross-striations, slight tingibility upon vital staining with carmine, or slight disintegration of the nuclei.

3. The interstitial inflammatory proliferation and the diffuse parenchymatous degeneration described above may both be attributed directly to thyroid intoxication.

4. The hearts showing such myocarditic lesions are functionally inferior to normal hearts.

5. In their histological appearance the myocarditic lesions resulting from thyroid administration are closely related to those observed by Aschoff, Tawara and many others in the hearts of individuals suffering from rheumatism.

6. The myocarditic lesions occurring in experimental hyperthyroidism induced by thyroid administration correspond to those in goitre hearts, first noted by Fahr, in the sense that they both consist of a chronic non-suppurative interstitial myocarditis. It is evident, therefore, that thyroid administration can cause not only tachycardia or hypertrophy, but also myocarditic lesions, all of which simulate the functional and anatomical changes found in human goitre hearts.

7. This evidence lends support to the theory that the cardiac disturbances associated with goitre are due to thyroid intoxication, and further, to an excess of thyroid secretion.

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CHANGES IN THE BLOOD PRESSURE IN A CASE OF HYPERVAGOTONIA CAUSED BY THE INTRAVENOUS INJECTION OF ADRENALIN

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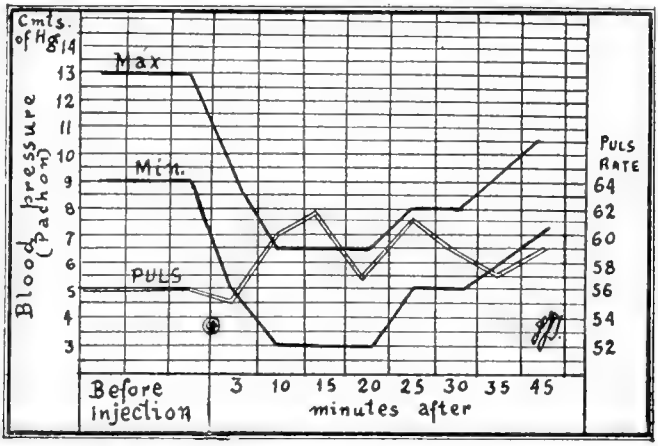
Among the experiments which were made on a hypervagotonic individual and which were reported in a paper at the first meeting of the *Sociedad Mexicana de Biologia* certain interesting changes in the blood pressure following the intravenous injection of adrenalin seemed worthy of special mention. In the study of this patient the blood pressure was first taken, with Pachon's oscillographic apparatus, and found to be 130 and 90 mm. as maximum and minimum respectively, and then one cubic centimeter of adrenalin, 1:1000, that is to say, one milligramme of adrenalin was intravenously injected in a vein of the forearm. The response was instantaneous and very intense. The patient became exceedingly pale, his bucco-pharyngeal mucous membrane was dry, his breathing was irregular and labored and an intense pharyngeal constriction was present. During the first few minutes after the injection, I was unable to determine the arterial tension, on account of the extreme agitation of the patient. At three minutes (see the graph) the fall of pressure reached 40 mm.; at ten minutes it fell to 65 mm. and remained at this level during the next ten minutes. After this time, the pressure rose very slowly and 45 minutes after the injection, when the observations were discontinued the initial value had not yet been regained.

The variation of the blood pressure had been produced as described by Dresel, but with greater intensity. Dresel believes, that in normal individuals, five minutes after the injection of adrenalin the blood pressure rises above 10 mm. of mercury. In the next five or ten minutes, it rises 20 to 30 mm., reaching at that time its greatest height and then descends slowly to the beginning. In the vagotonic individual the indirect stimulus to the vagus is at once apparent, immediately after the injection of the adrenalin at which time the direct stimulus to the sympa-

thetic is not in evidence. In this case the indirect action upon the vagus predominates over the direct action upon the sympathetic. In the first ten minutes after the injection of adrenalin, the blood pressure not only does not rise but even in individuals strongly vagotonic, it may fall a few millimeters; five or ten minutes later, the pressure may rise 20 or 30 mm. and then slowly fall. In these observations the drop in pressure reached 65 mm. notwithstanding the intense constriction of the peripheral vessels, shown by the extreme pallor of the patient. Furthermore, it was not followed by a rise above the initial value.

Now if the adrenine injection operates only through the sympathetic increasing its tone, how can the fall of the blood



⊙ Injection of 1.c.c. of adrenalin 1p. 1000 in the vein.

pressure be explained, since this indicates excitation of the vagus in the hypervagotonic individuals? Guillaume, in his interesting book on the sympathetic, classifies adrenine as clearly tonic for the sympathetic, without including it among the substances partially sympathetic and parasympathetic tonicals. To explain its different action in the vagotonic individual, Dresel speaks of an indirect action exercised upon the vagus, which predominates over the action exercised upon the sympathetic, but he fails to describe its nature, while Guillaume does not speak at all of it.

I believe that the phenomenon can be explained without casting doubt on the exclusiveness of the action of the adrenine

on the sympathetic. The vagus contains a certain number of very interesting fibers which, forming a group may be considered as constituting the depressor nerve of Cyon: the sensory cardiovascular nerve, which is mainly derived from the vagus, but which probably possesses important connections with the cervical sympathetic in man. The sympathetico-tonic stimulating action of adrenine would cause an increase in blood pressure, which at the moment of its initiation would become an exciting agent of sensory fibers of Cyon's nerve coming from the aorta and with their trophic centers in the plexiform and jugular ganglia, which through the sensory column of the tenth cranial pair would connect with the vago-spinal nucleus; this *vagus-vagus* reflex would then produce a fall in the arterial pressure. From this point of view the phenomenon would not be considered as excitement of the pneumo-gastric but would be looked on as an exaggerated reflex action resulting from the increased aortic pressure.

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Editorials

WHAT IS ENDOCRINOLOGY?

There is a class of writers who affect the term "*so-called endocrinology*," the implication seeming to be either that the existence of endocrine organs is doubtful or else that the voluminous literature pertaining to them is of such uncertain significance as not to deserve formal recognition. That the literature does include an intolerable deal of twaddle, no well-informed reader can deny. Such pretentious nonsense might well be designated *pseudoendocrinology*.

The proponents of this sort of literature are coming in for criticism on all sides. A recent editorial in the Journal of the American Medical Association concludes: "How much longer will our profession continue to merit such criticism? Just so long as our profession continues to give serious consideration to pseudoscientific rubbish promulgated by exploiters of organic extracts." The writer might well have added: "and by clinical incompetents seeking easy paths to fame."

Upon the members of the Association for the Study of Internal Secretions a special responsibility devolves lest a long suffering medical profession in disgust with the rank growth of weeds in our fertile field in reformatory zeal uproot wheat and tares alike.

It fortunately happens that the pseudoendocrinologists have developed such a characteristic array of methods that they are relatively easy to identify. They are strikingly addicted to theorizing. If, in a given article, the "explanatory" portion bulks larger than ten or twenty per cent. of the original data adduced, one is rarely in error in classifying it as "pseudoscientific rubbish." As Elliott has sagely remarked: "Medicine owes no thanks to him who, without proof, would formulate her theories." Those who are attempting to elicit our gratitude in this way often put forth the specious plea that they are pointing the way to research,—as though the competent investigators in this field were not beset with an almost bewildering array of problems.

The pseudoendocrinologists are much given to appeals to "physiology." But the physiology cited, one seeks in vain in any first class treatise on that subject. The guesses of novices and the deductions of shallow thinkers are habitually quoted as on a par with substantiated facts. Gross distortion of the evidence is constantly encountered. Such data as support the preconceived theories of the writer are cited while opposing data are ignored. This is not infrequently carried to the point of actual mendacity. Systematized delusions masquerading as the "teachings of experience" are not uncommon. Marvel mongering is also an ear-mark, though this is going out of style.

Examples could be cited by the volume. One recent paragraph, and it by no means the worst available, may be quoted: "I have frequently been asked why adrenal gland and pancreas can be given together in hyperthyroidism. . . . This is readily explained. . . . Adrenal extract is a cardiac tonic and slows and strengthens the heart. Further, when administered in this form, its influence upon the adrenal glands and the factors controlled by them is supportive rather than stimulative. . . . In the complex hormonic mixture in the blood all the hormones, both antagonists and stimulants, are to be found and the remarkable selective capacity of the organism to avail itself of those which are needed, and in proportion as they are needed, explains why, when antagonists are given simultaneously, benefit may accrue in both directions represented by the opposing principles. Suffice it to say that . . . the antagonistic value of pancreas over adrenal *medullary* irritability as well as the thyroid itself makes the pluriglandular idea not so unreasonable after all."

Space and patience are lacking for a full analysis, but a few of the violations of sound physiology may be indicated. That adrenal extract given by mouth has any effect on the circulation is without evidence that competent pharmacologists can now accept. "Its influence is supportive rather than stimulative" is only verbalism that obscures rather than clarifies. The "complex hormonic mixture of the blood" is quite possibly nonexistent. In few cases has it been proved that the endocrine organs contribute anything to the blood stream. They may function by a process of subtraction rather than addition. Hormonic "antagonists" are, so far as proof is concerned, largely

mythical. That epinephrin is rapidly destroyed in alkaline media and that pancreas extract is alkaline comprise the sum total of clean-cut evidence on the point. The "remarkable selective capacity of the organism" is, so far as can now be determined, a mere figment of the imagination, which is being grossly overworked as an excuse for haphazard, pluriglandular dosing. If the body cells were possessed of any such critical acumen as postulated, why should we ever encounter a case of acromegaly or hyperthyroidism? It is definitely proved that the cells will take up thyroxin or epinephrin in lethal quantities, when exposed to excess of these substances. Finally, the "value" of pancreas extract as a source of hormone is, according to all reliable evidence, nil.

That given endocrine gland substances may be valuable in given clinical conditions may or may not be true, as a matter of empirical observation. That enlightened empiricism may lead to further valuable therapeutic deductions is not improbable. Such results are to be expected, however, not from promiscuous dosing with hit-or-miss mixtures, but from carefully controlled experiments carefully analyzed. Rigid critique and rigid logic are indispensable. Any data adduced must stand on their own merits as data. Confusing the issue by the introduction of impressionistic physiology is deplorable.

In the endocrine field, as in all other fields of medical science, progress depends upon intelligent discrimination. Sound workmanship deserves every support, mere tinkering, none. Pseudo-endocrinology will disappear as soon as it ceases to be profitable. The medical profession at large can alone determine when this time will arrive. —R. G. H.

Book Reviews

HARROWER'S MONOGRAPHS ON THE INTERNAL SECRETIONS. HYPERTHYROIDISM: MEDICAL ASPECTS. By Henry R. Harrower, Glendale, Calif., 1921. The Harrower Laboratory. 119 p. 8°.

The author's use of words in this caption is unfortunate. The article is not a monograph in any adequate sense of the term and "hyperthyroidism" is applied promiscuously to all such conditions as Graves' disease, toxic adenomatosis, puberty hyperplasia, etc.

The brochure is published with the declared purpose of enhancing the reputation of the commercial laboratory from which it emanates. This is seemingly a euphemistic admission that it is motivated as an advertising circular. *Caveat emptor.*

The topics discussed receive an interesting presentation, but permeated with no little "pseudoscientific nonsense" and here and there a generous touch of autogenous laudation. It is apparently addressed to those unfortunately credulous clinicians who hope to get a command of present day endocrinology without the labor of serious study. Such readers should realize that "easy endocrinology" in the current state of our knowledge is on a par with Euclid for the nursery or Einstein made simple. It is, in short, sheer futility. Altogether, the "monograph" is entertaining, but unreliable.

R. G. H.

MECHANISMUS UND PHYSIOLOGIE DER GESCHLECHTSBESTIMMUNG. By Richard Goldschmidt, Berlin, 1920. Gebr. Borntträger. 251 p.

For review see Ber. ü. d. ges. Physiol. u. exper. Pharmak., Berl., 1921, **6**, 38-41.

EXOPHTHALMIC GOITRE AND ITS NON-SURGICAL TREATMENT. By Israel Bram, St. Louis, 1920. C. V. Mosby Co. 438 p. 8°.

The work is largely a republication in convenient book form of chapters that appeared originally in the periodical literature as independent articles. These have been previously abstracted in this journal, hence need not again be summarized. The author writes frankly as a partizan of the teaching that in nearly all

cases exophthalmic goitre can and should be successfully treated by non-surgical means. These means are discussed at some length. The work is subject to adverse comment in that a judicial attitude is sacrificed to vigor of debate and that little is made of the author's personal experience. The book may serve an important end in counteracting the extreme teaching, unfortunately common, that surgery is the only successful type of therapy in exophthalmic goitre.

R. G. H.

DIE INNERER SEKRETION. By Dr. A. Weil, Halle. Berlin, 1921. Verlag von Julius Springer. 140 p.

This is one of the few books written with a new idea. We are used to our textbooks dealing with each endocrine gland one after the other. Weil, however, first gives a short review of the embryology and histology of each gland and then discusses: circulation of the blood, respiration and formation of voice, metabolism, growth, procreation, sexual feeling, and psyche and how they are influenced by the endocrine organs. In this way a most interesting, readable little book has been made. It is, however, a pity that many problems are treated in a very superficial way. So when the author discusses homosexuality he quotes the histological changes in the testicle as described by Steinach, but he does not write that many authors have never confirmed this. It would not be difficult to find other examples. On the whole the book is interesting and valuable, but demands critical reading.—J. K.

MICROSCOPISCH EN MACROSCOPISCH ANATOMISCH ONDERZOEK NAAR DE ONTWIKKELING VAN HET OVARIUM VAN HET RUND (Microscopic and Macroscopic Anatomical Studies on the Embryology of the Ovary of the Cow). By W. F. van Beek. Gonda, 1921. 143 p.

This book deals in an exhaustive way with the embryology of the ovary in the cow, on which the author has carried out many studies. It is not possible to give a short review of the contents. For those interested in the question and understanding Dutch, the study of the work will prove of great use. The 38 microphotographs are excellent.—J. K.

KRANKHEITEN DES BLUTES UND DER DRUESEN MIT INNERER SEKRETION (Diseases of the Blood and of the Glands With Internal Secretion). By Prof. Dr. O. Naegeli, Zürich. Leipzig, 1920. Verlag von Georg Thieme. 72 p.

This little book is a part of a collection of similar books which appear under the title: Diagnostic and therapeutic mistakes and how to avoid them (Diagnostische und therapeutische

Irrtümer und deren Verhülung). Professor Naegeli has most brilliantly discussed the problem how to deal with the principal mistakes made in diagnosing or not diagnosing endocrine disease in 17 pages (the rest of the book is taken by the blood-diseases). He discusses: Graves' disease and warns against calling every neurosis with a small goiter by this name, and warns to be careful with the diagnosis of formes frustes or even formes "frustissimae"; thyroid insufficiency; tetany; diseases of the hypophysis; dysgenitalism; and Addison's disease. In each sentence the clinician with an enormous experience is heard and, therefore, this booklet may even prove useful to medical men who have made a special study of the diseases of the endocrine apparatus.

—J. K.

DAS VEGATATIVE NERVENSYSTEM (The Involntary Nervous System). By Prof. Dr. L. R. Müller. Würzburg, Berlin, 1920. Verlag von Julius Springer. 299 p.

Professor Müller is a clinician and, therefore, it is highly interesting to see that in his book he devoted 298 pages to the anatomy and physiology of the vegetative nervous system, and 17 lines to the clinic. *He considers our knowledge of this system absolutely insufficient to think even of clinical application at this moment.* What he writes about anatomy and physiology is good, with beautiful illustrations. Only the chapter on the involuntary nervous system and the blood is superficial and incomplete. There are no fantasies in this book; it has not at all the brilliant style of other works on the same subject, but from a severely scientific point of view it is by far the best book on the anatomy and the physiology of this part of the nervous system.

—J. K.

ENTWICKLUNG, BAU UND BEDEUTUNG DER KEIMDRUESENZWICHENZELLEN (Development, Structure and Significance of the Interstitial Cells of the Gonads). By Dr. W. Stieve. Münich and Wiesbaden, 1921. Verlag von J. F. Bergmann. 249 p.

Stieve calls his book "a criticism of the teachings of Steinach on the 'Pubertätsdrüse' (Interstitial gland)." It is true that in the sexual glands there exist two kinds of cells, interstitial cells and "Keimzellen." It is also true that the sexual gland has a double function, a sexual one and a function regulating growth. In puberty in man as well as in animals the testicle produces an increased number of spermatozoa, in the ovary the number of egg-cells increases. Is not it much more probable that these histological processes are related to the onset of puberty than the interstitial tissue, as Steinach believes? The interstitial cells develop from simple connective tissue and their function is

to gather the substances necessary for the metabolism of the germ cells. When these last cells are damaged, the interstitial cells increase in number and contain more substances that will be wanted by the new germ cells after regeneration. Total degeneration of the germ cells, however, always produces total degeneration of the interstitial gland. In lower animals there exist specimens that have no interstitial cells; in these animals the sexual characters are perfectly developed. It is not possible to believe that in higher animals a differentiation has taken place because we ought to believe then that a function originally due to epithelium would have been given gradually to connective tissue. In testicle as well as in ovary the endocrine sexual function is due to the "germ cells" or to cells derived from them (Sertoli-cells). A special endocrine function of the interstitial gland has never been proved and is even not probable. As to Steinach's rejuvenation, after the operation (ligation of the vas deferens), an unimportant atrophy of the epithelium and an unimportant small growth of interstitial elements is seen during a short time, but soon a perfect regeneration of the sperm elements takes place. Steinach's histological work is of little value, according to the author, as he compares in his book "Verjüngung" the testicles of senile animals with the testicles of animals of one year, which had been operated upon, and from this comparison between two absolutely different organs he draws his conclusions. As to the cases of Lichtenstein, we ought not to forget that cure from a disease as hypertrophy of the prostate itself can produce a real rejuvenation, with or without ligation of the vasa-differentia. These are only a few points from this highly important book. It is impossible to give more detail, as it would be necessary to translate the greatest part of it.—J. K.

Abstract Department

The effect of ADRENALECTOMY upon the total metabolism of the cat. Aub (J. C.), Forman (J.) & Bright (E. M.), Am. J. Physiol. (Balt.), 1921, **55**, 293.

The metabolism of three epinephrectomized cats was determined by means of a Benedict unit apparatus and a small water-sealed copper box. The experiments were carefully controlled. The conclusion seems justified that adrenal ablation in the cat causes a 25 per cent. reduction in the basal metabolism.—T. C. B.

X-ray treatment of ADRENALS in diabetes (Röntgengestrahlung der Nebennieren bei Diabetes). Beumer, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 369.

The influence of x-rays on the adrenals in diabetes, as first recommended by Dresel, was tried in a boy of 6 years with diabetes and serious acidosis. An enormous fall of blood sugar occurred, but the carbohydrate tolerance was not increased. The acidosis became much less serious; the diacetic acid disappeared from the urine. —J. K.

ADRENAL GLYCOSURIA, its connection with the method of administration (Glycosurie adrénalique, ses rapports avec la voie d'administration). Bordier (E.) & Stillmunkès (A.), Compt. rend Soc. de biol. (Paris), 1921, **84**, 613-615.

Protocols of experiments on rabbits and dogs, in which it is again shown that glycosuria follows subcutaneous injections of adrenalin, whereas intravenous injections are not followed by glycosuria in normal animals, within the limits of dosage of about 0.33 mgm. per kilo of body weight.—T. C. B.

Epilepsy and ADRENALS (Epilepsie und Nebennieren). Brüning (A.), Therap. Halbmonatsh. (Berlin), 1921, **35**, 297-301.

In some cases the author saw a good result from removal of an adrenal (see the abstract from his article in Zentralb. f. Chir., 1920, p. 1314). The operation is specially indicated in patients of 15-25 years, in whom fits are occasioned by emotions and probably in status epilepticus. The author recommends further to remove one adrenal in cases of serious juvenile diabetes. He does not describe cases in which this operation has been carried out.—J. K.

Carbohydrate metabolism in animals without ADRENALS (Métabolisme hydrocarboné chez les animaux sans surrénales). Catan

(M. A.), Houssay (B. A.) & Mazzocco (P.), Compt. rend Soc. de biol. (Paris), 1921, **84**, 164-166.

The experiments of Lewis raise the question whether ablation of the adrenals causes a disturbance in carbohydrate metabolism which could account for the sensitiveness of rats to various poisons. Rabbits and rats were decapsulated and the glycemia determined by the Benedict method. Comparatively little disturbance was found and the conclusion is, that the sensitiveness to toxic substances is not due to disturbed carbohydrate metabolism.—T. C. B.

Remarks on the extirpation of an ADRENAL for epilepsy (Bemerkungen zu der Extirpation der Nebenniere zur Behandlung von Krämpfen). Cordua (E.), Zentralbl. f. Chir. (Leipzig), 1921, **48**, 116-167.

Brunings has operated on some cases of epilepsy and removed one adrenal. Cordua does not believe that these cases prove much as the results were published only 5 months after the operation. Probably the loss of blood may temporarily have a good influence on the spasm. This the author proves by citing a case in which, during a brain operation, much blood was lost and the same temporary effect was observed.—J. K.

Sudden death and total caseous tuberculosis of the two ADRENAL capsules (Mort subite et tuberculose caséeuse totale des deux capsules surrénales). Creyx & Ragot, Compt. rend. Soc. de biol (Paris), 1921, **84**, 127-128.

A description of two cases of sudden death in which autopsy showed the suprarenals to be nothing but blocks of caseous material, without a trace of normal tissue. There were no premonitory symptoms, and the authors point out the fact that sudden death may occasionally be the first sign of adrenal insufficiency.—T. C. B.

(ADRENAL, BLOOD SUGAR) Fetter hyperglycemia and glycosuria of rabbits (Über Fesselungshyperglykämie und Glykosurie beim Kaninchen). Fujii (I.), Tokohu J. Exper. Med. (Sendai), 1921, **2**, 9-64.

Boehm and Hoffman reported in 1878 that fettering a cat to an operating board would suffice to cause glycosuria. Cannon, Shohl and Wright in 1911 observed that such glycosuria resulted only in animals that were emotionally disturbed. Fujii of the Tohoku University has subjected the problem anew to extensive study. Male rabbits served as experimental animals. It was found that fettering for several hours resulted in a marked rise in the blood sugar, as well as a slight fall in body temperature and some depletion of the chromaphil material in the suprarenals. Fettering for a few minutes to an hour evoked a less extensive though positive reaction

When the animal's body temperature was prevented from falling the reaction was much diminished. Cutting the splanchnic nerves on both sides lessened the degree of blood-sugar reaction and prevented the suprarenal depletion. For numerous details the original should be consulted.—R. G. H.

(ADRENALS) Hypernephroma (Zur Hypernephromfrage). Gagstatter (K.), Wien. klin. Wchnschr., 1921, **34**, 225-226.

Of no endocrine interest.—J. K.

The vasomotor action of the SYMPATHETIC fibers on the ADRENAL gland (L'action vasomotrice du sympathique sur la glande surrénale). Hallion (L.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 515-517.

According to Biedl, stimulation of the peripheral end of the splanchnic nerve causes vasodilation in the adrenals. The author has found vasoconstriction as a result of the same stimulation. He has, therefore, repeated the experiments with his plethysmograph, and demonstrates that the sympathetic supply to the adrenals is undoubtedly a vasoconstrictor. It is doubtful if there are vasodilators. When vasodilation occurs it is probably passive. The results are discussed at some length.—T. C. B.

The principles of ADRENAL support. Harrower (H. R.), Med. Record (N. Y.), 1920, **98**, 391-392.

The (hypothetical) functions of the adrenal glands in regulating the tonicity of unstriped muscle, and in responding to toxic substances are briefly described, and the clinical picture of so-called hypoadrenia is outlined. The author believes most cases of neurasthenia to be the result of adrenal insufficiency. Emotional shocks are said to deplete the adrenals. Fatigue, asthenia, lack of energy and ambition are pictured as characteristic of hypoadrenia. Low blood pressure is usually noted. Most tonics containing strychnine are contraindicated in this condition, according to the author, because they stimulate the adrenals to increased function when they are already worn out. Hypoadrenia should be treated by administration of adrenal preparations, together with some thyroid, which helps to stimulate cellular activity, and spermin the assumed endocrine principle from the interstitial cells of Leydig.—H. L.

(ADRENALS) Epithelial pigmentation and its relation to Addison's disease (Ueber das Hautpigment und seine Beziehung zur Addisonschen Krankheit). Heudorfer (K.), München. med. Wchnschr., 1921, **68**, 266-267.

Meirowsky discovered that when small pieces of skin are kept during some days at 55° they become rich in pigment. Heudorfer

found that this is more intense in pieces of skin which normally contain much pigment. The same result is obtained after boiling, so it is not caused by some ferment-action, but is probably due to chemical changes (perhaps oxidation) of colorless products, formed by the skin. Bloch has stated that pigment is formed by the action of enzymes on some organic substances. He observed that when dioxyphenylanalin was added to a section of skin the epithelial cells became grey or black. The more pigment the cells contained the more intense was the reaction (Dopa reaktion of Bloch). This, too, has been confirmed by Heudorfer, but when the skin was boiled for two hours the reaction was just as clear as in the fresh skin. From this it may be concluded that ferments do not play a part in the reaction. The same effect as with the dopa reaction was obtained when nitrate of silver was added. Why is the quantity of pigment increased in Addison's disease? Heudorfer considers the skin as a gland with an internal secretion. Extracts of skin dilate the pupil, so they stimulate the sympathetic. The pigment when isolated as pure as possible contracts blood vessels. So the skin has a similar relation to the sympathetic as the adrenals. The author believes that when the function of the adrenals is lowered the low blood pressure causes an increased functioning of the skin. This increase in function is the cause of the formation of pigment.—J. K.

(ADRENAL) The effect of certain dietary deficiencies on the suprarenal glands. Kellaway (C. H.), Proc. Roy. Soc. (London), 1921, **B. 92,** 6-27.

McCarrison's observations (see Endocrinol., 1920, **4,** 641, and abstract elsewhere in this issue) on the occurrence of enlargement of the adrenals with increased store of adrenalin in pigeons fed on polished rice, are confirmed. It is further shown that these changes still occur when either protein or fat is added to the diet, but are prevented by the addition of an adequate ration of yeast extract. The addition of such a ration of yeast extract to a basic diet of polished rice with extra fat or protein does not prevent the increase in the store of adrenalin, though in this case the glands are not enlarged. It is suggested that the enlargement of the adrenals is due partly to congestion and oedema of the gland tissues and partly to the storage in the cortex of the gland, of lipoids set free by the breaking down of body tissues. The investigation of the cholesterol content of the adrenals of normal and polyneuritic pigeons does not support this theory of lipoid storage, though a well-marked hypercholesteraemia occurs in the latter. The artificial production of hypercholesteraemia in rabbits and pigeons by feeding with cholesterol appears to be associated with a small increase in the adrenalin-content of the suprarenals. The increased content of adrenalin in the suprarenals of birds on deficient diets is attributed to diminished output of adrenalin as a result of lowered body metabolism. The

oedema which occurs in some cases of experimental polyneuritis is not due to increased output of adrenalin, since the daily administration of adrenalin to birds fed on normal or polished rice does not cause oedema, nor does it accelerate or retard the onset of polyneuritis in pigeons on a polished rice diet.—L. G. K.

Sensibility to toxic substance of rats deprived of ADRENALS (Sensibilité des rats privés de surrénales envers les toxiques). Lewis (J. T.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 163-164.

White rats with both suprarenals removed were given doses of various toxic substances, such as cobra venom, curare, veratrine, morphine, etc. In all cases the rats died from smaller doses than did the controls. This may be due to the fact that the adrenals normally neutralize these substances, or that the decapsulated animals undergo some modification of metabolism by which the cells are sensitized—possibly a disturbance of lipoid equilibrium.—T. C. B.

(ADRENAL) The genesis of oedema in beriberi. McCarrison (R.), Proc. Roy. Soc. (London), 1920, **B. 91**, 103-110.

In a series of cases of avian beriberi (polyneuritis gallinarum) oedema was found to be associated with massive enlargement of the adrenal glands. Of pigeons having massive enlargement of the adrenals, 83.3 per cent. had oedema in some form. The enlargement of the adrenal glands was a true hypertrophy in so far as the medulla was concerned; no conclusions were drawn with regard to the cortex. The adrenalin content of the hypertrophied adrenals, as estimated by the chemical method of Folin, Cannon and Dennis, was slightly less per gram of gland in cases of wet beriberi than in health or in dry beriberi. Nevertheless, in 100 per cent. of the cases of wet beriberi the quantity of adrenalin greatly exceeded that found in health; in 83 per cent of the cases it was also in excess of that found in dry beriberi. The conclusion is drawn that "whatever the function of the adrenal medulla may be, the excessive production of adrenalin under conditions of 'vitaminic' deficiency is concerned with the causation of the oedema found in this order of cases. It must, therefore, be taken into consideration as a possible factor in the causation of oedema in general." (See also Endocrinol., 1920, **4**, 641).—L. G. K.

The muscles of the human ADRENAL veins and their importance for its function (Die Venenmuskulatur der menschlichen Nebennieren und ihre funktionelle Bedeutung). Maresch (R.), Wien. klin. Wchnschr., 1921, **34**, 44-46; München. med. Wchnschr., 1921, **68**, 193.

In the vena suprarenalis there exist longitudinal muscle columns which follow the ramifications of this vein. In the newly born child

they are absent. Circular muscle-fibers are always absent, even in adults. When these fibers contract the lumen of the vessel becomes narrower. Therefore, the author suggests that when via the splanchnicus these muscles contract, the blood stagnates in the gland and has a more intense contact with the endocrine cells. Another thing is possible: when all these muscles in the veins are contracted the organ becomes smaller and the products of the endocrine function would be forced into the blood. The author tried to prove that this contraction really exists. In using an oncometer he proved this for the adrenals of the guinea pig.—J. K.

The relation between the "Hungerblockade" and ADRENAL function Ueber die Beziehungen der Hungerblockade zur Funktion der Nebennieren). Peiser (B.), München. med. Wchnschr., 1921, **68,** 521.

The author determined the adrenalin content of the adrenals after autopsy and found that the adrenalin content is now much lower than before the war. This is also of importance for the treatment of underfeeding.—J. K.

(ADRENALS) The SUPRARENAL apparatus of Teleosts (Sur l'appareil surrénal des Téléostéens). Ramalho (A.), Compt. rend. Soc. de biol. (Paris), 1921, **84,** 589-591.

Histological.—T. C. B.

(ADRENALS) Spasms and blood picture (Krämpfe und Blutbild). Schaps, Deutsche med. Wchnschr. (Berlin), 1921, **47,** 472.

Schlund has stated that spasms may produce a temporary exhaustion of the **chromaffin system.** So they must have the same influence as the removal of an **adrenal.** This theory is false. Only after an attack of epilepsy symptoms may be seen as observed after removing an adrenal. After the epileptic fit or removal of adrenal the number of lymphocytes may go down. But other spasms (as chorea minor or "tic convulsif") may produce an increased number of lymphocytes. Schlund also states that the blood picture after removal of one adrenal is just the opposite of the blood picture after injection of adrenalin and he believes that after removing an adrenal a hypofunction of the chromaffin system occurs. This is, according to Schaps, a much too mechanical theory. We know too little of the extremely complicated relations between adrenals, chromaffin system and other organs and the blood picture to draw such simple conclusions from two cases, that have even not been properly studied. —J. K.

The action of drugs upon the output of epinephrin from the ADRENALS. VII. Physostigmine. Stewart (G. N.) & Rogoff (J. M.). J. Pharmacol. & Exper. Therap. (Balt.), 1921, **17,** 227-248.

Using the cava pocket method, blood was collected and assayed on rabbit intestine. The intravenous or subcutaneous administration of physostigmine increased the output of epinephrin to 10-15 times the initial output. The stage of augmentation is prolonged and is preceded by a transient diminution. Section of the splanchnic and other nerves to the adrenals appeared to abolish the physostigmine effect.—F. A. H.

The epinephrin output estimated by collecting the ADRENAL blood without opening the abdomen. Stewart (G. N.) & Rogoff (J. M.), Am. J. Physiol. (Balt.), 1921, **56**, 213-219.

The rate of epinephrin output is approximately the same whether it is estimated on adrenal vein blood collected without opening the abdomen or after opening the abdomen.—T. C. B.

Post-operative depletion of the epinephrin store of the ADRENALS. Stewart (G. N.) & Rogoff (J. M.), Am. J. Physiol. (Balt.), 1921, **56**, 220-229.

"The question of the relative importance of the anesthetic and the trauma in causing post-operative depletion of the epinephrin store of the adrenals, was tested (in rabbits) by removing one adrenal under local anesthesia, and 5 to 7 hours later, killing the animal and removing the other adrenal. In 12 out of 15 rabbits no evidence of depletion was found." In the remaining three there was a moderate depletion of the second adrenal. In 25 rabbits which had been previously thyro-parathyroidectomized, 19 showed no depletion; 9 showed undoubted depletion of the adrenal last removed. —T. C. B.

ADRENAL hemorrhage in new born (Delle emoraggie surrenali nel neonato). Tronconi (S.), Pediatria (Napoli), 1921, **29**, 266-274.

After referring to infections and dystocia as determining causes of hemorrhage of the adrenals, Tronconi reports from the Pediatric Clinic of milan a case in a girl, four days old. She was born with intense icterus and very poorly developed. Delivery was effected in the beginning of the ninth month, owing to marginal placenta praevia. One hour after delivery the mother died of what the author calls "latent hemophilia." The infant died on the fourth day and autopsy revealed a right adrenal as large as a hen's egg, adherent to the kidney, the diaphragm and the head of pancreas; the gland was transformed into a mere hemorrhagic pocket. The left adrenal was the size of a pigeon's egg. It was adherent to kidney, diaphragm, tail of the pancreas and spleen. It was very much congested, soft and friable, with a pocket of blood, and still retaining a thin stratum of cortex. Version, which was done, is easy in a pluripara, hence cannot account for the hemorrhage. There would be more danger from the artificial respiration (Schultze's method)

which was instituted. The author suggests hemophilia as, on the whole, the most probable cause of the adrenal condition.—G. V.

(ADRENALS) The nervous regulation of purine metabolism (Die nervöse Beeinflussung des Purinstoffwechsels). Ullmann (H.) Deutsche med. Wchnschr. (Berlin), 1921, **47**, 578.

The author tried to determine if the excretion of uric acid after "piqure" or stimulation of the central nervous system with caffein goes via the splanchnic and adrenals as in the "piqure de Barnard" for glucosuria. The increased excretion in the rabbit of allantoin after injection of caffein does not take place after section of the splanchnics, so it is probable that in the reaction the splanchnic and the adrenals are of importance.—J. K.

Changes in the ADRENAL bodies and the THYROID resulting from inanition. Vincent (S.) & Hollenberg (M. S.), J. Physiol. (Lond.), 1921, **54**, lxix-lxxi.

The authors reported previously (see Endocrin., 1920, **4**, 408), that in the early stages of inanition there was an increase of adrenin in the adrenals, while later the amount was greatly reduced. They now confirm these results by chemical determination of the amount of adrenin by the method of Folin, Cannon and Denis. The thyroids, as well as the adrenals, hypertrophy during inanition, but the colloid substance is almost entirely lacking.—T. C. B.

The technic of the removal of an ADRENAL in spasms (Zur Technik der Exstirpation der Nebenniere bei Krämpfen). Vorschütz. Zentralbl. f. Chir. (Leipzig), 1921, **48**, 370-372.

Of technical surgical interest.—J. K.

Notes on ADRENAL action. Ward (E. H. P.), Med. Record (N. Y.), 1920, **98**, 845-851.

Speculative endocrinology.

Inverse ADRENIN action (Über inverse Adrenalinwirkung). Amsler (C.), Arch. f. d. ges. Physiol. (Bonn), 1920, **185**, 86-92.

Nicotine and ergotamine in large doses paralyze the end-apparatus of the sympathetic in the frog's heart. After their action on the ventricle, adrenaline acts in an inverse manner, producing either diastolic standstill or negative ino-and chrono-tropy.—A. T. C.

Studies on the changes in fluid volume under ADRENALIN, PITUITRIN, pilocarpine and atrophine. Becht (F. C.), Am. J. Physiol. (Balt.), 1921, **55**, 277.

By connecting the subdural space through a needle with a Mariotte bottle, the volume of fluid displaced by the action of drugs

can be accurately measured. The conclusion was reached that the movement of fluid was due entirely to alteration in blood volume within the skull.—T. C. B.

The effect of the simultaneous administration of ADRENALIN and glucose (Ueber die Wirksamkeit peroraler Adrenalinanwendung bei gleichzeitiger Zufuhr von Traubenzucker). Beumer (H.), Berl. klin. Wchnschr., 1921, **58**, 206-207.

Beumer administered adrenalin by mouth when glucose was given at the same time, and studied the effect on the amount of blood sugar. No change could be detected in the normal course. —J. K.

Have injections of ADRENALIN an influence on the formation of antibodies (Hat Einspritzung von Adrenalin einen Einfluz auf die Fähigkeit zur Antikörperbildung)? Bijlsma (U. G.), Centralbl. f. Bakt. (Jena), 1921, **86**, 246-247.

Borchart (Endocrinology, 1920, **4**, 455, and 1921, **5**, 253) has stated that injection of adrenalin in man increased the formation of agglutinins after anti-thyroid vaccination. Bijlsma has tried to do the same in rabbits, but came to the conclusion that neither injection of adrenalin, nor removal of one adrenal had the slightest influence on the formation of agglutinins.—J. K.

On the action of ADRENALIN injections (Über die Wirkungsweise der probatorischen Adrenalininjektion). Billigheimer (E.), Deutsches Arch. f. klin. Med. (Leipzig), 1921, **136**, 1-32.

After injection of adrenalin the protein content of the serum quickly rises, but is normal again or even lower one hour after the injection. In rare cases immediately after the injection the protein content sinks. This may be explained by retrograde filtration of fluids from the tissues into the capillaries caused by a decreasing pressure in the dilated vessels or perhaps it is due to a change in the permeability of the vessels. The hyperglycemia after injection of adrenalin has nothing to do with the changes of concentration of the blood. It is caused by irritation of the sympathic fibers of the liver. The irritability may be diminished (low glycemia, gradually setting in and passing away), or normal (maximum glycemia+ ½ hour after the injection and lasting during+1 hour. In osteomalacia the irritability is increased, in Addison's disease or sclerodermia diminished. Pilocarpin increases the irritability, atropin diminishes it. The injection of adrenalin may, however, not be used for the functional diagnosis of the sympathic system, for its effect depends also on other facts (irritability of the kidney, quantity of glycogen in the liver, etc.). The most constant change after injection of adrenalin is the change in blood picture (absolute and relative leucocytosis, first increase in lymphocytes, then an increased

number of polynuclear cells with decrease in the eosinophil cells). It probably acts on the blood-forming organs also. How otherwise can be explained the diminished number of red corpuscles after injection of adrenalin while the concentration of the blood is high. There exists three types of angioneural influence of adrenalin: I. Sympathic form; rapid rise and slow fall of the systolic pressure and rise of the diastolic pressure. This is often accompanied by a diminished pulse rate (stimulation of vagus). II. Parasympathetic form: Systolic and diastolic blood pressure both fall; no influence on the pulse. III. Mixed forms: The tracing of the blood pressure depends on the irritability of the vasomotor nerves and on the local conditions of the heart and vessels.—J. K.

Reversal of the depressor action of small doses of ADRENALIN. Collip (J. B.), Am. J. Physiol. (Balt.), 1921, **55**, 450-454.

The depressor effect of small doses of adrenalin may be converted into a pressor effect by increasing the depth of the anesthesia, and vise versa. Decreasing the H-ion concentration of the blood by sodium bicarbonate will convert a depressor effect into a pressor effect. The same procedure will increase the pressor effects of moderate doses of adrenalin, while raising the p. H. of the blood will lessen the pressor effects of moderate doses.—T. C. B.

(ADRENIN) On the presence of vasoconstrictor substances in the blood of ricket (Sulla presenza di sostanze vasocostrittrici nel sangue dei rachitici). Cozzolino (O.), Pediatria (Napoli), 1921, **29**, 1-11.

Blood from two normal and fifteen rachitic patients was tested by the frog preparation method, in an attempt to demonstrate the presence or absence of adrenin or other vasoconstrictor substance. Results were negative and are reported as indicating "the uselessness of trying to reach valuable conclusions either in favor of, or opposed to adrenal or other endocrin pathogeny of rickets."—G. V.

The influence of papaverin on the increase of blood pressure by ADRENALIN in man (Die Wirkung des Papaverins auf die Adrenalinblutdrucksteigerung beim Menschen). Csépai (K.), Wien. klin. Wchnschr., 1921, **34**, 186.

Pal has stated that papaverin inactivates the influence of adrenalin on blood pressure. This is true in the dog, but not in man. In man papaverin increases the rise in blood pressure, when it is already raised by adrenalin.—J. K.

The influence of ADRENALIN on the blood (L'azione dell' adrenalina sul Sangue). Dazzi (A.), Il Morgagni (Milano), 1921, **64**, 93-112.

The injection of 1 milligram of adrenaline in man is always followed by an increase in the number of red corpuscles and of leu-

cocytes. This augmentation is not very important and is transitory for the red corpuscles. In the white corpuscles, first the lymphocytes increase in number, then the polynuclear neutrophils increase, while the lymphocytes have reached their normal number again. The lymphocytosis is due to the action of adrenalin on the **spleen**, by stimulating the muscle fibers to contract. The increase in number of polynuclear cells is due to the action of adrenalin on the blood vessel coming from the bone-marrow.—J. K.

(ADRENIN) The role of acids in carbohydrate metabolism. IV. The relation of acids and alkalies to adrenalin glycosuria (Ueber Rolle der Säure im Kohlenhydratstoffwechsel. IV. Mitt. Die Bezeihung von Säure und Alkali zur Adrenalinglykosurie). Elias (H.) & Sammartino (U.), Biochem. Ztschr. (Berl.), 1921, **117**, 10-40.

Acid glycosuria differs from that produced by puncture or adrenalin in that it causes no increase in volume of the liver. Subcutaneous adrenalin injection produces a marked acidosis in rabbits and a 3-fold increase in the lactic acid content of the liver. This increase in lactic acid production begins within the first hour after the adrenalin injection and lasts for at least 3.5 hrs. Further perfusion experiments on livers of cold blooded animals showed that the sugar mobilization effect of adrenaline is inhibited by alkali. This inhibition can be removed if the alkali is neutralized by acid. It is, therefore, concluded that the acid produced by the injection of adrenaline is an important factor in the origin of the subsequent glycosuria.—F. S. H.

Researches on the reaction of human heart to ADRENIN (Ricerche sulla reazione del cuore umano all'adrenalina). Fulchero (A.), Riforma med. (Napoli), 1920, **36**, 1147-1150.

Fulchero, at the University of Torino, carried out an experimental study on 59 human subjects. His results indicate that contrary the affirmation of Roth, epinephrin injections (1.0-1.5 mgm.) cannot be regarded as always affording evidence of cardiac lesions. The epinephrin test of the functional condition of the heart may bring out different reactions according to the condition of the endocrine system of each patient. The test might be valuable as an index of myocardial tonicity; i. e., an accentuated hypertension without extrasystoles would indicate right myocardial involvement only; a moderately increased pressure with extrasystoles would indicate involvement of the left myocardium. Due allowance should be made for increased excitability. Increased excitability and diminished tonicity of the myocardium are best shown by adrenalin injections. This condition is especially found in severe myocarditis, in cardiosclerosis and very often in pernicious anemia. In this latter

condition the adrenalin test is recommended as affording a valuable auxiliary sign.—G. V.

Hypertension produced by isotonic solutions following injection of ADRENIN (Sur l'hypertension produite par les solutions isotoniques a la suite d'une injection d'adrénaline). Garnier (M.) & Schulmann (E.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1619-1621.

If a rabbit is given an injection of an active dose of adrenalin there is a rise of blood pressure which is transitory; it returns to normal in about two minutes and a half. But the animal remains under the influence of the adrenalin, for the injection of 1 to 2 cc. of physiological saline solution will cause a second rise of pressure that may be as marked as the first. The duration and degree of hypertension depends upon the time which elapses between the injection of adrenalin and the injection of saline. For instance, if seven minutes elapse, the saline causes but a feeble hypertension. —T. C. B.

(ADRENIN) V. Further studies on the antagonistic action of epinephrin to certain drugs upon the tonus and tonus waves in the terrapin auricles. Gruber (Chas. M.), J. Pharmacol. & Exper. Therap. (Balt.), 1921, **16**, 405-413.

The increased tonus produced by nicotine is decreased by strong solutions of adrenalin chloride. Likewise the increased tonus and tonus waves produced by digitalis are reduced by adrenalin. Adrenalin acts similarly toward the tonus waves set up by barium chloride, except to a lesser extent.—F. A. H.

The influence of ADRENIN on gastric secretion (Der Einfluss des Adrenalins auf die Sekretion des Magensaftes). Hess (W. R.) & Gundlach (R.), Arch. f. d. ges. Physiol. (Bonn), 1920, **185**, 122-136.

Adrenaline inhibits gastric secretion (dogs) at whatever phase of secretory activity it be injected, and whether injected intramuscularly or intravenously. The intensity of action is independent of the amount injected. The effect lasts at least 15 minutes (intravenous injection) and at most 200 minutes (intramuscular injection). Usually both total quantity and concentration are decreased. These results do not agree with Yukawa's. The cause is not psychic. The results suggest that the (thoracic) autonomic nervous system has a marked effect on the activity of the gastric glands, antagonistic to the chief factor in vagus action, and also that the secretory and motor functions of the stomach are associated in like sense, and their regulation is associated with physiological additions of adrenaline to the blood.—A. T. C.

On the diminished permeability for sugar of the kidney in experimental ADRENALIN diabetes (Ueber die sogenannte Nierendichtung gegen Zucker beim experimentelle Adrenalindiabetes). Hildebrand, Berl. klin. Wchnschr., 1921, **58**, 422.

Data reported elsewhere.—J. K.

The action of ADRENALIN on striated muscles (Ueber die Wirkung des Adrenalin auf die Skelettmuskulatur). Lange (H.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 578.

Adrenalin diminishes the permeability of the sarcolemma and changes the irritability of the muscle. Only a small note without details.—J. K.

The change of blood pressure after injection of ADRENALIN as a method of determining the tonus of the vegetative nervous system Die Blutdruckverändrung nach Adrenalininjektionen als Gradmesser für den Tonus im autonomen und sympathischen Nervensystem). Lehmann (G.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 41-42.

Dresel has published a method for the easy diagnosis of vagotonia or sympathicotonia. He injects 1 cc. of adrenalin solution and measures the blood pressure. In healthy individuals the line of blood pressure has a parabolic form, in vagotonia S-shaped, in sympathicotonia the blood pressure rapidly increases and rapidly falls to the norm given. Lehmann controlled this method and compared it with the result of pharmacological tests and with the reflexes of Czermst and Aschner (influence of pressure on vagus or on the eyes upon the heart). The results of these tests are nearly never the same and the author believes that Dresel's method has no clinical value. The tracings of the blood pressure as they are given by Dresel are extremely rare.—J. K.

(ADRENIN) On the duration of constriction of blood vessels by epinephrin. Meltzer (S. J.) & Auer (John), J. Pharmacol. & Exper. Therap. (Balt.), 1921, **17**, 177-196.

The effect of epinephrin on the vessels of the ear was studied by ocular examination. A subcutaneous injection of epinephrin into the ear of rabbits causes a constriction of all the vessels of that ear. Smaller doses (1 cc., 1:100,000) affected the arterioles more, causing but a moderate constriction of the central artery; with larger amounts (0.3 cc. to 1.0 cc., 1:1,000) the central artery was greatly constricted and the veins decreased in size. The constriction endured for three to eight hours. The latent period of the constriction is shorter the nearer the site of injection to the central artery. In subcutaneous injections the epinephrin apparently reaches the muscular sheath through the adventitia and not through the intima

from the lumen of the vessel. Constricted vessels tend to become dilated when constriction passes off. Simultaneously with the constriction in the injected ear there appears to be a transient dilatation of the vessels in the opposite ear.—F. A. H.

The action of ADRENIN on protein stored in the liver (Die Wirkung des Adrenalins auf das in der Leber gespeicherte Eiweiss). Stübel (H.), Arch. f. d. ges. Physiol. (Bonn), 1920, **185**, 74-85.

Stübel of Jena reports the results of an investigation of the effects of adrenin in the liver. It was found that injections of this drug result in the disappearance of the microscopically visible protein stored in the liver.—A. T. C.

(ADRENIN) Epinephrin hyperglycemia. Tatum (A. L.), J. Pharmocal. & Exper. Therap. (Balt.), 1921, **17**, 336-337.

It was found that phloridzin sufficient to produce hypoglycemia produces a fall in alkaline reserve capacity of whole blood. Epinephrin injected subcutaneously in conditions of low reserve from "phloridzin acidosis" causes a rise in blood sugar without further fall in alkaline reserve capacity of blood. Hydrochloric acid by stomach produces a marked fall in reserve capacity with but little change in sugar. Epinephrin injected under these conditions produces the usual amount of glycogenolysis with no further significant change in alkaline reserve capacity. For a given fall in reserve by hydrochloric acid by stomach and by epinephrin subcutaneously injected, the resultant glycogenolysis from epinephrin is so very much greater than that produced by hydrochloric acid as to be essentially incomparable. Previous induction of acidosis by hydrochloric acid does not considerably increase or decrease the efficacy of epinephrin as a glycogenolytic agent. There appears to be no demonstrable evidence of any interdependence between epinephrin glycogenolysis, as judged by hyperglycemia, and the fall of alkaline reserve capacity as usually found to occur after subcutaneous injections of epinephrin in normal animals. Glycogenolysis and acid production appear to be merely concomitant and independent phenomena following epinephrin injections.—F. A. H.

The influence of injections of ADRENALIN on the white cell count (Die Veränderungen des weissen Blutbilden nach Adrenalininjektionen). Walterhöfer (G.), Deutsche Arch. klin. Med. (Leipzig), 1921, **135**, 208-223.

Subcutaneous or intravenous injection of adrenin always causes a leucocytosis. This increase begins quickly after the injection and is transitory. Neutrophil cells as well as lymphocytes are increased. The lymphocytosis passes quicker than the neutrophil leucocytosis; the so-called "biphasical-blood picture" is not often observed. The intensity of lymphocytosis is independent of histological changes in

the organs. It has been said that the lymphocytosis is due to contraction of the spleen, but this is not proven. The contraction of the spleen does not go parallel with the number of lymphocytes. The leucocytosis after injection of adrenalin is not due to an unequal division of the cells in the body, but to an actual increase in number. —J. K.

[Blood sugar in ether narcosis]. Böggild (D. H.), Ugesk. f. Laeger. (Copenhagen), 1920, **82**, 1365.

Böggild determined the glucose content of the blood in 38 cases of ether narcosis, using the Hagedorn-Jensen method. Hyperglycemia was constantly found and is considered a typical phenomenon. This hyperglycemia should not be considered as a result of diminished oxydation of the organism as former authors have regarded it; the long duration of the hyperglycemia indicates a certain resemblance between the conditions of narcosis and those of diabetes mellitus.—K. H. K.

(CAROTID BODY) A case of perithelioma of the ganglion intercaroticum. Thomson (J. Oscar), China M. J. (Shanghai), 1920, **34**, 32-33.

The tumor "1½ by 1 inch in diameter was a chronic, circumscribed, primary perithelial neoplasm" and on its removal, the patient made an uneventful recovery. The literature is briefly discussed.—E. V. C.

(CORPUS LUTEUM) The ovarian cycle of swine. Corner (G. W.), Science (Garrison, N. Y.), 1921, n. s. **53**, 420-421.

The author studied 22 sows covering practically every day of the 21-day cycle. It was found that one or two days before the onset of the oestrous some of the follicles enlarge from one and one-half to twice the diameter of the reserve follicles. Ovulation occurs on the second of the three days of oestrous. The corpora lutea reach full histological complexity about the seventh day. They remain in a state of full development until the fourteenth or fifteenth day after discharge of follicles, when they begin to disintegrate. By the time of the next ovulation they have diminished to a little more than their original size. During the second interoestral interval they shrink further so that they are not readily distinguishable. That the corpus luteum persists until the fourteenth to fifteenth day harmonizes with the hypothesis that it aids in the fixation of the ova for the embryos gain attachment from the tenth to fifteenth day after ovulation.—F. A. H.

The CORPUS LUTEUM of pregnancy. Is it a cholesterol-forming organ? (Le corps jaune de la grossesse. Est elle une organe

cholestérinigénique)? Gross (A.), Gynec. et Obst. (Paris), 1921, **3**, 73-80.

A critical review of the literature and ideas concerning the origin and function of cholesterol in the organism, the result of which leads Gross to the opinion that the hypercholesterinemia of pregnancy is not connected with any alleged cholesterol forming power of the corpus luteum.—F. S. H.

The influence of the lipoids of the CORPUS LUTEUM and PLACENTA on bleeding, menstrual cycle and other phenomena (Der Einfluss eines Corpus luteum resp. Plazentar lipoids auf Blutungen, menstruellen Zyklus und Ausfallserchеinungen). Herrmann E.), Monatschr. f. Gebs. u. Gynäk. (Berl.), 1921, **54**, 152-164.

Clinical studies of the effects of the injection of lipoid material from corpus luteum and placenta on menstruation, etc. Seventy-three cases in all were studied, divided into the 6 groups: pollakomenorrhagia (8 cases), menorrhagia (15 cases), metrorrhagia with inflammation (16 cases), metrorrhagia with normal genitalia (15 cases), juvenile metrorrhagia (5 cases), climacteric metrorrhagia (4 cases), others (24 cases). In 60% of the cases and 6 to 8 months after cessation of treatment, all the cases that were observed showed an altered menstruation cycle, which lasted for several months. Moreover, the excessive bleeding was controlled in 83% of the cases after 5 to 9 injections of the lipoid. The cases of menorrhagia and metrorrhagia with normal genitalia reacted best. Climacteric disturbances were temporarily improved, but not permanently.

—F. S. H.

The CORPUS LUTEUM of menstruation and pregnancy. A review of a monograph by John C. Dalton, Jr., M. D. Morley (W. H.), N. York M. J. (New York), 1921, **113**, 230-232.

Review of a paper by Dalton which appeared in the transactions of the American Medical Association, 1851, volume IV

—H. W.

(DIABETES) Physiology and pathology of carbohydrate metabolism (Zur Physiologie und Pathologie des Kohlenhydratstoffwechsels). Arnoldi, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

By estimation of blood sugar and gas analysis it is possible to prove that the administration of glucose, injections of suprarenin, psychic excitement, CO_2 baths, have all a marked influence on metabolism, but not the same in the healthy persons as in persons with diabetes. (No details given).—J. K.

Experimental facts on "working" treatment of DIABETES (Experimentellen Grundlagen einer Arbeitstherapie der Diabetes). Bürger, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 611.

Blood-sugar falls during work and for some time after. In artificially increased blood-sugar less is excreted during work than during rest. When sugar is given the respiratory quotient rises less during work than when the patient rests. Work tends to diminish the glucosuria but to increase the glycemia.—J. K.

Sudden death in DIABETES without coma (Plotzlicher Tod bei Diabetes ohne Koma). Denecke (G.), München. med. Wchnschr., 1921, **68**, 398-399.

A patient with serious diabetes died in 5 days without "Kussmaul-respiration" or acetone or diacetic acid in the urine. Probably the cause of death was situated in the heart. No post-mortem is reported.—J. K.

The changes in the brain in DIABETES and the pathophysiology of sugar regulation (Die zerebralen Veränderungen beim Diabetes mellitus und die Pathophysiologie der Zuckerregulation). Dresel (K.) & Lewy (F. H.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

The brains were examined in 4 patients who had died in coma diabeticum. In all cases pathological changes were found in the globus pallidus; the nucleus periventricularis was normal. The authors believe that the relative amount of blood sugar is regulated on the nucleus periventricularis, the absolute amount is regulated in the globus pallidus.—J. K.

(DIABETES) Hyperglycemia and glucosuria (Zur Hyperglykämie und Glykosurie). Eisner (G.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

An increase of carbohydrates in the diet produces a temporary rise of blood sugar. This rise is specially marked in patients with sympathicotonia or with increased function of the **chromaffin system. Hypophysin** diminishes **adrenalin** hyperglycemia as well as the alimentary form. Therefore, it is possible that the alimentary hyperglycemia is due to glycogen-mobilization in the liver via the sympathetic and chromaffin system. If this is true there does not exist a real difference between adrenalin and alimentary hyperglycemia. —J. K.

DIABETES. Elias, Wien. klin. Wchnschr., 1921, **34**, 190.

By intravenous injection of solutions of Na_2HPO_4 or NaH_2PO_4 it is possible to decrease the blood sugar in diabetes or in alimentary glucosuria. These injections have no influence on the normal blood sugar. In one case of very serious diabetes with acidosis and lipemia no influence on the blood sugar was seen. Injection of other salts tend to increase the blood sugar.—J. K.

DIABETES of bearded women (Le diabetes des femmes a barbe). Emile-Weil (P.) & Plichet, Compt. rend Soc. de biol. (Paris), 1921, **84**, 13-15.

Description of a woman who, at the age of twenty-six, developed a facial hypertrichosis, and at thirty-one, diabetes. Autopsy showed total sclerosis of the ovaries. No microscopic lesions of the suprarenals nor of other blood vascular glands were found. Two other reported cases are given and discussed from the viewpoint of the interfunctional relation of the endocrine glands.—T. C. B.

(DIABETES) Studies on the threshold for GLYCOSURIA. Faber (K.) & Norgaard (A.), Acta med. scand. (Stockholm), 1921, **54**, 289-322.

There are described two cases of chronic glycosuria, persisting all through the twenty-four hours even though the blood sugar volume did not exceed the normal. After the ingestion of carbohydrates the blood sugar percentage rose in the normal way and glycosuria increased. By five days fasting the blood sugar value in the first patient might be forced down to 0.06%, the glycosuria being then kept at 1.5%, whereas at an ordinary diet rich in carbohydrates it was 5-6%. The persistent, and in the one case, considerable, glycosuria caused no morbid symptoms, the patient feeling perfectly well on ordinary diet. In both cases the glycosuria was shown to have been present during many years. In one case similar relations were found in a brother. The cases are most readily explained by assuming an individual low renal threshold for glycosuria. Under the term of cyclic glycosuria are described cases of glycosuria in which the urine is regularly sugar-free in the morning, but contains sugar in the course of the day after the ingestion of meals rich in carbohydrates. In certain cases such cyclic glycosuria appears without the blood sugar value exceeding the normal level. These cases are termed cyclic glycosuria of the renal type. Such a new case is described, in which glycosuria appeared even though the sugar value did not exceed 0.102%. In 32 diabetics the renal threshold for glycosuria has been determined at the point of time when the patient's glycosuria is about to cease consequent on a fasting treatment. The threshold values varied between 0.08 and 0.19%. In 16 of these patients the threshold level was determined several times (up to four times) in the same patient under identical conditions; that is to say, during fasting. The threshold in these cases was found to lie at the same level. The longest interval between the determinations was 20 months. There are thus great individual variations for the threshold level in diabetes.—J. A. H.

DIABETES (Die Mehlfrüchtekur). Falta, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 609.

See Endocrinol., 1921, **5**, 233.—J. K.

Renal DIABETES (Ueber Nierendiabetes). Frank (E.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

The cause of renal diabetes is unknown. It is not true, as often stated, that the quantity of sugar excreted is perfectly independent of the quantity that is ingested. The glucosuria in pregnancy is a form of renal diabetes. The prognosis is good. For the diagnosis, determination of the blood-sugar is necessary.—J. K.

Trauma and DIABETES (Trauma en diabetes). van Gelderen (D. N.), Geneesk. Tijdschr. Ryksverzekeringsbank (Amst.), 1921, **6**, 78-88, 104-112.

A man suffering from diabetes stuck a nail into one of his feet. He died some time later in coma diabeticum. The author believes that in this case death was caused by the injury.—J. K.

Assimilation of caramel in DIABETES (Ueber Assimilation von Karamel bei Diabetikern). Grafe, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

The author recommends the use of caramel (Karamose from Merck) in wine or cognac during acidosis. It is possible to make caramel not only from sugar, but from all kinds of flour when some fat is added. In most cases the tolerance for these preparations is very much higher than for carbohydrates.—J. K.

Frequency of disturbances of arterial permeability in the lower limbs in diabetics (Fréquence des troubles de la perméabilité arterielle aux membres inférieurs chez les diabétiques). Heitz (J.), Bull. et mém. Soc. méd. de hôp. de Par., 1921, **45**, 706-711.

Not of endocrine interest.—F. S. H.

The theory of the treatment of DIABETES (Zur Theorie der Diabetestherapie). Isaac (S.), Therap. Halbmonats. (Berlin), 1921, **35**, 129-134.

The author recommends carbohydrate cures, preceded and followed by "vegetable days." Urine-analysis does not give sufficient information to establish the tolerance. For this blood-sugar estimations are necessary.—J. K.

Fasting treatment of DIABETES (Les cures de jeune chez les diabétiques). Labbe (M.), Bull. et mem. Soc. méd. d. hop. de Par., 1921, **45**, 684-694.

In diabetes where denutrition has not occurred the fasting method of treatment leads to good results. The glucosuria disappears, no acidosis appears if it has not already been present, although some slight acetone and diacetic acid excretion may take place. There is some loss of nitrogen, and body weight. The arte-

rial pressure is but little less during the treatment. In cases where emaciation is present the fasting treatment affords only a passing relief.—F. S. H.

(DIABETES) The decomposition of carbohydrates in muscle (Ueber den Abbau der Kohlenhydrate im Muskel). Laquer (F.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

The author shows that glycogen is more readily used by the muscle than is glucose. He believes that in diabetes the formation of glycogen from glucose is insufficient and that this is the reason why insufficient carbohydrate is oxidized.—J. K.

Creatinuria and acidosis in DIABETES (Kreatinurie und Azidosis bei Diabetes). Lauritzen (M.), Zeitschr. f. klin. Med. (Berlin), 1921, **90**, 375-385.

Creatin may be found in urine in acidosis, but it may also be present in light cases of diabetes without acetonuria. Probably acidosis as well as creatinuria are due to defective carbohydrate metabolism. A marked permanent creatinuria is a bad prognosis. —J. K.

(DIABETES) The blood sugar in old age (Das Verhalten des Blutzuckers im höheren Alter). Löffler (W.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

In elderly people the administration of 20 grams of glucose in 100 cc. water by mouth produces a rise in blood sugar above that found in younger persons. The fall to the original level is also much prolonged. The same reaction is seen in diabetes, hence it can only be very carefully used for the diagnosis of diabetes in the aged. —J. K.

Organotherapy in DIABETES (Organtherapie des Diabetes). Löning (K.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

A new substance has been prepared from pancreas, and is called metabolin. It antagonizes adrenalin glucosuria. A similar substance can be made from yeast. The author obtained good results with it in diabetes.—J. K.

Gangrene in DIABETICS (A propos des gangrènes des mèmbres chez les diabétiques). de Massary (E.) & Girard (J.), Bull. et mém. Soc. méd. d. hôp. de Par., 1921, **45**, 670-674.

Not of endocrine interest.—F. S. H.

Old and new in the treatment of DIABETES (Das Neue und das Alte in der Diabetestherapie). Minkowski, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 609.

Real diabetes is due to a disturbed function of the pancreas. The other endocrine organs have an influence on the degree of glucosuria. How the pancreas acts is unknown. It certainly does not act only by diminishing the formation of sugar in the liver. Pancreatic diabetes cannot be explained as an adrenalin glucosuria. A normal function of the pancreas is necessary for a normal carbohydrate metabolism. The Allen treatment, if carefully used, may be followed by splendid success.—J. K.

The use of a high fat diet in the treatment of DIABETES mellitus. II. Newburgh (L. H.) & Marsh (P. L.), Arch. Int. Med. (Chicago), 1921, **27**, 699-705.

A report of the effects of a high fat diet on the blood sugar which indicates that in uncomplicated diabetes the blood sugar is reduced when a high fat diet is instituted and maintained.—F. S. H.

Treatment of DIABETES (Diabetestherapie). von Noorden, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 609.

A description of the dietetic treatment.—J. K

Syphilitic origin of DIABETES (L'origine syphilitique du diabete). Pinard (M.) & Velluot, Bull. et mém. Soc. méd. d. hôp. de Par., 1921, **45**, 760-771.

Favors the idea of a syphilitic causation of diabetes.—F. S. H.

Emaciation in DIABETES (L'amaigressement des diabétiques). Rathery (F.), Bull. gén. de thérap. (Paris), 1921, **172**, 216-217.

Three varieties of diabetic emaciation are distinguishable: the pathological, the dietary and the therapeutic.—F. S. H.

The alveolar carbon dioxide tension in DIABETES (La tension de CO_2 dans l' air alveolaire chez les diabétiques). Rathery (F.) & Bordet (F.), Bull et mém. Soc. méd. d. hôp. de Par., 1921, **45**, 498-502.

Since in general there is found a lower CO_2 tension of the alveolar air in diabetes the authors consider that the determination of this furnishes suggestive information to the clinician with regard to the condition of acidosis of the patient.—F. S. H.

The differential diagnosis between DIABETES and glucosuria in pregnancy (Die Differentialdiagnose der Schwangerschaftsglykosurie und des Diabetes bei Schwangerschaft). Salomon (H.), München. med. Wchnschr., 1921, **68**, 386-388.

There exist three forms of glucosuria in pregnancy: 1. Traces of sugar are excreted even when no carbohydrates are given. 2. When a certain amount of carbohydrates are given sugar is found

in the urine. When, however, more carbohydrates are given the sugar does not increase or very little. 3. A certain percentage of the carbohydrates are excreted as sugar. These very rare cases may only be distinguished from diabetes by determining the amount of blood sugar. Generally, when the blood sugar is not increased, there is no diabetes, but glucosuria. The groups 2 and 3 are always more or less looked on with suspicion and the diagnosis glucosuria is often only possible after many years.—J. K.

The therapeutic importance of acidosis in DIABETES (Ueber die therapeutische Bewertung der Azidosis im Diabetes). Salomon (H.), Wien. klin. Wchnschr., 1921, **34**, 185-186.

The author recommends the use of a strict non-carbohydrate diet in diabetes. From time to time some carbohydrate-days may be allowed. Practitioners are too much afraid of acetonuria or ketonuria. Many patients have a marked ketonuria during many years without going into coma. It is, however, not advisable to begin this strict diet at once, but to change the diet gradually. It is important not to give too many proteins or too much fat (Cream!). Alkalies must be given regularly. When the quantity of acetone increases a carbohydrate-day is indicated. It is necessary to attend to the general condition of the patient.—J. K.

Identification of the aldehyde-like body in the urine of patients with DIABETES (Identifizierung der aldehydartig reagierenden Substanz im Harn von Diabetikern). Stepp (W.) & Feulgen (R.), Deutsche med Wchnschr. (Berlin), 1921, **47**, 610.

Stepp had preveiously found in the urine of patients with acidosis an aldehyde which was probably acetaldehyde (Endocrinology, 1921, **5**, 261). He now identifies it as acetaldehyde by estimation of the melting-point of its compound with dimethylcyclohexandion. Even 50% of the total acetone may consist of acetaldehyde. Traces of it may be found in normal urine.—J. K.

The relation between blood sugar and acidosis and its importance for the pathogenesis of DIABETES (Ueber die Beziehungen des Blutzuckers zur Blutazidose und derem Bedeutung für die Pathogenese des Diabetes mellitus). Toenniessen (E.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

There is no relation between the absolute amount of sugar and ketone-bodies in the blood.—J. K.

(DIABETES) Acidosis and administration of fat (Acidosis und Fettzufuhr). Uhlmann (R.), Ztschr. f. ärztl. Fortbild. (Jena), 1921, **18**, 189-192.

A short article in which the author points out that in serious diabetes it is not enough to reduce the quantity of carbodydrates

and proteins in the diet, but that the amount of fat must be also restricted.—J. K.

Changes in inorganic metabolism in DIABETES (Ueber eine mineralische Stoffwechselstörung beim Diabetes mellitus). Veil (W. H.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

The author studied the polyuria in diabetes. He found most remarkable changes, for in a patient in a sugar-free period with a low elimination of chlorine, a large dose of NaCl produced glucosuria and ketonuria. Extract of ovary raised the NaCl elimination and diminished the glucosuria.—J. K.

DIABETES INSIPIDUS. Van der Heide (C. C.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65**, 590.

Data reported elsewhere.—J. K.

A case of hereditary DIABETES INSIPIDUS (Een geval van hereditairen diabetes insipidus). Janzen (E.) & Broekman (J.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65**, 2519-2531.

A description of a patient with diabetes inspidus and tuberculosis of the lungs. The x-ray of the sella turcica did not show any changes. It was remarkable that in the same family many other cases were observed. The familiar diabetes insipidus is very rare. In these cases the patients feel quite well, are able to do their work and can reach an old age. The symptoms generally begin in infancy and increase till the age of 25. Later on the symptoms gradually disappear. Blood pressure is normal. Sometimes during pregnancy the thirst and polyuria become worse. There are many points of resemblance between diabetes insipidus and diabetus mellitus. Both may be of endocrine origin; both may be produced experimentally from the mid brain; in Graves' disease glucosuria as well as polyuria may occur. There exist hereditary forms of both diseases. Both diseases may be observed in one family.—J. K.

DIABETES MELLITUS with INFANTILISM (Diabete mellito con infantilismo). Amenta (F.), Pediatria (Napoli), 1921, **29**, 249-253.

A report of a case of diabetes in a boy 8 years old. The condition began when he was one year old. He is now an underdeveloped rickety child, with rosary and dark skin. According to Amenta, the case might be classified as diabetes mellitus with Bramwell and Rentoul's pancreatic infantilism, but it is believed by the author that the infantilism is due merely to chronic acidosis and intoxication.—G. V.

A case of DIABETES MELLITUS treated successfully by novarsenobenzol. Porter (F. J. W.), Lancet (London), 1920, **(ii)**, 1051.

A case is recorded of a diabetic patient in which the administration of three doses of novarsenobenzol caused the disappearance of sugar from the urine, and the patient had remained practically sugar-free for the 7 months since the treatment. The diet is not indicated, except that the amount of carbohydrate had been gradually increased without any apparent ill effect.—L. G. K.

DIABETES MELLITUS. Toenniessen (E.), Münch. med. Wchnschr., 1921, **68**, 523-524.

A general review.—J. K.

DWARFISM and GIANTISM. Case of each reported. Shuman (J. W.), Med. Herald (Kas. City), 1921, **40**, 49-51.

Report of a case of dwarfism and one of giantism with few data. Nothing new.—C. M. W.

The EMOTIONS (Breve ensayo sobre la edad y la emoción). Marañon (G.), Arch. de med. cirug. y especialid. (Madrid), 1921, **3**, 337-351.

A general theoretical discussion including a consideration of the part played by the endocrin organs in the genesis and manifestation of emotion.—R. G. H.

(ENDOCRINE) The clinical significance and therapeutic indications of abnormal blood pressure. Blumgarten (A. S.), Med. Record (N. Y.), 1920, **98**, 856-859.

The hypertension of nephritis, that of arteriosclerosis, and also essential hypertension are discussed. The group of climacteric hypertension cases is then referred to; outside of obesity and very high systolic pressure, in these nothing abnormal is found. **Lutein** or **ovarian extract** is often highly beneficial in reducing the blood pressure in these cases. Hypotension, unassociated with such conditions as anemia, tuberculosis, hemorrhage, etc., is usually merely an individual marking of an endocrine disturbance such as **acromegaly** or **Fröhlich's syndrome**, or **adrenal** insufficiency. The author has not obtained much benefit from administering **pituitary, thyroid** or **adrenal** for such hypotension, though he recommends their trial.
—H. L.

ENDOCRINASTHENIA. Garretson (W. V. P.), N. York M. J. (New York), 1921, **113**, 221-225.

According to the writer, it is an expression of ignorance to label a patient with such terms as hysteria, psychasthenia, neurasthenia, functional neuroses, etc. Individuals so classed are sufferers of "endocrinasthenia," that is, dysfunction or perversion of the endocrine dominance. When endocrine exhaustion occurs, then, and

not until then, does the psychoneurosis or psychosis, as the case may be, become apparent. Endocrinasthenia not only occurs as a result of exhaustion reactions as expressed through the nervous system, but is always present as a sequel to every disease process, and more particularly the acute infections. All toxic states exhaust the glands of internal secretion and the degree of infection and toxemia depends upon the qualitative and quantitative balance of the hormones. That to which we have loosely referred as body resistance is dependent upon this balance. We all possess in varying degrees bisexual traits psychical (evident or repressed) as well as structural. The many victims of sexual perversion are those in whom there exists inherently an endocrine predominance (gonadal with either pituitary or suprarenal valencies) creative of heterosexual characteristics. The psychic manifestations of these pitiable types are purely symptomatic; the basis of the conditions is a physical one. By psychoanalysis an interpretative symptomatic understanding may be obtained, but here again to produce the complete and permanent cure, an attempt to effect physiological hormonic adjustment is essential. Every anaphylactic or shock reaction produces hypoadrenia with resulting vagotonia. Vaccines or sera serve to stimulate selectively the endocrine system to the further production of hormones which are the immunizing factors of the body. Four case reports of "endocrinasthenia" appended.—H. W.

A case showing ENDOCRINAL disturbance. Pope (C.), Kentucky M. J. (Bowling Green), 1921, **19**, 21-25.

Report of a case of a boy, age fifteen, who, after a series of profound toxaemias—influenza, suppurative appendicitis, gastro-intestinal toxaemia, suppurative bed sores, and burns—developed marked disturbances of pluriglandular nature, involving especially the pituitary. There was a marked change in growth, mentality and disposition. The body growth shows some signs of early hypersecretion and later hyposecretion of the pituitary gland.—C. M. W.

Amenorrhea and sterility due to functional ENDOCRINE disturbances. Watkins (Thomas J.), Surg. Clinics of Chicago (Phila.), 1919, **3**, 1477-1479.

A woman, aged 31, whose illness consists in irregular menstruation with periods of amenorrhea, rapid increase in weight, sterility, and extensive and abundant growth of hair over various parts of her body is reported. Improvement followed dilation of the cervix uteri and the administration of five grain capsules of **corpus luteum** three times daily. Later **thyroid** extract was added to the medication.—J. F.

Congenital cardiopathies; hemolytic jaundice; hypertrophic cirrhosis; pluriglandular ENDOCRINE DYSFUNCTION and infantilism from

hereditary syphilis (Cardiopatia congenita; Icteria hemolitica; Cirrosis hipertrofica; Disendocrinia pluriglandular y juvenilismo por heredosifilis). Padilla (T.), Rev. Assoc. Med. Argen. (Buenos Aires), 1920, **32**, 306-316.

Report of a case of nanism of hereditary syphilitic origin.
—B. A. H.

ENDOCRINE exhaustion. Hoxie (G. H.), N. York M. J. (New York), 1921, **113**, 225-227.

Cites two cases illustrating the various points of difference between true neurasthenics and those with endocrine exhaustion. All endocrine anomalies are not congenital, but many are the result of accidents occurring in adolescence and early adult life. Subjects of these latter furnish material for gratifying therapy. An endocrine want or exhaustion may be considered responsible for many so-called neurotic conditions, especially when the neuroses disappear following glandular therapy. The entire paper manifests a conservative attitude, such as is unfortunately rare in articles along this particular line.—H. W.

Influence of ENDOCRINE SECRETIONS on phloridzin glucosuria (Einfluss von Inkreten auf die Phloridzinglucosurie). Grote, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

Sympathicotonic persons, especially when thyreotoxic symptoms are present, show a very marked glucosuria after the injection of phloridzin. Patients with cancer or myxedema excrete very little sugar after such an injection. Injection of **thyroid** extract tends to augment phloridzinglucosuria, injection of thymus to diminish it.
—J. K.

(ENDOCRINE GLANDS) Epithelial and paraepithelial glands (Glandes épithéliales et glandes paraépitheliales). Bujard (E.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 498-500.

A grouping of all glands according to their morphological affinities. In this classification the endocrine glands are paraepithelial.—T. C. B.

The ENDOCRINE GLANDS—a caution. Editorial, J. Am. M. Ass. (Chicago), 1921, **76**, 1500-1501.

This editorial sounds a much needed note of caution against undue enthusiasm and credulity regarding the numerous poorly substantiated claims that are being made in the name of endocrinology. It is pointed out that much of the physiology of the internal secretions is in a state of chaos and that correspondingly it is futile to select bits uncritically from this chaos to bolster up clinical theories. It is suggested that the difficulties in the field and the

importance of the problems should stand as a challenge to the well-trained clinician to lend his constructive aid toward their solution; also that the solid work of well-trained investigators should be critically differentiated from the specious claims of gullible enthusiasts. The former should be supported, the latter condemned.—R. G. H.

(ENDOCRINE GLANDS) Miculicz disease, sympathicotonia and fruste pluriglandular syndrome (Maladie de Miculicz avec état de sympathicotonie et syndrome polyglandulaire fruste). Mery (H.), Girard (L.) & Mercier-Desrochettes, Bull. et mem. Sec. méd. d. hôp. de Par., 1921, **45**, 406-412.

Not endocrine.—F. S. H.

(ENDOCRINE ORGANS) Further studies on substances with specific action prepared from single organs. II. (Weitere Studien über die von einzelnen organen hervorgebrachten Substanzen mit Spezifischer Wirkung. II.). Abderhalden (E.), Arch. f. d. ges. Physiol. (Bonn), 1919, **176**, 236-262.

Thyroid, thymus, pituitary, gonad, adrenal, and **placenta** were administered to tadpoles, and the effects compared with those of hydrolysed preparations of these glands. Abderhalden states that the most important conclusion from his experiments is that the same results are obtained whether the organs themselves are administered, or their hydrolysed products, so that the active substances must be of simpler nature. Usually the action is quantitatively the same. —A. T. C.

(ENDOCRINE ORGANS) Studies on substances with specific action prepared from single organs. IV. (Studien über die von einzelnen Organen hervorgebrachten Substanzen mit specifischer Wirkung. IV.). Abderhalden (E.) & Brammertz (W.), Arch. f. d. ges. Physiol. (Bonn), 1921, **186**, 265-271.

The "optone" (completely hydrolysed products) of **corpus luteum** fed to tadpoles produced an increase in their oxygen-consumption, that of **thymus** had no effect, neither had that of **ovaries** from which the corpus lutea had previously been removed. Optones of **testis** and **pituitary** produced an increase, as did all the products obtained from yeast cells.—A. T. C.

(ENDOCRINE ORGANS) Further studies on substances with specific action prepared from single organs. V. (Weitere Studien über die von einzelnen Organen hervorgebrachten Substanzen mit specifischer Wirkung. V.). Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Bonn), 1921, **187**, 243-268.

The "optones" obtained by enzymic decomposition of organs possess specific actions which depend entirely on their content of organic substances of simpler nature. **Corpus luteum-, testis-,** and

thymus-optones produce on heart-strips (atropinised or not, but not on the whole heart, nor on strips connected to atrium and sinus), slowing of the spontaneous contractions and slight negative-inotropic action, and on the surviving oesophagus (frog) an increase of tonus, with, after a slight inhibition-period, positive-intropic and positive-chronotropic action. **Pituitary** and **thyroid** optones produce an opposite action on the oesophagus. Anterior pituitary optone excites, posterior pituitary optone inhibits the automaticity of the frog's oesophagus. These optones, and to a lessor degree those of the thyroid testis, and **ovary** produce an exciting, tonus-increasing action on the surviving uterus of the guinea pig, while those of corpus luteum and thymus decrease the tonus.—A. T. C.

(ENDOCRINE ORGANS) Experiments on the central regulation of carbohydrate metabolism in the medulla oblongata (Experimenteller Beitrag zur zentralen Regulation des Zuckerstoffwechsels in der Oblongata). Brugsch (T.), Dresel (K.) & Lewy (F. H.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 610.

The amount of blood sugar is increased only when the nucleus dorsalis vagus is wounded, because of an increased amount of adrenalin poured by the **adrenals** into the blood. No other lesions of the medulla oblongata produces the same effect. When a lesion is made in the nucleus vegetativas vagi the blood sugar diminishes. When the **pancreas** is removed special cells in the nucleus vegetativus degenerate. In the medulla oblongata there are two centers, one for increasing the blood sugar, via the sympathetic and **adrenals** and one for diminishing it via the pancreas.—J. K.

ENDOCRINE ORGANS and the x-ray (Streustrahlung oder endocrine Drüsenwirkung). Fränkel (H.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 242-243.

The effect of x-ray treatment in malignant tumors may partly be due to endocrine phenomena. Probably the endocrine organs have an influence on the cancer-cells. If in a cancer of the eye x-rays are used, the hypophysis may be stimulated to produce a hormone that acts against the carcinomatous-degeneration of normal cells. In the same way x-ray treatment of tumors of the mediastinum involves the **thyroid** and the **thymus**. In considering these facts, the author comes to the conclusion that for treating malignant growth smaller doses than are generally used are wanted.—J. K.

(ENDOCRINE ORGANS) Chronic colitis with secondary endocrine disturbances and their importance for the constitution (Chronische Kolitiden mit sekundärer inkretorischen Störungen und ihre Bedeutung für die Konstitution). Grote (L. R.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 379-380.

Three relations between the alimentary tract and the endocrine organs are possible: 1. The endocrine disturbance is primary (diarrhea in Graves' disease, hyper- or an-acidity in Graves' disease, constipation in acromegaly, etc.). 2. The endocrine disturbance and the disease of stomach or intestines are due to the same cause (necrosis of the stomach with thyrotoxicosis; constipation due to changes in the tonus of the involuntary nervous system). 3. The endocrine disturbance is caused by the changes in the abdominal organs. a. By direct influence: when a chronic enteritis reaches the pancreas and produces glycosuria. b. Through indirect influence. It is not so rare that in the cause of an intestinal disease symptoms of thyrotoxicosis are observed. This may be seen in + 20% of the chronic postdysenterical colitis. The most constant symptom in these cases is the increased excretion of sugar after injection of phloridzin.—J. K.

(ENDOCRINE ORGANS) A case of myasthenia gravis and its importance for constitutional pathology (Ein Fall von Myasthenia gravis als Beitrag zur Konstitutionspathologie). Hase (H.), Berl. klin. Wchnschr., 1921, **58**, 176-177.

Report of a case. Mother had diabetes; father gout. The patient had bilateral exophthalmos, nervous irritability and loss of flesh. Probably in these cases the endocrine symptoms, as well as the neurological symptoms, are due to constitutional abnormalities. —J. K.

(ENDOCRINE ORGANS) The effect of pregnancy upon the size and weight of the organs of the body. Herring (P. T.), Brit. M J. (London), 1920, **(ii)**, 886.

In the healthy albino rat the occurrence of pregnancy had little effect upon the length and weight of the body, excluding the increase of weight due to the uterus and its contents. The heart, kidneys and spleen were little effected; there was certainly no enlargement of the heart during pregnancy. The liver was greatly enlarged. The **thymus** had undergone rapid involution and was much diminished in size. The **suprarenals** were slightly hypertrophied. The **thyroids** were diminished in size, and there was a notable diminution in weight of the **pituitary** body, attended by histological changes in its glandular lobe.—L. G. K.

(ENDOCRINE ORGANS) A case of myasthenia gravis pseudo-paralytica. Hutter (A.), Psychiatrische en Neurologischebladen (Amsterdam), 1920, —, 352-356.

In this case at post-mortem no changes in the **thyroid, adrenals, testicles or hypophysis** were found. No trace of **thymus** tissue could be detected. The patient was 25.—J. K.

(ENDOCRINE ORGANS) A case of chondrodystrophia in an adult (Ueber einen Fäll von Chondrodystrophie bei Erwachsenen). Marum (G.), Inaug. Diss. (Cologne), 1919-1920.

Report of a post-mortem examination of a woman of 33 years with chondrodystrophia. She died from influenza. Her height was 108 cm. She first menstruated when she was 19. There were follicular cysts in the left **ovary**; no changes in the **thyroid, thymic** residues, **hypophysis** or **adrenals**. Only three **parathyroids** were found; these were smaller than normal. Microscopically there were no important changes in the parathyroids; they were very rich in blood; colloid was not present.—J. K.

(ENDOCRINE ORGANS) Myxedema and pluriglandular insufficiency (Myxödem mit pluriglandulären Insuffizienz). Meissner (R.), München med. Wchnschr., 1921, **68**, 488-490.

In 1920 Meissner described some cases of myxedema. One of the patients died. The post-mortem report is now given. It showed a highly atrophic **thyroid** with growth of lymphatic tissue in the gland; atrophy of the **ovaries** and increased pigmentation of the **adrenals** and **hypophysis**. The cause of death was a cerebellar disease.—J. K.

(ENDOCRINE ORGANS) The endocrine causes of pathological senescence (Die innersekretorischen Ursachen des pathologischen Alterns). Pribram, Berl. klin. Wchnschr., 1921, **58**, 366; Deutsche med. Wchnschr. (Berlin), 1921, **47**, 459; München. med. Wchnschr., 1921, **68**, 470.

A sarcomatous ovary was removed from a girl of 6 with well developed mammae. After this all symptoms of adult development retrogressed. A woman of 32 developed puerperal fever after manual removal of the placenta. She did not get well again, but showed many symptoms of senium praecox. Post-mortem changes were found in the **hypophysis, thyroid** and **adrenals**. The ovaries were normal.—J. K.

(ENDOCRINE ORGANS) The form of the blood vessels of the nail-wall (Zur Formenlehre der Nagelfalzgefässe). Rosenberger (F.), Zentralbl. f. inn. Med. (Leipzig), 1921, **42**, 26-28.

The author examined the capillaries of the nail wall with a microscope. He distinguished four different types: hairpin forms, repeatedly winded forms without anastomoses between each other, "crescent" forms and the form of the violin-key (&) in music with anastomoses. The hairpin forms and the violin-key vessels seem to have some relation to the kidney and the blood pressure; repeatedly winded capillaries seem to depend on the **thyroid**; the "crescent" forms are only seen in sympathicotonia. A patient with a small

goiter received during some days small doses of iodine. The goiter increased and the capillaries which were not coiled before took on the "thyroid-type." This type disappeared when the administration of iodine was stopped.—J. K.

(ENDOCRINE ORGANS) Osteomalacia and osteomalacia-like diseases (Osteomalazie und osteomalazieartige Erkrankungen). Schlesinger (H.), Wien. klin. Wchnschr., 1921, **34**, 213-214.

The opinion is expressed that this is a pluriglandular disease. Changes have been found in the **thyroid, ovaries, hypophysis, adrenals** and particularly hyperplastic changes in the **parathyroids.** Whether they are affected by a toxin, a micro-organism, a want of vitamines or another cause is unknown.—J. K.

Blockade and ENDOCRINE ORGANS (Blockade und innere Sekretion). Sehrt (E.), München. med. Wchnschr., 1921, **68**, 268-270.

Undernutrition during the war has caused a hypofunction of the endocrine organs. The iodine content of thyroids of the sheep is much lower than before the war. Hemorrhages per vaginam are often observed in women which are stopped by the administration of thyroid. Much larger quantities of thyroid are needed now than before the war. In animals the adrenals contain much less adrenalin; in man often a low blood pressure is observed. After operations hemotomas are often seen, much more frequently than before the war.—J. K.

(ENDOCRINE ORGANS) X-ray in epilepsy (Röntgenstrahlen bei Epilepsie). Strausz, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 524.

Strausz believes that epilepsy is due to a hypofunction of the endocrine glands. He recommends methodical x-ray treatment of the **thymus, spleen, liver,** and **adrenals.** Local treatment with x-rays of the cerebral cortex is not to be recommended.—J. K.

Mikulicz's disease and the ENDOCRINE ORGANS (Miculischer Symptomenkomplex und innere Sekretion). Taschenberg (E. W.), München. med. Wchnschr., 1921, **68**, 332.

A girl of 21 observed that regularly before the onset of menstruation symptoms of Mikulicz's disease (swollen salivary glands) appeared. This would make probable a relation between the ovaries and the salivary glands.—J. K.

The role of the ENDOCRINE system in internal medicine. Blumengarten (A. S.), N. York M. J. (New York), 1921, **113**, 233-239.

A consideration of the relation of the endocrine organs to the general picture of disease. Patients may show endocrine diseases as secondary factors resulting from other lesions.—H. W.

(ENDOCRINE SYSTEM) The individual factor in disease. Pottenger (F. M.), Med. Record (N. Y.), 1920, **98**, 647-649.

Symptoms of disease are produced through either the nerves or the internal secretions, and either from physical or psychical stimuli. A perfect man should be possessed of an anatomically perfect body and physiologically balanced nervous, endocrine and psychical systems; each part is interdependent upon the other. Pottenger then discusses the vegetative nervous system, and notes the symptoms and signs of vagotonia and sympathicotonia. A disease will affect an individual differently if he already be preponderantly vagotonic than if he be sympatheticotonic in type. Likewise, disease will appear differently in an individual exhibiting hypofunction of one or more endocrine glands than in one showing hyperfunction. Clinical syndromes will also vary with the psychic status of the patient.
—H. L.

Homoplastic and heteroplastic ENDOCRINE transplants. Swingle (W. W.), Anat. Record (Phila.), 1921, **20**, 195.

Various parts of the hypophysis from three species of frogs were ingrafted intraperitoneally into immature larvae of the bull frog. Grafts of the anterior lobe accelerated metamorphosis; those of the pars intermedia caused certain color changes. Grafts of the **adrenal** glands were negative. Implantation of the **thyroid** was the most effective means for hastening metamorphosis. It was found possible to ingraft a thyroid into an immature larva, induce metamorphosis, re-ingraft the same gland into another larva, induce metamorphosis, then repeat the procedure on yet a third animal.—W. J. A.

ENDOCRINOLOGY and the heart. Satterthwaite (T. E.), Med. Record (N. Y.), 1920, **98**, 510-511.

Among the prominent signs of **hypoadrenia** are muscular asthenia, sensitiveness to cold, hypotension, weak cardiac action and pulse, subnormal temperature, loss of appetite, anemia, slow metabolism, indigestion, constipation, psychoasthenia, perhaps Sergent's white line, a dry skin, and no capacity for sustained effort. For patients having such manifestations the author has achieved very satisfactory improvement by dried **suprarenal** extract, giving 2½ grain capsules, three times a day and adding 1/10 grain posterior lobe of pituitary to supplement and sustain the action of the former. The endocrine preparations are more effective when given in combination with one another. The pituitary usually provides an initial stimulation to activity of other preparations. The beneficial effect upon the circulation would seem to be obtained by direct action of the glandular secretion on the myocardium, and by stimulating the cerebrospinal nerves which govern the muscles of the heart.
—H. L.

Contributions to the physiology of the stomach. LXVII. The response of the stomach glands to GASTRIN before and shortly after birth. Sutherland (G. F.), Am. J. Physiol. (Balt.), 1921, **55**, 398-403.

In dogs and cats there is a secretory response to gastrin in fetuses a few days before term, and the response increases with age, at least for the first few days.—T. C. B.

On a case of GERODERMA GENITODYSTROPHICA with convulsions (Sopra un caso di geroderma genito-distrofico in soggetto frenastenico con attacchi epilettici). Gadani (Angelo), Riforma med. (Napoli), 1920, **36**, 1073-1074.

The case reported, while belonging without doubt to the geroderma syndrome in that the appearance of the skin, the atrophy of the genitals and the feminine voice show the additional symptoms of absence of the right lobe of the thyroid, marked abnormality of the intelligence, epileptic seizures and exaggerated development of the arms (1.87 M. as compared with the legs, 1.14 M.). The author believes this to be a case of a pluriglandular lesion and intends to subject the patient to glandular treatment and later report the result.—G. V.

(THYROID) Goitre produced experimentally by waters from the province of Salta (Bocio producido experimentalmente por agua de la provincia de Salta). Houssay (B. A.), Rev. del. Inst. Bacteriologico del Dep. Nacional de Higiene (Buenos Aires), 1920, May, II, No. 5.

Goiter has been produced in rats in Buenos Aires by giving them water from Cerrillos (a northern town affected with endemic goiter) to drink.—B. A. H.

(GONADS) Glandular hermaphrodism (Sur l'hermaphroidisme glandulaire). Ancel (P.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1642-1644.

Observations on four pigs in which there were present both ovary and testicle, either on one side or on both sides. Chiefly of embryological interest.—T. C. B.

(GONADS) Case of androgenous pseudo-hermaphroditism, with an intra-abdominal tumor consecutive to the ablation of a genital gland. Disappearance of the tumor under the influence of radiotherapy (Un cas de pseudo-hermaphoditissme androgyne avec tumeur intrabdominale consécutive a l'ablation d'une glande genitale. Disparition de cette tumeur sous l'influence de la radiothérapie). Béclére & Siredey, Bull d'obst. et gynéc. (Paris), 1921, **10**, 91-99.

The title tells the story.—F. S. H.

(GONADS) The work of Steinach on rejuvenation (Steinach's Arbeiten und die Verjüngungsfrage). Boruttan (H.), Ztschr. f. ärztl. Fortbild. (Jena), 1921, **18**, 129-131.

A very short review on the well known work of Steinach.—J. K.

(GONADS) Atypical structures of two OVOTESTES in the pig (Structures atypiques de deux ovotestis de porc). Bujord (Eug.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 112-114.

Histological.—T. C. B.

(GONADS) The genesis of the OVOTESTIS in mammals (De la genèse des ovotestis chez les mammifères). Bujord (Eug.), Histological and embryological.—T. C. B.

Compt. rend. Soc. de biol. (Paris), 1921, **84**, 114-116.

(GONADS) Nervous disturbances of genital origin in the female (De quelques troubles nerveux d'origine génitale chez la femme). Dalché (P.), La Gynécol. (Paris), 1920, **19**, 437-468.

This article is an extensive general discussion of the association of headaches during puberty, pregnancy and the menopause with disturbances of the endocrine organs and general physical condition. —F. S. H.

GONADS and sex development (Keimdrüse and Geschlechtsentwicklung). Halban (Josef), Arch. f. Gynaek. (Berlin), 1921, **114**, 289-303.

Halban reviews the recent evidence supporting his idea that at the moment of fertilization not only is the sex determined, but also the entire primary and secondary sex characteristics are laid down, whether male or female. A rather vigorous criticism of Steinach's conclusions is made, which is somewhat weakened by the statement that the ovarian and testicular secretions are identical in nature or effect, and that the placenta is not entirely a female organ, but is a mixed-sex gland, a sort of enlarged ovo-testis.—F. S. H.

The fat of the GONADS of Rhizostoma cuvieri (Untersuchung des Fetts der Gonaden von Rhizostoma Curvieri). Haurowitz (F.), Ztschr. f. physiol. Chem. (Berlin u. Leipzig), 1921, **112**, 28-37.

Chemical studies of the gonads of Rhizostoma cuvieri, particularly the lipoid constituents are reported in this paper, the results of which at present have no particular endocrine interest.—F. S. H.

(GONADS) The dissociation of the seminal and interstitial gland determined by experimental alcoholism. Sterility without impotence (Sur la dissociation de la glande séminale et de la glande interstitielle déterminée par l'alcoholisme expérimentale. Sterilité

sans impuissance). Kostitch (A.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 569-571.

White rats were progressively intoxicated by daily doses of absolute alcohol. There was a rapid influence on the genital glands. As an example, one rat was killed after thirty-seven days, having taken 53 cc. of absolute alcohol. It had the appearance of perfect general condition. The penis, vesiculae seminales and prostate were normally developed. Microscopic examination of the testes showed advanced atrophy of the seminal gland, with marked hyperplasia of the interstitial gland. The conclusion is that the spermatogenic tissue is more susceptible to alcohol than the interstitial. The fact that the integrity of the interstitial gland coincides with the integrity of the secondary sex characters, and the sexual appetite, confirms the opinion that they are dependent on the internal secretion of the interstitial glands. The hypertrophy of the interstitial gland indicates that it plays a rôle in the defense of the seminal elements against toxic substances. Atrophy of the seminal tissue shows that a certain degree of alcoholic intoxication may provoke sterility without determining impotence.—T. C. B.

(GONADS) The influence of ligation of the funicules spermaticus on metabolism (Der Einfluesz der Samenstrangunterbindung auf den Stoffwechsel). Loewy (A.) & Zondek (H.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 349-350.

If it is true that Steinach's operation renews sexual characteristics it must be possible to prove that the operation produces an increase in metabolism. In some cases this was really so, in some patients this increase was only temporary. The changes in metabolism and the influence on sexual functions do not go parallel. Some patients are described in whom the operation had no effect on the sexuality but in whom the metabolism was increased.—J. K.

(GONADS) Sex glands transplantation and the modifying effect in rats and guinea pigs. Moore (C. R.), Anat. Record (Phila.), 1921, **20**, 194.

In the white rat testicular tissue grafted into young spayed females will persist for a period of nine months. Associated with the testicle graft the behavior of the animal is decidedly male-like. Ovaries transplanted into young castrated males will persist and grow for several months. In the white rat ovarian grafts will persist for eight months in a male with one normal testicle. There seems to be no deleterious influence of secretions from either sex gland upon the opposite one.—W. J. A.

(GONADS) The influence of castration on patients with sexual neurosis (Der Einflusz der Kastration auf Sexualneurotiker).

Mühsam (R.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 155-156.

Report of three cases: two with sexual neurosis and one with homosexuality. Castration had in all three cases a good effect. One patient had a temporary restoration of his sexual desires.—J. K.

(GONADS) Eugenic prevention of conception and the biological fundamentals of generative prophylaxis by vasectomy and autotransplantation of the testicles (Ueber eugenetische Konzeptionsverhinderung und die biologischen Grundlagen generativer Prophylaxe durch Vasectomie und Autotransplantation der Hoden). Ottow (B.), Monatschr. f. Geburtsch. u. Gynäk. (Berlin), 1921, **54**, 219-227.

A review and discussion of the subject in the title.—F. S. H.

(GONADS) Implantation of testicles in prostatism (Hodeneinpflanzung bei Prostatismus). Rohleder, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 185-186.

One year ago (See Endocrinology, Vol. IV, p. 311) Rohleder stated that the administration of testicle had a good influence on prostatism. In many cases, however, no effect is seen. This may be due to the fact that the artificial extract that is given is not at all identical with the testicular hormone. This may account for the fact that in homosexuality never any result is obtained with testicle preparations. Further, we know that when glandular extracts are taken by mouth they undergo changes in the alimentary tract. Last, but not least, the commercial extracts are made from bull's testicle and we do not know whether they are absolutely identical with human organs. Then an injection of a hormone can never take the place of its regular excretion by an organ. Therefore, the author recommends the transplantation of slices of testicle in cases of prostatism, but only in cases in whom organo-treatment has had at least some effect. It is recommended to administer cryptorchic testicle. No clinical cases are reported. It is even doubtful whether the author has ever tried this operation.—J. K.

(GONADS) Hermaphroditismus glandularis. Steindl (A.), München. med. Wchnschr. 1921, **68**, 412.

A bicornate uterus was found in a girl of 9 during a laparatomy. There were two tubes, and on one side an ovary, on the other a testicle. The patient was classed as a female.—J. K.

Specific sex action of GONAD-extracts (Geschlectsspezifische Wirkungen von Keimdrüsenextrakten). Weil (A.), Arch. f. d. ges. Physiol. (Bonn), 1920, **185**, 33-41.

Subcutaneous injections of testicular extracts (cattle) corresponding to 30 grams of fresh organ per kilo body-weight produce in guinea pigs specific sex changes in the CO_2-curve (measured by a modified Haldane method). With young males, castrated males, and pregnant females there is a sudden fall followed by a steeper rise to above normal; no action is produced in adult males and (non-pregnant) females. In the former cases and in adult females ovarian extracts produce slight fall and slow rise to normal, but they are without action on adult males. Typical nervous symptoms are produced by both extracts, also sex-specific, and connected with rises in temperature. They cannot be evoked after fourteen days, but the influence on gas-metabolism persists.—A. T. C.

The effects of transplantation of the several parts of the adult HYPOPHYSIS into tadpoles in Rana pipiens. Allen (B. M.), Anat. Record (Phila.), 1921, **20**, 192.

Parts of the gland were transplanted into normal tadpoles and into those from which the hypophysis had been ablated. The latter showed a tendency toward metamorphosis and the thyroid glands were restored almost to normal size when the anterior lobe was implanted. Transplantation of the united intermediate and neural lobes caused the tadpoles to revert to the original black color after having become white as a result of prior pituitary extirpation. Transplantation of the intermediate lobe does not stimulate the development of the thyroid gland; for this reason it likewise has no effect upon metamorphosis.—W. J. A.

(HYPOPHYSIS) Acromegaly (Acromegalia). Bellavitis (C.), Riforma Med. (Napoli), 1921, **37**, 403.

Report of a case of complete acromegaly (mandible, nose, tongue, limbs involved, kyphosis and clavicles thickened) lasting nine years in a man 59 years old. The familial and personal history was otherwise negative. Radioscopy showed a normal sella turcica, and there were no intracranial pressure symptoms. Nothing abnormal was detected in the other endocrine glands. The only abnormality found was in his blood, leukopenia with 15 per cent. eosinophils. The red cell count was 5,500,000. There were traces of albumin in the urine.—G. V.

The HYPOPHYSIS in hypothyreosis and some remarks on the hypophysis in pregnancy (Die Hypophyse bei Hypothyreose nebst Bemerkungen über die Schwangerschaftshypophyse). Berblinger (W.), Mitt. a. d. Grenzgeb. Med. u. Chir. (Jena), 1921, **33**, 92-112.

In all textbooks one may find that thyroidectomy is followed by a compensatory hypertrophy of the hypophysis. This is certainly not

true in all animals. There are animals (goat) in which thyroidectomy has no influence on the hypophysis. Berblinger carefully examined the hypophysis in 5 people with hypofunction of the thyroid, dying from intercurrent disease. He found an increased number of chromophobe cells; the cells are richer in protoplasm than normally. The number of eosinophil cells is augmented. In the syncytial cells degeneration of the nucleus was seen. In 3 of the 5 cases the hypophysis was heavier than normal. This increase in weight is only due to the increase in chromophil cells. In one case the hypophysis was much lighter than had been expected. In this gland a great many naked nuclei without protoplasm were found. The increased number of chromophil cells is typical for hypothyroid conditions. This is, however, found also during pregnancy, but it is not regularly seen in myxedema. The author injected into male and female rabbits extracts of placenta or of fetus and always observed that the hypophysis gained in weight and the number of chromophil cells increased—although it never reached the number observed in pregnancy. When other substances were injected no effect was seen, only injection of peptone produced a similar effect. Of course, these changes are only to be observed in the anterior lobe and they are most marked in the female animals. Boiled extracts of placenta and fetus have the same influence as do unboiled extracts. The histology of the hypophysis in a rabbit after thyroidectomy or thyroidectomy+ castration is the same as in the pregnant animal. Berblinger does not believe that the enlargement of a hypophysis after thyroidectomy is compensatory.—J. K.

Experimental DIABETES INSIPIDUS and HYPOPHYSEAL opotherapy (Diabete insipide expérimental et opotherapie hypophysaire). Camus (J.) & Roussy (G.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1578-1583.

The authors have adduced evidence that the polyuria usually attributed to a lesion of the hypophysis is in reality due to a lesion of the base of the brain. In the present paper they give the results of a study of the effect of different extracts of the pituitary upon diabetes insipidus experimentally induced. The usual lesion was made at the base of the brain, and after polyuria was established, various extracts of the hypophysis (posterior lobe, the whole gland, hypophysine, pituitrin) were injected either subcutaneously or intravenously. The results obtained were inconstant. Sometimes the quantity of urine was lessened, sometimes it was increased in spite of treatment. When oliguria occurred it was not lasting.—T. C. B.

(HYPOPHYSIS) Dystrophia adiposo-genitalis. Chiari, Wien. klin. Wchnschr., 1921, **34**, 42.

A woman of 25, who was an alcoholic, became fat, menstruation was regular, no eye-symptoms; infantile sexual-organs, polydipsia,

polyuria, Wassermann test positive. Improved by antisyphilitic treatment.—J. K.

(HYPOPHYSIS) [Acromegaly with myxoedema]. Christoffersen (N. R.), Ugesk. f. Laeger. (Copenhagen), 1920, **82**, 794.

The author presented the case of a man, aged 48 years, who 19 years ago suffered traumatism of the head. Nine years ago headache and vomiting supervened and 3 years later acromegalic symptoms. Presently the face assumed the typical acromegalic characteristics, but the condition of the skin and hair of the scalp indicated well marked myxedema. The reactions to adrenalin and to hypophysin were found to be normal. The radiogram showed a dilated sella turcica. The mentality was slow and dull. The metabolism was depressed. The increase of blood sugar after 100 grammes glucose was strikingly slow.—K. H. K.

The effect of feeding the anterior lobe of the HYPOPHYSIS on the oestrous cycle of the rat. Evans (H. M.) & Long (J. A.), Anat. Record (Phila.), 1921, **21**, 62.

The length of the oestrous cycles was not appreciably altered. —W. J. A.

(HYPOPHYSIS) Heat polyuria in children (Poliuria estiva infantile). Funaioli (G.), Gazz. de osp. (Milano), 1921, **42**, 189-190.

The author observed in Africa many cases of polyuria in young children. This always began at the beginning of the hot season. Administration of hypophysis had no influence. Only belladonna was useful. Even without treatment the symptoms disappear rather quickly.—J. K.

(HYPOPHYSIS) The induction of labor with pituitary extracts. Gallie (J. G.) & Scott (W. A.), Canad. M. Monthly (Toronto), 1920, **4**, 143-146.

Induction of labor by means of intramuscular injections of pituitary extract can be successfully accomplished in the great majority of cases, especially if the patient is at or past term. The initial dose is ½ cc., and this is repeated every half hour until regular uterine contractions occur. The administration is then discontinued. If the contractions begin to die away, the dose is immediately repeated. If the contractions are allowed entirely to cease, the whole process has to be repeated. The advantages of this method of induction are that (1) there is no instrumentation, and consequently less liability to sepsis; (2) no anesthesia is required; (3) there is less reluctance on the part of the patient than there is to submitting to the introduction of a bag. A series of 65 cases is reported, in 55 of which labor was successfully induced by the use of pituitary extract.—L. G. K.

HYPOPHYSEAL syndrome and decompressive craniotomy (Sindrome ipofisaria e craniotomia decompressiva). Gianettasio (N.), Riforma med. (Napoli), 1921, **37**, 177-179.

A report of a somewhat typical case with marked improvement following decompression.—G. V.

Action of HYPOPHYSEAL extracts on the bronchial muscles (Action de l'extract hypophysaire sur les muscles bronchiques). Hallion (L.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1587-1590.

The injection of very small doses of extract of hypophysis causes an augmentation of the amplitude of the respiratory movements. This occurs in dogs that have shown a diminished lung volume under larger doses of the extract. It is thought that this effect of small doses is due to a lowering of the pulmonary blood pressure, as the same result is obtained by compressing the vena cava.—T. C. B.

(HYPOPHYSIS) The influence of pituitary extract on gastric secretion (Der Einflusz von Hypophysenextrakt auf die Magensaftsekretion). Hess (W. R.) & Gundlach (R.), Arch. f. d. ges. Physiol. (Bonn), 1920, **185**, 137-140.

There is no marked effect. The initial slight decrease in secretion-volume is probably psychic.—A. T. C.

Tumor of HYPOPHYSIS (Hypophysentumor). Hirsh (O.), Wien klin. Wchnschr., 1921, **34**, 79-80.

Demonstration of a man of 27 who had been operated upon for tumor of the hypophysis 4 years ago with splendid success. Three years after the operation the eye symptoms reappeared. It is impossible to completely remove tumors of the hypophysis when the method of Krause is used. Therefore, this operation must be followed by a treatment with radium. In two cases of acromegaly the patients were cured by its use. Not all cases end so happily. In 28 cases a splendid result was obtained 5 times.—J. K.

The influence of the HYPOPHYSIS on growth (Versuche über den Einfluss der Hypophyse auf das Wachstum). Klinger (R.), Arch. f. d. ges. Physiol. (Bonn), 1919, **177**, 232-238.

Weekly injection of fresh pituitary emulsion, or implantation of anterior pituitary into young guinea-pigs for from two to five months did not produce any definite influence on growth.—A. T. C.

Tuberculosis of the sphenoid and its relation to the HYPOPHYSIS (Ueber Tuberkulose des Keilbeins mit Beziehungen zur Hypophyse). Kurzak (H.), Inaug. Diss. Cologne, 1919-1920.

The author reports a case of a patient in whom the clinical diagnosis of empyema of the sinus sphenoidalis was made. Post-

mortem, a tuberculosis of the sphenoid was found, which had reached the hypophysis. This is one way in which the hypophysis can become the seat of tuberculosus changes; it is rare that a tubercular meningitis is the primary cause. Tuberculosis of the hypophysis as the cause of a miliary tuberculosis does not seem to be so very rare. There do not exist typical symptoms of tuberculosis of the hypophysis. In cases in which there are eye symptoms, as they are seen in hypophyseal disorders, without symptoms of acromegaly we must think of the possibility of a tuberculosus infection of the hypophysis.—J. K.

(HYPOPHYSIS) Tumor of the pituitary. McArthur (L. L.), Surg. Clinics of Chicago (Phila.), 1918, **2**, 691-700.

The report of a patient 35 years of age who has been suffering from severe headaches at intervals for two years. The diagnosis of pituitary tumor was based upon the symptoms of intra-cranial pressure and the x-ray findings. Operation was carried out through the McArthur frontal approach.—J. F.

Removal of HYPOPHYSIS (Hypophysenexstirpationen). Oehlecker, München. med. Wchnschr., 1921, **68**, 121.

A short note. In a case of acromegaly and another one of dystrophia adiposo-genitalis, a good result was obtained after removal of the hypophysis. In three other cases a tumor of the brain invaded the hypophysis. In two of them the outcome was at once fatal, in the third one a temporary remission was seen before death. —J. K.

Tumors of HYPOPHYSIS (Hypophysentumoren). Oehlecker, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 228.

The author demonstrated two patients who had been operated upon by the method of Schloffer-Chiari. One with acromegaly has slightly, the other one with dystrophia adiposo-genitalis largely improved.—J. K.

(HYPOPHYSIS) Experiments with pituglandol in DIABETES (Einige Versuche mit Pituglandol bei Diabetickern). Schild, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 611.

Injections of pituglandol are followed by a decrease in the quantity of sugar in the urine.—J. K.

The influence of the anterior lobe of the HYPOPHYSIS in the development of the albino rat. Sisson (Warren R.) & Broyles (Edw. N.), Johns Hopkins Hosp. Bull. (Balt.), 1921, **32**, 23-30.

The desiccated powder of the anterior lobe of the hypophysis of young calves was fed to albino rats of a standard stock. The experi-

ments were begun when the animals were three weeks old and lasted for periods of 8-10 weeks. Sixty-eight animals were used, one-half serving as controls. They were observed for differences in activity, in the condition of their fur, in their nutrition, and in their skeletal development. Special emphasis has been laid upon differences in external sex characters, changes in body weights and differences in the microscopical findings in the reproductive organs and the endocrine glands, after hypophysis feeding. Dietary precautions were taken in order to differentiate the effects of food and the gland substance. The hypophysis-fed animals developed normally and showed no significant deviation beyond the normal variation of their species. Careful autopsies revealed no significant differences in organ weight or structure.—J. F.

Some modifications induced by parabiotic union of the hypophysectomized to the normal tadpole. Smith (P. E.), Anat. Record (Phila.), 1921, **21**, 83.

Hypophysectomized tadpoles were united at an early stage to normal larvae. Both members of four pairs completed metamorphosis, and several pairs reached a nearly maximal larval size. In every case the pigmentary and endocrine disturbances typical of hypophysectomy were modified. Albinism, though evident, was only partial. The **thyroids** of the hypophysectomized member, instead of being diminuitive, as would otherwise have been the case, were nearly normal in size, while those of the normal mate exhibited a slight hypertrophy. The **adrenal** cortex, while reduced, did not appear to suffer the same reduction as that which occurs in the typical albino.—W. J. A.

Upon the essentiality of the buccal component of the HYPOPHYSIS for the continuance of life. Smith (P. E.), Anat. Record (Phila.), 1921, **21**, 83.

When hypophysectomized and normal tadpoles were joined into parabiotic pairs by the tails, both completed metamorphosis. The members of a pair were liberated, when, in metamorphosis, the tails were resorbed. The hypophysectomized members soon died. The separation in no way embarassed the normal members of the pairs; they continued to display their usual activity.—W. J. A.

(HYPOPHYSIS) Does the administration of anterior lobe to the tadpole produce an effect similar to that obtained from THYROID feeding? Smith (P. E.) & Cheney (G.), Anat. Record (Phila.), 1921, **21**, 84.

The evidence indicates that a similarity of response is not evoked by thyroid and hypophyseal administration. The author concludes that the anterior lobe preparation used by Hoskins and

Hoskins contained an unusual amount of iodine and displayed an altogether unique activity.—W. J. A.

(HYPOPHYSIS) On narcolepsy (Zur Narkolepsiefrage). Somer (W.), Wien. klin. Wchnschr., 1921, **34**, 132-133, 147-149.

A description of two cases of narcolepsy. A cause could not be detected. It is possible that endocrine disturbances, especially of the **hypophysis**, play an important part. Jolly has described a case of narcolepsy with enlarged sella turcica. In the cases of Somer the sella was normal, but in one of them a calcium-infiltration of the **pineal** was suspected from the x-ray picture.—J. K.

Relations between the various cellular forms of the anterior lobe of the HYPOPHYSIS (Sur les relations unissant entre elles les diverses formes cellulaire du lobe antérior de l'hypophyse). Stewart (F. W.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 49-50.

Histological.—T. C. B.

The relation of the pars intermedia of the HYPOPHYSIS and the PINEAL gland to pigmentation changes in anuran larvae. Swingle (W. W.), Anat. Record (Phila.), 1921, **21**, 87.

Reported in full elsewhere. Previously abstracted.

(HYPOPHYSIS) Studies in metabolism. II. The metabolism of a very obese child with a small sella turcica (Typus Fröehlich?). Talbot (F. B.), Am. J. Dis. Child. (Chicago), 1920, **20**, 331-336.

The boy studied was 2 years and nine months old, had been born at full term and fed for the first nine months on drawn breast milk because his mouth would not open widely enough to permit him to nurse. He was thin and poorly nourished until one year of age, when he commenced to gain. His weight on entering the hospital was 54 pounds, 9½ ounces. The mentality was that of a 10-month child; he recognized the family, but did not talk, did not feed himself and was unable to stand alone. His voice was hoarse, his skin like satin, hair slightly coarse and great rolls of fat were present all over the body. Total basal metabolism was found to be that of a boy of the same age, that is 631 calories. Total metabolism in comparison with boys of same weight was found to be 37 per cent. below the average. Heat production per kilogram of body weight when compared with that of boys of same age was found to be 56 per cent. below the average and when compared with boys of same weight was 40 per cent. below the average. Talbot thinks that in children and infants there is a tendency for the fatter individuals to have a lower metabolism both per kilo of body weight and per square meter of body surface than for children of the

average weight. The child was given pituitary extract and it was found that when he did not receive the extract he gained in weight and presumably put on fat very rapidly, even on a diet containing relatively few calories. After the extract was supplied he lost weight and commenced to develop mentally.—M. B. G.

HYPOPHYSEAL anomalies (Hypophysäre Störung). Weggand, München. med. Wchnschr., 1921, **68**, 317.

The author demonstrated a mentally deficient girl with dwarfism, adiposity and glycosuria. Menstruation was normal. This disease is probably due to the hypophysis. He also showed a photograph of a very fat giant with atrophy of the genitals, but normal psychical functions. There was a hydrocephalus which certainly had an influence on the hypophysis. In another girl with adiposity and blindness a tumor of the hypophysis was found at autopsy. The photograph of Napoleon during the last period of his life shows adiposity; we know that he had had epileptic fits. Perhaps this was a hydrocephalus which influenced the hypophysis.—J. K.

The excretion of enzymes and the influence of the HYPOPHYSIS in diabetes insipidus (Ueber Fermentausscheidung und Hypophysenwirkung bei Diabetes insipidus). Wolpe (L.), Berl. klin. Wchnschr., 1921, **58**, 101-103.

In normal urine trypsin is not regularly found. In a case of diabetes insipidus trypsin was never found in the urine; pepsin and diastase were found, but not regularly. The influence of pituglandol injections on the quantity proves, according to the author, the importance of the hypophysis as the origin of the disease. (The work of Camus and Roussy, Aschner, Leschke and others, proving that the hypophysis has no relation to diabetes insipidus seems to be unknown to the author).—J. K.

INTERNAL SECRETIONS as conceived from the point of view of the practical physician. Kaplan (D. M.), N. York M. J. (New York), 1921, **113**, 227-230.

A characteristic article explaining to the uninitiated the almost unbelievable wonders of "the endocrines." The present article, as several previously published, is concerned with the various "endocrine tropisms" through which all physical, mental and spiritual peculiarities find an explanation. Indeed, Kaplan would have us believe that the entire purpose of life rests upon a thoroughly established endocrine basis. The **thyroid** is the chief equilibrizer of the human organism and is particularly endowed to maintain equipoise among the endocrine organs. The **pituitary** dominates dimension. The **adrenal** system is the chief source of energy. The **gonads** "insure the preservation of the race, being so endowed by nature and

through them the ego of man is conscious of his immortality." "Such states as lack of courage, melancholy, suicidal tendencies, dementia praecox, precocious adolescence, and immature senility, sadism and masochism, are all possible manifestations in a gonadatrop individual." "More than one living man has been cured of his so-called incurable and manifold complaints by the judicious administration of ovarian extract." "We know that measles, typhoid fever, diphtheria, mumps, and even syphilis in a patient does not signify that the infection was contracted by some unexplainable accident. On the contrary, we believe that the ability to contract these infections lies in the makeup of the individual. He selects this or that malady, and it is not the malady that selects him. The infectious diseases of childhood determine the tropism of the pathocrine constitution."—H. W.

(INTERNAL SECRETIONS) Obesity following encephalitis lethargica (L'obesité consécutive a l'encéphalite léthargique). Livet (L.), Bull. et mém. Soc. méd. d. hôp. de Par., 1921, **41**, 656-659.

Report of a case of obesity following encephalitis lethargica in which disturbances of menstruation occurred. The total syndrome suggests a repercussion of the infectious process to the endocrine organs, particularly: **hypophysis, thyroid** and **ovaries.** Hypophyseal therapy was beneficial.—F. S. H.

(INTERNAL SECRETIONS) Acrocephaly and scaphocephaly with symmetrical malformations of the extremities. Park (E. A.) & Powers (G. F.), Am. J. Dis. Child. (Chicago), 1920, **20**, 235-315.

In a consideration of the possibility of disorders of internal secretions as etiological factors in these conditions, Park and Powers state that, although they cannot offer evidence as striking as that contained in the work of Harrison to prove that growth and development of the limb buds is not determined by any organ or combination of organs of internal secretion of the fetus, they can bring forward considerations sufficient to render any such view extremely improbable. All facts at their disposal indicate that the embryo is dependent for its proper growth and development, not on its own, but on the parental organs of internal secretions. Though the medical literature is full of examples of abnormal conditions attributed to disturbances in the fetal organs of internal secretion and abounds in explanations of congenital defects and disease of the basis of insufficiency in the fetus' own endocrine glands, there is not one single pathologic condition which in the present state of our knowledge can be referred to that cause with any justification whatsoever. Furthermore, clinical observation teaches that disturbances in the function of the endocrine glands may give rise to changes in the body as a whole or at least in a variety of tissues (gigantism, acro-

megaly, dystrophia adioposo-genitalis, myxedema, hyperthyroidism, eunuchism) or to altered metabolic states, such as those seen after removal of the pancreas or parathyroids, but gives no indication that they produce alterations in parts of the body which are composites of tissues, such as the head, extremities, etc., to the exclusion of other parts. It is impossible to conceive that an organ of internal secretion can cause changes to occur in the bone muscles, connective tissue, fat and integument of certain divisions of the body and not act at all on the same tissues elsewhere.—M. B. G.

The organs of INTERNAL SECRETION in anaerobic infections (Les organes a sécrétion interne dans les infectiones a microbe anaérobies). Van Gehuchten (P.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 459-461.

A study of the glands of internal secretion **(adrenals, hypophysis, thyroid)** in sixty-five guinea pigs that had died of anaerobic infections. The changes observed were comparable to those occurring in other infections.—T. C. B.

[Metabolism and internal secretion]. Christoffersen (N. R.), Ugesk. f. Laeger. (Copenhagen), 1920, **82**, 838-850; 879-885.

The author reports some examinations on the metabolism made on 3 patients with endocrine disturbances. The first case was a man, aged 45 years, with signs of insufficiency of the **thyroid, adrenals** and **pituitary** glands, hypotonus of the **vagus** and **sympathetic** and possibly hyperfunction of the **parathyroids.** The other patient showed uncomplicated myxoedema. The third patient had acromegaly and myxoedema. The results of the examinations were as follows: Good renal NaCl-secretion is maintained in thyroid insufficiency when the adrenals are healthy and the pituitary either normal or diseased. Perturbed secretion is noted when thyroid, pituitary and adrenals are simultaneously affected. In some cases the NaCl-secretion is diminished after thyroid treatment. The secretion can be increased in a single day by pituitrin and hypophysin. The secretion can be increased very considerably by treatment with adrenalin. The data as a whole indicate that the regulation of the NaCl-secretion is mediated in man by the adrenals and pituitary.—K. H. K.

Mental disturbances at the MENOPAUSE and opotherapy (Troubles mentaux an cours de la menopause et opotherapie). Marie (P.), Bull. gén. de thérap. (Paris), 1921, **172**, 215.

Advocates opotherapy in combatting the mental disturbances of the menopause. The doses should be increased when the periods are expected and treatment should be carried out for long periods. —F. S. H.

The white blood picture during menstruation (Ueber das leucocytäre Blutbild während der Menstruation). Garling (K.), Deutsches Arch. f. klin. Med. (Leipzig), 1921, **135**, 353-357.

The blood was examined during menstruation in women who did not show changes in the irritability of the vegetative nervous system. The lymphocytes and monuclear cells had a tendency to increase, though this was by no means constant. A constant relation between eosinophilia and menstruation does not exist.—J. K.

Metabolism in vascular hypertonia (Ein Beitrag zum Stoffwechsel bei der vaskulären Hypertonie). Hitzenberger (K.) & Richter-Quittner (M.), Wien. Archiv. f. inn. Med., 1921, **2**, 189-216.

In primary as well as in secondary vascular hypertonia there always exists a hyperglycaemia, which is independent of the quantity of carbohydrates ingested. It is not due to a disturbed sugar metabolism, but to a permanent over-production of sugar. In cases of hypertonia with **diabetes** the blood sugar is always higher than the amount that would correspond to the quantity of sugar that is excreted with the urine. In vascular hypertonia the quantity of uric acid in the blood is often increased. This is not due to a retention, for the quantity of endogenous and exogenous uric acid excreted is often higher than normal and when an increased quantity of purin-bodies are given, they are excreted as usual. Thus this hyperuricemia cannot be compared to the hyperuricemia in gout. It is possible, though not sure, that hyperuricemia may be due to increased secretion of **adrenalin**.—J. K.

MONGOLIAN IDIOCY. Pardee (I. H.), Arch. Ped. (N. Y.), 1920, **37**, 10.

Data published elsewhere. See Endocrin., **4**, 662.—M. B. G.

(OVARY) The oestrous cycle in the mouse. Allen (E.), Anat. Record (Phila.), 1921, **21**, 43.

Diagnosing oestrous by the cell contents of the vaginal fluid, it was found that the average duration of the cycle in the mouse is from four to six days. There is little uterine discharge. Not all mice ovulate spontaneously during oestrous.—W. J. A.

(OVARY) Ovogenesis in the sexually mature mouse. Allen (E.), Anat. Record (Phila.), 1921, **21**, 44.

Allen finds that ovogenesis is not complete at birth or at puberty in the mouse, but continues on into sexually mature life. He concludes that the germinal epithelium of the ovary is homologous with that of the testis tubules.—W. J. A.

Invagination of the superficial epithelium and neoformation in the transplanted OVARY of the guinea pig (Invaginations de l'épi-

thelium superficiel et néoformation ovulaire dans l'ovaire transplanté chez le cobaye). Athias (M.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1647-1649.

Histological.—T. C. B.

An address on the nature of the OVARIAN function and the medical and surgical methods adopted to secure the benefits of the ovarian secretions. Bell (W. Blair), Lancet (London), 1920, **(ii)**, 879-884.

The author advances the view that normally the sex-development of the individual is not primarily dependent on the nature of the gonad, but the character of the sex pervades all the tissues of the foetus, including the sex-gland itself. The primary sex-characteristic is the predominance of maleness or femaleness in the fertilized ovum, and this predominance may be so slight as to be disturbed. This conception is advanced as an explanation of such experiments on the determination of sex, as the influence of nutrition on the final sex-characterization of the frog. All the glands of internal secretion are said to control the sex-functions, sex-characteristics, and sex-metabolism from the beginning as much as do the gonads, and, primarily, all owe their directive tendencies to the predominating sex-potentiality in the zygote. Certain partial hermaphrodites have all the mental and physical aspects of the opposite sex, in spite of their gonads, consequently when the sex-glands are out of co-ordination with the other organs of internal secretion, in regard to sex-characterization, they have little influence in this respect, and should not, therefore, be termed the primary characteristic on which the denomination of sex is based. Removal of the ovaries in a young sexually-active woman of a feminine type may cause very serious results. Consequently, if the ablation is unavoidable, substitution therapy should be undertaken. Ovarian whole gland substance, gr. v-x, with thyroid gland gr. ½, taken 3 times a day after food, is recommended. In cases of pelvic infection autoplastic ovarian grafting is advised. The ovaries should be implanted into the rectus muscle. This does away with the danger of the ovaries later having to be removed from the normal situation because they had become bound down with adhesions and become cystic. Of the author's cases menstruation occurred following ovarian grafts in 66.6 per cent of the cases in which menstruation was possible (38 out of 57 cases).

—L. G. K.

Cyclic changes in the OVARIES and uterus of the sow, and their relation to the mechanism of implantation of the embryos. Corner (G. W.), Anat. Record (Phila.), 1921, **21**, 52.

Oestrous in the sow averages twenty-one days in length. Ovulation is found to occur during oestrous; the **corpora lutea** complete their formation about the seventh day, and remain in full develop-

ment from the seventh to the fifteenth day, thus surviving just long enough to cover the period of attachment of the embryos. If no embryos are present the corpora lutea degenerate about the fifteenth day. At the same time changes are taking place in the uterus. The results indicate that there is a correlation between the state of the corpus luteum and that of the uterus by which the uterus is prepared, after ovulation, to receive embryos.—W. J. A.

(OVARY, THYROID) The effect of thyroidectomy on the oestrous cycle of the rat. Evans (H. M.) & Long (J. A.), Anat. Record (Phila.), 1921, **21**, 61.

Following thyroidectomy there was a pause in the oestrous cycle of from 6 to 27 days, but this was succeeded by normal cycles. Operations on young animals did not appreciably influence either the time of maturity or the length of the oestrous cycles when these appeared. Regenerated thyroids were found at autopsy in several of the latter group.—W. J. A.

Activity of the OVARY in pregnancy (interstitial cells) [Ueber die Tätigkeit des Ovarium in der Schwangerschaft (interstitielle Zellen)]. Fellner (O. O.), Monastchr. f. Gebs. u. Gynäk. (Berl.), 1921, **54**, 88-94.

Experiments are reported on rabbits in which the injection of ovarian lipoid material is shown to be more active in producing uterine hypertrophy than is corpus luteum lipoid, from which Fellner concludes that the interstitial cells of the ovary are likewise active as secretory agents, that they produce the same lipoid as the corpus luteum and that the activity of the interstitial cells in pregnancy is just as marked as is the activity of the corpus luteum. He also is of the opinion that the ovarian activity is increased during pregnancy. His experiments, however, are few and hardly seem sufficient to justify such sweeping conclusions.—F. S. H.

OVARIAN influence on blood-sugar (Beitrag zur Frage der Beeinflussung des Blutzuckers durch das Ovarium). Hürzler (O.), Monatschr. f. Geburtsh. u. Gynäk. (Berlin), 1921, **54**, 215-219.

Using rabbits as the experimental animals it was found that when that dose of **adrenine**, which when injected into healthy animals failed to produce a hyperglycemia, was injected into the same animals after removal of the ovaries, there occurred a marked increase of the blood sugar.—F. S. H.

(OVARY) The influence of lactation on the sexual cycle in the rat and guinea pig. Loeb (L.) & Kuramitzu (C.), Am. J. Physiol. (Balt.), 1921, **55**, 443-449.

Ovulation is suspended in the rat during lactation, but it continues to take place in the guinea pig. A possible explanation is that

in the rat the corpus luteum of lactation functions for a longer period of time than in the guinea pig.—T. C. B.

On the rapid maturation of the OVARY by transplantation of the youthful gonad to adults. Long (J. A.) & Evans (H. M.), Anat. Record (Phila.), 1921, **21**, 60.

Ovaries from immature rats, when transplanted to adults, become functional in from six to eight days. The authors think it is apparent that endocrine influences of the adult tissues are responsible for provoking this sudden maturation of the sex gland, which normally occurs from one to two months later.—W. J. A.

(OVARY) The interstitial gland ("Ein Mahnwort zum Kapital" Interstitielle Drüse). Meyer (R.), Zentralbl. f. Gyn. (Leipzig), 1920, **45**, 593-601.

The author studied the "interstitial sex gland" in women and comes to these conclusions: An interstitial gland does not exist. The Pubertätsdrüse is a word without any physiological meaning. Some authors have stated that this gland is situated in the cells of the theca, but girls in puberty have no increase in theca cells and these cells are already found in the sixth month of fetal life. A woman does not need ovaries for the development of the secondary female characteristics. A person without ovaries in whom interstitial cells of testicles are found may develop perfect female characteristics. A function of the theca cells is unknown, but it is highly improbable that it has anything to do with sexuality. The interstitial uterus gland that has been invented by some authors does not exist.—J. K.

(OVARY) The interpretation and clinical significance of uterine hemorrhage. Novak (E.), Med. Record (N. Y.), 1920, **98**, 43-46.

The underlying cause of menstruation is the **ovary**, and the **corpus luteum** the responsible constituent. The author outlines 3 types of uterine bleeding: (1) the purely anatomical type, as in uterine cancer; (2) the combined mechanical and functional group, as in myomata, adnexitis, etc., in which functional disturbance of the ovary is partially responsible, and (3) cases in which hyperplasia of the endometrium with hemorrhage is due to ovarian endocrinopathy.—H. L.

Grafts of the OVARIES of the goat or sheep (Sur la greffe d'ovaires de chevre ou de brebis). Retterer (Ed.) & Voronoff (S.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 104-106.

If an ovarian graft is successful, do all the elements of the ovary continue to survive? Is the ovary capable of producing mature ova and can it furnish an internal secretion? Two experiments on goats

are described. In one case, after double ovariotomy, one ovary was implanted in the interior of the right horn of the uterus; the other ovary was introduced into the left horn in such a way that one-fourth of the ovary was inside the horn, the other three-quarters outside. The graft was removed after nineteen months. In the second case, after double ovariotomy, half of an ovary taken from another goat was introduced into the right uterine horn, while half of one of its own ovaries was transplanted to the exterior of the uterus at a level with the bifurcation of the cornua. The grafts were removed in thirty-three days. The microscopic appearances are described. En résumé, all the elements of the graft in the cavity of the uterine horn were the seat of degeneration. In spite of this, the presence of the ovary in the uterus of a spayed goat determined the development of the maternal placenta. There is a brief critique of the work of others.—T. C. B.

Evolution of maternal placenta or caruncles after OVARIAN grafts (Evolution des placentas maternels ou caroncules après le greffe d'ovaires). Retterer (Ed.) & Voronoff (S.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 187-189.

Histological description of the uterine mucosa of the two goats in which the ovaries had been grafted into the cavity of the uterine horn, with a discussion of the results.—T. C. B.

(OVARY) The non-atresic graafian follicle in the rabbit (Sur le follicule de de Graaf non atrésique de la lapine). Salazar (A. L.), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1658-1660.

Histological.—T. C. B.

The Pflüger's cords of the adult rabbit OVARY; their atresia (Sur les cordons ovigènes de l'ovaire adulte de la lapine: leur atrésie). Salazar (A. L.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 235-237.

Embryological.—T. C. B.

(OVARY) The concentric corpuscles of the atresic granulosa of the rabbit (Chromatolytic period) [Les corpusules concentriques de la granulosa atrèsique de la lapine (période chromatolytique)]. Salazar (A. L.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 237-239.

Histological.—T. C. B.

OVARIAN function. Ovulation, corpus luteum and menstruation (Études sur la fonction des ovaries. Ovulation, corps jaune et menstruation). Schickele (G.), Gynec. et Obst. (Paris), 1921, **3**, 170-196.

Macroscopic and microscopic studies of the ovaries removed from a large number of patients because of one pathological condition and another, accompanied by observations of the menstrual period and uterine condition lead to the conclusions that the corpus luteum can be found in active condition during the week after the completion of menstruation; that the latter part of the menstrual period is accompanied by a hyperemic and secretory metamorphosis of the uterine mucosa, which may persist after cessation of the periods; that in consequence, a developing corpus luteum often is seen to coincide with a uterine mucosa in the state of metamorphosis, but that the degree of development is not necessarily the same for both; in fact, the uterine metamorphosis can take place without corpus luteum, and corpus luteum can develop without uterine transformation. There is accordingly a reciprocal independence of the two, and it is stated as a certainty that menstruation can occur in the absence of corpus luteum.—F. S. H.

The influence of optones from the OVARY on the secretion of milk (Die Wirkung der Ovarialoptonen auf die Milchsekretion). Weil (A.), München. med. Wchnschr., 1921, **68**, 520-521.

Abderhalden has prepared "optones" from different organs, which underwent sterile autolysis. In one case Weil could prove that injections of optones from the ovary increased the secretion of milk in woman.—J. K.

Formation of the definitive cortical layer in the rabbit OVARY (Formation de la couche corticale définitive de l'ovaire de lapin). Winiwarter (H. de), Compt. rend. Soc. de biol. (Paris), 1920, **83**, 1559-1561.

Histological.—T. C. B.

(PANCREAS) Carbohydrates in the surviving liver of depancreatized dogs (Sul comportamento degli idrati di carbonio nel fegato sopravvivente di cane spancreatizzato). Lombroso (Ugo), Riforma med. (Napoli), 1921, **37**, 429.

After removal of the pancreas the liver content of carbohydrates is very low—less than 1 per cent. During the survival period the liver hardly consumes them as well as the carbohydrates of the circulating blood. Upon adding a large amount of glucose to the circulating blood its consumption is remarkable, though a great deal less than that in the liver of a normal dog, during the digestion period. Therefore, the fat of the liver in dogs without pancreas is not used to form glucose, as some authors claim, in explanation of pancreatic diabetes.—G. V.

(PINEAL) A contribution to the study of the function of the glandula pinealis. Zandrén (Sven), Acta med. scand. (Stockholm), 1921, **54**, 323-335.

A youth of 16 years, 9 months, exhibited a number of abnormalities in development, namely, a considerable retardation of physical growth, retention of teeth, small testes and the absence of all secondary sexual traits. The anamnesis showed that he had developed normally to the age of ten, but that he had entirely failed to undergo the characteristic changes of puberty, and at the age of nearly 17 presented the appearance of a boy of 12. The clinical ensemble seemed to indicate **thyroid** insufficiency. But the absence of myxedematous affections of the skin, despite the very marked aberrations in development, may possibly argue against thyroid insufficiency. Four days before death ejection of blood occurred and laparatomy was performed on suspicion of ulcus perforans ventriculi; no ulcus nor peritonitis found. Collapse and death followed. Autopsy disclosed: Thyroid, 19 gm.; hypophysis, 9 gm.; thymus and adrenals, normal; testes hypoplastic with a microscopic appearance which fully corresponds with that of a 1-2 years old baby. Pineal gland missing (proved by microscopical search in serial sections). The function of the pineal gland is without doubt essentially of an internal secretory nature. Its principal task is the initiation of puberty, which probably is effected by an interaction between the epiphysis and the sexual glands. The granulation of the pineal cells observed by the anatomists at the age of 8 or 9 may possibly be the anatomical basis of the secretion. The absence of complete involution even at mature age argues that the gland has internal secretory functions also after puberty. The described case affords no support for a purely mechanical function, nor for any connection of the symptoms adiposity, cachexia and idiotism with disorders of the pineal gland.—J. A. H.

Postoperative tetany and transplantation of PARATHYROIDS (Postoperative Tetanie und Epithelkorperchenüberpflanzung). Burk (W.), Zentralbl. f. Chir. (Leipzig), 1921, **48**, 10-12.

Tetany developed after an operation for goiter in a boy of seventeen. As organotherapy and autotransplantation were unsuccessful 35 hours after operation a homotransplantation was carried out with temporary benefit. Death occurred in 6 days. However, at autopsy organs which had been transplanted were found to have been lymph-glands. The parathyroid that had been transplanted with autotransplantation had become necrotic.—J. K.

(PARATHYROID) Guanidin poisoning in mammals and its physiopathological importance (Guanidinvergiftung beim Saügetier und seine physiopathologische Bedeutung). Frank (E.), (Stern (N.)

& Rothmann (M.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 578.

Guanidin causes tetanic contractions of muscles. Still more poisonous is diurethylguanidin. This poison produces all symptoms of tetany. Guanidin and diurethylguanidin do not stimulate but increase the irritability of nerves and muscles. It is a function of the **parathyroids** to neutralize their influences.—J. K.

On the formation of the PARATHYROID immune bodies. Kishi (Isami), Tokyo, Igakkwai, 1920, **34**, (No. 9).

Correction Endocrinol., **4**, 678. The author immunized rabbits with horse's parathyroid gland tissue and made studies on complement fixation, precipitin, and cytolytic reactions. He found that the immune serum affects not only parathyroid, but also **thyroid, pineal, hypophyseal, suprarenal,** and lymph glands of the horse, while it was without influence on parathyroid tissue of dogs and rats. The serum, therefore, contained no genuine specific antibody.—Author's correction.

(PARATHYROID) Calcium metabolism and calcium in the blood of a patient with tetania parathyreopriva (Kalkstoffwechsel und Blutkalkunterssuchungen in einem Falle von Tetaniaparathyreopriva). Klein (C. J. J. G.), Deutsches Arch. f. klin. Med. (Leipzig), 1921, **135**, 161-172.

Report of a case of tetany after an operation for goiter. There was an enormous retention of calcium in the body. The more calcium was retained, the less intense were the symptoms and the less was the galvanic irritability of the peripheral nerves. When parathyroids were given by mouth the retention of calcium was somewhat increased. When an extract of parathyroids was injected the amount of retained calcium was a bit more. Much more calcium was retained when thyroid tabloids were given, though metabolism was markedly increased. The amount of calcium in the blood was normal and remained normal when parathyroids were given. However, it reached four times its original amount when 3 gr. lactate of calcium was given daily.—J. K.

(PARATHYROIDS) Treatment of tetany during the first years of life (Behandeling van de tetanie der eerste levensjaren). de Lange (C.), Neuratherapie (Amsterdam), 1920, —, 30-36.

Of no endocrine interest.—J. K.

On the internal secretion of Sandstroem's glands, PARATHYROID hypofunction and eclampsia. Massaglia (A. C.), Am. J. Physiol. (Balt.), 1921, **55**, 317-318.

After removal of two or three parathyroids (in dogs or cats) there are no nervous symptoms; they are in a condition of "latent

parathyroid insufficiency." Toxic substances in the blood may bring on tetanic symptoms, for the remaining gland will not be able to function efficiently. This gives a method for determining what poisons are neutralized by the parathyroids. Waste products were increased by means of pregnancy, impairment of kidney function, derangement of the liver, muscular fatigue and lead poisoning. The parathyroids neutralize the toxins from pregnancy, muscular fatigue and from the intestines; they do not neutralize phosphorus or lead poisoning. Hypofunction—especially in pregnancy—causes auto-intoxication which injures the liver and kidneys. Parathyroid hypofunction produces symptoms similar to eclampsia. This does not preclude the possibility of other etiological factors. In eclampsia caused by parathyroid hypofunction, prompt treatment with parathyroidin gives good results.—T. C. B.

Transplantation of PARATHYROIDS in postoperative tetany (Epithelkörperchenüberpflanzung bei postoperativer Tetanie). Polya (E.), Zentralbl. f. Chir. (Leipzig), 1921, **48**, 223-224.

The author tried to find at autopsy the parathyroids and examine them histologically. In many cases the organ that was believed to be a parathyroid proved to be a tuberculous lymph-gland. Therefore, he advises the transplantation of a part of the thyroid with its adnexae from a person recently dead. Histological examination is less useful. While the aspect under the microscope may be that of a parathyroid the largest part of the graft may consist of lymph or other tissue.—J. K.

(PINEAL) Pubertas praecox. Frank, München. med. Wchnschr., 1921, **68**, 29.

A boy of 11 became suddenly stupid, dull and complained of giddiness, headache and vomiting. The sexual organs developed rapidly, hair around the genitalia and on the legs, largely developed and a choked disk (optic neuritis) was observed. An x-ray was negative. The diagnosis is a probable teratoma of the pineal.—J. K.

(PINEAL) Pubertas praecox. Huebschmann, München. med. Wchnschr., 1921, **68**, 220.

Clinical details are not given. Post-mortem: Tumor of the pineal, large heart and larynx, the testicles were completely developed (age of the patient not given).—J. K.

(PINEAL) Lipodystrophia: report of a case (Ueber Lipodystrophie nebst Mitteilung eines Falles). Klien (H.), München. med. Wchnschr., 1921, **68**, 200-208.

In this case the atrophy of the subcutaneous fat was combined with nasal hydrorrhea, hypertrichosis, polakiuria and slight polyuria.

The author believes that these symptoms as well as the lipodystrophia itself may be due to changes in the pineal.—J. K.

(PINEAL) Pubertas praecox. Weigeldt, München. med. Wchnschr., 1921, **68**, 220.

Report of a case of a girl of 13 years and 8 months with normal female development. The author considers this as a case of hypergenitalism, because the girl had already menstruated. (It would be of interest to know what age the author considers as the normal age of puberty).—J. K.

The diuretic action of PITUITRIN. Stoland (O. O.) & Korb (J. H.), Am. J. Physiol. (Balt.), 1921, **55**, 305-306.

Experiments were made on large, healthy female dogs with a bladder fistula. The urine was collected in clean flasks packed in ice and determinations made every four hours. The results seem to show that pituitrin acts as a stimulant to the kidney in that it produces such a marked secretion of urine that the nitrogenous content of the blood falls far below normal.—T. C. B.

Dangers of injections with PITUITRIN (Gevaren van de inspuiting van pituitrine). Westerbeck van Eerten (B. J.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65**, 513-515.

In one case a dead child was born after an injection of pituitrin. In another an injection of pituitrin was given, the patient collapsed after the accouchement. The author's proof that these accidents were due to pituitrin is not very convincing.—J. K.

Maternal PLACENTA experimentally produced in the guinea pig (Placenta maternel expérimental de la chévre). Retterer (Ed.) & Voronoff (E.), Bull. d'obst. et gynéc. (Paris), 1921, **10**, 32-34.

These investigators transplanted ovaries into the uterine cornua and observed that the neighboring uterine mucosa produced tissue analagous to the maternal placenta during the degeneration of the implant.—F. S. H.

Action of the PROSTATIC liquid on the contents of the vesicular glands of new born or very young guinea pigs (Action du liquide prostatique sur le contenu des glandes vesiculaires des cobayes nouveau-nés ou tres jeunes). Camus (L.) & Gley (E.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 250-252.

It is shown that the coagulating action of "vesiculase" (prostatic ferment) on "vesiculine" (vesicular contents) is delayed in very young guinea pigs, due to the minute quantity of ferment present. —T. C. B.

Endocrinological studies of the PROSTATE. Macht (D. I.), Am. J. Physiol. (Balt.), 1921, **55**, 311-312.

Feeding prostate hastens metamorphosis of frog and salamander larvae, but unlike thyroid it causes no shrinkage of the animals. Extracts of prostate have no particular influence on the contraction of smooth muscle (fallopian tubes, bladder, etc.). Prostatic extracts hasten coagulation of blood, but it is due to kephalin, not to a specific substance. There is no effect on the intelligence (behavior) of albino rats. A study of the innervation of the prostate warrants the statement that it is more richly supplied by the true sympathetic system than by the sacral autonomics.—T. C. B.

(SEX) Is castration indicated in pseudo-hemaphroditic males (A propos d' un cas de pseudo-hermaphrodisme a type androgynoide regulier. La castration estelle indequée chez les pseudo-hermaphrodites males). Bérard (L.) & Dunet (Ch.), Gynec. et. Obst. (Paris), 1921, **3**, 226-232.

A description of a case of pseudo-hermaphroditism as given in the title, accompanied by a discussion as to the advisability of removing the gonads in such cases. In view of the possibility of development of a malignant tumor from the ectopic sex residue, and since the endocrine importance of such abnormalities is not proven, the authors consider total castration justified.—F. S. H.

(SEX) The early history of the germ cells in the brook lamprey, Entosphenus wilderi (Gage), up to and including the period of sex differentiation. Okkelberg (P.), J. Morph. (Phila.), 1921, **35**, 1-151.

The germ cells are segregated very early in the life of the animal even before the germ layers are definitely established. They are first recognizable when the mesoderm separates from the entoderm. The definitive germ cells take their origin from no other source than the primordial germ cells and the germ cells take no part in the production of somatic structures. Numerous germ cells are produced which do not become functional, and these degenerate and disappear during the process of development. The germ cells of each germ gland are usually of two kinds, namely, those showing a tendency toward rapid division (katabolic) and those showing a tendency toward growth (anabolic). The former are regarded as having a male, the latter a female potentiality. The relative proportion of anabolic and katabolic cells determines whether the larva becomes a male or a female. During this period the larva may be described as a juvenile hermaphrodite. The author feels warranted in concluding that each larva of this species carries the potentiality of both sexes, and that sex, therefore, is not irrevocably fixed at fertilization. When sex is once established, the germ cells belonging to

the opposite sex disappear or remain in the gland in a rudimentary condition.

(SEXUAL GLANDS) Rejuvenation by extirpation of the uterus (Totalextirpation des Uterus und Verjüngung). Leipmann (W.), Zentralbl. f. Gyn. (Leipzig), 1921, **45**, 302-303.

A short note. In many cases the women made a younger impression and showed stronger sexual desires. (It is not told why the patients have been operated. We know how the removal of a tumor, etc., may have an influence on a patient in relieving the symptoms.)—J. K.

Treatment of SPASMOPHILIA by calcium chloride and phosphated cod-liver oil (Le traitement combiné des manifestations spasmophiles par le chlorure de calcium et l'huile de foie de morus phosphorée). Rhomer (P.) & Vonderweidt (P.), Le Nourrisson (Paris), 1921, **9**, 87-95.

Feeling that the discontinuous effects of calcium administration in conditions of spasmophilia may in part be due to defective absorption, the authors made several studies of various methods of giving the compound, and checked their results by observations on the changes in the galvanic reactions of the patients treated. Twelve cases in all were studied. As a result of the investigation the conclusion is reached that from the first day on, large doses of calcium chloride (5 to 6 grams of the anhydrous salt or 10 to 12 grams of the crystalline salt) should be given accompanied by 5 grams of phosphated cod-liver oil (0.01 gram of Phosphorus per 100 grams of oil) twice a day. This medication is continued without interruption for 12 days. The calcium chloride is then omitted and the oil continued for several weeks. Good results are obtained.—F. S. H.

The action of SPLEEN extract on the activity of the frog's heart in situ and of the isolated perfused mammalian heart [Ueber die Einwirkung des Milzextraktes (Lienins) auf die Tätigkeit des Froschherzens in situ und des isoliert durchströmten Säugetierherzens]. Rothlin (E.), Arch. f. d. ges. Physiol. (Bonn), 1920, **185**, 111-121.

Stern and Rothlin's work on spleen extract (named by them "Lienin") suggests at least a specific metabolic product if not a hormone (J. de Physiol. et de Path. gén., 1919, **18**, 441), having a marked vasoconstrictor action on all surviving vessels. The action of "Lienin" on the heart is marked by two phases, the first occupying 10 to 15 seconds. The curarised frog's heart (in situ) shows first a decrease of tonus, slowing of frequency, and lowering of height of contraction, followed in the second phase by a decrease of frequency, with increase of height of contraction and slow recovery of tonus. The perfused mammalian heart shows at first an increase

of tonus, with decrease of frequency and extent of contraction, these being followed by increases in the second phase. Repeated injections give the same results, and will produce marked activity in a heart originally scarcely beating or at standstill. "Lienin," histamine, and "Pituglandol" have in these respects qualitatively the same action; quantitatively that of histamine is greater. This suggests that histamine is present as an active principle in "Lienin" and "Pituglandol."—A. T. C.

(TESTES) The existence of secretory phenomena in the vas deferens (Sur l'existence de phénomènes sécrétoires dans le canal déférent). Benoit (J.), Compt. rend. Soc. de biol. (Paris), 1920, **83,** 1640-1641.

Histological proof that the vas deferens is secretory.—T. C. B.

(TESTES) Interstitial gland grafting (Sugli innesti della ghiandola interstiziale). Falcone (R.), Riforma med. (Napoli), 1920, **36,** 1177-1180.

Falcone, of the University of Naples, reports four cases of grafting of ram testicle into the abdominal wall. The subjects were men, 74, 63, 53 and 69 years old, respectively, all of them sexually impotent. As regards the sexual condition and general health, all of the patients showed a remarkable improvement; in two patients even exaggerated sexual excitability resulted. Psychic influence was excluded since the patients did not know what effect was expected from the graft; and furthermore no psychical effect, the author adds, would explain the increased size of the testicles that followed. Without trying to draw definite conclusions from cases too recently operated upon, the author believes that from heterologous grafts encouraging results may be obtained as regards the sexual function, general euphoria, psychic condition and organic improvement.—G. V.

A case of transplantation of the TESTICLE (Ein Fall von Hodentransplantation). Förster (W.), München. med. Wchnschr., 1921, **68,** 106.

A testicle of a man of 20 was transplanted without success into a man of 55 with praecox senilis. The patient died 3 months after the operation; both the grafts had become necrotic.—J. K.

Quantitative experiments on the endocrine function of the TESTICLE (Quantitative Untersuchungen über die innersekretorische Funktion der Testikel). Lipschütz (A.), Deutsche med. Wchnschr. (Berlin), 1921, **47,** 350-351.

In guinea pigs one testicle was completely and the other one partly removed. When in a young animal only one testicle is removed the other one hypertrophies. If, however, the second testicle

is partly removed, the piece left behind does not become hypertrophied. When about 1/140 part of the normal testicles are left behind the animal develops normally. When still more testicular tissue is removed sexual development becomes slower. The histological examination of the piece, left behind in the body, shows marked changes. Degeneration of the spermatozoa may be found; at last they disappear completely. The same changes are observed after exposure to x-ray, transplantation or cutting of the vasa deferentia. On the other hand, the interstitial cells in the residues left behind are enormously increased in number and volume. These results are found in guinea pigs; in rabbits no growth of interstitial cells or degeneration of the spermatogeneous tissue could be detected. —J. K.

Two remarkable cases of TESTICLE implantation. Lydston (G. F.), N. York M. J. (New York), 1921, **113,** 232-233.

Case 1. Hypopituitarism was manifested in a subject, age 34; he showed feminine secondary sex characteristics and had sexual organs the size of those of a child of one year. He was inefficient mentally, physically and sexually. Left scrotal implantation of a single testicle was made. The implantation resulted in an improvement of nutrition, the appearance of frequent and violent erections and the power of coitus, a marked growth of pubic and axillary hairs and an enlargement of the penis and testis. The marked enlargement of the patient's own testis will probably make permanent the results of the implantation.

Case 2. A man, age 36 years, who at the age of 30 lost both testes because of a tubercular condition of these parts. The castration operation was followed by the loss of the beard, the acquirement of much fat of feminine distribution, alterations in the voice, loss of sexual power and mental and physical efficiency. Double implantation was made 2 years ago without much improvement. Ten months after first operation a single gland was implanted. This was followed by a decided physical improvement, a loss of 26 pounds in weight, disappearance of the nervous condition and pronounced sexual improvement. The author believes the results of this operation can be maintained by repeated implantations. —H. W.

The TESTICLE of a glandular hermaphrodite (Der Hoden eines Drüsenzwitters). Meixner (K.), Wien. klin. Wchnschr., 1921, **34,** 142-144.

In a child with female internal sexual organs a part of the left sexual gland was removed and proved to be a testicle. No clinical details are given.—J. K.

Further experiences on the transplantation of TESTICLE (Weitere Mitteilungen über Hodenüberpflanzung). Mühsam (R.), Deutsche med. Wchnschr. (Berlin), 1921, **47,** 354-355.

In a case of bisexuality and two cases of homosexuality favorable results were obtained. These results, however, were not observed immediately after the transplantation. In both cases of homosexuality it took 6 and 4 months before heterosexual signs were observed.—J. K.

Influence on sexual life of TESTICULAR transplantation (Beeinflussung des Geslechtslebens durch freie Hodenüberpflanzung). Mühsam., Berl. klin. Wchnschr., 1921, **58**, 182.

In two cases of homosexuality and in one case of eunuchoidism caused by castration a good result was obtained. No clinical details are given.—J. K.

The development of the antlers and its relation to the internal secretion of the TESTICLE (Ueber die Geweihentwicklung und ihre Abhängigkeit von der inneren Sekretion der Hoden). Olt., Deutsche med. Wchnschr. (Berlin), 1921, **47**, 491-492.

In the deer the development of the antlers depends upon the function of the gonads. Normally, when the antlers are full grown they become necrotic. When such an animal is castrated new antlers begin to develop. These show abnormal growth and finally kill the animal through cachexia. These abnormal antlers may be compared to a kind of papilloma.—J. K.

The mode of development of tumors of the interstitial gland of the TESTICLE of the horse (Sur le mode de développement des tumeurs de la glande interstitielle du testicule chez le cheval). Peyron (A.), Compt. rend. soc. de biol. (Paris), 1921, **84**, 461-464.

Of pathological interest.—T. C. B.

A case of tumor in an ectopic TESTICLE (Un caso di tumore in testicolo ectopico). Pizzagalli (L.), Il Morgagni (Milano), 1921, **64**, 133-119.

Of no endocrine interest.—J. K.

The results of ligation on the TESTICLE with special reference to the question of the puberty-gland (Unterbindungsbefunde am Hoden unter besonderer Berücksichtigung der Pubertätsdrüsenfrage). Tiedje (A.), Deutsche med. Wchnschr., 1921, **47**, 352-354.

If one testicle is removed in guinea pigs and on the other side the vas deferens is ligated the testicle develops normally in young animals, or in older ones first shows a degeneration, followed by a complete regeneration. If the ligation is made on both sides the results are the same. If only one side is ligated without removal of the other gland the testicle on which the operation is performed becomes atrophic, the other one hypertrophical. According to the author the spermatogenous part of the testicle is the cause of the

sexual characteristics. It has never been proved that the so-called interstitial cells have an endocrine function. There is not one reason to believe in a Pubertätsdrüse" as described by Steinach.
—J. K.

Contribution to the anatomical and pathological study of the THYMUS in infancy (Contributo allo studio anatomico e patologico del timo nella prima etá). Canelli (A.), Pediatria (Napoli), 1920, **28**, 1003-1019; 1056-1070; 1108-1122.

Canelli reports from Foa's laboratory at Turin University a study of 119 thymuses, 7 per cent of which were derived from cases of status thymicus or thymico-lymphaticus. From the study of his own cases as well as of those published by others, he draws the following conclusions: In new born children, either premature or not, there may be found status thymicus or thymico-lymphaticus (congenital), as indicated by hyperplasia of the lymphoid elements of the gland. These conditions may be clinically connected with mors thymica, though the anatomo-pathological finding does not always show this. Owing to the constant hyperplasia of the lymphatic tissue in both varieties we may conclude that in new born there may be either a status lymphaticus or a s. thymico-lymphaticus. Nearly all thymus glands in these conditions are above the normal weight (13.8 gm.), but as regards the cortico-medullary index there is no characteristic change, nor is there in the number and size of the Hassel's corpuscles in the nuclear picnosis, nor in the number of the eosinophiles. Hyperplasia of the lobules is constantly found. There is always augmented development of the follicles of the spleen (number and volume), but neither congestion nor increased weight is characteristic. The peripheral lymphatic glands may be macroscopically normal, but microscopically, they always show in their cortex many compact follicles. The lymphatic tissue in the rhinopharynx is always involved; it is doubtful, however, whether the hyperplasia of the palatine and lingual tonsils is due to a lymphocytic proliferation or to diapedesis of lymphocytes through the epithelium. Eventually the vermiform appendix in such cases may be of a considerable length (8 cm.), but what is more important, nothing can be stated with certainty about the involvement of the lymphatic intestinal tissue in these cases. There is no lymphoid reaction of the bone marrow. The process of ossification is not influenced. Hyaline degeneration of the renal glomeruli is not found, nor is fetal lobulation of the kidney, such as is frequently seen in status thymolymphaticus of adults. The hematopoietic foci that can be found in the liver are independent of status thymolymphaticus. Hypoplasia of the blood vessels, especially of the aorta, is of doubtful occurrence in status thymolymphaticus of the new born. Characteristic lesions of the adrenals are not surely demonstrated in such cases, yet in two of Canelli's cases there was accentuated hypoplasia

of the medulla and a poor development of the chromaphil elements. This might lead to an imbalance in the interrelational functions of the endocrine glands. Nothing significant was noted in the hypophysis. Congenital thyroid struma is frequent, though not found in every case. Nothing abnormal was seen in the seminiferous tubules, but increase of fat in the canalicular epithelium was noted. There may be congenital malformations, though no relation can be demonstrated with the status thymolymphaticus. The color and condition of the skin are not characteristically altered. The length of the body is not above normal, but in some cases the weight may be increased.
—G. V.

Congenital bone fragility and the THYMUS. Contribution to the study of bone dystrophy in relation to the ENDOCRINE GLANDS (Fragilitá ossea congenita e timo. Contributo allo studio delle distrofie ossee in rapporto con le ghiandole endocrine). Frontali, Riv. di clin. pediat. (Firenze), 1920, —, —, (May); Abst., Pediatria (Napoli), 1921, **29**, 334-335.

The author reports a case of congenital fragility of bones in an infant three months and a half old, whose skull bones were of a parchment consistence and whose long bones, all very much reduced in size, had 33 fractures. The calcium metabolism and the calcium content in the blood showed no detectable abnormality. The thymus showed marked atrophy and sclerosis. Frontali thinks that a marked alteration of the thymus in the prenatal life might have influenced the osteogenesis. The other endocrine glands did not show any abnormality.

[Park and McClure's recent careful studies render very dubious the theory that the thymus has an influence on osteogenesis.]—G. V.

(THYMUS) A case of status thymolymphaticus with rickets (Un caso die stato timico-linfatico accompagnato a rachitismo). Gemma (G.), Pediatria (Napoli), 1921, **29**, 126-130.

Gemma of the University of Naples reports a case of rickets in which autopsy revealed parenchymatous hyperplasia of the lymphoid tissue of the thymus with hypertrophy of the spleen. The Wassermann reaction was negative in the child, but positive in the mother, hence syphilis might have played a part in the abnormality of the thymus and the development of rickets. Usually the condition of status thymolymphaticus is observed in cases of rickets with florid appearance. The marasmatic condition of the present case the author regards as probably due to insufficiency of the thymus with relative atrophy of Hassal's corpuscles.—G. V.

Lymphosarcome du THYMUS. Harvier (P.), Bull. et. mem. Soc. méd. d. hop d. Par., 1921, **45**, 374-381.

A case report of thymic tumor of no particular endocrine interest.—F. S. H.

Extirpation and transplantation of THYMI in larvae of Rana pipiens. Hoskins (Margaret M.), Anat. Record (Phila.), 1921, **21**, 67.

When one thymus is removed there is no compensatory hypertrophy of the remaining one, and the engrafting of thymic tissue does not affect the thymi of the host. None of the operations affects the spleen in size or appearance. The **gonads, thyroids**, and **parathyroids** remain unchanged. In some instances the **hypophysis** of the thymectomized larvae appear to be hypertrophied, but this is not always the case. Histologically, the hypophyses of the operated animals are normal.—W. J. A.

The effect of the THYMUS and MAMMARY on menstruation. Jacoby, (A.), N. York M. J. (New York), 1921, **113**, 243-244.

Mammary and thymus extracts alone or in combination, administered in 5 gr. doses three times a day over a period of 1 to 6 months, resulted in a diminution of both the duration and quantity of blood lost during the menstruation in 53 cases or 75 per cent of those considered. Such changes did not follow the administration of thymus extract alone (4 cases). Inhibition of the ovary alone is not sufficient to influence menstruation as shown by the failure of thymus extract to cause any change in the menstruation. On the other hand, a combination of the thymus and mammary extracts is quite effective in the control of the menstrual flow.—H. W.

The developmental topography of the THYMUS, with particular reference to the changes at birth and in the neonatal period. Noback, (G. J.), Anat. Record (Phila.), 1921, **21**, 75.

This is a topographical study in the fetus and new born.

W. J. A.

The results of THYMUS extirpation in the dog, with a review of the experimental literature of thymus extirpation. Park (E. A.) & McClure (R. D.), Am. J. Dis. Child. (Chicago), 1919, **18**, 317-521.

Park and McClure summarize the results of a careful and extensive series of experiments on the extirpation of the thymus in the dog as follows: Thymectomy failed to cause death. It did not produce rickets or any disease of the skeleton. It was impossible to be certain that it caused any alteration in the animal. A great minority of experiments suggested the possibility that removal of the thymus had caused a retarded or diminished growth of the skeleton and, therefore, of the animal as a whole; some experiments suggested that removal had provoked changes in the **thyroid** in the nature of hyperplasia, hypertrophy of the **suprarenal** or retarded

development of the testes. There is a cogent reason, however, which they wish to emphasize for believing that the changes in the various parts of the body mentioned were actually due to some other cause than deprivation of thymus function; they did not occur in combination in the same animal. It was concluded that the thymus gland is not essential to life in the dog. Extirpation of the thymus produces no detectable alteration in the hair, teeth, contour of the body, muscular development, strength, activity or intelligence of the experimental animal. Extirpation of the thymus does not influence growth or development. The possibility that it may cause retardation in development and delayed closure of the epiphysis, however, cannot be excluded absolutely. Extirpation of the thymus probably produces no alterations in the organs of internal secretion. It is possible that it produces well marked changes in the organs of internal secretion in the period immediately following thymectomy which was not covered in their experiments.—M. B. G.

The influence of the administration of THYMUS on weak animals (Die Beeinflussung minder veranlagter, schwächlicher Tiere durch Thymusfütterung). Romeis (B.), München. med. Wchnschr., 1921, **68**, 420-422.

Romeis has shown that when thymus is given to tadpoles they grow quicker and show metamorphosis before normal control animals. The same influence is observed when the fats and lipoids are removed from the thymus. The fats and lipoids themselves have, on the contrary, an inhibiting influence on the growth of the animals. In each generation of tadpoles many specimens are weak and are less developed than the others. Romeis has examined the influence of thymus on these weak animals, and found a most marked effect, for after some time the weak individuals had reached or even surpassed the control animals in size and development.—J. K.

The influence of x-ray treatment of the THYMUS on the excretion of uric acid (Ueber die Beeinflussung der Harnsauerausscheidung durch Röntgenbestrahlung der Thymusdrüse). Rother & Szego, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 578.

In some cases of Graves' disease the excretion of uric acid was largely increased after exposure of the thymus to x-rays.—J. K.

(THYMUS) Status thymo-lymphaticus. Stahr (H.), München. med. Wchnschr., 1921, **68**, 405-406.

An isolated status thymicus is not known with certainty, the existence of a status thymicus has never been proved. Status thymo-lymphaticus plays an important part in fatal diseases of children. —J. K.

Surgical treatment of hyperplastic THYMUS (Zur operativen Behandlung der Thymushyperplasie). Wirtz (C.), Inaug. Diss. (Cologne), 1919-1920.

A hyperplastic thymus from a child 5 weeks old. This organ was partly removed, because of the pressure from an intercurrent disease.—J. K.

(THYROID) The influence of specifically formed iodine compounds on the metamorphosis of frog larvae (Ueber den Einfluss spezifisch gebauter Jodverbindungen auf die Metamorphose von Froschlarven und von Axolotl). Abelin (J.), Biochem. Ztschr. (Berl.), 1921, **116**, 138-164.

Studies are reported of the influence of KI, NaI, NH_4I, KIO_3, Lugol's soln., di-iodo-salicyclic acid, di-iodo-phenyl-salicylate, iodopyrine, di-iodo-tyrosine, di-iodo-di-thymol, iodo-gallicin, iodized protein, non-iodized proteins, and tyrosine on metamorphosis of tadpoles. The results showed that certain type of organic I_2 protein derivates such as di-iodo-tyrosine and iodized protein are of importance at the beginning and during the course of frog larvae metamorphosis while the other compounds of non-protein derivative nature were ineffective. The active compounds act as does the thyroid substance itself. Their activity is to be taken into account when thyroid extracts or thyroid decomposition products are used. Similar results were obtained with axolotl.—F. S. H.

(THYROID) The presence of pathogenic cryptococci in the lymph-nodules of goitrous goats (Sur la présence de cryptocoques pathogènes dans les ganglions des chevreaux goitreux). Bachmann (A.), Bull Soc. path. exot. (Paris), 1921, **14**, 199-202.

Noting that the inguinal and axillary lymph-nodes were enlarged in a goat having a goiter, Bachmann examined the glands histologically. There was found to be present an organism which to all appearances was similar to that present in epizootic lymphangitis of the horse.—F. S. H.

(THYROID) Diagnostic methods in exophthalmic goitre, with special reference to quinine. Bram (I.), Med. Record (N. Y.), 1920, **98**, 887-891.

Bram stresses the importance of early diagnosis in this disease before all four cardinal symptoms have necessarily appeared. This is the period when treatment is most beneficial. Marked hyperthyroidism may occur without goitre or without exophthalmos. At this time differential diagnosis may be difficult. Kocher's blood picture of leukopenia with relative lymphocytosis is not a positive diagnostic test of exophthalmic goitre. Harrower's **thyroid** extract test is condemned because it may aggravate the disease and is not

always reliable. Administration of digitalis for diagnostic purposes is of no value. Complement fixation tests are still in the experimental stage. The **hyperglycemia** test is also not reliable, being positive in other endocrine diseases. **Basal metabolism** observations are valuable aids in diagnosis, but not always available and require intricate, costly apparatus with highly trained technicians. Bondouin and Porak's posterior lobe **pituitary** injection test is valuable. The Goetsch **adrenalin** hypersensitiveness test has lately been questioned as to accuracy, having been found positive in 48 per cent of 103 soldiers with the effort syndrome. Furthermore, it depends on aggravation of the symptoms. The author then describes a quinine test which he has employed in 160 cases, 67 of which were instances of thyroid toxemia. It is simple of application and harmless. Most normal individuals react to large doses of quinine by fullness and roaring in the head, tinnitus, impaired hearing, etc. Subjects of thyrotoxemia, on the other hand, are exceptionally tolerant to quinine, almost "immune" to it. The patient is given a dozen capsules, each containing ten grains of the neutral hydrobromide of quinine. He is instructed to take one capsule four times a day, to be washed down by an ample quantity of lukewarm water, an hour or two after meals and at bedtime. Patients susceptible to the drug complain after the first or second dose; normal individuals, as a rule, after thirty, forty, fifty grains, whereas the hyperthyroid subjects will not only not complain after over a hundred grains, but feel definitely improved. Bram thinks there may be a 5 to 10 per cent error in the use of his quinine test, but believes its simplicity and harmlessness offsets this.—H. L.

(THYROID) Epilepsy, anaphylaxis and dysthyroidism (Epilessia, anafilassi e distiroidismo). Buscaino (V. M.), Arch. Suisses de Neurol. et de Psych. (Zurich), 1920, **7**, 304-315.

Buscaino refers to a previous publication, in which he cited evidence that in genuine epilepsy as well as in epileptic crises, as found in paresis, and arteriosclerotic dementia, there is a form of dysthyroidism, characterized by formation by the thyroid of octahedric crystals of protein, which by entering into the circulation determine the epileptic seizure. The author especially insists on the participation of the endocrine action on epileptic fits, as demonstrated by the unbalance of the leucocytic formula and vagotonia. In his research on protein crystals in the thyroid he found their presence in 15 per cent of patients supposed not to be epileptic and in 84 per cent of epileptics or patients affected with epileptiform seizures, in cases of paresis, arteriosclerotic dementia, idiocy, cerebral tumor and urema presenting epileptiform convulsions.

—G. V.

The comparative effects of THYROID and of iodide feeding on growth in white rats and rabbits. Cameron (A. T.) & Carmichael (J.), J. Physiol. (Lond.), 1921, **54**, lxxiv-lxxvi.

The conflicting results of thyroid feeding on growth are due to inaccurate dosage; results depend on the proportion of thyroid to body weight. The method was, therefore, to base the amount of thyroid on the daily weight of the rat fed. Continual small doses of desiccated thyroid lead invariably to a decrease in the rate of growth, and hypertrophy of the organs concerned with increased metabolism—heart, liver, kidneys, adrenals. Sodium iodide has no effect on the rate of growth, and there is no hypertrophy. Full details are promised.—T. C. B.

Action upon the THYMUS of the ingestion of THYROID gland (Action sur le thymus de l'ingestion de glande thyroïde). Courrier (R.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 226-228.

A study of the functional correlation between the thymus and thyroid. The experiments were made on white rats and on cats. From 0.5 to 5 gms. of fresh thyroid were given daily. In one set of experiments the animals were kept on a diet that was insufficient to compensate for the augmentation of metabolism; they were in negative balance. In another series the diet was sufficient to keep the animals in positive balance. In the case of negative balance it is found that there was atrophy of the thymus caused by general lack of nutrition, but a comparative examination of all the organs showed a selective action on the thymus. In the case of positive balance, there was hypertrophy of the thymus, apparently due to a specific action of the thyroid. The author expects to show later that the above results confirm the theory that the thymus is the principal reserve organ for nucleoproteins.—T. C. B.

Morphology of THYROID (Morfologia della tiroide). Castaldi (L.), Gazz. de osp. (Milano), 1920, **41**, 1115-1116.

The author compared the weight of thyroids (found post-mortem) in Italians from different regions. All thyroids with abnormalities were excluded. The thyroid of people living in the mountains had a higher average weight than in people living on the plain. Goiter and hyperthyroidism are frequently observed on the mountains. A well developed pyramid of the thyroid and a large isthmus are much more found on the mountains than in the plain. These differences become clear after some years; at birth no constant differences are found.—J. K.

(THYROID) The blood in myxedema (Blutuntersuchungen beim Myxödem). Deusch (G.), München. med. Wchnschr., 1921, **68**, 297-298.

Data have been reported in Deutsche Arch. f. klin. Med., Vol. 130.—J. K.

(THYROID) Should the wound after operation for goiter be closed at once or drained? (Primärer Wundschlutz oder Drainage nach Strumectomie)? Dorn (J.), Zentralbl. f. Chir. (Leipzig), 1921, **48**, 111-114.

Of technical surgical interest.—J. K.

The effect of THYROID feeding on the oestrous cycle of the rat. Evans (H. M.) & Long (J. A.), Anat. Record (Phila.), 1921, **21**, 61.

In all cases thyroid feeding was accompanied by an increased consumption of food, but by a decrease in body weight. On the one hand, when the doses were very large, the cycle was lengthened or inhibited. With moderate doses, on the other hand, the oestrous cycles were usually not greatly disturbed. There consequently do not appear to be specific effects of thyroid substance on the oestrous cycle.—W. J. A.

(THYROID) Hereditary goitrous cretinoid degeneration (Sulla degenerazione gozzo cretinica ereditaria). Ferrara (M.), Riforma med. (Napoli), 1921, **37**, 117.

An interesting study of endemic thyropathy. Ferrara has observed that the children born of cretinous parents from Lavanone (Val di Sabbia) may be healthy, whereas the offspring of healthy parents who have migrated to Lavanone tend to be cretins. There seems to be no doubt of the endemicity of cretinism in this region, but there is no recognized difference between the condition of this and surrounding non-cretinous territory, as regards either water supply or terrain. Consanguinity of the parents was found to play an important role; with successive generations from affected parents the degenerative condition progresses from goitrous cretinoid to a true cretin state.—G. V.

(THYROID) Role of basal metabolism in diagnosis and treatment of hyperthyroidism. Freund (H. A.), J. Mich. M. Soc. (Grand Rapids), 1921, **20**, 35-37.

Discussion of the value of basal metabolism tests in diagnosis, especially in borderline cases in which the pulse may be normal. Report of five cases of hyperthyroidism with basal metabolism determinations.—C. M. W.

Carcino-sarcoma of the THYROID (Contributo alla conoscenza dei carcino-sarcomi della tiroide). Giavotto (G.), Pathologica (Genova), 1921, **13**, 95-98.

A case of carcino-sarcoma of the thyroid is described and illustrated.—R. G. H.

Creatinuria. III. The effect of THYROID feeding upon creatinuria. Gross (E. G.) & Steenbock (H.), J. Biol. Chem. (Balt.), 1921, **47**, 45-52.

The feeding of sheep's thyroid to a pig on a nitrogen-free diet calls forth a marked stimulation of creatine formation. This is accentuated when creatine precursors from exogenous sources are available. It is suggested that creatine formation is primarily dependent upon the balance that obtains between the arginase and oxidative systems whereby arginine is destroyed. Furthermore, it is suggested that the thyroid principle may be active in causing creatine formation by accelerating the oxidative system of arginine destruction at the expense of the effect of arginase and that in the thyroid mechanism is to be sought the variable responsible for the difference in reaction of men and women in protein feeding.

—F. S. H.

(THYROID) Strumitis (Beitrag zur Kenntnis der Strumitis). Hagenbuch (M.), Mitt a. d. Grenzgeb. der. Med. u. Chir. (Jena), 1921, **33**, 181-195.

A tedious description based on 47 cases, without novel data.

—J. K.

The THYROID gland and thyrotoxicosis. Hammer (A. W.), N. York M. J. (New York), 1921, **113**, 245-247.

Review of general interest; nothing new.—H. W.

Studies of the THYROID apparatus. I. The stability of the nervous system as a factor in the resistance of the albino rat to the loss of the PARATHYROID secretion. Hammett (F. S.), Am. J. Physiol. (Balt.), 1921, **56**, 196-204.

At the Wistar Institute there are maintained, among others, two colonies of albino rats which are descended from the same original pair. One of these, the "Experimental Colony," has been "gentled" and gives a uniform picture of placidity. Their threshold of neuromuscular reactions is very high. The other colony, the "Standard" stock, has come into only such human contact as is incident to cage cleaning and feeding. The picture as a whole is one of high irritability and neuromuscular tension. The author noticed that, following parathyroid ablation, not all animals died of tetany, and that the greater percentage of survivals occurred in animals from the "Experimental" colony; hence the present report. In all, 304 rats were operated upon. Complete thyro-parathyroidectomy resulted in a mortality from acute parathyroid tetany of 79 per cent in

the "Standard" rats, but only 13 per cent in the "gentled" rats. The same ratio was found when parathyroidectomy alone was done. "Gentled" rats of the third generation, when put from weaning under conditions exactly similar to those of the "Standard" stock, still showed a mortality of only 14 per cent. "Standard" rats had their mortality reduced to zero, when "gentled." There were no significant sex, size, weight or dietary variations. It is concluded that stability of the nervous system induced by petting produces a marked resistance to the loss of parathyroid secretion. The reason for this is briefly discussed.—T. C. B.

Acute hyperplasia of the THYROID with dyspnea. Harger (John R.), Surg. Clinics of Chicago (Phila.), 1919, **3**, 1417-1423.

Report of the case of a girl of 12 years who complained of marked dyspnea upon exertion associated with rapid enlargement of the thyroid gland of three months duration.—J. F.

(THYROID) Hypothyroidism, infiltration and hypertension. Harrower (H. R.), Med. Record (N. Y.), 1920, **98**, 854-856.

The occasional successful reduction of hypertension by thyroid extract is the basis for a theory that essential hypertension may be due to an infiltration of the tissues, "myxedeme fruste," with resultant pressure on, and narrowing of, the lumina of the arterioles in the precapillary areas, which cellular infiltration is a characteristic of hypothyroidism. Harrower considers this mechanical factor important in the production of hypertension. With this cellular clogging there is chemical stagnation, elaboration and absorption of toxins which in turn affects the adrenal mechanism. "In other words, thyroid therapy in cases of hypothyroidism with high blood pressure not merely removes a part of the accumulated toxemia, but at the same time favors a change in this mechanical obstruction in the circulation in these so-called 'precapillary areas.'" [It seems difficult to reconcile this theory with the hypertension not infrequently met with in cases of hyperthyroidism.]—H. L.

(THYROID) Diffuse colloid goiter (Die diffuse Kolloidstruma). Hellwig (A.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 324-325.

The surgery of goiter generally accepts two principles: Operation is wanted when the pressure on other organs is too marked or when there are toxic changes as in Graves' disease. It is generally believed that the ordinary goiter only acts in a mechanical way by pressure. This is not true. The author examined about 20 colloid goiters. Degeneration with atrophy as described by Lücke, Wölfler and others was never observed. A retention of colloid could never be detected. This proves that Breitner's theory that the colloid

goiter is produced by a retention of colloid and in this way gives rise to a hypothyreosis is not right. Always there were histological signs of hyperplasia with hypersecretion of colloid. Clinical symptoms are always symptoms of hyperthyreosis or of "formes frustes" of Graves' disease (perspiration, marked intelligence, tremor of hands and feet, goiter heart). On the other hand, the goiters of patients with Graves' disease prove to develop from a diffuse colloid goiter. The author considers patients with colloid goiter as very apt to get Graves' disease; operation may be desirable even when there are no symptoms of pressure.—J. K.

The effect of THYROID-feeding and of thyro-parathyroidectomy upon the pituitrin content of the posterior lobe of the pituitary, the cerebro-spinal fluid, and blood. Herring (P. T.), Proc. Roy. Soc. (London), 1921, **B. 92**, 102-107.

Six adult cats were fed with large quantities of fresh ox thyroid for from 2 to 3 weeks in addition to their ordinary diet. Six other cats were subjected to thyro-parathyroidectomy and then killed in from 3 to 6 days after the operation. The pituitrin content of the posterior lobes of the pituitary bodies of these two series of animals was found to be unchanged from that of a series of normal cats, when tested by the action of the extracts upon the contraction of the rat's uterus and the blood pressure of the pithed cat. There was no evidence of the presence of pituitrin in the cerebrospinal fluid of the fourth ventricle in normal, thyroid-fed or thyro-parathyroidectomized cats. The defibrinated blood of the three series of animals showed no appreciable differences in its action upon the rat's uterus. The blood of the thyroid-fed cats had a greater depressor action upon the circulation than had that of the normal animals. The blood of the thyro-parathyroidectomized cats exercised a pressor effect upon the circulation, accompanied by a contraction of the kidney and a diminution in the secretion of urine. It is suggested that this might have been due to the presence of guanidin, or allied bodies, in the blood of these animals.—L. G. K.

(THYROID) How to stop bleeding after operation for goiter (Zur Stillung von Blutungen aus dem Kropfrest nach Strumentomien). Hilgenberg (F. C.), Zentralbl. f. Chir. (Leipzig), 1921, **48**, 366.

Of technical surgical interest.—J. K.

THYROID removal from the horse (La tiroidectomia en los caballos). Houssay (B. A.) & Hug (E.), Rev. del Inst. Bacteriologico del Dep. Nacional de Higiene (Buenos Aires), 1920, May 11, No. 5.

Thyroidectomy in young horses determined an evident delay in body growth (size of body, sexual organs, teeth, etc.) and sometimes it produced cachectical death in a few months. Adult horses did not

present any apparent perturbation. Nearly every thyroidless horse experienced passing hypothermy. In some cases there appeared very prominent edema; and generally a depression in normal vitality was noticed.—B. A. H.

(THYROID) Does x-ray treatment of goiter produce adhesions (Experimentelles Beitrag zur Frage der Verwachsungen nach Strumenbestrahlung). von der Hütten, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 284.

The experiments prove that x-ray treatment of goiter produce adhesions which make an operation much more difficult. Therefore, it is advised not to use x-rays in treating goiter.—J. K.

(THYROID) Recent studies on the Flajani-Basedow's disease (Studi recenti sulla malattia di Flajani-Basedow). Japelli (A.), Riforma med. (Napoli), 1921, **37**, 82-84.

A review of recent literature and theoretical discussion of well known data. The author ascribes considerable importance to syphilis and tuberculosis as etiologic factors. Radiations of the thyroid and thymus are favored as therapeutic proceedure.—G. V.

The action of the THYROID on tadpoles (Ueber die Wirkung der Schilddrüse auf Kaulquappen). Jarisch (A.), Arch. f. d. ges. Physiol. (Bonn), 1920, **179**, 159-176.

The well known stimulating effect of thyroid substance on the development of tadpoles was proven on larvae of Bufo vulgaris by the use of differential diets. The effect was particularly marked in fasting animals with those running a close second which were fed protein, egg-yolk or starch plus the thyroid substance. The process by which the animals are hastened in their development is in fact a hastening of the disintegration of the larval form, not a hastening of the formation of the adult stage. This is attributed to the metabolic stimulating properties of the active principle of the thyroid.
—F. S. H.

[Standardization of THYROID preparations by use of Axolotl]. Jensen (C. O.), Hosp.-Tid. (Copenhagen), 1920, **63**, 505-515.

Standardization of thyroid preparations by measurements of the iodin content is not satisfactory, since the iodin content does not correspond to the therapeutic effect. Neither is the Reid Hunt acetonitrile method adequate on account of the varying resistance of the mice to the poison. Jensen investigated further, therefore, the availability of the tadpole metamorphosis method. He has continued Gudernatsch's experiments, especially on axolotls, and found that thyroid feeding and injection brought about metamorphosis. The experiments showed that injection of inorganic and some organic

iodin compounds (starch-iodin, iodized albumin) had no effect on the development; iodo-thyrosin had some influence, but not so much as thyroid preparations. Various of these preparations (iodothyrine, thyreoidine, etc.) were investigated. It was found that the effect was constant in any given preparation, but varied in the different preparations and was not dependent on the iodin content. Thyroidine of Vermehren had the same effect as the iodothyrine from Friedr. Bayer, although its iodin content is only 1/10 that of iodothyrine.—K. H. K.

Laryngeal function in THYROID cases. Judd (Edward Starr), Ann. Surg. (Phila.), 1921, **73**, 321-327.

The author concludes that the functional results following thyroidectomy, as concerns both phonation and respiration, are extremely good; that the disturbances which sometimes follow immediately after operation are temporary and normal functions will be restored in from a few days to a few weeks; that there is a very small group of patients who, following thyroidectomy, have a bilateral abductor disturbance which is slow in onset but very persistent. Its cause is not known.—J. F.

The action of THYROID and THYMUS on frog larvae (Zur Frage der Wirkung von Schilddrüse und Thymus auf Froschlarven). Kahn (R. H.), Arch. f. d. ges. Physiol. (Bonn), 1916, **163**, 384-404.

Aqueous solutions of fresh thyroid or thyroid tablets are thermostable and produce the same effect on frog larvae as thyroid gland. Thyroid and thymus tablets have the same action as fresh gland. Partial separation of the active constituent of thyroid can be made by extraction with 96 per cent alcohol, evaporation nearly to dryness, and removal of the "lipoid" substances which separate. The cloudy aqueous solution which remains is very active.—A. T. C.

(THYROID) Idiocy (Idiotie). Kellner, Berl. klin. Wchnschr., 1921, **58**, 424.

In some cases of idiocy thyroid therapy gave good results. No details are given.—J. K.

Extirpation of uterus and REJUVENATION (Totalexstirpation des Uterus und Verjüngung). Lahm (W.), Zentralbl. f. Gyn. (Leipzig), 1920, **45**, 601-602.

Leipmann has stated that rejuvenation may take place after extirpation of the uterus. He considers the ligation of the vas deferens as the same operation as extirpation of the uterus, for in both operations the natural excretory duct of the sexual gland is taken away. This is not at all true, for after ligation of the vas deferens histological changes occur in the testicle. The function of

the ovary is not changed after removing the uterus. It is, of course, possible that women with diseases of the uterus feel younger after removing this organ, but this has nothing to do with real rejuvenation.—J. K.

(THYROID) Eserine sulfate in the treatment of tachycardia (Le sulfate d' éserine dans le traitement des tachycardies). Lian (Camille) & Welti (H.), Bull. et mem. Soc. méd. d. hôp. de. Par., 1921, **45**, 559-566.

Favorable report from the use of 1 mg. of eserine sulfate after meals in the relief of tachycardias of thyroid origin.—F. S. H.

(THYROID) Healing by first intent or drainage after goiter surgery (Primärer Wundschlusz oder Drainage nach Strumectomie). Lotsch (F.), Zentralbl. f. Chir. (Leipzig), 1921, **48**, 589-590.

Of technical surgical interest.—J. K.

(THYROID) Myxedema. McGraw (T. A.), J. Mich. M. Soc. (Grand Rapids), 1921, **20**, 27-30.

Complete report of a case of myxedema with secondary involvement of pituitary and gonads. Trouble began five years ago. The first symptom noticed was oedema around the eyes. Menses became irregular and profuse, with occasional severe hemorrhages. Symptoms of myxedema gradually increased. The patient showed an unusual feature for myxedema, namely, pulse of 112 and temperature of 98.6. Physical examination showed the ordinary signs of myxedema plus prominent malar bones and chin with spacing of the upper teeth, all suggestive of acromegaly. She was given four grains of thyroid daily and began to improve, but in two weeks started to develop symptoms of hyperthyroidism. When by mistake in directions, ten grains of pituitary extract were combined with the same dose of thyroid, the symptoms of hyperthyroidism disappeared and did not return. After two months treatment all the symptoms of myxedema disappeared, menstruation became normal, and the patient later gave birth to a healthy full term child.—C. M. W.

(THYROID, TESTIS, HYPOPHYSIS) Researches on complement deviation in dementia praecox (Richerche sulla deviazione del complemento nei dementi precoci). Magauda (P.), Riforma med. Napoli), 1920, **36**, 908-909.

Following the negative results of Pellacani, Magauda chose as antigens testis, thyroid and hypophysis extracts from the glands of 8 patients. The material was obtained 12 to 14 hours after death. The sera were taken from cases of dementia praecox, choosing subjects preferably at the initial stage of the disease and showing paranoid and catatonic symptoms. Disregarding instances of incomplete

hemolysis, the author obtained with 20 sera deviation of the complement eight times with testis antigen and seven times with thyroid antigen. As regards the subjects affording antigens two showed complement deviation with both testis and thyroid antigens, one with testis antigen and two with thyroid antigen. Notwithstanding all the possible causes of error (more or less fresh antigens, period of the psychosis at the moment of death, the acuteness or chronicity of accompanying sickness, apt to determine endocrine disturbances) the results, though not all positive, are certainly such as to encourage further researches.—G. V.

Differential diagnosis between perichondritis laryngis and THYRIDITIS or strumitis (Zur Differentialdiagnose zwischen Perichondritis laryngis und Thyreoiditis bzw. Strumitis). Maier (M.), Berl. klin. Wchnschr., 1921, **58**, 230-232.

Of no endocrine interest.—J. K.

(THYROID) The emotional factor in the pathogenesis of hyperthyroid states (Le facteur émotionnel dans la pathogénie des états hyperthyroidiens). Marañon (G.), Ann. d. Méd. (Paris), **9**, 81-93.

Marañon reports and discusses his observations on some 48 cases of hyperthyroidism in connection with the emotional conditions present. He comes to the conclusion that the emotions have an indisputable influence in the pathogenesis of Basedow's disease; in general in all cases of hyperthyroidism. In the majority of cases emotion acts on subjects having a predisposition to hyperthyroidism and consequently sensitized to emotional shocks. In a much smaller number of cases emotion acts as a first cause in normal subjects from the thyroidal point of view. This pathogenetic action of emotion on the thyroid is well explained on the basis of our actual knowledge of the intervention of the endocrine glands in the emotional act and does not contradict the generally accepted idea of the thyreogenous origin of Basedow's disease. These facts explain the great etiologic importance of prolonged emotion; and the great frequency of cases of Basedow's disease of emotional origin at the critical age and particularly in women.—F. S. H.

(THYROID) Exophthalmic goiter: removal of the right lobe and the isthmus. Moorhead (Edward Lewis), Surg. Clinics of Chicago (Phila.), 1919, **3**, 1205-1214.

Report of a case in a seamstress of 20 years with goiter, prominent eyes, and a rapid heart. The differential diagnosis and treatment are discussed. Emphasis is placed on the surgical cure of the disease.—J. F.

Multiple tumors of the THYROID. Moorhead (E. L.), Surg. Clinics of Chicago (Phila.), 1920, **4**, 1051-1054.

A case report of a woman of Austrian descent, aged 53, who had a swelling in the region of the right lobe of the thyroid for 32 years. She was the mother of four children. One daughter had been operated upon at 26 years for exophthalmic goiter.—J. F.

(THYROID) Graves' disease and x-ray treatment (De ziekte van Basedow en Röntgenbestralingen). Orbaan (C.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65**, 1576-1578.

Careful x-ray treatment may be useful.—J. K.

(THYROID, HYPOPHYSIS) Biddy and the coal bin. A case of polyglandular disease. Pitfield (R.), Med. Record (N. Y.), 1920, **98**, 351-352.

A picturesque sketch of a pathetic, gloomy, shrivelled woman of 42, evidently an example of infantile **myxedema**, with added pathological conditions due to **oophorectomy**, magically transformed, as it were, by administration of thyroid and pituitary.—H. L.

(THYROID) Specific dynamic action of thyroxin. Plummer (H. S.) & Boothby (W. M.), Am. J. Physiol. (Balt.), 1921, **55**, 295-296.

The specific dynamic action produced by intravenous injection of varying amounts of thyroxin in sixty-nine cases of myxedema and hypothyroidism is reported, with tables. Thyroxin undoubtedly has a specific dynamic action, increasing the metabolic rate in proportion to the quantity actively present in the body.—T. C. B.

Organ therapy in THYROID and allied disorders. Rogers (J.), Med. Record (N. Y.), 1920, **98**, 631-639.

Rogers finds the nucleoproteins of thyroid glands less toxic and more beneficial than the dried entire organ extracts. The pig had a higher iodine content than the sheep thyroid, and beef thyroid was not satisfactory. Standardizing by iodine content, 1 per cent, 2, 5 or 10 per cent, corresponded to 1/100, 1/50, 1/20, or 1/10 grain pig or sheep thyroid nucleoproteins, which clinically and for dosage is equivalent to ⅛, ¼, ½ or 1 grain of the dried powder from the entire gland. Nucleoprotein preparations of **pituitary, parathyroid, adrenal, ovarian** substances, etc., were then made and found more efficacious than any desiccated entire gland. Hypodermically, nucleoproteins or coagulable portions of aqueous thyroid extract excited no immediate response, but the residue given subcutaneously or intravenously excited prompt and vigorous reactions. Alcoholic extracts of thyroid were found to have the same physiological action as the non-coagulable hydrolyzed aqueous extract or residue. The thyroid nucleoproteins seemed more efficacious in typical myxede-

matous conditions; the residue, which is a vigorous vasodilator and stimulant, seemed most useful in chronic hypothyroid disturbance accompanied by high blood pressure or deficient gastrointestinal function. The varying types of hyper- and hypo-thyroidism and mixed states, and the manner in which one often merges into the other, are discussed. If thyroid is administered (injection of alcoholic extract or hydrolyzed residue) to voluntary muscles the end plates of which are fatigued but not exhausted, muscular vigor is immediately restored. The flow of gastric secretion, pancreatic secretion, urine, saliva, and involuntary peristalsis is similarly accentuated. The tachycardia of hyperthyroidism is not due to direct stimulation of the cardiac accelerator nerve by the thyroid product, but is an accompaniment of increased metabolism. Adrenal extract acts exactly opposite to thyroid—it will stop the stimulation previously induced by thyroid extracts. The adrenal nucleoprotein will inhibit gastric secretion more than 1:1000 solution of adrenalin. These adrenal extracts act upon the terminal filaments of the sympathetic system ("check" system, the vagus being termed the "drive" system). A case of myxedema with high blood pressure is presented; sufficient desiccated thyroid to relieve symptoms produced more troublesome signs of hyperthyroidism. When thyroid nucleoprotein was used no unpleasant symptoms appeared. Another patient, diagnosed as having forme fruste of hyperthyroidism, but in reality hypofunction, who had formerly been made worse by thyroid tablets, improved on thyroid nucleoprotein. Several other interesting case histories are added with observations on therapy with thyroid nucleoprotein of varying iodine strength, thyroid residue, and alcoholic extracts. Rogers claims to have seemingly saved life in some acute post-operative toxemias following thyroid extirpation by prompt administration of thyroid residue. Peculiar neuralgias and subjective dyspnoea are curiously relieved by the alcoholic extract of thyroid, but not by the nucleoproteins or residue. These peculiarities are not explained. Typical hyperthyroid cases are sometimes improved by adrenal therapy, since the latter checks the former through the sympathetic check mechanism. Several illustrative cases accompany the discussion. Some cases of gastric hyperirritability with high acid values and vomiting are remarkably improved by adrenal nucleoprotein; cases of gastric hypofunction and hyposecretion are improved by thyroid residue.—H. L.

A note on the relation between the weight of the THYROID and the weight of the THYMUS in man. Scammon (R. E.), Anat. Record (Phila.), 1921, **21**, 25-27.

The writer has utilized the recent data of Dustin and Zunz on the weight of the thyroid and the thymus in young adults who died within forty-eight hours after receiving wounds in battle. These

data have been compared with other figures on the weight of these glands in the new born, and the standard of deviation, the coefficient of variation and the coefficient of correlation between the two organs determined. These figures indicate that any correlation which may exist between the weights of the thyroid and the thymus is inconstant in postnatal life, and they offer little if any support to the theory of a direct functional relation between the two organs. —W. J. A.

Hyperplasia and hypersecretion of the THYROID in the young (Hyperplasie und Hypersekretion der Schilddrüse bei Kindern und Jugendlichen). Schlesinger (E.), München. med. Wchnschr., 1921, **68,** 531-532.

Hyperplasia of the parenchyma of the thyroid in countries with goiter may begin in newborn infants. It begins most frequently at the age of 6 in girls or 9 in boys. Then the number of cases rapidly increases with the age: ⅙ of the number of boys and ⅓ of the number of girls with hyperplasia of the thyroid have cardiovascular disturbances and often symptoms of hyperthyroidism. They are mostly very intelligent and show sexual precocity. Often the cases are complicated with a scoliosis and myopia.—J. K.

(THYROID) Graves' disease, its pathogenesis and treatment (De Ziekte van Basedow, haar pathogenese en Behandeling). Schulte (J. E.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65,** 1243-1251.

A general review.—J. K.

[A case of THYROGENOUS edema]. Scheel (V.), Ugesk. f. Laeger. (Copenhagen), 1920, **82,** 369.

A woman, aged 61 years, showed an ordinary edema (not myxedema) of her face and arms, but none on the lower limbs. The skin was dry and desquamating. There was no albuminuria or other signs of heart disease. Thyroid treatment was without effect on the edemata, but it made the patient nervous and tachycardia appeared. The patient died of bronchopneumonia. Autopsy showed atrophy of the thyroid gland, no abnormality of the heart and the kidneys, nor thrombosis of the veins.—K. H. K.

[Cases of papillomatous tumors of the THYROID gland]. Sennels (A.), Hosp.-Tid. (Copenhagen), 1920, **63,** 337-341.

Sennels describes two cases of papillomatous tumors of the thyroid gland. In one of the cases there had been slight symptoms of Graves' disease, but they had disappeared; after that the papillomatous tumor had developed. Such tumors seem to be rare; only 17 cases have been published before. The tumors seem ordinarily

to be malignant. The author mentions that corresponding tumors of the thyroid are found commonly in certain American salmon, caused by a nematode (Gayland and March). —K. H. K.

THYRO-PARATHYROIDECTOMY in the sheep. Simpson (Sutherland), Am. J. Physiol. (Balt.), 1921, **55**, 281.

Five animals, four of which were pregnant ewes, over five years of age were operated upon. A sixth was kept as control. The chief point of interest is that no manifestations of acute tetany were observed, even in the pregnant state, to follow removal of the parathyroids, except in one case, after many months. Autopsy on two of the sheep showed no accessory parathyroids, but some thyroid tissue.
—T. C. B.

(THYROID) Changes in the muscles in myxedema (Muskelveränderung bei Myxoedem). Slauck, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 172.

Heidenheim has found that in myotonia atrophica there are so-called circular fibers; these are fibers that surround the ordinary muscle-fibers. Slauck found these circular fibers still more distinctly in myxedema with hypoplasia of the ordinary muscle-fibers. In cachexia strumipriva this was seen too. It was not possible to get these circular fibers in an animal by removing the thyroid. In dystrophia musculorum progressiva or myasthenia these fibers are not seen.—J. K.

(THYROID) The management of toxic goiter with radiation. Stevens (J. T.), N. York M. J. (New York), 1921, **113**, 247-248.

Metabolism tests show that at least 90 per cent of toxic goiters can be cured by proper röntgen therapy.—H. W.

(THYROID) A study of the correlation of the basal metabolism and pulse rate in patients with hyperthyroidism. Sturgis (C. C.) & Tompkins (Edna H.), Arch. Int. Med. (Chicago), 1920, **26**, 467-476.

This report shows that there is a fairly constant relation between the resting pulse rate and the basal metabolism in hyperthyroidism. Determinations were made on 154 patients with hyperthyroidism. A tachycardia of 90 or more was found associated with a plus basal metabolism of 15 per cent or more in 84 per cent. When the metabolism fell to normal there was a drop in the pulse rate in 78 per cent of the cases studied. This is of practical importance in differentiating nervous conditions from hyperthyroid conditions.
—F. S. H.

(THYROID) Surgical treatment of Graves' disease (Chirurgische Behandlung der Basedowschen Krankheit). Sudeck, München. med. Wchnschr., 1921, **68**, 499.

There are three forms: 1, the classical Graves' disease, which is a typical dysthyroidism and has a typical bloodpicture; 2, thyroidism; 3, formes-frustes. The best treatment of the classical disease is resection of both lobes of the thyroid with ligation of the 4 arteries. In some cases the whole thyroid is removed and thyroid tablets are given the patient. From these last cases he reports 100 per cent cases. Removal of the **thymus** is not necessary. In thyroidism the effect of surgical treatment is not so good. Perhaps the **thymus** plays a certain part in these cases.—J. K.

(THYROID) Endemic goiter as a public health problem. Tolman (Mayo), Am. J. Pub. Health (Concord, N. H.), 1920, **10**, 434.

This paper presents briefly the results of a survey of the state of West Virginia made by its Health Department to ascertain the frequency and distribution of goiter within this commonwealth. —J. F.

(THYROID) The MAMMARY glands of thyroidectomized goats (Die Milchdrüse thyreopriver Ziegen.) Trautmann (A.), Arch. f. d. ges. Physiol. (Bonn), 1919, **177**, 239-249.

Thyroidectomy produces harmful effects of a degenerative nature on the lactating mammary gland.—A. T. C.

(THYROID) Thyreo-tuberculosis or pseudo-Basedowian pulmonary tuberculosis (Thyreotuberculose ou tuberculose pulmonaire pseudo-Basedowique). Vanowski (W.), Ann. de méd. (Paris), 1920, **8**, 418-434.

This paper presents an extended discussion of the sign-posts and frequent concurrence of thyroid disorders and tuberculosis. The similarity of the symptomatology in its gross manifestations is noted both from the subjective and the objective points of view, and the literature on the subject is well covered. The opinion is expressed that prognosis is favorable in 90 per cent of the patients coming under observation providing a proper orientation between patient and physician is obtained.—F. S. H.

(THYROID) A case of erysipelas terminating in acute thyroiditis. Weeks (L. M.), Brit. M. J. (Lond.), 1920, (ii), 476-477.

A case is described in which, following recurring attacks of erysipelas on the face and buttocks, a long standing swelling of the thyroid gland increased in size and became very tender and hard. There was pain on swallowing, and within a few days fluctuation was felt. An incision was made and a cupful of pus evacu-

ated. From this a pure culture of streptococcus was obtained. The wound did not heal for three months, and during this period signs of myxoedema were noticed. The hair fell out, the skin became dry, the pulse was slow and mental depression was present. These signs as well as the original swelling disappeared with the closure of the sinus. About six months later a similar swelling was opened and a pure culture of streptococcus again obtained. Vaccine treatment is now being carried out.—L. G. K.

Acute malarial THYROIDITIS (Tiroiditis aguda de origen palúdica). Wieland (F.), Cron. méd. (Lima), 1920, **37**, 259-262.

Wieland cites a case of inflammatory process of the thyroid, presumably due to weak circulation or loss of blood in the capillaries of the glands as it was characterized by sphygmothermic dissociation and diarrhea. The former may be regarded as the exterior manifestation of lack of equilibrium in the sympathetic nervous system due to perturbations in the production of the thyroid hormones which also causes tachycardia. The diarrhea, according to the author, is a predominant sign of the sympathetic activity which is always constant in functional hyperthyroidism.—I. O.

The abstracts in this number have been prepared by the staff, assisted by

C. M. Wilhelmj, St. Louis.

With the permission of the editors, certain abstracts have been quoted from "Physiological Abstracts," "Chemical Abstracts" and from "Surgery, Gynecology and Obstetrics."

Vol. V. No. 6. Serial No. 22. *November, 1921.*

Endocrinology

The Bulletin *of the*
Association *for the* Study *of*
Internal Secretions

CONTENTS

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THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

COUNCIL

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THE object of this Association is to correlate the work and interests of many physicians and students throughout the world who are engaged in the study of the internal secretions and organotherapy, and by concerted effort to broaden knowledge in this field.

This Association is not limited to specialists. It includes in its membership physiologists, pathologists and other investigators in addition to a large number of physicians in active practice—leading men in this field in the United States and thirty other countries.

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ENDOCRINOLOGY

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ENDOCRINOLOGY is the official bulletin of the Association for the Study of the Internal Secretions. It is published in volumes of 600-800 pages. At present it appears as a bimonthly. It comprises original articles, authoritative reviews, critical abstracts of the endocrine literature and editorial discussions of timely topics.

Manuscripts of three types of original work are desired for publication:

a. *Clinical studies* of endocrine diseases and the part played by the endocrine organs as contributing factors in other diseases;

b. *Systematic studies* on endocrine therapy;

c. *Laboratory investigations* of endocrine problems.

Articles are accepted for publication with the understanding that they will appear in this journal only.

Manuscripts may be submitted in any modern language, and if found suitable for publication will be translated into English without expense to the authors. To insure a version, however, satisfactory to the author, it is desirable that the article be submitted, when feasible, in English.

Readers who encounter articles of endocrine interest in unusual periodicals or under captions not indicating such interest are requested to submit abstracts for publication.

Bibliographic form: Since ENDOCRINOLOGY is to a considerable extent a bibliographic journal, it is desirable that references should be given in *complete form*, quoting title of article, author, periodical, year, volume number and page. The references should be segregated on separate sheets for publication at the end of the article. Footnotes should be used sparingly and included with the text.

Illustrations: A reasonable number of illustrations suitable for zinc line reproduction may be included. Half-tone reproductions will ordinarily necessitate a reasonable charge to the author.

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Manuscripts may be addressed to the Editor, Prof. R. G. Hoskins, Ohio State Univ., Med. School, Columbus, Ohio, or to any of the members of the staff.

Correspondence relating to advertising and business matters should be addressed to Dr. W. H. Morley, Managing Editor Pontiac, Mich.

COMPLETION OF VOLUME V

This number of ENDOCRINOLOGY completes its fifth volume. You will observe that there is a total of 828 pages exclusive of the annual index. This is 114 pages more than the preceding volume, which was the largest to that time.

In this volume there have appeared thirty-nine original papers and editorials. The abstract department has contained 1174 items. The annual index in this issue makes all of this material readily accessible for study or reference.

For those individuals and libraries who bind their journals, a Title Page and Table of Contents will be found just preceding page 699 of this issue. This is a separate signature and may be removed by the binder and transferred to the beginning of the volume.

We wish to thank all who have contributed to the successful year just closing, and assure you that your co-operation is appreciated. On another page will be found the titles of some of the papers which will appear in the early numbers of Volume Six.

We wish you all a Merry Christmas and a Prosperous New Year.

1917 NUMBERS WANTED

We are very anxious to get hold of one or more sets of ENDOCRINOLOGY Vol. I (1917). If any of our readers wish to sell their set, or any single numbers of it, we would be glad to have you write us.

BACK VOLUMES FOR 1918, 1919 AND 1920

These back volumes can now be furnished complete at $5.00 per volume. If you have not secured these back volumes and wish them to complete your reference library on this subject we would advise ordering early as there are but a few sets of some years available.

VOL. V, NO. 1 (January-March, 1920)

Early this year we sold a number of sets for 1920 without the first number. We have recently secured additional copies and have been supplying this number to those who bought the broken sets. If you have been overlooked, send us $1.25 and we will send this number by return mail.

IN FUTURE NUMBERS

The following manuscripts are in the hands of the editorial department and will be published in early numbers of ENDOCRINOLOGY:

Effect of tissues other than thyroid upon the basal metabolic rate. J. C. Aub, Boston.

Spontaneous tetany following epidemic encephalis. L. F. Barker and T. P. Sprunt, Baltimore.

Early observations bearing upon pituitary function. Harvey G. Beck, Baltimore.

Some factors modifying the epinephrin reaction. J. B. Collip, Toronto.

Pathological and clinical significance of diffuse adenomatosis of the thyroid. Emil Goetsch, Brooklyn.

Childhood myxedema in North America. Murray B. Gordon, Brooklyn.

Water and salt metabolism in diabetes mellitus. J. Koopman, The Hague.

Hypopituitarism and its treatment. H. Lisser, San Francisco.

Influence of adrenal feeding upon the iodine content of the thyroid. J. Rogers, New York.

Studies on the cortical substance of the suprarenal capsule. Y. Tokumitsu, Igakushi, Japan.

Adrenal enlargement in rabbits. T. L. Squier and G. P. Grabfield, Ann Arbor and Boston.

Diabetes insipidus, pathogenesis and therapeutics. T. Stenstrom, Lund, Sweden.

Effect of iodothyrine and iodine on metamorphosis. E. Uhlenhuth, New York.

STATEMENT OF THE OWNERSHIP, MANAGEMENT, CIRCULATION, ETC., REQUIRED BY THE ACT OF CONGRESS OF AUGUST 24, 1912,

Of Endocrinology, published quarterly at Los Angeles, California, for October 1, 1921.

State of California } ss.
County of Los Angeles }

Before me, a notary public in and for the State and county aforesaid, personally appeared Paul C. Mason, who, having been duly sworn according to law, deposes and says that he is the Business Manager of The Endocrinology, and that the following is, to the best of his knowledge and belief, a true statement of the ownership, management, etc., of the aforesaid publication for the date shown in the above caption, required by the Act of August 24, 1912, embodied in section 443, Postal Laws and Regulations, printed on the reverse of this form, to wit:

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Business Manager.

Sworn to and subscribed before me this 30th day of September, 1921.
(Seal) ELIZABETH F. HILLMAN.
(My commission expires October 6, 1921.)

The Abstract Department

Beginning with January, 1916, the periodical literature on the internal secretions is abstracted exhaustively. The morphology, physiology, pharmacology and pathology of the thyroid, parathyroid, pineal and adrenal glands, the chromaffin tissues, the pancreas, gonads, hypophysis and thymus are included. Articles on the spleen, mammae, prostate, stomach, liver and intestines are dealt with only as they are of endocrine interest.

Especial attention is given to diseases of known or supposed endocrine origin, as diabetes, acromegaly, exophthalmic goitre, Addison's disease, the various dystrophies, scleroderma, etc. Articles on growth, menstruation and other functions subject to hormone control are included when they are of explicit or implicit endocrine interest.

Organtherapy is treated in detail.

The literature on the physiology, pharmacology and pathology of the autonomic nervous system is included as of presumptive endocrine interest.

In general contributions on surgical technique and on the spleen are omitted and those of highly technical interest are merely indicated as such. Articles which include nothing new either in the way of data or of significant viewpoint are ordinarily treated very briefly with a notation as to their general character.

The material is fully cross indexed. The index is checked with "Chemical Abstracts," "Physiological Abstracts," "Index Medicus" and other special bibliographies to insure completeness. Readers who chance to note omissions of articles of endocrine interest, and especially any which appear in unusual publications or under captions which do not indicate such interest, are requested to notify the editor.

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Boston Medical and Surgical Journal
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Endocrinology

The Bulletin *of the*
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Internal Secretions

November, 1921

CLINICAL REPORT OF A CASE OF GRAVES' DISEASE WITH RAPID IMPROVEMENT FOLLOWING THE ORAL ADMINISTRATION OF FRESH OX SUPRARENAL GLAND

S. SHAPIRO and DAVID MARINE

From the Laboratories of Montefiore Hospital, New York.

The following clinical report of a case of exophthalmic goiter presents several unusual features in addition to the classical manifestations of profound asthenia, emaciation, tachycardia, thyroid hyperplasia, tremor and exophthalmos. The more important of these were:

(1) Periods of pyrexia for which no assignable cause could could be found;

(2) Very low systolic blood pressure;

(3) Purpura with prolonged bleeding time, decreased platelet count, swollen and bleeding gums and a history of profuse menstrual hemorrhage; and,

(4) A rapid gain in weight and muscular strength, rise in blood pressure and decrease in bleeding time associated with administration of fresh ox suprarenal gland, but without any noteworthy changes in the pulse rate, exophthalmos or thyroid gland.

Case History: R. B., the patient, is a female, age 30 years, single, and a stenographer by occupation.

Family History: This is unimportant.

Past History: Aside from measles and diphtheria, the patient has never had any serious illness.

Habits: The appetite is always good. The bowels were regular until about two years ago. Since then she has been irregularly constipated.

Weight: Her average weight before the present illness was about 125 pounds.

Menstruation: Began at the age of thirteen and has been regular up to August, 1919.

Present Illness: During June of 1919 the patient first noticed the occurrence of irregular large and small black and blue spots on her thighs. She consulted her physician, who treated her without improvement. Soon the spots spread so that they were present on the abdomen and chest. These purpuric spots continued to develop for more than a month when, early in August of 1919, the patient developed a sudden profuse menstruation which lasted for sixteen days. She became so exsanguinated that a blood transfusion was performed. She also became very nervous, complained of palpitation of the heart, persistent dryness of the mouth, and increased muscular weakness. Nocturia two or three times each night developed about this time. A second uterine hemorrhage occurred at the time of the next menstrual period and is said to have ceased following the administration of thromboplastin. At this time abnormal prominence of the eyes was noted, her nervousness became more marked, the palpitation of the heart and dryness of the mouth persisted. She was losing weight steadily in spite of a good appetite. Physical weakness became profound. Purpuric spots covered her chest, abdomen, upper and lower extremities.

Her case was now recognized as one of exophthalmic goiter and she was advised to go to the mountains for a rest. She remained in the mountains two months and returned home in December of 1919 feeling better. Her menstrual periods during October and November of 1919 were within normal limits. In December of 1919 she had another profuse menstrual hemorrhage lasting fifteen days, which is said to have been controlled by the administration of thromboplastin. She then went to the country and remained until March, 1920. During these three months the menstrual periods appear to have been normal. However, her exophthalmos had increased so that her ability to read was impaired. There was further loss of weight and muscular strength. Her pulse rate averaged about 150 at that time. There has been amenorrhea since May of 1920.

Early in June of 1920 she went to a western sanitarium, where she remained for four months. Examination of the blood at that time revealed: Red cells, 3,300,000; white corpuscles, 12,700; hemoglobin, 73 per cent. The blood pressure was 150-60. The Wassermann reaction was negative; non-protein blood nitrogen was 25.3; and blood sugar, 100. The urine showed no albumin, sugar, casts or blood cells. The basal metabolic rate in June was + 68. Soon after her arrival at the sanitarium she had, according to her physician, a hemorrhage into the medulla, causing paralysis of the muscles innervated by the 7th, 9th and 12th cranial nerves on the left side. In the course of a few weeks the paralysis cleared up entirely. The purpuric condition,

however, persisted, so that she had considerable oozing from the gums and purpuric spots over the body. X-ray and radium applications to the thyroid were followed by violent reactions. Ligation of the left superior thyroid artery was performed September 1, 1920, and of the right superior thyroid artery on September 25, 1920. Following this, she improved sufficiently to return to New York about October 15th, at which time her metabolic rate was + 49.

She entered Montefiore Hospital October 20, 1920, complaining of nervousness, palpitation of the heart, profound muscular weakness and marked loss in body weight.

Physical Examination: General: The patient is a female adult, white, markedly emaciated and so weak that she is scarcely able to stand long enough to have her weight taken. The weight is 70 pounds. She perspires freely. The *Head* is normal in size and shape. The *Hair* is very thin and dry. The *Eyes* show marked bilateral exophthalmos. The pupils are equal and react sluggishly to light and accommodation. Von Graefe's and Stellwag's signs are present. Iritis is present in the left eye. The left fundus shows a petechial hemorrhage near the center of the disc. The right fundus is normal. *Ears:* The hearing is good. No tophi, no discharge, no mastoid tenderness are found. *Nose:* There are scab-like crusts of old and recent hemorrhages on the mucous membrane just within the external nares. *Mouth:* The teeth are fairly well kept, the gums are swollen and spongy; there is oozing of blood from the gum margins The tongue protrudes in the mid-line, is markedly tremulous and dry. Facial muscles show no abnormalities. *Neck:* A transverse scar is seen just above the level of the cricoid cartilage. The thyroid gland is symmetrically enlarged; a thrill is felt and bruit heard over each lobe. Carotid pulsations are forcible and visible. The cervical lymph glands are not enlarged. The *Chest* is of the flat type. The mammary glands are atrophic. The ribs are very prominent. Purpuric spots are seen over the chest. Marked suprasternal pulsations are visible. The lungs are clear and resonant throughout. *Heart:* The cardiac rate is 128. The beat is regular. The apex is in the fifth interspace in the mid-clavicular line; the apex beat is diffuse but forcible. The area of cardiac dulness is not increased. A soft, blowing, systolic murmur is heard over the apex; it is not transmitted. The *Abdomen* is scaphoid. Purpuric spots are seen chiefly over the lower portion. The abdominal wall is very thin. The liver, spleen and kidneys are not palpable. No masses are felt; no tenderness is detected. *Extremities:* No abnormalities are palpable in the long bones. There are a few purpuric spots on the arms and legs. The outstretched fingers show fine tremor. *Reflexes:* The knee jerk and ankle jerk are active. The abdominal reflexes are present. *Temperature:* The temperature of the patient has been ranging between 100° and 102° since admission.

Subsequent Notes: October 26. The patient's temperature still varies between 100° and 102°. She perspires readily, although kept

quiet in bed. Bleeding along gum margins is seen; calcium lactate, 1 gram t. i. d., is prescribed. Blood examination on this date showed: red cells, 3,800,000; white cells, 9,000; neutrophils 64%, lymphocytes 30%, mononuclears and transitionals 4%, eosinphils 2%; bleeding time eight minutes. The blood pressure was 95-60, the weight, 72½ pounds. Urine had a specific gravity of 1010, was acid, showed a very faint trace of albumin, with no sugar and no casts.

October 27. Glucose tolerance test using 50 grams of glucose gave no glycosuria in three hours.

October 31. The tolerance test was repeated, using 100 grams of glucose. No glycosuria appeared in three hours.

November 1. Started desiccated suprarenal gland, 0.3 grams t. i. d. The bleeding time was eight minutes. The weight was 70½ pounds.

November 4. The patient still complains of persistent dryness of the mouth. The temperature is normal for the first time since admission. The blood pressure is 100-60.

November 9. The patient is on a full diet. She is out of doors most of the day, but still unable to walk. Her weight is 73 pounds.

November 13. The blood pressure is 105-65.

November 16. The weight is 74 pounds.

November 18. Dryness of mouth and sweating persist. Coarse tremor of fingers is apparent.

November 22. Fresh ox suprarenal gland, 10 grams, t. i. d., is substituted for the desiccated suprarenal. The weight is 75½ pounds. The blood pressure is 115-75.

November 23. The patient had nausea and vomiting associated with cramp-like pains in the abdomen, probably due to the excessive administration of fresh suprarenal gland. This is discontinued.

November 27. Desiccated whole suprarenal gland, 0.3 gram, t. i. d., is started. The blood pressure is 110-70.

November 29. Desiccated suprarenal gland is discontinued and the administration of fresh whole ox suprarenal, 5 grams daily, begun. The weight is 75 pounds.

December 2. Temperature has remained normal since November 28. Between November 6 and November 28 the temperature has fluctuated between normal and 102°. The bleeding time is four minutes. The patient no longer complains of dryness of the mouth nor of sweating—symptoms that have been present since admission. She is now able to walk from bed to porch. New growth of scalp and axillary hair is visible. Urine examination shows: specific gravity, 1012; acid, very faint trace of albumin; no sugar; no casts.

December 6. The weight is 77 pounds. The blood pressure is 110-70.

December 12. Blood examination shows: red cells, 4,000,000; white cells, 7,500; neutrophils, 62%; lymphocytes, 30%; mononuclears and transitionals, 6%; eosinophils, 2%.

December 13. The weight is 83 pounds. The blood pressure is 115-70.

December 21. The weight is 87¼ pounds. The blood pressure is 115-70.

December 27. The exophthalmos seems slightly increased. The outstretched fingers show marked lessening of tremor. The patient is able to walk about the ward without dyspnea. The purpuric spots have disappeared. The weight is 94 pounds. The blood pressure is 115-70.

January 1. Temperature arose to 100.2° today. The abdomen is distended with gas. Nausea is complained of. Colonic irrigation and light catharsis are administered.

January 3. The temperature is normal. The abdomen is soft.

January 4. The weight is 99¼ pounds. The blood pressure is 120-70.

January 9. Fresh suprarenal gland is discontinued (for a control period). The patient still receives calcium lactate.

January 11. The weight is 101¾ pounds.

January 15. The blood pressure is 125-70.

January 18. The weight is 108 pounds. The temperature has remained normal since January 3. The patient feels quite comfortable. Palpitation and tremor are improved. The blood pressure is 120-70. The bleeding time is four minutes. Urine examination shows: specific gravity, 1010; very faint trace of albumin; no sugar; no casts.

January 25. The weight is 113 pounds.

January 31. The weight is 117¼ pounds. The bleeding time is five minutes.

February 1. Purpuric spots reappear over chest and thighs. Feeding 5 grams of fresh ox suprarenal cortex daily is begun. Blood examination shows: red cells, 4,150,000; white cells, 4,500; platelets, 40,000; neutrophils, 64%; lymphocytes, 26%; mononuclears and transitionals, 10% The bleeding time is 4½ minutes.

February 5. The patient is menstruating for the first time in nine months.

February 6. The temperature is elevated to 101.4°. The patient complains of headache and diarrhea.

February 7. The temperature is 100.8°.

February 8. The temperature is 101.8°. Diarrhea is still present. The blood pressure is 125-70.

February 9. The temperature is 102.4°.

February 10. The temperature is 102.8°. A severe chill was experienced during the night. The blood pressure is 125-70. The abdomen is distended. Tenderness is elicited over both ovaries. The bleeding time is four minutes.

February 11. The temperature is 102.8°. The stools are normal. The purpuric spots have disappeared.

February 13. The temperature is 99.4°. Desiccated ox suprarenal cortex, 0.3 grams, t. i. d., is substituted for the fresh suprarenal gland.

February 14. The weight is 112½ pounds. The temperature is normal.

February 21. Purpuric spots have returned. Desiccated whole suprarenal gland is substituted for the desiccated cortex. The weight is 115¾ pounds.

February 24. The blood pressure is 125-80.

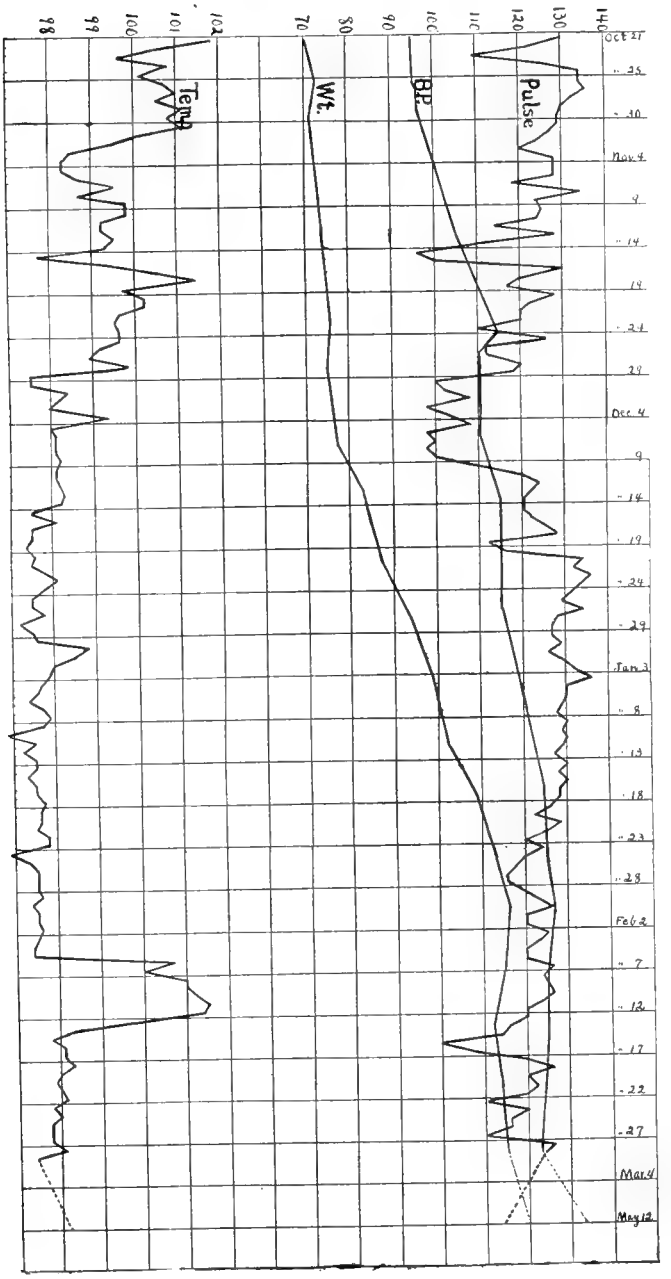
March 1. Purpuric spots are still present on the chest. The patient feels quite comfortable and is able to take considerable exercise without fatigue. She leaves the hospital today.

May 12. The patient returns for observation after having spent approximately 2½ months in the country. The temperature is 98.2°; the pulse, 112; blood pressure, 120-76; weight, 133 pounds. There is no tremor of the outstretched fingers. Muscular strength is excellent. Exophthalmos is possibly slightly less. There is no abnormal sweating. She sleeps well. Her appetite is good. A thick coat of scalp hair has grown. The skin is normal. The neck measures 34 cm. in circumference; the thyroid gland is vascular. The menstrual function has been regular. Purpura is absent. Subjectively the patient is quite comfortable and able to take considerable exercise daily without fatigue. Since leaving hospital the patient has taken one gram desiccated whole suprarenal gland daily.

DISCUSSION

Fever in uncomplicated exophthalmic goiter is rare, although patients suffering from this disease frequently complain of hot flushes and of feeling warm. If fever is present, it usually manifests itself as a very slight and fairly constant elevation of the temperature above normal. The febrile reaction in this case suggested a focal infection, but we were unable to find such a focus, and moreover there was no leukocytosis, nor did the pulse vary with the temperature.

Extensive studies on blood coagulation in exophthalmic goiter have been made in Kocher's clinic. These have uniformly shown a prolongation of the coagulation time in frank cases. Purpura is a rare complication. In our case exacerbations and remissions were observed which coincided with the withholding and administration of suprarenal gland. The bleeding time likewise increased and decreased with the appearance and disappearance respectively of the purpura. The patient showed a marked and rapid gain in weight, which began with the administration of desiccated suprarenal gland, and became more rapid after the fresh gland was substituted. Others, including Solis-Cohn and Crary, have observed rapid increases in the weight following the


Temp
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Pulse
98
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Oct 27
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Jan 3
Feb 2
Mar 4
May 12

administration of suprarenal gland. Oppenheim and Hoppe have reported similar rapid gains following the use of desiccated ovary and corpus luteum. Quite recently, Obregia has reported a series of twenty-one cases of exophthalmic goiter, including classical types as well as the so-called "formes frustes," in which he obtained a marked and rapid amelioration of the symptoms, excepting exophthalmos and tachycardia, by the administration of from 10-50 drops of a glycerol extract of whole fresh pig suprarenal gland by mouth. This author also claims that adrenalin alone seemed to have some beneficial effect, but negligible as compared with the glycerol extract of whole fresh gland. He was aware of the voluminous literature now available dealing with the untoward effects of adrenalin in exophthalmic goiter, and of the alleged hypersecretion of epinephrin in this disease.

Unfortunately, we were unable to make metabolic rate determinations during the period under observation, although in June a rate of + 68, and in September, a rate of + 49 were obtained in another institution. The right and left superior thyroid arteries were ligated September 1st and 25th, respectively. While increase in weight and general improvement frequently occur within two or three weeks after ligation, it is quite unusual to see such marked gains in weight unaccompanied by pulse and thyroid changes beginning after an interval of two months without improvement.

The systolic blood pressure remained relatively constant at 95 mm. for the first ten days after admission, and during the next 2½ months rose gradually to 125 mm. This likewise was coincident with the gain in weight and the administration of suprarenal gland. We do not believe there is any direct relationship between the administration of the suprarenal gland and the rise in blood pressure, and are inclined to believe that the improved vascular tone is more readily explained as a part of the general improvement. Other striking evidences of improvement were the return of the menstrual function and the new growth of scalp and axillary hair, the disappearance of the asthenia, the lessening of the tremor, the disappearance of abnormal sweating and dryness of the mouth, although the thyroid gland, as regards size, consistency, bruit and expansile pulsation, remained unchanged, as did also the pulse rate and exophthalmos throughout her stay of over four months in the hospital.

SUMMARY

Very rapid and striking improvement in the general nutrition of a case of exophthalmic goiter has been observed following the use of suprarenal gland. This improvement occurred during the administration of fresh ox suprarenal cortex, rather than during the administration of desiccated suprarenal gland. The observation contains an additional suggestion from the clinical viewpoint of a possible relative functional insufficiency of the suprarenal cortex as one of the underlying factors in exophthalmic goiter. Our experience suggests that fresh suprarenal cortex may be administered in five gram doses daily by mouth without untoward effects. Larger doses, especially of whole fresh suprarenal gland, caused nausea and vomiting, probably from direct irritation of the gastric mucosa by epinephrin. These doses are equivalent to much larger amounts of desiccated suprarenal gland than had been administered by the authors of the reports above referred to. Evidence, both experimental and clinical, is now rapidly accumulating that the suprarenal gland, and particularly its cortical portion, plays an essential and fundamental role in the etiology of exophthalmic goiter.

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TESTICULAR SUBSTANCE IMPLANTATION

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Brown-Séquard (1) in 1889 made a number of experiments with an extract produced from the testicles of various animals. He became so convinced of the beneficial effects of this material when injected into older animals, that he determined to experiment with it upon himself.

On May 15, with the assistance of his co-workers, he excised one of the testicles from a vigorous dog two years of age, cut it into pieces, ground it in a mortar with a small amount of water, and expressed the fluid. By filtration about 4½ c.c. of extract was obtained. He injected 1 c.c. of this extract subcutaneously into his own leg, repeating the injection about every five to ten days, until he had received ten treatments in all.

The last five were made from the extract of guinea pig testicles, which was injected under the skin of the abdomen and arm.

At this time Brown-Séquard was 72 years old, and so feeble that it was necessary for him to sit down after only half an hour's work in his laboratory. Although seated, he became very much fatigued after a few hours, and it was necessary to return home in a carriage, and immediately go to bed after a sparse and hurried supper. For the preceding ten years his weakness had been so great that he was unable to sleep, and arose excessively tired.

The day after the first injection, and still more after the others, he claimed that a radical change took place in him, and by the first of June he had regained all the force which he possessed a number of years before. A considerable amount of work in the laboratory scarcely tired him, and, to the astonishment of his principal assistants, he was able to experiment for many hours, and in walking about had no need for help. On May 23rd, after three and one-quarter hours of very fatiguing experimental work, he was so slightly tired that after dinner he was

able to begin work on the report of some very difficult problems. It had been twenty years since he had done any work after supper.

Because of a natural impetuosity, Brown-Séquard had the habit, up until he became sixty years old, of running up and down stairs. This gradually lessened, and it became necessary for him to hold to the balustrade, but after the second injection he regained his lost propensities, and without realizing it regained his old habit.

His limbs showed a very noticeable increase in strength. The flexors of his right arm registered 34 kilograms before, but after the treatments increased to 41. Particular attention had been paid for many years by him to the registering of this strength by the dynamometer.

He observed the force of the jet of urine, and affirmed that the greatest length of the stream during the six days preceding the first injection was at least a quarter less than that which followed during the next twenty days.

He commented, moreover, that perhaps the most distressing misfortune of old age consists in the inability to defecate. With him the expulsion of fecal material had become most laborious during the preceding twelve years, and had become almost impossible without the aid of purgatives and artificial means. During the two weeks which followed the first injection, a radical change took place in the reflex of defecation. He had less use for laxatives, and the expulsion of feces equally as large and hard was accomplished without mechanical assistance or lavage. There had been a return to normal state of many years before.

He added that intellectual effort had become easier than for many years, and that many other forces not lost, but decreased, had been notably increased.

Subsequent to his experiments upon himself, Brown-Séquard reported other cases which were benefited. He believed that the testicular extract had an influence particularly on the spinal cord.

Brainard made injections in over two hundred people, using extracts from the testicles of healthy young rams. He tied the spermatic veins and vasa of the ram as far away from the testicle as possible, and then expressed the fluid. Mixing this with distilled water, and filtering, he injected from 15 to 60 minims

in the deltoid muscle. After the first injection in many cases of weakness without definite disease, he noticed a beneficial effect. In three cases of locomotor ataxia, Brainard states, more favorable and pronounced effects resulted than in any others. Five cases of muscular rheumatism and four of sciatica were relieved or entirely cured of pain. Some of the cases of Brainard reported as not improved, were thought by Brown-Séquard to have received insufficient injections.

In cases of tuberculosis, Brown-Séquard noticed beneficial effects, as increase in appetite, strength, and a fall in temperature. He gave daily injections of 1 c.c of testicular material. He also reports cases of other diseases in which conditions of mental depression, hemiplegia, and myopathies were greatly relieved.

In the latter part of 1918, the first experiments of engrafting human testicles from recently executed prisoners to senile recipients were begun at San Quentin Penitentiary, and to date twenty-one such cases have been treated.

In 1920, animal glands were substituted for the human, and were not grafted to the recipients testes, but were merely laid in the pampiniform plexus of the scrotum. Many of these sloughed out, for too large a piece was used. After a time, varying from three days to as many weeks, the site of operation would open up and discharge a quantity of yellowish necrotic material, usually devoid of bacteria.

Later smaller pieces were used. A cross section of a ram's testicle about the size of a dollar was cut and placed in the scrotum. Many of these remained without sloughing, and very gradually were absorbed.

As the scrotum is subject to considerable trauma, and is difficult to keep clean, it was determined to imbed the section of ram's testicle on the fascia, overlying the rectus muscle of the abdomen. With the skin injected with ½ per cent novocain, an incision was made down to the rectus; closed curved Mayo's scissors were then run along on top of the fascia at right angles to the incision, opened and withdrawn, leaving a tunnel between the fascia and fat. This was held open with retractors, and the section of testicle carefully inserted. The incision was closed with two silkworm gut sutures. With this procedure there were

very few sloughs, but it was necessary for the patient to "go easy" for a week, until the wound had healed.

A number of these implants were removed after a variable time, and it was found that they were not alive, but were necrotic, and were being gradually absorbed.

Believing that all the testicular substance would undergo the same process, however placed in the system, it was determined to inject it by syringe without undue maceration.

The syringe employed is one devised by Joseph Beck, for paraffin. It holds about 4 grams. The barrel of the syringe is filled with strips of the fresh testicle. The piston is attached and the substance slowly injected through a large needle, the skin being first infiltrated with a few drops of novocain. About one gram of the testicle is injected in each of four places, radially from the single point of entrance.

With this method the danger of slough is reduced to a minimum. The patient does not have to "go easy" for a week, but may continue with his work.

There is usually no inconvenience, although there may be some redness for the first few days about the site of injection on the abdomen, and later on a sense of itching. The injected substance may be felt under the skin for weeks and months, until it is all absorbed.

The material used is best taken from a ram, goat, or boar which has reached maturity, preferably a year to eighteen months old. As soon as the animal is killed, the whole scrotum is resected between clamps and brought to the hospital. Here the external hair is clipped off, the skin painted with iodine, and with absolutely aseptic technic the skin incised. The edges are grasped with hemostats and held back. The next layer is likewise grasped and retracted. There are many coverings before the tunica is reached, and each may be carefully and aseptically opened.

The tunica vaginalis is then opened and the testicle caught with a large hemostat and removed to a sterile towel or basin. Here it is opened, and the strips cut for filling the syringe.

The abdomen or site of injection of the patient is cleaned with alcohol. After the operation the needle hole in the skin is covered with Tincture Benzoin Compound, and a little cotton. This may be in turn covered with a small strip of adhesive tape.

Because it is not always possible to obtain testicular material just when it is wanted, a plan for preserving was devised. As soon as the testicle is removed aseptically, it is immersed in pure vaseline, warmed to liquid state. This keeps out all air. Then the container is placed in the refrigerating vats of the ice plant and kept frozen at –12° F.

When ready for use the testicle has the consistency of an ice cream brick. Glands preserved in this way have been used as long as thirty days after death of the animal. Refrigeration does not seem to affect the potency.

Up to the present time over three hundred cases have been treated with animal testicular material. These were not selected but were taken in order of their application. After the first twenty or thirty prisoners had received the glands and reported among their fellow prisoners the good results they had obtained, many applications were received.

As there is very little pain, and no inconvenience to the process, many were willing to test it.

Among those treated were cases of neurasthenia, senility, asthma, paralysis agitans, epilepsy, dementia precox, diabetes, locomotor ataxia, impotency, tuberculosis, paranoia, gangrene of toe, atrophied testicles, rheumatism, and, in fact, many other illnesses of chronic character not amenable to treatment.

Finding that the injection of animal testicular substance caused no ill effects, and at most only a slough, it was thought worth while to try it on any case which presented.

From these experiments it may be said that animal testicular substance injected into the human body does exert decided effects.

Some of those receiving this treatment claim that their eyesight is improved, the appetite is increased, that there is a feeling of buoyancy, a joy of living, an increased energy, loss of tired feeling, increased mental activity and many other beneficial effects. These results are not easy to demonstrate, and one must rely to a considerable extent on the patient's statements.

However, when the psychology of a prisoner is considered, one may be assured that if no beneficial effects were derived, the news would rapidly spread among the inmates and it would be impossible to induce others to take the treatment. As a

matter of fact, applications come in every day from the convicts for the "glands" and the demand is very great. Some even want a second and third injection, feeling that if one does good, more will do better.

In the series, eight cases of asthma have been treated. All have been helped, and four claim that they have had no recurrences.

If it be true that there is an inter-relation between the various glands of internal secretion, the theory might be advanced that the injection of testicular substance so acts upon the adrenal glands, that an increase of adrenin is thrown into the system, thereby influencing the asthmatic attacks.

In four cases of acne, young men from 18 to 25 years of age have received injections. The eruptions have been markedly decreased. As acne is usually a disease of early manhood, may it not be possible that the maturing interstitial tissue has less influence on the sebaceous glands than that which the patient acquires as he grows older? Acne generally disappears when the patient enters manhood.

In tuberculosis in the various stages and conditions, eleven patients were treated. Most of them showed a temporary gain in weight, appetite, sexual manifestations, and general well-being. Three advanced cases, however, died. The injections were made only as a last resort, with little hope of their being of any value.

This procedure has been carried out in about sixteen mental cases, ranging from neurasthenia to manic-depressive insanity. Most of the subjects showed some change. One case of paranoia has apparently lost his delusions of persecution, improved physically, and works very well.

Almost all the subjects report increased sexual activity. Many who have not had erections for years claim that their virility has been restored.

One melancholiac, who would not talk or show any activity whatever, was observed to have an erection a few days after an implantation. He died several months later from inanition due to refusal to take food.

Experimentation is now under way with six white rats in separate revolving cages, to compare the amount of work done before and after implantation of testicular substance.

Further work will also be done on prisoners, testing the effects of single and multiple injections.

These observations were undertaken with an unbiased mind, and with the endeavor to pursue the truth, wherever it may lead.

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THE IMPORTANCE OF VISUALIZING ESTABLISHED SCIENTIFIC DATA WITH REFERENCE TO THE SIZE OF THE BODY CELLS AND THEIR CHEMICAL SUPPLIES IN THE CIRCULATING BLOOD

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Knowledge only becomes our mental property after it has been visualized. Scientific data can be visualized only by correlating them to familiar conceptions, quantities or measures. An attempt has been made in this paper to form a clearer conception of well-known data concerning the size and the numbers of certain body cells and of the chemical supplies in the circulation. The information thus obtained proved to be interesting and instructive: it gave food for thought in connection with great medical problems. It revealed unsuspected elements of humor in sober scientific facts and showed that "relativity" is by no means restricted to Einstein's famous theory. The data which have been considered are (1) the size of the body cells; (2) the total blood volume in relation to the total number of erythrocytes and leukocytes in the circulation; (3) the total amounts in which important chemical blood constituents (iodin, urea, sugar, cholesterol, natrium chlorid, and so forth) are present in the total blood volume; (4) the relative size of electric ions or electrons with reference to the hydrogen-ion concentrations of the blood, and (5) the concentration in which epinephrin is physiologically active.

The size of the body cells.—It is well-known that in normal blood counts the number of cells contained in 1 c.mm. ranges from 4,000,000 to 5,000,000 for the erythrocytes and from 6,000 to 10,000 for the leukocytes. It is less well known that the actual size of a millimeter may be visualized by merely pressing the point of a fairly soft pencil on paper: the resulting dot will be found to measure 1 mm. To form a mental picture of objects, 5,000,000 of which find room in a mere dot of three dimensions, is by no means easy. However, microscopic measurements have

proved that the size of the cells in the human body ranges from 5 to 40 microns, micromillimeters, one micron being equal to the one-thousandth part of one dimension of the aforementioned dot or to the one twenty-five thousandth part of an inch. The largest cell in the body, the ovum, measures 40 microns; the erythrocytes vary from 5 to 8 microns, and the leukocytes from 10 to 15 microns (Nichols and Vale). While it is impossible to form a very definite mental picture of even the largest body cell, it will help our imagination considerably to recall that this cell covers the same area as five of the largest erythrocytes, of which 5,000,000 practically fill 1 c.mm.

The total blood volume.—Various methods have been used to determine the total blood volume. MacCallum mentions the method of Haldane-Smith as the most accurate; it consists in administering a known amount of carbon monoxid and in estimating the concentration of the gas in several blood samples.* By this method the total blood volume was found to represent from 5 to 5.3 per cent of the total body weight. The recent investigations of Ashby (1), based on the injection of a known quantity of Group IV blood serum followed by numerous blood counts, seem to indicate that the total blood volume is likely to be higher, from 7.5 to 8.5 per cent of the body weight. According to Haldane-Smith the total blood volume of an adult, weighing 154 pounds (70 kg.) is 3500 gm., that is, 3.5 liters or slightly less than 1 gallon; according to Ashby (2) the blood volume of this adult would be approximately 5900 gm., that is, practically 6 liters or 1.5 gallons. The latter amount only half fills an average pail or bucket, of the type used for household purposes.†

The figures given in the following calculations are based on the total blood volume of an adult weighing 154 pounds, with a blood volume of 5000 gm. (a compromise between the data of Haldane-Smith and Ashby); erythrocytes 5,000,000, leukocytes 6,000 per 1 c.mm.

The total number of erythrocytes and leukocytes in the total blood volume.—In order to estimate the total number of erythro-

*The determination of the carbon monoxid concentration in blood by the carmin method, used by Haldane, has not proved satisfactory; a new method is in elaboration at the U. S. Bureau of Mines, according to information received from Dr. A. C. Fieldner.

†The accuracy of this comparison has been verified by pouring 6 liters into an average bucket; all the other "visualized" data have been similarly controlled by measure or weight, whenever this was possible.

cytes and leukocytes in the blood of the adult, the following facts must be borne in mind: the specific gravity of blood and of water is practically identical; 1 gm. of blood represents the content of 1 c.c. or 1000 c.mm. Hence a total blood volume of 5000 gm. is equal to $5000 \times 1000 = 5{,}000{,}000$ c.mm. The figures for the total number of erythrocytes and leukocytes per 100 c.c. and in the total blood volume are given in Table 1.

TABLE 1

BLOOD CELLS IN CIRCULATION

Per 100 c.c.	Per total blood volume
Erythrocytes 500,000,000,000 (five hundred billion)	Erythrocytes 25,000,000,000,000 (twenty-five trillion)
Leukocytes 600,000,000 (six hundred million)	Leukocytes 30,000,000,000 (thirty billion)
Adult, weight 154 pounds; blood volume 5000 c.c.	

Figures which contain from nine to twelve zeros are likely to convey little information. It may be advisable to recall a certain unscientific conundrum, when an attempt is made to visualize "the countless hosts" of blood cells in the circulation. Question: If a fortune of seven billion silver dollars were to become the personal property of any one who finished counting the coins, when would the prospective owner be entitled to enjoy the fruits of his labors? Answer: At the end of 400 years, assuming that the aspirant had counted day and night without any intermission whatsoever.

The relative proportions and the total amounts of important blood constituents.—The work of numerous investigators (Folin and Wu, McLean and Van Slyke, Benedict, Menten, Bloor, Grigaut, Chauffard, Laroche and Grigaut, Kendall (25, 26), and Hawk, to name but a few) has furnished definite data concerning the proportions in which important chemical constituents are present in the blood. It has become customary in this country to express the values obtained by blood analyses in milligrams per 100 c.c. of blood; in other countries, France for instance, they are usually expressed in terms of milligrams per liter, whereas Italian and German research workers generally give their

findings in terms of percentage. The presentation of an analysis in milligrams per 100 c.c. is clear and convenient and its universal acceptance would undoubtedly further the progress of science; neither the American nor the foreign mode of expression, however, gives a very definite idea of the total amounts found in the circulation for the use of the whole body. A far more vivid conception of the (often ludicrously small) quantities with which the body works may be obtained by correlating the number of milligrams per 100 c.c. to the total blood volume and by visualizing the values thus found through comparison with familiar quantities. This has been done in Table 2. It need hardly be pointed out that the figures given in this estimate only apply to the chemical supplies of the body which are in circulation in the blood, and not to the reserve deposits in organs and tissues. To form even an approximately correct idea of, for example, the urea or creatinin content of all the tissues might prove a difficult task. The relative size of different organs in different persons and many other factors would have to be taken into consideration, and large series of determinations, such as have been made of the blood, have not been made of the majority of organs. An amusing, if not very precise, estimate of the total chemical composition of "the average man" has recently been published by a big industrial company*; it may be summarized as follows: fat enough for seven bars of soap; iron enough for medium-sized nail; sugar enough to fill a shaker; lime enough to whitewash a chicken coop; phosphorus enough to make 2,200 match-tips; magnesium enough for a dose of magnesia; potassium enough to explode a toy cannon; sulphur enough to rid a dog of fleas. Many items in this estimate are left largely to the imagination, such as the size of the dog and the number of his tormentors, but the total cost of the ingredients is given as ninety-eight cents, which is neither expensive nor calculated to foster megalomania. The total amounts of the blood constituents presented in Table 2 are based on Hawk's data, with the exception of the values for iodin (Kendall, 25, 26) and for cholesterol (Luden). Kendall proved that the total quantity of thyroxin, the thyroid hormone containing 65 per cent of iodin, present in the tissues (exclusive of the thyroid gland) is approximately 14 mg., that is, roughly, ¼ gr. of hormone and slightly more than ⅛ gr. of iodin; these values are

*The Marathon Paper Mills Company.

TABLE 2

RELATIVE AND TOTAL AMOUNTS OF IMPORTANT CHEMICAL CONSTITUENTS IN NORMAL BLOOD

(Adult, body weight 154 pounds)

	Per 100 c.c.	Per total volume (5000 c.c.)		Equivalents
	Milligrams	Milligrams	Grains	
Iodin	0.013	0.65	0.01	Average dose atrophin or hyosin.
Creatinin	1.0 to 2.0	50 to 60.0	1 to 2.0	Average dose ferrous lactate,
Uric acid	1.0 to 3.0	50 to 150.0	1 to 3.0	caffein or aloes.
Acid Phosphorus	2.0 to 6.0	100 to 300.0	5.0	Small dose acetylsalicylic acid (aspirin).
Lipoid phosphorus	6.0 to 12.0 Milligrams	300 to 600.0 Grams	10.0 Grains	Large dose acetylsalicylic acid (aspirin).
Urea	20.0 to 40.0	1 to 2	15 to 30.0	Average dose sodium bromid or quinin (malaria).
Sugar	80.0 to 120.0	4 to 6	60 to 80.0	1 teaspoonful.
Cholesterol	10.0 to 140.0	4 to 6	60 to 80.0	24 egg yolks.
Sodium chlorid	650.0	32	480.0 (1 oz.)	1 tablespoonful.
Fat	100.0 to 720.0	5 to 36	60 to 480.0 (1 oz.)	1 tea to 1 tablespoonful.

comparable to the "average doses" in which morphin is given hypodermically after operation. The iodin content of the total blood volume, according to Kendall's findings, is equal to the average 1/100 gr. dose of atropin sulfate, hyoscine bromid or nitroglycerine (Bastedo, Bethea). Plummer's determinations of the basal metabolic rate show that "the average daily exhaustion of thyroxin in the tissues is 0.5 to 1 mg." approximately 1 120 to 1/60 grain or the usual dosage of physostigmin salicylate (Bethea, Powell). "A shift of 1 mg. of thyroxin in the tissues is accompanied by a corresponding rise or fall of between 2 and 3 per cent in basal metabolism" (Plummer). I determined the cholesterol values shown in Table 2 according to the Bloor I and II methods for blood and for egg yolk (28, 29, 30). The yolk of eggs contains no "split cholesterol" (Luden), the Bloor I and II values being identical, its cholesterol content is roughly nine times that of normal human blood: the normal Bloor I cholesterol value of whole blood, upper limit, is 100 mg. per 100 c.c.; that of egg yolk is 888 mg. per 100 c.c. The sugar concentration in the total blood volume is especially worth considering.

The fact that there is but one medium-sized teaspoonful of sugar in the one-half bucketful of blood, which represents the entire circulation of an adult weighing 154 pounds, may even help us to take a lenient view of certain acrimonious traits which we sometimes encounter in fellow human beings.

The hydrogen ion concentration in the blood and the relative size of electrons.—The terms "acidosis" and "alkalinosis" are familiar because of their frequent use in modern medicine. The clinical conditions to which they refer are of great importance: "A rise in the hydrogen ion concentration of the blood is significant because it indicates failure on the part of the protective mechanism to preserve the proper reaction" (Hawk). Yet the statement that in clinical acidosis the hydrogen ion concentration values range from P_h 7.3 to P_h 7.1; that the normal values are from P_h 7.6 to P_h 7.4, and that the extreme alkalinosis observed by Menten in a case of gastric cancer was 8.44, conveys anything but a clear picture of these values to the majority of physicians. Rowntree's admirable comparison on the other hand: "The 'acidity' in acidosis and the 'alkalinity' in alkalinosis may be likened with perfect scientific accuracy to the 'acidity' of distilled water and the 'alkalinity' of tapwater." promptly fur-

nishes a usefully vivid conception of the extremely narrow limits in which the balance of health is known to swing. Any one who has stained microscopic sections with hematoxylin knows that the sections left in distilled water, no matter how long, consistently decline to assume the desired blue tone, but that emersion in tap-water will make them do so in from five to fifteen minutes, according to an alkalinity of the water. But, even Rowntree's simile does not throw any light on the relative size of the electric ion, that minute electric charge which plays such an important part in chemical reactions. The recent investigations of Millikan, professor at the University of Chicago, make it possible to form some idea at least of the size of these electric units. A special apparatus was devised by Millikan; it somewhat resembles a water tank combined with a projecting lantern and a telescope with a scale fixed in the eye piece. By means of this apparatus minute particles of oil, which by special methods have been compelled to carry only one or two electrons, are made visible. The speed at which the droplet travels along the scale shows whether it carries a single or a double electric charge and permits the determination of the number of electrons in a given concentration. Table 3 gives a conception of the infinitesimal size of the

TABLE 3

COUNTING ELECTRONS

Volume of electricity contained in the filament of a 16 candlepower lamp	1.0
Price of the given current in cents	0.00001
Number of people counting electrons	3,000,000.0
Rate of counting per second	2.0
Time required in years	20,000.0

electron. According to this estimate it would take 3,000,000 persons no less than 20,000 years to count the electrons contained in the electric current of a 16 candle-power lamp, when the cost of the current amounted to one one-hundred-thousandth part of one cent (Howard).

The concentration in which epinephrin is physiologically active.—The numerous and interesting experiments of Stewart and Rogoff (8) have furnished conclusive data concerning the concentration of epinephrin in the blood. They proved that "the range of epinephrin output per kilogram (body weight) per

minute is surprisingly narrow, not only for animals of the same species, but of different groups. Cats, dogs, baboons, monkeys (M. rhesus), and rabbits were used in these experiments. The epinephrin output "worked out at 0.0002 mg. per kilogram per minute" (42). According to this estimate the total epinephrin output in twenty-four hours of the adult weighing 154 pounds (70 kg.) would not exceed 20.16 mg., that is, slightly less than ⅓ grain. The test objects, by means of which Stewart and Rogoff secured demonstrable evidence in the form of tracings, were segments of the intestine or of the uterus of rabbits. The delicacy of the method (bio-assay) is shown by the fact that the intestinal and uterine segments "gave a distinct reaction with 1 : 330,000,000 epinephrin in indifferent blood, a stronger reaction with 1 : 160,000,000, and a marked effect with 1 : 80,000,000" (46). In other words, the tiny strips of animal tissue detected and recorded the presence of epinephrin even in a dilution of 1 : 330,000,000 (one in three hundred thirty million). Bio-assay proved further that "adrenalin in the concentration of a 1/500,000 molecular solution" is equal to "a normal concentration in adrenal vein blood" (44). It should be recalled in this connection that the blood of the adrenal vein contains the highest concentration of epinephrin and that, after dilution of the blood of the adrenal vein in the total blood volume, the concentration in the peripheral circulation will be even less than 1 :500,000. That notwithstanding the almost inconceivably small amount of epinephrin in the blood, "the steady, spontaneous discharge of epinephrin is of sufficient magnitude to cause definite physiologic effects in the organism," was shown in an experiment on a cat (45). The customary "vena cava pocket" which Stewart and Rogoff employed in all of their experiments, was made by "tying off the lumbar and renal veins and all the small branches which enter the cava from the liver to the bifurcation of the iliacs; thus, a clamp adjusted just below the liver and one just above the iliacs completes a blind pouch into which only the adrenal veins are emptied. Blood collected in such a pocket is released by removing the upper clamp (42). As the amount of blood which collects in the cava pocket is only "about 1 to at most 2 c.c. the results obtained" could have nothing to do with any effect which the abstraction of such a small quantity of blood as was col-

lected in the pocket could have had on the filling of the heart''* (45). By way of preliminary experiment an injection of 1:500,000 epinephrin was made into the cat's jugular vein: a marked cardiac arrythmia was immediately produced within a few seconds. One minute after the injection the cava pocket was closed off, and after a latent period of six or seven seconds the cardiac irregularity completely disappeared. ''During the two minutes for which the pocket was closed, no trace of irregularity could be discerned.'' The pocket was then opened by releasing the upper clamp, the accumulated blood of the adrenal vein entered the circulation, and in seven or eight seconds the irregularity reappeared. During the experiment the cava pocket was opened and closed repeatedly at suitable intervals. At first, while the animal was still in good condition, the releasing of blood from the adrenal vein into the circulation produced arrythmia after a short latent period, whereas the closing of the pocket caused re-establishment of the normal rythm. Towards the end of the experiment, however, when the heart had become weary and the muscle had begun to deteriorate, the reverse effect was obtained; closing the pocket now produced arrythmia, which vanished when the pent-up blood in the adrenal vein was released into the circulation. Stewart and Rogoff (45) point out that there is ''nothing really puzzling'' in these dissimilar results, as they merely resemble the effects produced ''by flogging an exhausted and a fresh horse.'' The experiment proves conclusively that the minute, spontaneously liberated amounts of epinephrin entering the circulation at the normal rate produce a demonstrable effect on the heart. The concentration of epinephrin in the blood in the adrenal vein, 1:500,000, may be visualized by diluting a small glass of whisky (10 c.c.) with the combined content of two standard city sprinkling carts. A standard sprinkling cart holds 625 gallons of water. The lowest concentration in which epinephrin was detected by the intestinal or uterine segments in bio-assay, 1:330,000,000, is comparable to the dilution of the same small amount of whisky in the combined content of 1320 sprinkling carts, that is in 826,000 gallons, or,

*If the weight of the cat be taken at 2 kg., its total blood volume computed at 8 per cent of the body weight would be approximately 160 c.c. The temporary exclusion of 1 c.c. from the circulation would therefore be only the one hundred and sixtieth part of the total blood volume, or comparable roughly to the loss of 30 c.c. of blood by a man with a blood volume of 5000 c.c., a negligible quantity since often more than ten times that amount is withdrawn for a single transfusion.

roughly, 13,000 "hogshead" of water. It might be mentioned, incidentally, that a procession of 1320 sprinkling carts would be about six miles long.

The practical value of visualized scientific data lies not only in the stimulation of memory through the imagination, but also in the food for thought which they offer and in their bearing on great medical problems. If mental pictures of the billions and trillions of blood cells crowding, jostling, and possibly struggling for a share of the mere teaspoonful of sugar in the total blood volume of a full-sized man, or the endless procession of sprinkling carts representing the epinephrin concentration to which animal tissues respond, appeal to one's sense of humor, they also do much more than this. They bring home (1) the delicacy of the adjustment by which the human body mechanism is regulated; (2) the extent to which this fine adjustment may be disturbed by seemingly trivial factors; (3) the obligation of both laymen and physicians not to ignore the "slight" tokens of distress of the body engine; and (4) the value of comparing the quantities used in the body chemistry with the "dosage" in therapeutics.

1. Langfeldt has furnished evidence suggesting that the hydrogen ion concentration of the blood together with the pancreatic hormone play important parts in regulating the sugar concentration in the blood; Henderson, Haggard, and Coburn have devised means by which the post-operative depression resulting from a decrease in the blood alkali may be combatted successfully: yet even in extreme "alkalinosis" the alkalinity of the blood is no greater than that of tap water.

2. Hamilton (15, 16), in her admirable survey of industrial diseases, has shown that minute amounts of lead and arsenic may produce severe clinical symptoms. The effects of prolonged inhalation of imperceptible quantities of carbon monoxid have been discussed by Wilmer, Harris, McGurn, Luden (31) and others. Haldane mentions that in his first series of experiments the inhalation of 0.06 per cent (6:10,000) of carbon monoxid "produced no symptoms except shortness of breath on exertion" in several hours; that the blood saturation did not exceed 28 per cent, and that no further absorption occurred up to five hours." But he adds: "About a year later we tried a similar experiment and found that 0.06 per cent was far too much for us;" and

when the experiment was again repeated, later at Oxford, it was found that "even with 0.03 per cent the saturation gradually crept up during four or five hours to over 30 per cent." Findings which show that the body did not handle one-half the concentration of the "toxic" gas quite as successfully in the later experiment as it had handled the greater concentration in the first series of experiments, suggest hypersensitization as much as previous acclimatization; they also tend to show that the oxygen deficit created by the inhalation of the "toxic" gas had been "registered" by the body as a whole, and had been resented. If the body works with and animal tissues respond to "home products," such as iodin and epinephrin, in concentrations comparable with 0.01 grain or to 10 c.c. diluted with the volume content of six miles of sprinkling carts, is it to be expected that the body cells should be entirely indifferent to far greater concentrations of a gas, the action of which is admittedly highly toxic, even though no immediate or grossly demonstrable changes may be produced? The investigations of Green show that the cancer incidence is influenced by the amount of combustion products in chimney smoke. The increase of cancer throughout the world has been proved by Hoffman's (21, 22) statistics; that such an increase exists is now generally admitted. May not the carbon monoxid content of combustion products be a factor, though not the only one, promoting the admitted increase of cancer by furthering the chemical disbalance which underlies malignant proliferation (Luden, 30). This idea may not prove to be as far-fetched as it may at first appear, for the work of Teague has proved that the exhaust gas of a smoothly running automobile contains 4 per cent of carbon monoxid and that of a truck with "racing" engine as much as 9 per cent; the numerous and recent investigations of Henderson, Haggard, Teague, Prince and Wunderlich have demonstrated that the air near the taxi-stand of the New York Grand Central station contains, under ordinary circumstances, a considerable amount of exhaust gas. Henderson says in this connection, "It appears from these data that the air is occasionally vitiated for a time with as much as two parts of carbon monoxid in 10,000, but that with the ventilation provided by large fans the concentration soon falls again decidedly below one part in 10,000." But what about the concentrations in narrow streets lined by sky-scrapers,

on windless days and in the absence of large fans? Are the severe headache lasting for from five to seventy-two hours, the dizziness, nausea and faintness, or weakness, which inhalation of from six to nine parts of carbon monoxid in 10,000 during one hour produced in Henderson's heroic volunteers, entirely "forgiven and forgotten" by the organism as a whole, after the symptoms themselves have passed off? The statistics of the Automotor Industries show that the number of motor-driven vehicles in America alone increased from 1,000,000 to close to 9,000,000 between 1912 and 1920* (41).

3. Mackenzie, in "The Future of Medicine," urges that the consideration which small details deserve should be given them in clinical observation, in order to insure "the recognition of the diseased state before it has produced gross structural changes and of the condition that predisposed to, or indeed induced the disease." Cushing (51) has recently repeated this warning and suggested that "we are prone to lose sight of the patient as a whole." In an automobile the faint "knock" indicating lack of water or of oil receives prompt attention. The delicate human engine should deserve as much consideration. If this were borne in mind the number of "hopeless" cases that physicians encounter would be diminished greatly.

4. In modern therapeutics, fortunately, the "horse-power" dosage of fifty years ago has been discredited. The era of modern medicine is characterized by a growing interest in the activities of the glands of internal secretion. Organotherapy still resents innumerable problems, but it can also point to unquestionable victories (Kendall, 24, Timme, 48, 49, 50). It is in connection with this new type of therapy, with the preparations of the pharmacopeia and with the great problems of medicine that the diminutive size of the body cells and the infinitesimal quantities with which the body works, and to which organs and tissues respond, are well worth remembering.

SUMMARY

1. Established scientific data may be visualized, that is, transformed, into vivid mental pictures by comparison with familiar conceptions, weights and measures.

*These figures are based on "the revised total registrations after careful checking with the final records of the various secretaries of state."

2. Visualized data stimulate memory by appealing to the imagination. Visualized data concerning the size of the body cells, the number of erythrocytes and leukocytes in the total blood volume, the hydrogen-ion concentration in the blood, the size of electrons, and the concentrations in which epinephrin is physiologically active, are presented in this paper.

3. The practical value of visualized data lies chiefly in the food for thought which they offer in connection with great medical problems. Illustrations are given showing the bearing of visualized data on the cancer problem and on other subjects of medical interest.

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SOME NOVEL EFFECTS PRODUCED BY STIMULATING THE NERVES OF THE LIVER

W. B. CANNON, J. E. URIDIL and F. R. GRIFFITH

After removal of the adrenal glands, splanchnic stimulation will cause a faster beat of the denervated heart. Since this occurs when the inferior cava and the portal vein are closed below the liver, and since it does not occur when the hepatic nerves are cut, the inference is drawn that some agent arising in the liver is the occasion of the faster beat.

Stimulation of the hepatic nerves will cause an increased rate of the denervated heart, an effect appearing later than the similar adrenin effect and lasting for a longer time.

Stimulation of the hepatic nerves will cause a rise of blood pressure. The following evidence is adduced to show that this is not the consequence of a retarded blood flow through the liver. It does not occur on closure of the hepatic artery and vein; it occurs on hepatic stimulation though all abdominal viscera have been removed except the liver, and, unlike stimulation of splanchnic blood vessels alone, it long outlasts the period of stimulation.

Asphyxia is very promptly depressive in its influence on the effectiveness of hepatic stimulation.

The increments of heart rate vary widely. They are slight, if the animal has been fasting, or is in poor condition; they are much greater if the animal is digesting meat. These differences can account for the discrepancies in Cannon's and Stewart and Rogoff's results of splanchnic and reflex stimulation after adrenal ablation. The inference is drawn that a substance is given off by the liver into the blood stream which, carried to the denervated heart, raises its rate.

None of the known or supposed products of hepatic activity —glucose, urea, catalase—when injected into the blood stream have the effects produced by exciting the hepatic nerves.

Watery extracts of the liver are ineffective. Liver extracted by boiling acid and nearly neutralized augments the heart rate, but so do extracts of other organs.

The efficiency of hepatic stimulation in causing a faster heart rate, when meat is being digested, is not seen if an animal is digesting carbohydrate, or fat, or has been fed for several days on either of these foodstuffs. On the other hand, stimulation is more effective after amino acids have been injected into the intestines.

The tentative conclusion is drawn that the effects noted are probably not due to a true internal secretion produced by the liver, but to a discharge from its cells of amino acids, or amines, which are sympatho-mimetic in character.

THE NEW VIEWS AS TO THE MORPHOLOGY OF THE THYMUS GLAND AND THEIR BEARING ON THE PROBLEM OF THE FUNCTION OF THE THYMUS

By J. Aug. Hammar

UPSALA

(This paper was begun in the September, 1921, issue.)

4. A CLEAR DISTINCTION MUST BE MADE BETWEEN THYMUS ASTHMA DUE TO THE EFFECT OF PRESSURE AND DEATH CAUSED BY THIS AND SO-CALLED "THYMUS DEATH": THERE IS NOTHING TO INDICATE THAT "THYMUS DEATH" IS PRIMARILY DUE TO AN ABNORMAL CONDITION OF THE THYMUS.

Before proceeding to put forward a view of the functional conditions of the organ, based on the facts given here, I must touch a little upon the question of the so-called "thymus death," as it is obvious that if there are cases in which changes in the thymus are directly harmful to the organism, even, as has been stated with regard to "thymus death," causing apoplectiform death, not only can such cases not be disregarded in judging of the function of the organ, but they might almost be expected to be more fitted than others to afford information about this.

A perusal of the exceedingly abundant literature dealing with cases coming within this field soon shows that these cases, far from always present the same clinical features, and, as regards the cases that are best observed and described, there is little difficulty in referring them to two distinct groups: cases with thymus asthma and cases without the symptoms characteristic of this.

Thymus asthma is characterized, above all, in most cases by attacks of inspiratory dyspnoea, inspiratory stridor and the so-called Rehn's symptom, the expiratory swelling of a tumour —the cranial thymus end—in the jugulum. In an attack of this kind, possibly even in the first, death may occur, under the form of so-called suffocation death.

It seems to be proved quite conclusively that in certain cases of this kind it really is the thymus that has produced the fatal symptoms by pressure on the air-passages. Not only has thymectomy led to a recovery in certain cases; in others it seems

to have been sufficient merely to carry out ectopexy, to sew the organ forward and fix it in the jugulum. In some cases it has been possible to observe at the operation itself that merely by pulling the thymus forward towards the jugulum the breathing was made easy, while the symptoms of stenosis appeared once more when the organ was allowed to take up its original position (Purrucker 1899, Rehn 1906, Ollivier 1911, Schumacher 1913). That under such circumstances the obstruction cannot have been situated in the upper thoracic aperture, as has been generally assumed, but farther down, at the tracheal bifurcation or probably still more frequently at the very root of the lung, and that a continuance or a reappearance of the broad shape of the thymus that occurs towards the end of foetal life plays a part in this, are special matters which I have tried to explain in a special paper (1915:2), with reference to the topographical conditions of the thymus.

But it is by no means in every case that death occurs in immediate connection with difficulties in respiration. *Death* has frequently occurred quite suddenly and unexpectedly *in an apoplectiform manner.* Pott (1892) gives a graphic description based upon the observation of no less than four cases that occurred before his eyes. Owing, on the one hand, to the importance of the matter, and on the other to the circumstance that these deaths happen mostly unobserved during sleep and seldom under the notice of the physician, I think I ought to give an extract of this account of Pott's. He says:

"Die Erscheinungen, unter denen der Tod erfolgte, waren stets die gleichen. Plötzlich biegen die Kinder den Kopf nach hinten zurück, machen eine lautlose, nach Luft schnappende Inspirationsbewegung, verdrehen die Augen nach oben, die Pupillen erweitern sich. Das Gesicht, namentlich die Lippen, werden blitzblau und schwellen an. Die Zunge zeigt sich zwischen die Kiefer eingeklemmt, schwillt um das Doppelte im Dickendurchmesser an, ist ebenfalls stark cyanotisch, etwas nach oben umgerollt und fest an den harten Gaumen angepresst. Die Halsvenen, stark geschwellt und prall gefüllt, treten als dicke Stränge deutlich hervor. Die Hände werden mit eingeschlagenen Daumen zur Faust geballt, die Finger cyanotisch. Der Unterarm steht in krampfhafter Pronations—und Adductionsstellung. Die unteren Extremitäten sind gestreckt, die grosse Zehe etwas abducirt und dorsal flectirt. Die Wirbelsäule wird in Bogen stark nach hinten gekrümmt. Einige blitzartige Zuckungen der Gesichtsmuskeln und einige vergebliche schnappende Inspirationsbewegungen erfolgen, aber kein Laut, kein zischendes Eindringen von Luft durch die Stimmritze wird gehört. Auf einmal löst sich der Krampf, das Gesicht verfärbt, sich, wird aschgrau, die Cyanose lässt nach, die Zunge und die Lippen werden livide, und nach höchstens 1—2 Minuten ist das Kind eine Leiche."

"Urin und Fäces gingen jedesmal bei den ersten künstlichen Atembewegungen unwillkürlich ab. Die Herztätigkeit hörte mit Eintritt des Anfalles sofort auf. Herztöne sind nicht mehr zu hören, ebensowenig ist ein Puls fühlbar. Die Reflexerregbarkeit ist gänzlich erloschen. Auf das Einführen des Fingers in den Mund und auf die Berührung des Kehldeckels, resp. der Stimmbänder, welche ich in Medianstellung, fest aneinanderliegend, gefühlt zu haben glaube, erfolgen weder Würgbewegungen noch Hustenreiz. Ebenso bleibt der Lidschluss bei Berührung der Cornea aus. . . . Meine Ueberzeugung nach wird der Tod durch einen plözlichen Stillstand des Herzens bedingt."

I think that anyone who reads Potts's account must agree with his conclusion that in these cases it was not a question of death from suffocation, but death from heart failure.

This fact, that two quite different syndromes, cases of death from suffocation and death from heart failure, have been grouped under the heading "thymus death," was clearly pointed out by Ganghofer in 1902. Christeller (1919) has also recently assumed both a thymus death due to autointoxication "hyperthymisation" and one produced mechanically. As a rule this has not been sufficiently taken into consideration. It is obvious, however, that this is what lies behind and explains the long prevailing difference of opinion as to the cause of "thymus death," whether it is to be considered as due to mechanical causes or constitutional or endocrine factors [lymphatism (Paltauf), hyperthymisation (Svehla)].

It is also obvious that the former of these syndromes, which might be called death in and through thymus asthma and in which the part played by the thymus is, of course, apparently a purely mechanical one, cannot be expected to afford any real information as to the function of the thymus. It is only deaths of the second kind that can be taken into consideration in dealing with this question.

The proof that in deaths of the latter type the thymus has really been the cause of death has been chiefly sought in the fact that in autopsies of such cases an abnormally large thymus has been found, while in other respects the post-mortem finding has been negative. In many cases, however, the presence of a capillary bronchitis has also been verified, in addition to the large thymus, and in such cases it has certainly depended to some extent on the subjective view of the pathologist whether the one or the other part of the findings has been registered as the cause of death.

In two papers (1915:1, 1917) I have reported the results of a microscopic analysis of a total of 37 cases of sudden death from internal causes in children, the majority of which cases can with good reason be considered to belong to the category referred to here. Comparisons made with thymi of equal age from children who had died from accidents while in good health showed that the organ exceeded the normal limits with regard to size in only four cases, and with regard to the amount of parenchyma in only five. A comparison with the cases—unfortunately not very numerous—in which the weight of the organ is mentioned in the literature shows that it, too, was as a rule normal. The idea of an abnormally large thymus in these cases of death is obviously due to a great extent to insufficient knowledge of the normal conditions of size in the organ and a misleading comparison between those glands that have not, as a rule, undergone accidental involution and those that have undergone such involution and are usually found post-morten after a preceding illness.

The structure, the amount of cortex, medulla and interstitial tissue, respectively, the index and the relative and absolute amount of the Hassall's corpuscles were all as a rule within normal limits also. In six cases, however, the absolute number of Hassall's corpuscles was subnormal, in relatively many—15—it was below the average without being subnormal. In two cases small Hassall's corpuscles (10 to 25 μ) were entirely absent, in two others their number was subnormal.

It is quite evident that an anatomical finding of this sort does not afford any support at all for the view that in these cases of death the *primary* cause of death was to be sought for in the thymus. Nor was the above-mentioned depression of the number of Hassall's corpuscles so regular that any certain conclusions could be based on it, as there were in the material three cases with a supranormal number of these corpuscles without any apparent cause. It is, however, conceivable, with the really negative characteristics that distinguish these sudden deaths, that in the three cases mentioned there was present another cause of death than in the rest—a latent infection or something similar. But even if, excluding such cases, one were to consider it possible to say that the deaths in question were characterized by a decrease in the number of the Hassall's cor-

puscles, the fact remains that it is only in exceptional cases that this decrease exceeds the normal limits.

If, nevertheless, I consider that we cannot quite exclude the possibility that in "thymus death" there is present in the organism a state of increased vulnerability, which is reflected in the thymus by a less than average number of Hassall's corpuscles, it is because I have also observed a reduced re-formation of Hassall's corpuscles in some cases of sudden death in elderly people, among them two in which the diagnosis was "paralysis of the heart." In order to prevent any misunderstanding I must state emphatically here that the reduction in the number of Hassall's corpuscles cannot in either case be reasonably supposed to be the *cause* of death, but only an expression of a state produced by other parts of the organism, possibly by other endocrine organs.

It is useless at present to discuss the nature of such factors as counteract the formation of Hassall's corpuscles in these cases, of the "cH-depressory factors"; our knowledge on this point is still too incomplete. When we consider, however, the well-known fact that it is especially well-nourished children that are subject to these deaths, it is, at any rate, not the most common factor of this sort that is present, the one that is operative in starvation, etc.

I shall only mention here in passing that even in some other cases the possibility of a cH-depression must be considered. Thus a comparison between the thymus in cases of suicide and in other cases of persons of equal age who have died from external causes (Hammar 1917:3) shows the possibility that in the majority of suicides there are less than the average number of these corpuscles present. Similarly the analysis of the thymus in some cases of epilepsy and eclampsia has given ground for the suspicion that in these forms of disease a cH-depression is present. Both these series of observations, however, need to be supported by a far greater material before they can be considered to constitute proofs. The same is true of the above-mentioned cH-depression in pregnancy.

5. THE FUNCTION OF THE THYMUS; DIFFERENT CH- AND LC-EXCITATORY AND -DEPRESSOR FACTORS RESPECTIVELY; ANTAGONISTIC FACTORS OF BOTH KINDS CONTINUALLY OPERATIVE; THE LC-EXCITATORY AND LC-DEPRESSOR AFFECT THE NUMBER OF ALL THE

LYMPHOCYTES IN THE ORGANISM, THE THYMUS ONLY INDIRECTLY; THE CH-EXCITATORY FACTORS ARE OF A TOXIC NATURE; THE ACTIVITY OF THE THYMUS IS ANTI-TOXIC.

When we have to try to work out a view as to the function of the thymus on the basis of the morphological and experimental data present, it is worth while first to mention the fact that in the case of the thymus we have no *morphological* observation that could justify the idea that the thymus carries out any secretory activity in the real meaning of this term.

The thick, milky juice that often runs out when a voluminous thymus gland, normal or pathological, is cut through in its fresh conditions, has not infrequently, not only in older works but even of late, been called a thymus secretion. The microscopical examination of the li uid that has thus run out shows, however, that it consists chiefly of lymphocytes in large numbers, a fact which has been known for a very long time. And if corresponding places in the fixed organ are investigated in sections, one finds that the lymphocytes are collected in certain, generally rather circumscribed, regions of the medulla, as a rule corresponding to the central parenchymatous cord. It will be seen that in doing this they have dispersed and broken asunder the ordinary medullary elements. The significance of these local surpluses of lymphocytes in the medulla and what has produced them is an unsolved problem. They do not seem to be purely post-mortal phenomena—due to post-mortal autolytic changes. One thing, however, is certain: they cannot be considered as products of any real secretory process in the organ.

Nor can any signs of a secretory function in the Hassall's corpuscles be proved, contrary to the statements of some investigators (Livini, Mensi, Magni, Dustin, etc.). The products that arise in connection with the degeneration of the central cells in the somewhat larger corpuscles vary in nature, being sometimes horny, sometimes hyaline products of an indeterminable nature; no signs are to be found of these degenerative substances being transferred into the blood. And it is furthermore, not to be forgotten that in by far the greater number of corpuscles, namely those that never attain great dimensions, these degeneration products are quite absent. In the lower vertebrates, in which, as a rule, there are no typical Hassall's corpuscles, there is certainly an analogous local hy-

pertrophy of cells in the medulla, but very seldom anything corresponding to the degenerative processes in the larger Hassall's corpuscles.

And it is obviously the former factor, the hypertrophy of certain groups of medullary cells, and not the degeneration, that is the constant and functionally important one in the case of the Hassall's corpuscles.

The negative attitude that already in 1910 I considered I must adopt with regard to the statement that there is a real secretory process in the thymus has only been more and more justified during the years that have since elapsed. E. R. Hoskins (1918) has recently taken up a similar position in a paper in this periodical. Dustin (1920) has also recently expressed the opinion that the thymus does not function by means of secretion and that in this respect the organ occupies a special position compared with other glands with internal secretion. As, however, he considers that the function of the organ is characterized "par fixation ou déstruction de matière sous forme d'éléments figurés" and he points to the small thymus cells as the medium for this function, it seems to me open to question whether this function is carried on by the thymus to any very much greater extent than by various other organs of the body.

In searching for functional changes in the thymus there are chiefly two facts that attract special attention: the variations in the number of lymphocytes in the parenchyma, especially the cortex, and the variations in the number of the Hassall's corpuscles. With the variations in the number of the lymphocytes are connected, as I have previously shown, changes in the reticulum cells (fat granulation of varied character, mitotic and reductive processes), so that both the primary parenchymous components may in this way be considered to take part in these variations. The changes in the reticulum cells are, however, not at all so striking as those in the number of the lymphocytes. The significance of the changes in the fat-granulation or the successive reduction of the reticulum cells that takes place in involution is not well enough known for these phenomena to be discussed at present. I limit myself accordingly to pointing out how these changes in the reticulum take place as a rule at the same time as those in the number of the lymphocytes.

The variations, both in the number of the Hassall's corpuscles and in the amount of the cortex, may be considerable. Only in exceptional cases, however, is their occurrence parallel; as a rule they appear independently of each other, a fact that scarcely fits in with the assumption of common causative factors. On the contrary, everything supports the idea that one has to take into account independent excitatory and depressor factors in the case of each category of these structure elements. Thus in hyperplasia in Graves' disease both eH-excitatory and le-excitatory factors exert their influence, but in a mutual relation that varies considerably from one case to another, so that sometimes the one, sometimes the other influence sets its special stamp on the case. In the earlier stages of infection involution, on the other hand, eH-excitatory factors are apparent at the same time as le-depressor. In acute infectious illnesses like poliomyelitis anterior acuta, which may cause rapid death before the general nutrition has suffered any reduction to speak of, cases may occur in which, under the conditions mentioned, only the eH-excitatory factor is perceptible, but the emigration of the lymphocytes has not yet assumed greater proportions than normal. In advanced cases of infection involution, on the other hand, with a specially marked involvement of the general condition the eH-excitation is gradually succeeded by a eH-depression. Thus we have so far conditions that agree with those prevailing in inanition involution, i. e., both eH-depression and le-depression. Finally, in certain cases of sudden death it seems as if we may assume a eH-depression, either alone or connected with a le-excitation.

The independence of the eH-excitatory and the le-excitatory and the corresponding depressor factors which is emphasized here has been illustrated in an interesting way by the comparison between the structure of the thymus in mother and foetus in certain cases of illness in pregnant women. One example may be mentioned. In a case of pregnancy in a woman with Graves' disease the size of the organ in the foetus was at the upper limit of what is normal for the age; the number of Hassall's corpuscles, on the other hand, was at the lower limit. The le-excitatory factor characteristic of Graves' disease seems here to have shown its influence even on the foetus, but not the eH-excitatory one.

It has already been pointed out above how the mention of an excitation or depression affecting the Hassall's corpuscles or the lymphocytes, respectively, must not be taken to mean that in the concrete case factors exclusively of a certain sort, excitatory or depressor, are in activity against this component of the structure. Thus le-depressor factors injurious to the general nutrition are connected with the majority of illnesses. If, nevertheless, in certain cases, as in most cases of Graves' disease, these factors do not make themselves perceptible, this is certainly due to the fact that antagonistic factors of superior potency then affect the organ. If these are weakened, le-depressory influences become visible even in the hyperplastic organ, i. e., an accidental involution is brought about. It is only from the point of view of an interchange of potentialities of this sort that we can explain the individual variations of a quantitative nature that occur from one case to another, even where, judging from external evidence, we may suppose quite similar conditions with respect to age, state of nutrition, etc., to be present.

What is the present state of our knowledge as to these excitatory and depressor factors?

In the case of the Hassall's corpuscles the question is easiest to answer as regards the excitatory factors. An increase in the number of the small Hassall's corpuscles has been shown beyond all doubt in Graves' disease, in the great number of acute infections of various sorts that have been subjected to investigation, and in the above-mentioned case of death from snakebite. A common characteristic of all these cases of disease is that in all of them a toxic factor is operative in the organism; in the case of bacterial and snake poison it is well known that this toxic factor causes the formation of an antitoxin, in the case of thyroid poison it may possibly do so. On the other hand, it has been impossible to establish any abnormal cH-excitation in investigated cases of poisoning by lye, hydrochloric acid, phosphorus, carbon monoxide and other substances that do not cause the formation of antitoxin, and this is true even when the intoxication has taken a somewhat protracted course.

As cH-depressor factors we have in the first place inanition and other comparable conditions that disturb the nutrition. Such influences appear so commonly in disease that one may say that there are comparatively few cases in which an illness of

long duration does not, at least in its final stages, cause an abatement or a stoppage in the new formation of Hassall's corpuscles, and this is also the case when the earlier stages of involution are characterized, as in acute infections, by a supranormal formation of such corpuscles. It is obvious that a cH-depression of this sort may be the result of a reduction in the power of reaction of the reticulum cells against cH-excitatory factors. Below, I shall discuss how in certain cases this reduction may possibly be supposed to be caused directly or indirectly by the rarefication of the lymphocytes in the organ.

It is not probable, however, that this method of explanation can be used in all cases. If it turns out to be correct that a cH-depression can appear even in cases where the number of lymphocytes in the organ is normal (as in certain cases of suicide or sudden death), or even where there is hyperplasia of the thymus, then the reduction in the reaction of the thymus reticulum must be considered to be caused, most probably, by other factors (changes in other endocrine organs?) or else it must be presumed that a weakening of the cH-excitatory factors themselves has taken place.

The most common of the factors that reduce the number of lymphocytes in the organ—the amount of cortex—are also disturbances in the general metabolism. In certain illnesses, however, such as Spanish influenza, one often finds a very marked involution of the thymus even in cases in which the fat and the musculature still seem to be normal or very slightly reduced. In these cases the question arises whether special lc-depressor factors have not exerted an influence by the side of the disturbances in the general nutrition. But these phenomena are too little known to be discussed here. Apart from these exceptions, which are in any case relatively rare, it is true of the lc-depression in general, as has already been mentioned, that there is no question at all here of conditions, special in principle, for the thymus, but of conditions that occur at the same time in the genuine lymphoid tissue and are also reflected in the number of lymphocytes contained in the blood. As has previously been indicated, the same may be said to be also true in the case of the more chronically operative lc-depression that begins with puberty, principally under the influence of the sexual glands.

This, too, has its correspondence in the real lymphoid tissue and in the blood.

A similar parallelism, but in the direction of a le-excitation, is perceptible in Graves' disease, as we have already seen. The hyperplasia of the thymus in this illness, which is chiefly a hyperplasia of the cortex, is often associated with hyperplasia in the real lymphoid tissue and with lymphocytosis. The question as to whether the same thing is true in castration seems at present to have been scarcely sufficiently investigated.

As far as the present deficient state of our knowledge permits us to judge, the lymphocytes thus seem in their conditions in the thymus to obey the same rules as usually regulate the total lymphocyte constituent in the organism. And therefore, it seems as if their variations in the thymus, no matter how great and striking, ought scarcely to be taken as direct expressions of the function of the organ. This does not at all mean that this function is independent of the lymphocytes of the organ, but I shall return to this question below.

Nor can the parallelism between the conditions of the lymphocytes in the thymus and in the organism in general lead to the idea that the thymus can, without reserve, be subordinated functionally to the lymphoid tissue. On the contrary, all the attempts made by v. Braunschweig (1891), Petrone (1904), Rudberg (1909) and Holmström* to produce in various ways an increased mitotic reaction in the thymus lymphocytes corresponding to that which takes place in the lymph glands show a negative result. Nor, as far as we can judge, is the regenerative activity of the thymus parenchyma increased in diseases of the blood. Basch (1906) looked in vain for a compensatory hypertrophy of the lymph glands in his thymectomized animals. The attempt made by v. Hansemann (1905) to explain the thymus as a regional lymph gland to the thyroid has not been confirmed, either. It is also very frequently found that the changes in the lymphocytes in the thymus, especially in accidental involution, are more far-reaching and occur more promptly than the corresponding processes in the real lymphoid tissue. And finally, as Hellman's investigations (1904) clearly showed, one has constantly to take into account differences of a purely local nature in the real lymphoid tissue, differences which apparently have no parallel in the thymus.

All these facts thus contain as many confirmations, from the point of view of the function, of the fact, well substantiated by the peculiar development and structure of the organ, that the thymus is not or does not consist of lymphoid tissue. But they do not alter the fact that the essential variations of the lymphocytes in the thymus are by no means anything special for the thymus, but obey laws that are applicable to the lymphocytic economy as a whole in the organism.

In spite of the far-reaching influence, morphological and functional, that both age involution and accidental involution undoubtedly have on the thymus, the question as to the significance of these variations is thus by no means a special thymus problem, but one that in a certain sense has a far wider scope. It passes into the problem of the importance of the lymphocytes to the organism in general, and a decisive answer to it has certainly not been given. But I wish, in passing, to mention the significance that, according to the investigations of Poulain (1902), Bergel (1909), Stheemann (1910), and others, may possibly be assigned to these cells in regard to the fat metabolism in the body.

If the view I have arrived at is correct, the two groups of functional changes that occur in the thymus parenchyma and leave their mark on it during different phases of the existence of the organ, namely, the changes in the number of Hassall's corpuscles and of lymphocytes, thus have a rather different significance with regard to the thymus function, and it is of prior importance to pay attention to the former kind of change in trying to explain this function.

From what has already been said with regard to the functional variations in the number of the Hassall's corpuscles, the conclusion may be drawn that the enlargement of cells or cell groups in the thymus reticulum which causes the formation of such corpuscles may be brought about by certain toxic substances that are produced by the organism itself or have entered into it. As these substances, as far as they are known, are of such a nature that they bring about the formation of antibodies, while toxic substances of other sorts have no effect in this direction, it is tempting to assume that this enlargement of cells is connected with an antitoxic activity in the cells concerned; this, of course, does not necessarily mean that these cells produce just

the antitoxic substances that have been proved serologically to exist in cases of this sort. The cell degeneration occurring in the Hassall's corpuscles, especially in the central cells, which are affected first and probably most strongly, has an analogy in other cases in which cells die away under the influence, for instance, of a bacterial toxin in a greater concentration than is compatible with cell life. It is then also easy to understand that the form of degeneration is not always the same, but that it may vary even in the same species, just as, of course, the nature of the factor that produces the degeneration varies considerably.

A fact shown even by histological and histogenetic investigation of the organ and strongly confirmed by its numerical analysis is that the Hassall's corpuscles are started as small formations and that only quite a small number of those so begun attain a greater diameter than 50-100 μ; the number of these larger forms is also less according as their dimensions are greater. If one tries to find the reason why the power of growth in different Hassall's corpuscles thus seems to be rather different, there is one especially important fact that is clearly shown as the result of the investigation of material from diseases. In no case* have I come across conditions indicating that the new toxic factor that affects the organ in and through disease can lead to an enlargement of already existing corpuscles, but in every case we have a formation of new small forms, which, if circumstances permit of it, seem in their turn to be able to some extent to assume greater dimensions, while the previously existing larger corpuscles not infrequently show regressive forms even at an early period of the disease. This state of affairs seems to me to indicate a certain specificity in the cells that are involved in the composition of the Hassall's corpuscles: they do not react to an additional toxic factor of another sort than that which originally caused their formation.

If this conclusion is correct, there are, as far as I can see, in the main two possible ways of explaining the fact that dif-

* A reservation may perhaps be necessary on this point with regard to typhoid fever, as in the few cases of this disease that I have had an opportunity to investigate there has been no increase in the number of small corpuscles, but certainly one in the number of large ones. The cases investigated are, however, from a late stage of the disease, when it may be assumed that the formation of fresh corpuscles has upon the whole ceased, and that a number of those formed earlier may have grown into larger forms. It is thus by no means necessary that the finding in question, which is practically unique in my material, should connote a deviation in principle from the other results, but it demands, of course, continued investigations with regard to the disease in question.

ferent Hassall's corpuscles in the same thymus attain to different degrees of development before they fall into regression. One is that toxic factors, which may be thought to be of a similar or heterogeneous nature, have ab initio affected one place in the parenchyma more strongly and with a greater area of extension, another place more slightly and to a less extent. The second possibility, which of course by no means excludes the first, is that a summation of similar stimuli may take place and proceed to a different extent at different places. Without wishing to adopt a decided standpoint in this matter, I shall only point out that certain cases in which there has been a relapse in an acute infectious illness without any observable increase of growth in the Hassall's corpuscles rather disfavour the latter alternative.

What has been said above shows quite well that Hassall's corpuscles do not arise everywhere in the parenchyma, nor under all circumstances, when a toxic factor of the kind indicated above is present in the organism. In trying to form a more detailed view as to the conditions under which these corpuscles arise, a fixed point of departure is afforded us by the fact that they originate only in the medulla, never in the cortex. It seems to me that we may all the more certainly consider it a fixed point, as the same is true of the different form of cell hypertrophy—"unicellular Hassall corpuscles," "myoid cells," epithelial cell groups of non-concentric arrangement—which apparently form an equivalent to Hassall's corpuscles in lower vertebrates.

The medulla is now characterized by a hypertrophy of the reticulum cells. This medullary hypertrophy of the reticulum cells thus seems to be an indispensable qualification if the latter are to show, against toxic substances, a group reaction of the sort that is expressed in the formation of Hassall's corpuscles. It is only after the formation of the medulla that these corpuscles arise, and this is the case both at the first development of the organ and at its regeneration. If the hypertrophy of the medullary cells regresses at accidental involution, the recruiting of the Hassall's corpuscles ceases, and this is also the case even when, as sometimes happens, the reticulum cells take up their position once more, side by side, in close epithelial union, which might seem to form a more than usually favorable mor-

phological condition for the origin of such formations. To use an expression borrowed from serology, one might say that only with the formation of the medulla are the reticulum cells sensibilized for the formation of Hassall's corpuscles. Of course this expression by no means contains any statement to the effect that this "sensibilization" in this connection is of the same nature as is usually denoted by this term.

With this view the medulla becomes the most peculiar part of the organ from a functional point of view, an opinion to which Shimizu (1913) was also led by the thymolytic experiments carried out by him, as in these the thymolytic changes were chiefly localized in the medulla. But these last-named investigations certainly need further confirmation before we can venture to build upon them. Weyermeersch (1908) seems to have found only ordinary accidental involution in corresponding experiments. Even Ogata's results (1917), to judge from the abstract, do not seem to have afforded morphological guarantees that the effect of the serum on the organ was anything but an indirect one.

If the cell hypertrophy that leads to the medullary differentiation is of such importance for the genesis of the centers of functional reaction constituted by the Hassall's corpuscles, it is especially to be regretted that our knowledge of the conditions under which medullary differentiation arises and is maintained is particularly slight and uncertain. As a matter of fact the actual question has only arisen quite recently in the literature. A case of thyreoaplasia (dystopic thyreohypoplasia) published by Hellman and myself (1920), in which the only noteworthy change that could be established in the thymus was a subnormal amount of medulla, gave rise to the question whether the secretion in the embryonal thyroid gland might be one of the factors producing differentiation of the thymus medulla. An investigation quoted in the same place, showed that in ontogenesis of amniota of different kinds, not only the oviparous but also the viviparous, the first traces of a secretion in the thyroid gland occur in a fairly fixed time relation both to the first appearance of the thymus medulla and to the appearance of the enchondral ossification or the starting of the medullary cavity in the larger cylindrical bones. These changes in the thyroid gland seem everywhere to belong to a period just before the above-

mentioned changes in the thymus and during ossification, so that to this extent we actually have the first condition for supposing that the function of the foetal thyroid gland may possibly influence the last-named processes. But we are still a long way from proving any real causality.

If under these circumstances we are confined chiefly to assumptions with regard to the factors that cause the formation of the thymus medulla, it is rather tempting to think in the first place of a chemical correlation, an endocrine influence. On the other hand, the occurrence of lymphocytes in the organ does not seem to be without significance for the medullary differentiation, if we are to judge from the fact that both in development and in regeneration the medullary differentiation does not take place until a considerable number of lymphocytes have infiltrated the organ. Likewise, in both accidental and age involution, when the number of lymphocytes in the organ has been reduced to a somewhat great extent, the hypertrophy of the medullary cells also undergoes regression.

That the lymphocytes are indispensable for the function of the organ is also shown by those cases in which, as sometimes in congenital lues, the parenchyma has partly assumed an epithelial character and is partly still infiltrated with lymphocytes. It is then solely the places infiltrated with lymphocytes that form Hassall's corpuscles, whereas the epithelial regions have no such newly-formed corpuscles. It is certainly an open question whether the influence of the lymphocytes is exerted directly on the formation of Hassall's corpuscles or only indirectly through their importance for medullary differentiation. It may possibly be considered that the latter alternative is supported by some cases in which, during convalescence after an acute infectious illness, the patient has fallen ill again with the same or another disease of an infectious-toxic nature. In some such cases the thymus has been found to be in reconstitution, with a relatively abundant infiltration of lymphocytes, but without any medullary differentiation. Under these circumstances it was impossible to establish any reaction on the part of the organ against the new illness in the form of an appearance of fresh Hassall's corpuscles. Before the formation of medulla has taken place the regenerating organ seems to be refractory to eH-excitatory factors.

At present no details can be given as to the nature of this influence of the lymphocytes on the antitoxic activity of the thymus. I shall only call to mind in passing that the presumed co-operation between the proper cells of a tissue and leucocytes is by no means without analogies in other cases in the theory of immunity.

If one starts out from the idea that the presence of the lymphocytes in the organ is of importance, directly or indirectly, for the antitoxic function of the organ, then certain phenomena in accidental involution become less difficult to understand. As, according to the laws otherwise governing the conditions of the lymphocytes in the organism, these cells are rarefied and disappear more or less completely in the thymus, the function of the organ also seems to be weakened and finally ceases altogether. The fact that this disappearance of the lymphocytes and the cessation of the function of the organ takes place especially during a reduction of the general state of nutrition does not fit it at all badly with our experience that during a reduction of this sort the power of resistance of the organism against infectious-toxic and other similar influences is actually reduced. This is, of course, not intended to be any expression of opinion as to how much of this decrease in the power of resistance is to be ascribed to the thymus and how much to other, synergistic organs. For it is of course quite certain that the thymus cannot sustain more than a part, more than some side that at present we are unable to define more closely, of the antitoxic activity in the organism.

The conclusion thus arrived at by my analysis of the morphological and experimental material put forward here is that *the lymphocytes in the thymus are necessary postulates for the function of the organ, but that the essential functional changes take place in the epithelial thymus reticulum in the form of an enlargement of separate cells or cell groups, causing in mammals the formation of the concentric cell complexes known as Hassall's corpuscles. These originate under the influence, direct or indirect, of the lymphocytes in the medullary reticulum, which is prepared and "sensibilized" by special influences (the thyroid?), and they form the morphological expression of an antitoxic activity.*

This view of the function of the thymus is the result of more than 20 years' study of this organ in different kinds of animals. In its most general features it has been indicated in an earlier essay (Hammar, 1918:2), but is put forward here for the first time in a somewhat more detailed form, after being tested, with a result that seems to me satisfactory, against a background of a total of between 200-300 normal and 400-500 pathological cases of human thymus, all subjected not only to a purely histological investigation but also to an analysis according to a numerical method. I hope to be able to make this material more accessible in print and so to help to form a concrete idea of the morphology of the human thymus, both under normal conditions and under the influence of different sorts of diseases. Here the observations gained from this material could only be mentioned as far as they were necessary for the present task.

It will certainly have been noticed that the detailed nature I have here tried to give to my exposition of the thymus function has caused me to enter on certain points into the sphere of working hypotheses. If, in spite of this, I considered that I could and ought to enter upon details of this sort, it was not only because my view seemed on the whole suited to contain all the not inconsiderable fund of assured knowledge with regard to the organ that we possess at present, but also and especially in the hope of facilitating in this way the experimental testing of the ideas developed here.

To a certain extent a testing of this sort is already possible now, namely with regard to the considerable experimental experience recorded in the literature, which, as it was arrived at without any close attention to the morphology of the organ, has not been taken into consideration in my exposition above. A detailed investigation of this point would, however, require much space and cannot be carried out here. But a few words must be said about the matter.

I may at first quite briefly call attention to the paucity of the positive results obtained from the attempts to incorporate more than a normal amount of thymus substance within the organism, whether in the form of an extract, by transplantation or by feeding. In this view I agree very much with what E. R. Hoskins (1918), among others, has stated in relation to this. In

all these attempts at hyperthymisation there has scarcely been one that indicates, still less proves, an internal secretion in the proper sense of the term. The lowering of the blood pressure that was shown, first by Svehla (1896-1900) and then by a number of other investigators, to be the effect of an intravenous injection of thymus extract seems, as far as it is not entirely due to intravascular coagulation, not to be any special characteristic of the thymus, but also belongs to other organs containing lymphocytes. And, according to Parisot and Lucien (1908) this effect is absent in the thymus from athreptics and is thus apparently connected with the presence of the lymphocytes.

And when Hedvig Müller (1917) and Del Campo (1918) state that by intravenous injection of thymus extract they have shown the existence of a specific capacity in the thymus to inhibit the occurrence of or even neutralize fatigue, such phenomena point rather to a fixation of poison than to a specifically secretory activity in the organ. An explanation of the same sort seems to be indicated by the cases, not very numerous up to the present, in which thymus medication has been employed in myasthenia (A. M. Hamilton, 1912). On the other hand the disappearance of myasthenic symptoms in patients with Graves' disease after thymectomy (Schumacher and Roth, 1912; Sauerbruch, 1912) seems to be compatible with the previous mentioned observations only if we may assume that here we are concerned with a dysfunctioning thymus.

Nor does there seem to be anything specific for this organ in the marked growth and delayed metamorphosis of thymus-fed amphibian larvae observed by Gudernatsch (1913-1914) and many others after him. It must be admitted that Uhlenhuth (1919) is correct in his view that the experiences gained on this point most probably indicate that the feeding of such larvae entirely on thymus is not likely to supply them with the substance necessary for metamorphosis. On the contrary, there seems to be no reason for assuming that there is present in the thymus any substance that has a positive inhibitory effect on the metamorphosis.

When, on the other hand, the last-mentioned writer is of the opinion that by proving "that the calf's thymus contains a specific toxin which is capable of producing tetany in salamander larvae and which can be antagonized by the parathy-

roids" he has shown "that the thymus actually does produce an internal secretion," I cannot agree with him. The observations in question show at the very most that a substance of this sort *is present* in the thymus; whether it has been formed there or perhaps only absorbed and possibly accumulated there must be considered as quite undecided.

The state of affairs with regard to the effect of the extirpation of the thymus may at first sight seem different. Ever since Restelli's experiments in 1845 until Klose's and Vogt's monumental investigations in 1910, as well as since that time, there is a whole series of works—by Basch, Soli, Matti, Hart and Nordmann, etc.—that can give us information about positive results of such interferences; not a few of these experimenters even come to the conclusion that the thymus is a vital organ. If one examines more closely the nature of the changes that are observed, which may consist in disturbances in the bone system and the lime metabolism, changes in the irritability of the nerves, delay in the occurrence of puberty, incomplete somatic and psychical development ("idiotia thymopriva")—to mention only some of the most important—one must admit that none of them is of such a nature that it cannot equally well be explained by assuming that the thymectomized animals are affected by injuries of a toxic nature which are neutralized in the intact animal.

We must also note that against these experiences there are experimental results that are entirely or partly negative. I may mention the results obtained by Ver Eecke (1899:1, 2), Pari (1905, 1906), Vincent (1904), the author (1905:2), etc., with regard to the frog by Allen (1920) in the earliest stages of tadpoles; those of Nordmann (1914), Pappenheimer (1914) Tangu (1916, 1917), Park (1917), etc., in mammals, in which thymectomy was carried out without any lasting disturbance in the condition of the animal. Park and McClure (1919) arrive at essentially the same negative results, on the basis of their own comprehensive experiments, in their large recently published monograph on this question. The detailed and careful historical and critical exposition in this work is well fitted to serve as a guide to this part of the thymus problem, and I refer the reader to it on this point.

If one starts out from the view of the disappearance of a specific organic function it seems comparatively difficult to explain this variation in the result of otherwise successful experiments that is actually present in thymectomy; on the other hand it is easy to explain it as the result of a reduced resistance against external injurious factors, which differ occasionally in occurrence and potency.

In one case the correctness of the latter explanation has been proved in an apparently convincing way by Pari's demonstration that the fatal syndrome that Abelous and Billard (1896) found in their thymectomized frogs and that they took to be a direct result of the operation, is really caused by the invasion of a bacterium against which animals without thymus are less resistent than those which are intact. Cosentino (1900) and Paton and Goodall (1904), among others, seem to have had similar experiences with mammals. And Park and McClure also suggest unfavorable conditions of milieu as the explanation of the disturbances in the condition of the animals, caused by thymectomy in so many of their predecessors' experiments.

As a matter of fact, several previous investigators, starting out from their experiments, have arrived at conclusions very similar in the main point, the antitoxic activity in the thymus, to those indicated by me from the point of departure of the structure of the organ and its variation. These statements, more or less firmly established, will be found collected in the book of Barbàra (1918). Here I shall mention two which have a broader experimental basis.

In the first place there is Brieger, Kitasato and Wassermann's work of 1892. They found that certain bacteria showed a reduced virulence when cultivated in thymus extract or when this extract was added to the culture medium. Thymus extract also appeared to possess the power of neutralizing bacterial toxin. In this the authors see an indication of an antitoxic activity of the organ; in the cases in which a comparison was instituted it turned out that the lymph glands had the same power. In the case of the tetanus toxin, however, the power of the thymus to prevent poisoning was not confirmed in a test carried out by Alfred Petterson (1911).

The conditions of both the thyroid and the thymus during infection have been recently submitted to a thorough clinical

and experimental investigation by Barbàra (1918). He records positive results for both organs. In the case of the thymus he comes to the conclusion that in this organ substances are formed that stimulate the phagocytes; they can be shown in an extract of the organ. In addition the thymus either forms complement or stimulates, by the formation of hormones, other organs to form complement. It also forms or increases the formation of opsonines, but it is uncertain whether it plays any part in the formation of agglutinins. The lack of equilibrium in the immunization apparatus that is at first brought about by thymectomy is gradually counterbalanced, except as regards the opsonins, in which case it seems to be permanent.

* * * * *

It is obvious that in all experiments on the function of the thymus we cannot disregard the very varied conditions that the organ may be in, on account of difference in age, different conditions of nutrition in the animal, etc., in each special case.

It is also extremely desirable that more attention than hitherto should be paid to each of the different structural components of the thymus separately, if our knowledge of the function of the organ is to be properly deepened. It would certainly be some gain if the detailed account of the problem of the function that I have tried to give above were to contribute to this.

In addition our lack of comprehensive knowledge of the factors of an excitatory and depressor nature that affect the thymus is especially noticeable. The filling of this gap seems to me one of the most important tasks that thymus investigation has to carry out in the immediate future. But it is obvious that this task cannot be accomplished by work directed merely toward the thymus. For it we certainly need, above all, a more extensive and a more profound knowledge of other endocrine organs and of the real lymphoid tissue.

Thus the special interests of thymus investigation result in a plea for the investigation of these last mentioned parts of the organism along the lines that not long ago (1920) I ventured, on more general grounds, to indicate, by ways of suggestion to the readers of this journal.

EDITORIAL SUMMARY

"Thymic asthma" due to pressure and "mors thymica" should be sharply differentiated. There is no reliable evidence that the latter is due to abnormality of the thymus.

The Hassall's corpuscles (c. H.) and the lymphoid cells (l. c.) vary independently. C. H. - excitatory and - depressor as well as l. c. - excitatory and - depressor factors can be recognized. L. c. - excitatory and - depressor factors affect the lymphoid tissues throughout the body. The c. H. - excitatory factors are of a toxic nature. The function of the thymus is antitoxic.

Much more study of these excitatory and depressor factors is needed as well as careful morphological analysis of the endocrine glands generally.

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• Signifies papers which have not yet been published.

EXPERIMENTAL DIABETES INSIPIDUS AND GENITAL ATROPHY.*

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(Preliminary abstract publication)

In order to throw further light on the pathogeny of certain symptoms commonly ascribed to deficiency of the hypophysis considered as an endocrine gland a series of experiments were performed on adult dogs. The chief purpose of the experiments was to differentiate between the effects of lesions in the juxta-hypophyseal region of the brain and of the hypophysis itself. Systematic punctures were therefore made in the hypothalamus. The lateral route of Paulesco and Cushing was employed; this gives a perfect exposure of the region and permits avoidance of the hypophysis with practical certainty, which is not true of the transphenoidal procedure hitherto employed for the purpose. The results of the experiments may be summarized as follows:

The consequences of the puncture depend strictly on the localization of the lesion and when the localization is correct, upon the extent.

A lesion, even an extremely minute one, of the parinfundibular region of the hypothalamus provoked with certitude (in 13 of 13 dogs) a polyuria which appeared in the first two days. According to the extent of the lesion it varied from a transient one lasting 6-8 days to an apparently permanent polyuria.

In the latter case other important symptoms were present, e. g., cachexia "hypophyseopriva," genital atrophy and adiposity.

The permanent polyuria realized has all the characteristics of diabetes insipidus in man, e. g., possibility of concentration when intake of fluids is restricted, when pituitrin is injected subcutaneously or in the presence of fever, excessive polyuric reaction to the administration of chlorides, and absence of theobromine effect.

The thirst may precede the polyuria. In 5 cases the increase in intake preceded the output by one day, and during several

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subsequent days there was a marked discrepancy between the intake and output. On the other hand, the polyuria may appear and persist without intake of water, e. g., in comatose animals.

The experimental diabetes insipidus does not depend upon a disturbance of a supposed nervous or vascular regulation of the kidney. It may be induced in animals whose kidneys have previously been denervated and when present persists with the same characteristics after denervation of the kidneys.

Lesion of the tuber cinereum has produced in two dogs a cachexia "hypophyseopriva" with genital atrophy, and in two other dogs an insidiously developing adiposogenital dystrophy. The integrity of the pituitary was in each case verified histologically.

An extensive lesion of the tuber cinereum is incompatible with life. The animals either die quickly or after a period of apathy in coma and convulsions.

Glycosuria was an inconstant result of the lesion and seemed probably to depend on the state of nutrition of the animal.

Even an extensive lesion of the base of the brain outside of the parainfundibular region may produce glycosuria, but never polyuria, the operative trauma being the same as in the previously mentioned polyuric animals. The relationship of the mammillary bodies to the polyuria is undetermined. Though involved in a few cases they were uninjured in other animals, which nevertheless showd polyuria and other symptoms.

The situation of this important nervous center and the minuteness of the lesion necessary to provoke characteristic symptoms probably explains the results of operations on the hypophysis in both young and adult animals. There is no evidence at present that the lesion acts by the intermediation of the pituitary.

A full report will be published later.

EXTIRPATION AND TRANSPLANTATION OF THE THYMI IN LARVAE OF RANA SYLVATICA

(With five plates—39 figures)

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INTRODUCTION

The following study has been prepared from notes and preserved material left by the late E. R. Hoskins. The experiments were made by him in the spring of 1919 at the University of Pittsburgh. They consisted of extirpations and transplantations of the thymi of larvae of Rana sylvatica, planned with particular idea of determining the relation of these glands to the lymphoid organs which they so closely resemble. In a previous paper, this investigator (Hoskins, '18) expressed the belief that the thymus is a lymphoid organ, producing no internal secretion. The suggestion was made that "in the lower animals there is relatively little lymphoid tissue other than the spleen and thymus, and experiments with the thymus in these forms should, therefore, be very instructive on account of the relative simplicity of the problem."

The experiments herein reported were of three sorts: complete extirpation, unilateral extirpation, and transplantation of thymic tissue. By making such a series of operations it was possible to study and compare normal animals, individuals with an excess of thymic tissue, those that had half the normal amount, and those that were entirely without any. In the following pages we shall consider the effect of the operations on the growth of the animals, on the normal thymi in cases where they were left intact, on the spleen, and on the endocrine organs.

MATERIAL AND METHODS

The tadpoles chosen for the experiments were from 11 to 16 mm. in length, and the operations were performed with fine knives and iridectomy scissors, the animals being anesthetized

with chlorotone (0.02% in 0.3% sodium chloride). When extirpation was to be performed, an incision was made at the side of the animal's head, and the thymus anlage was cut out. In making a graft, a flap of ectoderm was turned back on the lower jaw, and the thymic tissue which had been taken from another animal was implanted between the ectoderm and the muscles. The normal thymi of the hosts were not disturbed in the transplantation experiments.

The material chosen for histological study is largely from animals which had just completed metamorphosis, but some were also studied that were killed when at their maximum size, before the beginning of metamorphosis. The selection of a single, easily recognized stage eliminates the possibility of error arising from comparing tadpoles of the same size but of different stages of development.

Two methods were used in the study of the preserved material. Several animals from each set of experiments were studied from paraffin sections, and a large number of specimens were autopsied under the binocular microscope. The organs to be studied were dissected out from the surrounding tissues, and their outlines traced with the assistance of a camera lucida. The method is rather a crude one, but gives a general idea of the comparative sizes of the organs. It was expected that if significant variations of size were found, more exact measurements would be made from reconstructions, but the negative results obtained with the quicker method did not warrant the use of the more tedious process.

LITERATURE

Thymectomy has been performed by a number of investigators, on various animals. The results of all the experiments are critically summarized in a recent paper by Park and McClure ('19) and need not be reviewed in detail here. When the evidence is sifted, we find that thymectomy has not been satisfactorily shown to have a perceptible effect on the growth and development of any animals nor on any of their organs. In all cases in which experiments have been properly performed and controlled, they have yielded only negative results. Most of the work has been done on mammals, but some experiments with amphibia give similar results. It is certain that the high mor-

tality among the tadpoles operated on by Abelous and Billard ('96) was the result of an infection rather than of the operations. The experiments of Hammar ('05) showed that the thymus is not essential to the life of the tadpole. Adler ('14) reached the same conclusion, but claimed to have observed changes in the thyroids of thymectomized larvae, and hypertrophy of the gonads. He draws his conclusions from but three specimens, hence they amount to little more than guesses. Allen ('20) has extirpated the thymus from tadpoles, and studied a much larger number of specimens without finding any effect on their gonads or thyroids.

Thymus transplantation has not been performed by so large a number of investigators, and those who have done this operation have usually found that the graft was resorbed. Gebele has reported that the operation prevents the tetany which follows the extirpation of the thyroid and parathyroid, but others have been unable to confirm this statement. Dustin, who has worked on thymic grafts in amphibians and reptiles, has studied the different cellular elements in the grafts themselves, but not their effect on the rest of the body.

Other work on the thymus which is of particular interest in connection with the present study is that of Uhlenhuth. His views are not based on operative work, but on feeding experiments, and his general conclusion is that the thymus and the parathyroids act antagonistically in the body, the thymus producing a toxic substance which is neutralized by the parathyroids. Any disturbance of the balance existing between these organs, such as is caused by feeding thymus substance, results in a tetany which is similar to tetania parathyreopriva. The results obtained by Gebele are in opposition to this theory, since Gebele found that excess of thymic tissue prevented tetania parathyreopriva, instead of causing it.

Recently Dustin ('20) has proposed a different theory of the function of the thymus. He has made a very extensive study of the histology of the thymi in frog larvae, using both normal and thyroid fed animals at various stages of development. According to his observations, the small cells of the thymus are derived from the larger elements, and represent a stage in the loss of nuclein which the gland undergoes. The function of the organ is the elaboration of nuclein and giving it to the body.

Under conditions resulting from thyroid feeding the process goes on much more slowly. Nuclein is supplied to the body by the ingested thyroid substance and is not removed from the thymus, which shows a greater number of large cells than the thymus of a normal tadpole.

RESULTS

1. *Growth and development:* None of the operations performed seems to have affected the growth and development of the animals. Some measurements were taken during the growth period from the time of the operation until the animals attained their maximum size, and no significant difference between operated and normal animals was observed. As the tadpoles approached the period of metamorphosis each one was isolated, and

	TADPOLE		FROG	
	Max. Length	Max. Volume	Length	Volume
Control				
4/3	39.0 16.1	.69	13.0	.28
3/29	38.5 16.9	.71	13.8	.34
4/21	43.5 17.4	.....	14.3	.35
4/24	.....	.....	11.6	.22
Complete Extirpation				
4/10	38.6 16.2	.....	13.2	.25
4/11	39.3 16.2	.....	12.6	.27
4/21	39.8 17.1	.....	13.8	.33
Partial Extirpation				
4/24	39.3 17.1	.64	11.5	.17
4/25	42.7 15.5	.....	13.5	.29
Implantation				
4/11	40.0	.....	12.9	.27
4/21	37.4	.....	11.8	.19

was measured daily, so that we might be sure to have a record of its maximum size. Both body-length and total length were recorded, and the volume was measured by displacements. Table I shows a summary of these measurements, and of the measurements of the frogs developing from the experimental and the control subjects. Neither extirpation nor transplantation has any effect on the size of the animals. The only case in which a noticeable difference is present is in the three groups for 4/21. Here both the hosts in the transplantation experiments and the

completely thymectomized animals were smaller than the controls. This is doubtless an accidental variation; certainly it cannot be directly traced to the amount of thymic tissue present.

None of the experimental animals showed any loss of vigor, or any signs of tetany.

2. *Grafts and Normal Thymi:* Autopsies and sections showed that the operations were generally successful. Regenerated thymi were rare, while the grafts grew well in every case. Figures 1, 2 and 3 show sections through a graft and a normal thymus. They illustrate the position of the graft and the size relation between it and the normal thymus. The more ventral portion of the graft (A. Figs. 1 and 2) is undoubtedly the original tissue, while the smaller part (B. Fig. 2) is an off-shoot from it which has grown in behind the cartilage of the jaw. Figures 14 and 18 represent the outlines of the grafts obtained from autopsies. The thymi from the same frogs are shown in Figures 13 and 17, and it is evident that the grafts have more than doubled the amount of thymic tissue in the body.

Histologically, the grafts resemble the normal thymus of a tadpole. During metamorphosis the normal thymus undergoes a change which is represented in figures 6 and 9. The first of these shows the gland before metamorphosis. There are present in it a number of very large vesicular nuclei, which disappear during metamorphosis. According to Dustin ('20) they undergo "diminishing" divisions. Their place is taken in the thymus of the young frog by smaller vesicular nuclei. Connective tissue elements, also, which are prominent in the thymus of the tadpole, are less noticeable after metamorphosis, and the proportion of small dark nuclei is increased. The figures are taken from the central part of the thymus in both cases. The thymus of the tadpole has a cortex in which there are more dark nuclei than at the center, and this cortex increases in relative amount during metamorphosis.

A graft from a tadpole is shown in figure 4, and its close resemblance to the normal larval thymus (Fig. 6) is noticeable. This figure, also, is taken from the center of the graft which had about as much cortex as a larval thymus. The grafts do not undergo the same changes as the normal thymi at the time of metamorphosis. Figure 5 shows a portion of a graft from a frog,

illustrating its similarity to the normal larval thymus and the larval graft.

The normal thymi were studied, both from autopsies and from sections, to see if any regulation of the amount of thymic tissue takes place. Figures 12-19, which are representative of the entire series of autopsies, show that there is no regulation. Figures 12, 13, 14 and 15 show the different amounts of thymic tissue in three individuals with the length of 12½ mm. each. Figure 12 represents the two thymi of a normal frog, figures 13 and 14 the two thymi and the graft of a host in a transplantation experiment, and figure 15 the single thymus of a frog which had undergone unilateral extirpation. Figures 16, 17, 18 and 19 give a similar series for 12 mm. frogs. It might appear from the upper row of figures that the graft had exerted a retarding influence on the thymi shown in figure 13, since they are smaller than those of the control, but the condition is not repeated in the second series, in which the thymi of the host are larger than those of the normal animal. No proof of regulation is seen in the single thymus remaining after unilateral extirpation. In the smaller animals (Figs. 16-19) it is larger than either of the glands from the normal animal, but in the other series (Figs. 12-15) it is about the same size. The method of measurement, which is simply a comparison of outlines of the organs, is not very accurate, but as far as it goes it shows no indication that there is regulatory hypertrophy or atrophy of thymic tissue in these experiments.

The only detected effect of these operations on the thymus was a slight change in the histological appearance of the single thymus after unilateral extirpation. This is illustrated in figures 10 and 11, which represent the remaining gland in a tadpole and a frog respectively. In the tadpole the large cells have already become considerably smaller than those of the thymus of a normal larva (Fig. 6). The picture presented is scarcely distinguishable from that of the normal thymus of a frog. Also, in the single thymus after metamorphosis, a condition is found which may be supposed to be a later stage in the development of the gland. Pycnotic cells are not infrequent (p Fig. 11) although they are not to be seen in the normal thymus immediately after metamorphosis. Dustin has stated ('20) that the only activity of the organ which is morphologically demonstrable is the multi-

plication of cells, with increase of basichromatin and final pycnosis. It appears that though there is no compensatory hypertrophy of the gland, the rate of this activity is more rapid in the thymus left after a unilateral extirpation than in the glands of a normal animal.

Spleen: If the thymus is to be classed as a lymphoid organ, it is possible that its extirpation would affect the spleen, which is the only other large mass of lymphoid tissue in the body of the frog. Such does not, however, seem to be the case. Figures 20, 21, 22 and 23 show the spleens from a series of frogs with varying amounts of thymic tissue, and no significant size-differences are to be seen. Neither does a microscopic examination of the tissues show any effect of the operations.

Thyroids and Parathyroids: The thyroids have been studied from paraffin sections, as it is difficult to dissect out the whole gland on account of its irregular shape. I have not observed any significant changes in the form, size, or histological appearance of the thyroids of operated animals. My results on this point agree with those of Allen ('20) and differ from Adler's ('14). The thyroids of normal animals vary so much in size that a large amount of material must be studied in order to reach a definite conclusion with regard to the effect of the experiments on this gland. Within the limits of the material I have examined, no effect of thymectomy or grafting was to be seen in the thyroids.

The same condition is found in the parathyroids. Particular interest attaches to the condition of these glands in the frogs in which large amounts of thymic tissue have been implanted, owing to the theory of Uhlenhuth regarding the interrelation of the thymi and parathyroids. Nothing has been brought to light by this study which points to any special relation between these organs. The parathyroids of the thymectomized and normal frogs and tadpoles appear like those of the hosts for large grafts. They were studied from sections on account of their small size.

Hypophysis: Hypophyses were dissected out from a number of normal and completely thymectomized animals. From the first few autopsies and from sectioned material it appeared that the hypophysis had hypertrophied in the thymectomized specimens. Further investigations, however, made it seem doubtful whether this was anything but an accidental variation.

Figure 24 shows a median longitudinal section from a thymectomized frog, and figure 1 from a control. There is a striking difference in the size of the inferior lobe, particularly. Figures 26 and 27, however, show a pair which are practically equal in size. They were taken from a thymectomized and normal frog, respectively, the two being the same length (12 mm.) and nearly the same volume. Figure 28 shows the outline of the largest hypophysis found. It is from a thymectomized frog 13 mm. in length. The figure beside it (29) is from a normal animal of the same size. Figures 30 and 31 show a similar relation in hypophysis from thymectomized and normal frogs of 13½ mm. There seems to be a tendency for the hypophyses of thymectomized frogs to be abnormally large, especially in the larger animals. I have not found any of these glands in the normal specimens, which are as large as those shown in figures 28 and 30. I should hesitate, however, to say that the hypophysis had undergone a compensatory hypertrophy without examining a much larger amount of material than I have on hand. A histological study shows no change in the appearance of the gland as a result of the operations. The hypophysis of frogs with one thymus and those which had thymic tissue implanted in them are also normal as far as I have observed, and these show no variation in size.

Gonads: The gonads of all four groups of animals were studied from autopsies and representative specimens of testes are shown in figures 32 to 39. It has been found that castration delays the involution of the thymus in some animals, and we might expect this interrelation to be expressed by hypertrophy of the gonads after thymectomy. This does not occur, however. The two series, figures 32 to 35 and figures 36 to 39, are arranged in order according to the amount of thymic tissue present in the animal. They show no consistent differences in size which can be thought to indicate an influence of the thymus. The size relations seen in the ovaries are the same as these figures, and neither gonad shows any change upon histological examination. Here, also, our results agree with Allen's, and disagree with Adler's.

DISCUSSION

It is impossible to draw any definite conclusion as to the function of the thymus from the foregoing study. Owing to the great variation in the size of the organs of the normal frogs one

cannot obtain satisfactory results without a very large amount of material. Moreover, the smallness of the individual organs makes direct weight or volume determinations impossible, and methods of measurement must be either crude or excessively time consuming. The plan of the study was to look for any striking changes in the sizes of organs; and in case these presented themselves, to carry the work further by means of reconstruction. There is no indication, however, that such an undertaking with this material would be worth while.

A few negative results of the study may be pointed out. We agree with Allen that the thymus is not at all necessary for the life and development of the frog larvae, and that its loss does not affect the gonads or thyroids. We have also shown that excess of thymic tissue does not affect the tadpole in any perceptible way. The only endocrine gland which seems to be affected by any of the operations is the hypophysis, which is abnormally large in some cases after complete thymectomy. Since this gland does not always show evidence of hypertrophy, it is hardly likely that the overgrowth, when present, is of a compensatory nature.

Another point which is of some interest is the complete absence of regulation of the amount of thymic tissue. The larva seems to thrive as well with half as much or twice as much as the normal amount, and no attempt is made to restore the usual condition. This should be considered in judging the lack of effect produced by the operations on the spleen. If the thymus remaining after unilateral extirpation undergoes no hypertrophy, it is hardly to be expected that the spleen would show any overgrowth, even though it were of the same nature as the thymus.

On the ground of this lack of regulation, also, it would seem more reasonable to class the thymus among the lymphoid organs than to place it with the glands of internal secretion. It is known that the amount of lymphoid tissue in the body may vary greatly without producing any noticeable effects, while increase or loss of a hormone-producing gland is followed by some disturbances of metabolism and by easily recognized changes, especially in other glands of the endocrine series.

SUMMARY

1. Complete thymectomy does not affect the spleen of the larva or frog, nor any of the other organs with the possible excep-

tion of the hypophysis. The hypophysis appeared abnormally large in some of the thymectomized specimens, but the difference in size is probably not a true compensatory hypertrophy.

2. After partial (unilateral) thymectomy there is no attempt at compensatory hypertrophy on the part of the remaining thymus. Certain cellular changes go on more rapidly in the remaining thymus than they do in the glands of normal animals. No other organs are affected by unilateral thymectomy.

3. Grafting thymic tissue into a tadpole does not affect the size or structure of the normal thymi, the spleen, or any other organs.

4. Neither grafting nor extirpating the thymus affects the growth and development of the larvae.

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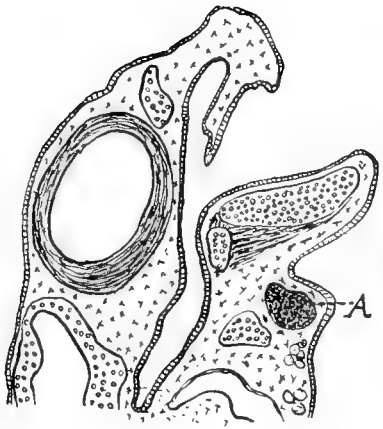
PLATES

PLATE I.

Fig. 1. Sagittal section, showing largest section of graft (A).

Fig. 2. Sagittal section, showing two parts of graft (A and B).

Fig. 3. Sagittal section through thymus (T) with small part of graft.



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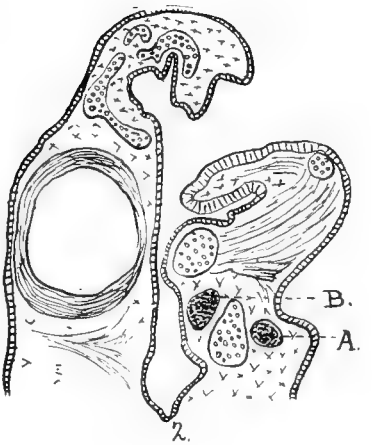

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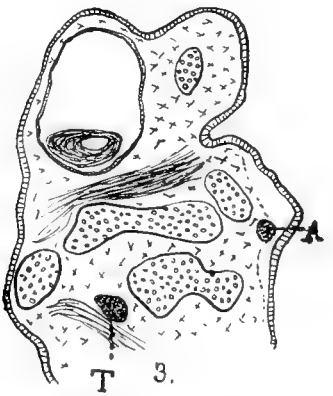

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PLATE II.

Fig. 4. Graft from tadpole.

Fig. 5. Graft from frog.

Fig. 6. Thymus from normal tadpole.

Fig. 7. Thymus from tadpole with graft.

Fig. 8. Thymus from frog with graft.

Fig. 9. Thymus from normal frog.

Fig. 10. Thymus from tadpole after unilateral thymectomy.

Fig. 11. Thymus from frog after unilateral thymectomy.

(Note pycnotic nuclei, at p—)

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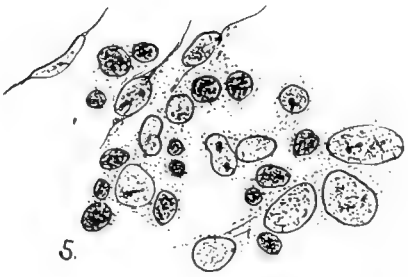

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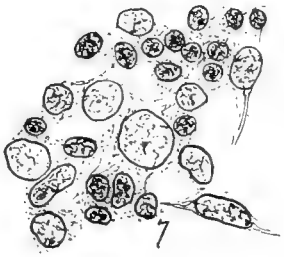

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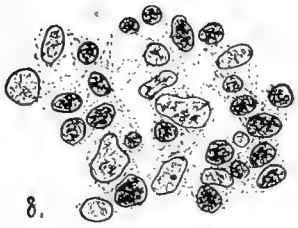

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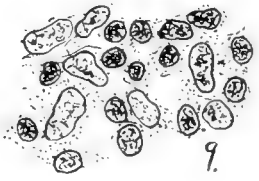

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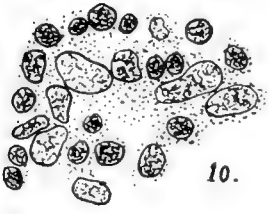

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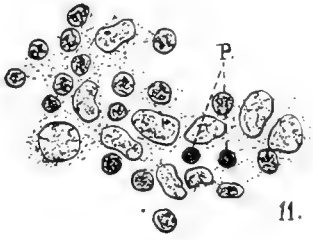

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PLATE III.

Fig. 12. Thymus normal frog (12.5 mm., vol. 0.22 cc.).

Fig. 13. Thymus of frog after grafting (12.5 mm., vol. 0.28 cc.).

Fig. 14. Graft, same frog as fig. 13.

Fig. 15. Thymus frog after unilateral thymectomy (12.5 mm., vol. 0.25 cc.).

Fig. 16. Thymus of normal frog (12 mm., vol. 0.20 cc.).

Fig. 17. Thymus of frog after grafting (12 mm., vol. 0.18 cc.).

Fig. 18. Graft, same frog as fig. 17.

Fig. 19. Thymus of frog after unilateral thymectomy (12 mm., vol. 0.18 cc.).

Fig. 20. Spleen, normal frog (12.5 mm., vol. 0.22 cc.).

Fig. 21. Spleen of frog after grafting (12.5 mm., vol. 0.28 cc.).

Fig. 22. Spleen of frog after unilateral thymectomy (12.5 mm., vol. 0.25 cc.).

Fig. 23. Spleen of frog after complete thymectomy (13 mm., vol. 0.3 cc.).

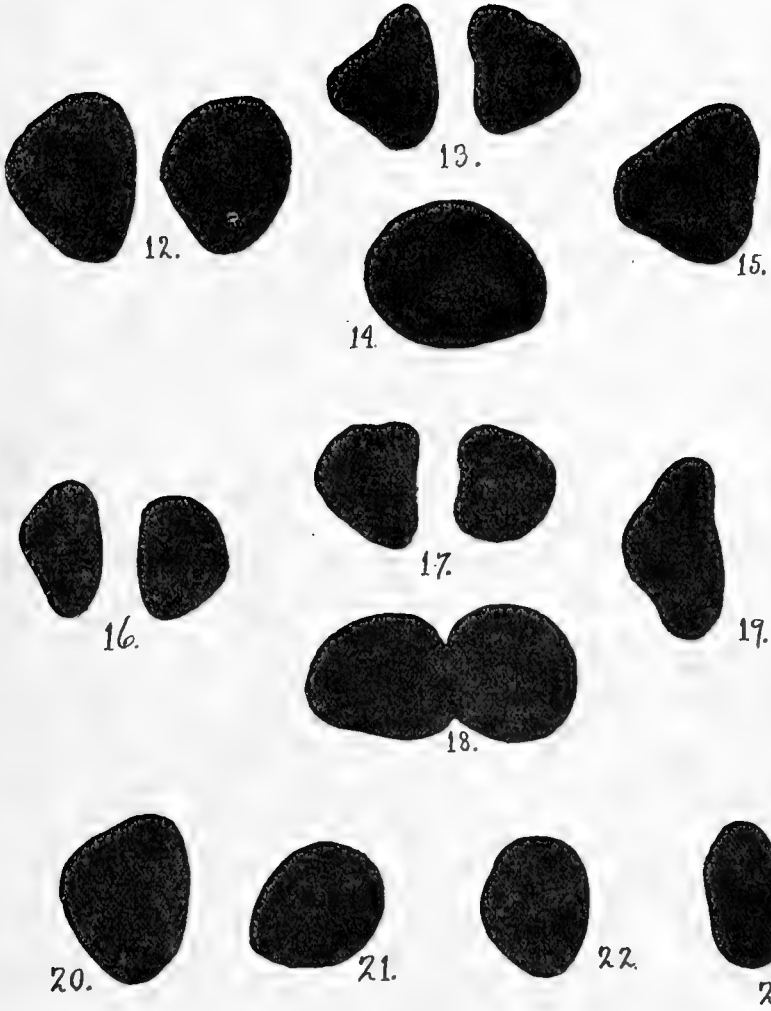
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PLATE IV.

Fig. 24. Median longitudinal section of the hypophysis of thymectomized frog.

Fig. 25. Median longitudinal section of the hypophysis of normal frog.

Fig. 26. Hypophysis after thymectomy (frog, 12 mm., vol. 0.18 cc.).

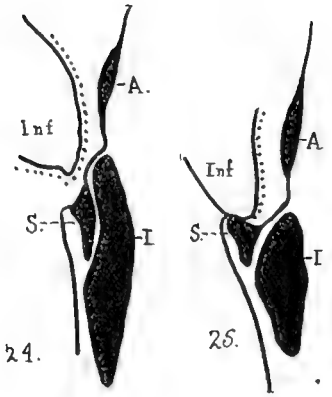
Fig. 27. Hypophysis of normal frog (12 mm., vol. 0.20 cc.).

Fig. 28. Hypophysis after thymectomy (frog, 13 mm., vol. 0.32 cc.).

Fig. 29. Hypophysis of normal frog (13 mm.).

Fig. 30. Hypophysis after thymectomy (frog, 13.5 mm., vol. 0.30 cc.).

Fig. 31. Hypophysis of normal frog (13.5 mm., vol. 0.33 cc.).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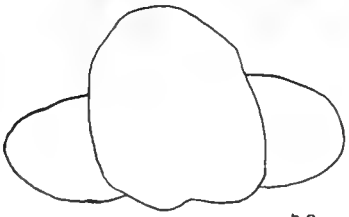
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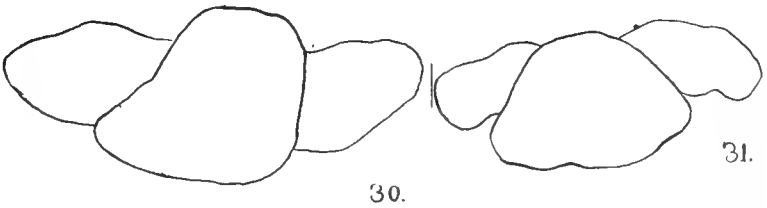
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PLATE V.

Fig. 32. Testes after complete thymectomy (vol. of frog, 0.25 cc.).

Fig. 33. Testes after unilateral thymectomy (vol. of frog, 0.25 cc.).

Fig. 34. Testes of normal frog (vol. of frog, 0.20 cc.).

Fig. 35. Testes after grafting (vol. of frog, 0.20 cc.).

Fig. 36. Testes after complete thymectomy (vol. of frog, 0.38 cc.).

Fig. 37. Testes after unilateral thymectomy (vol. of frog, 0.35 cc.).

Fig. 38. Testes of normal frog (vol. of frog, 0.37 cc.).

Fig. 39. Testes after grafting (vol. of frog, 0.38 cc.).


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ENDOCRINE THERAPY IN CASES OF LOW BLOOD PRESSURE

GEORGE H. HOXIE, A.M., M.D., F.A.C.P.

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Because the endocrine glands seem to be the catalyzers and energizers of the body it is natural to assume that the blood pressure, which is an index of vasomotor tone, must depend upon one or more of these products. The next step is to use these products in the therapy of disorders in which the vasomotor tone is thoroughly disorganized. This therapeutic experiment has been quite generally tried out these last two years throughout America. It is perhaps timely to seek an evaluation of the results.

For this purpose it would be well to classify the cases of blood pressure and note the results in each class. But here one finds his first difficulty in that there is no generally accepted etiological classification.

However the unprecedented prevalence of low blood pressure since the pandemic of influenza (or since the world war) has forced practitioners of medicine to set up working hypotheses and act upon them. Such a working classification would be the following:*

1. Infections:
   - Acute
   - Chronic
   - Focal
2. Exhaustions:
   - Nervous
   - Physical
3. Congenital:
   - Status hypoplasticus
   - Status thymico-lymphaticus

The congenital group, depending as they do upon constitutional anomalies for their symptoms, do not offer even theoretical

*Anaphylactic shock with its accompanying temporary fall in blood pressure is not under consideration here. For such cases of temporary low blood pressure the adrenal products have shown themselves worth while. We are considering here only the cases seen in ordinary practice.

encouragement for the administration of glandular extracts. Our experience has confirmed this theory. Nothing except systematic regulation of their diet, their activities, and their environment has succeeded in improving the condition of these unfortunates.

There remains, therefore, the consideration of the first two groups. Group 1 is extremely interesting since the blood pressure in these cases is a fair index of the body's success in its conflict with the infective agent or toxin. Just as in pneumonia we may gauge the patient's progress by the blood pressure curve, so in the chronic infections we find that as soon as the tissues win out, the blood pressure begins to rise. And we have noticed that many cases of high blood pressure are subsequent to a long season of low blood pressure when the body has been battling with a persistent infection. The high blood pressure with its hardened arteries is the body's defense against the depressant effects of the toxins.

The most persistent form of low blood pressure in this group has been that of the so-called focal infection wherein a chronic inflammation of, for instance, the tonsil, sinus, gall bladder, or seminal vesicle has depressed the vasomotor tone of the body for weeks and months. This is so general that in the presence of a persistently low blood pressure one should suspect the presence of such a focal infection.

Of the group of exhaustions, the most frequent example is that of the business man who has been straining every nerve to put through some business deal. In military life wonderfully good examples were seen in the soldiers who had participated in the battles of Chateau Thierry and the mad rush toward the Vesle. In these men the blood pressure was quite usually below 100, and remained so for two or three weeks. Then it gradually rose until in many cases it reached 160 and was accompanied by many signs of hyperthyroidism. This circumstance makes one wonder if the thyroid were involved in the syndrome, and the low blood pressure due to thyroid exhaustion. But the discussion of these possibilities would lead us too far afield.

The problem is whether the endocrine hormones are the link in the chain between the causal infection or exhaustion and the resulting low blood pressure (lowered vasomotor tone),—or

whether the cause acts directly through the disturbance of cell nutrition.

If, for example, the existence of a persistent focal infection has lowered the blood pressure, and if it does so by depriving the body of a needed hormone, we should by administering the needed hormone restore the vasomotor tone even while the infection persists. In the same way, if the body be exhausted, we ought (under this hypothesis) by substitution therapy to be able to maintain its tone while repairs are being made. Many practitioners have acted on this hypothesis, and the various glandular extracts have been tried and that under all sorts of conditions.*

The first thought for several years has been that the maintenance of vasomotor tone is the function of the adrenals. Hence among practitioners a great deal of adrenalin (medullary product), and also of the entire gland has been administered these last four years. The results have been such that practitioners are gradually abandoning the attempt. For even in the case of Addison's disease the vasomotor stability has not been restored. No better success has been obtained in the cases either of focal infection or of exhaustion. On the other hand, in a few of the acute fevers, such as pneumonia, adrenalin has once in a while stimulated the patient long enough for the exhausted tissues to recover their tone. But for this purpose its administration has had to be intravenous, and in a dose that might not overwhelm the weakened heart muscle.

Thus the experience with epinephrin is such that we can no longer regard adrenal dysfunction as one of the primary causes of low blood pressure.

The gland next tried out in practice has been the pituitary. Here the results have been more encouraging. The subcutaneous injection of pituitary extract has raised the blood pressure from a systolic of 90 to one of 110 in cases of exhaustion, especially of the nervous type. This rise will persist for 24 to 48 hours. But its continued use will not permanently stabilize the vasomotor tone, although it does give subjective relief.

Since the introduction of the study of basal metabolism, the question of its relation to thyroid secretion has become

*L. Borchardt in *Ergeb d. inn. Med. u. Kinderheilkünde* (Vol. 18, p. 331) says, "Organotherapy is partly organotropic, partly ergotropic, partly suggestive therapy, partly pharmacologic, partly ferment therapy." We have tried to recognize this complexity, and base our conclusions on objective and permanent results

increasingly acute. For, if the metabolic rate depended upon the presence of thyroxin and that alone, it would be easy to gauge the body's need for that hormone. But even if we grant that this is true, we are not permitted to believe that the blood pressure depends on the thyroid alone, for the basal metabolic rate does not run parallel to the blood pressure, nor is it uninfluenced by the type of infection present in the body. Yet in spite of all this we find that cases of persistent low blood pressure are more often benefitted by the administration of thyroid than by any other one extract. Even in cases in which the basal metabolic rate seemed fully normal and the blood pressure below 100, and the pulse pressure consequently between 20 and 30, the administration of thyroid has proven of advantage while the other curative processes were being applied.

The sex gland secretions,—in particular the extracts of the glands of Leydig and of the so-called "ovarian residue," have also been used by many practitioners with encouraging results. In fact, there seems to be more of a parallelism between vasomotor tone and the integrity of the sex glands than between it and any other one endocrine organ. Gonad administration therapeutically is rather difficult because, to be convincingly effective, its active principle needs to be isolated and prepared for intravenous, or at least subcutaneous, administration.

As a result then of our experience with low blood pressure, we are reaching the conclusion that the depressed vasomotor tone is not due to the exhaustion of any one gland, but to general nutritional causes in which the hormones are only one factor.

The use of such endocrine products therefore symptomatically is, to say the least, uncertain, and hardly possesses great superiority over other vasomotor stimulants of vegetable origin.

The prime requisite, on the other hand, in the treatment of low blood pressure is rest,—rest of both mind and body. In fact, to be really successful such rest must reach the stage of contentment (a condition just now hard to find). For every thoughtful clinician is made to realize that vasomotor tone depends on psychic as much as somatic influence,—and whether that influence is exerted through the endocrine organs must, in the light of our clinical experience, remain more than doubtful.

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Book Reviews

LA GLANDE GÉNITALE MALE ET LES GLANDES ENDOCRINES. Edouard Retterer and Serge Voronoff, Paris, 1921. Librairie Octave Doin, 233 p.

The poor impression of this book created by its wretched illustrations and worse paper is borne out by a reading of the text. The study is divided into two parts. In the first are described experiments on old sheep and goats that had lost their sexual desire. Implantation of a testicle from another animal was followed by increased strength and vitality as well as augmented libido. Histological examination of the graft disclosed absence of mitotic figures from the interstitial cells and a sort of fibrous degeneration of the spermatogenic elements. The authors believe that the interstitial cells take origin from the spermatogenic and that the internal secretion of the testis is merely resorbed material set free in the disintegration of the seminal cells. Merely superficial evidence for this view is adduced. The second part might well have been entitled "Endocrinology for the nursery." Although interesting and readable it discloses not a few fantastic views. The islets of Langerhans are represented as derived from the parenchyma of the pancreas and becoming changed into fibrous tissue, the pancreas thus resembling the testis. The lymphoid glands are considered as endocrine. In the thymus the epithelium and connective tissue are represented as changing into red and white corpuscles. The active principle of the thyroid is regarded as probably Baumann's iodothyrin, isolated in 1895. The important recent work of Kendall, Abelin, Hirschfeld and Klinger on this subject is ignored. These are a few of the many examples that might be cited to show the superficial and unreliable character of the book. It should be read very critically or, better, not at all.—J. K.

HUMAN BEHAVIOR, by Stewart Paton, M. D. New York, 1921. Chas. Scribner's Sons. 465 p.

The underlying theme of this book is that the individual should be studied from the broad biological point of view as a unit and not as a collection of unrelated segments. Throughout the course of the discussion this motif threads its way insistently and while to all broad-minded persons no argument is needed to justify the assertion, yet its continual and assertive repetition is

needed that those who run may read. In a thoroughly intelligible manner and yet withal by a somewhat circuitous method, Paton presents his study of the individual in relation to educational and social problems. He gathers his harvest from the fields of physiology, biochemistry, psychology and philosophy in expounding his conception of the adjusting mechanisms of the organism: the personality and its development: the controlling mechanisms or inhibitions; the factors in organization and synthesis or character, temperament and intelligence; the factors determining the trends of activities; habit formation and involution of the personality. In addition there are chapters on the resultants of imperfect organization of activities; methods of studying the personality and education. The role of the internal secretions in these various processes of human adaptation is brought to the fore wherever necessary and furnish the measure of a minor harmony. The importance of the endocrine organs in the development of the personality and in the adjustments as expressed in behavior is frequently mentioned, but an elucidation of the mechanism of their participation is lacking. The book should be read by all those interested in problems of the reaction of man to his heredity and environment.—F. S. H.

DIABETES: A HANDBOOK FOR PHYSICIANS AND THEIR PATIENTS. Philip Horowitz. New York, Paul B. Hoeber, 196 p.

For review, see J. Am. M. Ass. (Chicago), 1921, **76**, 402.

Abstract Department

A case of macrogenitosomia precox and ADRENAL tumor in a 3-year-old girl (Ein Fall von Makrogenitosomia praecox und Nebennierentumor bei einem 3 jährigen Mädchen). Ambrozic (M.) & Baar (H.), Ztschr. f. Kinderh. (Berlin), 1920, **27**, 135-142.

Report of a case af adrenal tumor in a three-year-old girl. When two years old she was observed to be large for her age. A year later pubic hair appeared and the voice became deeper. Menstruation did not appear. Her general appearance was that of a six-year-old, though an x-ray examination of the hand showed ossification comparable to that usually found at twelve. There was a marked hypertrophy of the external genitalia. The breasts were not affected. A palpable abdominal mass was present and operation showed this to be a tumor of the adrenal cortex. Metastasis to the lungs was found at autopsy. The authors review the literature on this condition and point out the superiority of the term macrogenitosomia over the earlier used pubertas praecox.—C. H. G.

(ADRENAL) Injection of gas to outline the kidney. Anon., J. Am. M. Ass. (Chicago), 1921, **77**, 1108; **Un nuevo procedimiento para explorar el riñon.** Carelli (H. H.) & Sordelli (E.), Rev. Asoc. Méd. Argentina (Buenos Aires), 1921, **34**, 424.

A method is described whereby the outline of the adrenal can be obtained on an x-ray plate. This should be of considerable importance in the diagnosis of adrenal hypertrophy or atrophy.
—R. G. H.

ADRENAL glycosuria. Caffein a paralyzing poison to the sympathetic (A propos de la glycosurie adrénalique. La caféine, poison paralysant du sympathique). Bardier (E.), Leclerc (P.) & Stillmunkes (A.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 281-282.

Fredericq and Descamps have shown that caffein has a paralyzing action on the sympathetic nervous system and it became of interest to observe its effect in experimental adrenin glycosuria. The double benzoate of caffein and sodium in 2 per cent saline solution was injected intravenously, followed by a subcutaneous injection of adrenalin. The urine contained no sugar, while control animals with adrenalin only, all gave sugar in the urine. The caffein inhibits the glycosuria by a paralyzing action on the sympathetic.
—T. C. B.

(ADRENAL) Tumor of the sympathetic (Sympatheticustumor). Barnewitz, Deutsche med. Wchnschr. (Berl. & Leipz.), 1921, **47**, 796.

The tumor was found in a woman of thirty-seven. It took origin from the medulla of the right adrenal. Metastases were found in both ovaries and in the left lung. The tumor contained microscopically immature sympathetic elements (sympathoblasts), but no neurofibrils or neuroglia.—J. K.

Syphilis and the ADRENALS (Syphilis y capsulas suprarenales). Bejaram (J.) & Covira (J.), Méd. Ibera (Madrid), 1921, **14**, 332.

The authors have observed various cases of syphilis in which, above all, at the end of the secondary period there appeared asthenia, pigmentations, and, at times, hypotension. They attribute these appearances to affections of the suprarenal glands. In these cases adrenalin is administered together with the antisyphilic treatment.—G. M.

The effect of radiation of the ADRENALS on the metabolism in DIABETES (Zur Wirkung der Röntgenbestralung der Nebennieren auf den Stoffwechsel bei Diabetes). Beumer (H.), Ztschr. f. Kinderheilk. (Berlin), 1921, **28**, 329-334.

Report of a diabetic boy of 6½ treated by radiation of the adrenals. One-half of the erythema dose of x-rays was applied on each side for three successive days. Following the first dose the blood sugar fell from 0.262 to 0.158 and remained at approximately this level for the week the child was under observation. A mild acidosis cleared up at the same time. In spite of the changes in the blood sugar there was no apparent change in the carbohydrate tolerance or the urinary excretion of sugar. The author discusses the different possible endocrine relationships involved in this case and concludes that the fall in blood sugar is an expression of a lessened adrenal secretion.—C. H. G.

A note on the relation between the ADRENALS and the THYROID. Crile (G. W.), N. York M. J. (New York), 1921, **113**, 389-391.

The adrenal glands are activators of the brain, and that their aid is promptly elicited when increased metabolism—increased work—is required, is shown by the fact that adrenalin alone produces nearly all the symptoms produced by the various causes of increased energy transformation, such as emotion, exertion, injury or infection. That is, adrenalin causes increased metabolism, increased thyroid activity, increased blood pressure, increased pulse, increased respiration, leucocytosis, increased sweating, dilation of the pupils, diversion of the blood to the surface, lowering of the threshold of the myoneural junction. Adrenalin causes hyperchromatism and later chromatolysis of the brain cells, just as do emotion, injury, exertion, infection; it causes an immediate increase in the electric conductivity of the brain, and when the adrenals are removed the brain cells rapidly degenerate, the animal rapidly loses the power to

fabricate heat, and muscular and mental action; death usually follows. We conclude, therefore, that the brain is dependent on the adrenals, both for function and for survival. "Experimental and clinical phenomena seem to indicate that the body is driven by electricity, which is fabricated in the brain cells with the aid of adrenalin. But we have no evidence that adrenalin covers more than the emergencies of moments and hours, or of days." It is assumed that the brain does not possess this power within itself, hence some other tissue is responsible for the maintained electric conductance. The tissue responsible is the thyroid which, throwing its secretion into the blood stream, activates the brain cells. The thyroid and adrenal glands, because of their secretions, therefore, are similar in that the processes of electrical phenomena are maintained by them in the cells of the nervous systems.—H. W.

(ADRENAL) Addison's disease. Report of an unusual case, Eidelsberg (J.), N. York M. J. (New York), 1921, **113,** 292-293.

A report of a rapidly fatal case of Addison's disease. The onset was characterized by marked gastric symptoms. Bronzing was represented by a general tan and slight buccal bronzing. There was no anemia. The patient probably had tubercular epididymitis. Both suprarenal bodies were markedly enlarged and soft and on cutting, except for a thin cortical portion, appeared to consist of a soft cheesy material. Typical tubercular lesions were demonstrated microscopically. The thoracic and other abdominal viscera were normal.—H. W.

Investigaciones embriologicas sobre la capsule suprarrenal. Forcada (F.), Laboratorio (Barcelona), 1920, **3,** 621-624.

Confirms the opinion commonly held.—E. B.

Possible relation of ADRENAL cortex to Graves' disease and to myxedema. Friedman (G. A.), Med. Record (N. Y.), 1921, **99,** 295-300.

The author atempts to find an increased activity of the adrenal medulla in **Graves' disease** and a corresponding mild deficiency of the medulla in **myxedema,** as suggested by autopsy findings, response to the Goetsch test, sugar tolerance, eosinophilia, etc. The independence but interrelationship of the adrenal medulla and cortex is then emphasized, and finally the conclusion is reached that the chief function of the cortex seems to consist in supplying the medulla either directly or indirectly with its products for the elaboration of epinephrin; and that the second function of the cortex is probably a detoxicating one. He quotes Bauer, who believes that uric acid is converted into the melanin of the cortex, and the epinephrin of the medulla elaborated by the reduction of the melanin. As an example of its detoxicating function it is assumed that the cortex prevents

the accumulation of uric acid in the body and in such a manner saves the organism from uremia. The cortical lipoids largely disappear in acute infections. Body weight is supposed to be largely under control of the adrenal cortex. Blood pressure is influenced by the cortex as well as the medulla. The cortex therefore is supposed to influence epinephrin production; regulates purin metabolism and pigment metabolism; destroys pathogenic bacteria; regulates weight; and somewhat controls blood pressure. The hyperpigmentation frequently seen in Graves' disease is explained as due to increased retention of uric acid due to decreased detoxication because of cortical hypofunction. In myxedema the opposite occurs. The cholesterin metabolism is decreased in Graves' disease and increased in myxedema. The loss of weight, myasthenia and asthenia in Graves' disease resembles that of Addison's disease and is therefore attributed to cortical deficiency. The obesity and atheroma of myxedema might be the result of hyperactivity of the cortex. The size of the mammae is mentioned as partly dependent on cortical activity. The author finally concludes that hyperthyroidism and myxedema are not monoglandular disturbances, that in Graves' disease there is hypofunction of the cortex, and in myxedema, hyperfunction. Fifty-five references are appended which form the experimental, histological, biological and clinical basis for the author's deductions. [A perusal of Stewart's critical review of adrenal insufficiency in a recent number of Endocrinology would make one hesitate before accepting much of the evidence presented in Friedman's article.]—H. L.

Consequences of the destruction of the ADRENALS in the toad and the frog [Consequences de la destruction des surrénales chez le crapaud (Bufo marinus) et la grenouille (Leptodactylus ocellatus)]. Giusti (L.), Compt. rend. Soc. de biol. (Paris), 1921, 85, 30-31.

Operations were made on 300 toads and 200 frogs. Two longitudinal incisions were made at the sides of the vertebral mass, instead of an abdominal incision, as the wounds heal better and more quickly, and the kidneys are more easily accessible. There were three groups of operations: (a) cauterization of both suprarenals; (b) cauterization of one suprarenal and the opposite kidney; (c) linear cauterization of both kidneys. The conclusion of Abelous and Langlois is confirmed, viz.: that destruction of the two suprarenals in batrachians produces a considerable mortality that cannot be attributed to operative traumatism.—T. C. B.

(ADRENAL) Sensibility to poisons, of toads decapsulated, or without the HYPOPHYSIS (Sensibilité aux toxiques des crapauds acapsulés ou sans hypophyse). Giusti (L.), Compt. rend. Soc de biol. (Paris), 1921, 85, 312-313.

Confirming J. T. Lewis' results on decapsulated rats, Giusti finds the lethal dose of various poisons to be less in decapsulated toads than in the normal.—T. C. B.

Persistence, after double ADRENAL ablation, of the salivary reflex caused by excitation of the sciatic nerve (Persistance, après la surrénalectomie double, du réflexe solitaire, causé par l'excitation du nerf sciatique). Gley (E.) & Quinquaud (A.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 706-708.

The salivation caused by stimulation of the central end of the cut sciatic is not modified by removal of the two suprarenals, as claimed by Forovsky. The flow of saliva is practically the same as before the operation. It is necessary, however, to wait 30 minutes before stimulation, as the flow is diminished during that time. A fall of temperature is also accompanied by a diminished flow.
—T. C. B.

Vasomotor reaction of the ADRENAL to ADRENIN (Reaction vasomotrice de la surrénale a l'adrenaline). Hallion (L.), Compt rend. Soc. de biol. (Paris), 1921, **85**, 146-149.

The author gives tracings showing typical curves of vasoconstriction, i. e., a diminution in volume of the adrenal coincident with the rise of blood pressure following the injection of adrenalin.
—T. C. B.

The ADRENALS play no role in the production of vascular effects of extract of HYPOPHYSIS (Les surrénales n'ont aucun rôle dans la production des effets vasculaires de l'extrait d'hypophyse). Houssay (B. A.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 35-36.

The injection of pituitrin produces exactly the same effect (hypertension and bradycardia) before and after ligature of the adrenal veins.—T. C. B.

Unilateral ADRENAL extirpation for epilepsy (Die Behandlung epileptischer Krämpfe durch Extirpation einer Nebenniere). Kutscha-Lissberg (E.), Wiener klin. Wchnschr., 1921, **34**, 299-300.

The author, following Bruning, has performed unilateral adrenal extirpation in two cases of epilepsy. No further seizures occurred during the 6 months and 7 weeks, respectively, that the cases had been under observation.—J. K.

The importance of the ADRENAL in spermatogenesis (Die Bedeutung des Interrenalorgans für die Spermiogenese). Leopold, Berl. klin. Wchnschr., 1921, **58**, 556; Deutsche med. Wchnschr. (Berl.), 1921, **47**, 665.

There seems to be a definite relation between the cholesterol content of the adrenal and the histological picture of the seminal epithelium in the mole during rutting time. In man, when the cholesterol content of the adrenal is diminished, the seminal cells degenerate, the lipoids from the latter being resorbed by the interstitial cells.—J. K.

ADRENAL opotherapy in Basedow's disease (Action de l'opothérapie surrénale chez les Basedowiens). Obregia (A.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 1024-1026.

The author has administered daily doses of a glycerin extract of fresh suprarenal glands in a series of cases, not only of typical Basedow's disease, but also cases which he calls "basedowoids," characterized by vibratory trembling, tachycardia and asthenia. In all cases there has been a rapid amelioration of the symptoms and a final cure. Pig's suprarenals have been the most active. A second series was treated with adrenalin, but while there was a constant amelioration, it was not as pronounced as in the case of the total gland. The explanation may be, as pointed out by Marinesco and Parhon, that there is an important relation between the thyroid and the lipoids and chromaphil substance of the adrenals, and it is necessary to have a combination of these two substances.—T. C. B.

ADRENAL extirpation in epilepsy (Nebennierenreduktion bei Epilepsie). Peiper (H.), Zentralbl. f. Chir. (Leipz.), 1921, **48**, 407-409.

The improvement that results from unilateral adrenal extirpation in epilepsy is merely temporary. The return of the seizures is perhaps due to compensatory hypertrophy in the other adrenal. —J. K.

(ADRENAL) Addison's disease and pregnancy (Enfermedad de Addison y embarazo). Puig & Roig, (Rev. españ. obst. y ginec (Madrid), 1920, **6**, 487-494.

The author says that Addison's disease is very rare among pregnant women. When the disease is present the patient is in a very grave situation; there is likelihood of abortion, premature parturition, autointoxication, infections, and sudden death. Dystocia is common on account of the hyperactivity of the uterine muscles or suprarenal disturbance.—E. B.

(ADRENAL) Symptomatology and treatment of hypernephroma (Beitrag zur Symptomatologie und Therapie der Hypernephrome). Thierry (H.), München. med. Wchnschr., 1921, **68**, 638-640.

Of technical surgical interest.—J. K.

ADRENAL cortex. Tokumitsu (Y.), Mitt. a. d. path, Inst. Univ. Sendai (Japan), 1921, **1**, 161; 211.

Tokumitsu describes what he calls a new function of the suprarenal cortex, which becomes manifest when a ligature is thrown around the pancreatic duct. The cortex proliferates and hypertrophies, evidently as a compensating process. The medulla of the suprarenal, on the other hand, seems to have an antagonistic action to that of the pancreas. The medulla and the cortex are separate organs. His research has confirmed that diabetes develops even with slight changes in the pancreas if the suprarenal cortex shows degenerative changes, while otherwise the diabetes develops only with pronounced changes in the pancreas. The article is in German, but is followed by a report, in English, of experimental research on the suprarenal cortex which demonstrated that it is indispensable to life, while the medulla can be removed without comparative harm.

—J. Am. M. Ass., **77**, 823.

ADRENAL hemorrhage in the new born (Della emorragie surrénale nei neonato). Tronconi (S.), Pediatria (Napoli), 1921, **29**, 266-274.

A case report without especial endocrine interest. The child was markedly jaundiced and the history suggested a latent hemophilia in the mother.—C. H. G.

(ADRENIN) The stimulating effect on the PANCREAS of the amino-acid hydrochlorides (Ueber die sekretorische Wirkung der salzsaüren Aminosäuren auf das Pankreas). Arai (M.), Biochem. Ztschr. (Berl.), 1921, **121**, 175-179.

5 to 10 cc. of H_2O solutions of various concentrations of the HCl salts of glycocoll, d-alanin, d-glutamic acid and glycylglycin were injected into the duodenum of dogs with temporary pancreatic fistulas. Pancreatic secretion was stimulated. Histidin and d-glucosamine hydrochloride did not act as stimulants. When the compounds were injected intravenously or subcutaneously no reaction was obtained. **Adrenalin** depresses the stimulating action of these amino-acid hydrochlorides.—F. S. H.

Hypersensibility to ADRENIN of animals narcotized with chloralose (Hypersensibilité a l'adrénaline des animaux chloralosés). Bardier (E.) & Stillmunkes (A.), Compt. rend Soc. de biol. (Paris), 1921, **84**, 766-767.

According to Gautrelet and Briault dogs having previously received an injection of adrenalin are rapidly put to sleep by chloralose, without the characteristic medullary hyperexcitability. In the course of experiments on adrenalin glycosuria the authors noticed on many occasions that rabbits anesthetized with chloralose died in from 3

to 8 minutes after an injection of adrenalin much smaller in amount than the minimal lethal dose. Death occurs with pronounced nystagmus and acute pulmonary edema. No explanation is given.—T. C. B.

Studies on the cerebro-spinal fluid. VII. A study of the volume changes of the cerebro-spinal fluid after ADRENALIN, PITUITRIN, pilocarpine and atropine. Becht (F. C.) & Gunnar (H.), Am. J. Physiol. (Balt.), 1921, **56**, 231-240.

Adrenalin does not increase fluid formation, because it can be shown by the authors' method that fluid flows out during the pressor stage, but returns in equal amount as vascular readjustment takes place. The same is true for pituitrin. These drugs therefore affect the cerebrospinal fluid output merely through their influence on the circulation.—T. C. B.

Atropine and ADRENIN as antidotes to morphine (Atropin und Adrenalin als Gengengifte des Morphiums). Bornstein (A.), Deutsche med. Wchnschr. (Berl.), 1921, **47**, 647.

The author, himself, took large doses of morphine and then studied the gaseous metabolism. Atrophine had no influence upon the respiratory center, at least in doses of 1 to 3 mgm. Adrenin increased the intensity of respiration and consequently appears to be a better antidote than atrophine in respiratory difficulty from morphine.—J. K.

(ADRENIN) The mechanism of the production of paroxysmal tachycardia. Heterotropic tachycardia produced in man by adrenin (Sur le méchanisme de production de l'accés dans la tachycardie paroxystique. Tachycardie hétéroptope provoquée chez l'homme a l'aide de l'adrénaline). Danielopolu (D.) & Danulesco (V.), Ann. méd. (Paris), 1921, **10**, 1-9.

The subcutaneous injection of 1.5 milligrams of adrenin in a case of tachycardia gave relief. This effect is attributed to an inhibition of the sino-auricular node function and an excitation of the heterotopic centers.—F. S. H.

Experimental ADRENIN hyperglycemia (Contribucion experimental al estudio de la hiperglucemia adrenalinica). Del Campo (G.), Estudios Médicos (Murcia), 1920, **7**, 3-32.

In numerous experiments carried out on dogs, the author has not been able to obtain hyperglycemia by subcutaneous or intravenous injections of adrenalin, although it is always elicitable in rabbits. This is correlated with injury to the hepatic plexus. Del Campo always employs, for determination of glycemia, the method of Bang, which he considers much the best.—E. B.

On the influence of ADRENALIN and pilocarpin on the calcium exchange in infancy (Über den Einflusz von Adrenalin und Pilocarpin auf den Kalkumsatz im Säuglingsalter). Schiff (E.) & Peiper (A.), Jahrb. f. Kinderh. (Berlin), 1920, **93**, 160-166.

The authors studied the Ca balance in four children before and after giving adrenalin and pilocarpin. The results were in no way conclusive, though they feel that there was a slight increase in the Ca excretion following adrenalin. They say that this may indicate that adrenal substance is not of therapeutic value in rachitis.

—C. H. G.

EPINEPHRINE hyperglycemia. Tatum (A. L.), J. Pharmacol. & Exper. Therap. (Balt.), 1921, **17**, 395-413.

Testing the blood sugar content and alkaline reserve following administration of epinephrine alone and in combination with phloridzin, morphine, acid or alkali, in the rabbit, has led the author to the conclusion that epinephrine glycogenolysis cannot be satisfactorily explained on the basis of hepatic asphyxia or acidosis. There is produced essentially the same quantitative glycogenolysis, as measured by hyperglycemia, regardless of whether or not acidosis pre-exists. The real mechanism of epinephrine mobilization of carbohydrates, therefore, is as yet undetermined.—W. J. A.

Über CHONDRODYSTROPHIE. Duken (J.), Ztschr. f. Kinderh. (Berlin), 1920, **26**, 65-84.

In his discussion of chondrodystrophy the writer finds himself in more or less agreement with the earlier remarks of Jansen, who believed that "the mechanical malformations characteristic of achondroplasia could be brought about by three compressing forces which act on the head-, the neck-, and the tail-bends of the embryo and—so to speak—roll it up in its long axis." Duken feels that these mechanical factors may produce results not only by direct amniotic pressure, but as well by secondary ischemic effects on the **endocrine organs**, especially the **pituitary**. He suggests the use of pituitary extract as a therapeutic procedure. Duken presents a case of chondrodystrophy in a 4¾-year-old boy in which he tested the response of atropine, **adrenalin** and pilocarpine and the Abderhalden ferment reaction as applied to **pineal, brain, gonad,** hypophysis and **thyroid.** These tests all showed an apparently normal response and the author does not attempt to draw conclusions from them.

—C. H. G.

Changes in the brain in DIABETES and pathophysiology of sugar regulation (Die cerebralen Veränderungen beim Diabetes mellitus und die Pathophysiologie der Zuckerregulation). Dresel (K.) & Lewy (F. H.), Berl. klin. Wchnschr., 1921, **58**, 739-740.

In the nucleus dorsalis vagus sympathetic cells were found, stimulation of which produced mobilization of sugar in the liver and hyperglycemia. In another part of this nucleus parasympathetic cells were found, stimulation of which seemed to increase the pancreatic secretion and the formation of glycogen in the liver. In the latter cases the blood sugar tended to fall. The authors claim that these two groups of cells are dominated by a nucleus which they call the "nucleus periventricularis." In four cases of serious diabetes, changes in both hemispheres were found, but the nucleus paraventricularis was normal. Large amounts of lipoids and new glial cells were found in the globus pallidus. In two cases the nucleus dorsalis vagus was poor in cells and showed gliosis. In all cases changes in the islets of Langerhans were noted.—J. K.

The importance of blood sugar estimation in the diagnosis and treatment of DIABETES. Johns (F. M.), New Orleans M. & S. J., 1921, **74**, 244-249.

A general article in which is emphasized the importance of careful blood sugar determinations in order to convince the physician of the seriousness of apparently mild cases. The use of a twelve hour fast previous to the determination is deplored as likely to mask the existence of a true glycosuric state.—R. G. H.

A review of carbohydrate metabolism as related to DIABETES. Knowlton (F. P.), N. York M. J. (New York), 1921, **113**, 591-592.

The author considers that it is not possible at the present time to state the relations of the endocrine system to carbohydrate metabolism.—H. W.

Fasting treatment of DIABETES (Les cures de jeûne chez les diabétiques). Labbé (M.), Ann. méd. (Paris), 1921, **10**, 32-57.

Fasting treatment of diabetes is useful. In cases of diabetes when there is no denutrition the treatment yields a speedy and complete cure, providing it is continued until the hyperglycemia as well as the glucosuria have disappeared. In cases of diabetes when denutrition exists the results of the treatment are incomplete, since the glycemia cannot be brought to normal. The benefit is transitory. The treatment should be used only in crises.—F. S. H.

The carbohydrate-fat ratio in relation to the production of ketone bodies in DIABETES MELLITUS. Ladd (W. S.) & Palmer (W. W.), Proc. Soc. Exper. Biol. & M. (New York), 1921, **18**, 109-110.

Eight diabetic and one non-diabetic patient were studied. The problem was to determine the minimal ratio of carbohydrate to fat that would prevent the appearance of augmented ketone excretion.

i. e., how much carbohydrate is necessary for oxidation of fat. The ratio varied in different cases between (CH:Fat) 1:1.9 to 1:4.6.

The mechanism of the excretion of sugar in DIABETES (Über die Vorgänge bei der Zuckerausscheidung in Diabetes). Schmiedeberg (O.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1921, **90**, 1-26.

The normal human organism can make glycogen or fat from nearly unlimited quantities of glucose or it is able to oxidize them to CO_2 and water. In diabetes it is assumed that the oxidizing power is the same, but that assimilated glucose has lost its power to be oxidized. After removal of the pancreas levulose is still stored in the liver as glycogen, although glucose is not. Hyperglycemia results. There exist cases of diabetes with hyperglycemia without glycosuria and other cases with glycosuria but without hyperglycemia. Glucose in the urine has the same properties as ordinary c.p. glucose. Therefore, it is suggested that in diabetes glucose is combined in the body with another substance which prevents its oxidation or transformation into glycogen. In the kidney the glucose is released. When fibrin is exposed to trypsin a substance is formed, which by injection produces glycosuria in CO intoxication. CO intoxication without injection of this substance does not produce glycosuria. The author suggests that, in diabetes, or after removal of the pancreas, there is a substance formed which prevents the oxidation of glucose.—J. K.

DIABETES INSIPIDUS and puberty (Diabete insipido e pubertá). Silvestri (T.), Rif. med. (Napoli), 1921, **37**, 412-415.

A case of extreme diabetes insipidus (14-17 liters) developed in a boy of three years, following a long period of gastro-intestinal disturbances. When 6 to 10 years old he had severe headache, which did not yield to any treatment; it then disappeared spontaneously. When 11 years old, he began to have severe colicky pains in the epigastrium (apparently pancreatic). Such crises were not affected by any treatment. When 13 years old he entered the hospital, where **thyroid** and **pituitary** treatment was given without any improvement. Besides the diabetic syndrome there was also noted underdevelopment of the external genitals and general underdevelopment, but no adiposity. At the beginning of his twentieth year suddenly he began to develop into a normal boy, with primary and secondary genital characters very well marked and the diuresis fell to two liters a day. A theoretical discussion is included. The author opines that intestinal infection stopped (or at least delayed) the general growth, affecting mostly the vegetative system and perhaps secondarily the endocrine functions (or interfunctions).—G. V.

(DIABETES) Blood sugar after oral administration of glucose (Das Verhalten des Blutzuckers nach peroraler Zufuhr kleiner Glukose-

mengen). Staub (H.), Ztschr. f. klin. Med. (Berlin), 1921, **91**, 44-60.

Oral administration of 10-20 gm. of glucose in a healthy person on an empty stomach increases the blood sugar. The curve of increase varies in different individuals. It seems to depend upon the intensity and persistence of the hyperglycemia. This is suggested as a test of the fixation power of the liver for glucose.—J. K.

The gastric juice in PANCREATIC DIABETES. Steinberg (M. E.), Am. J. Physiol. (Balt.), 1921, **56**, 371-379.

The secretion of gastric juice after total pancreatectomy in dogs with a Pavloff stomach pouch is different from that of normal dogs. The quantity in the first two hours is less, the total quantity on the same diet has been more than doubled, the pepsin concentration is increased. The acidity does not differ essentially. The chlorides are uniform. Acute gastritis developed on the second or third day.

—T. C. B.

Polyuria or DIABETES INSIPIDUS. Winslow (K.), Northwest Med. (Seattle), 1921, **20**, 16-17.

The author gives the several causes of polyuria and then states the etiology of diabetes insipidus to be hypofunction of the posterior lobe of the pituitary from disease, usually syphilis; injury such as fracture of the base of the skull; or tumor. He substantiates the extraordinary efficacy of injection of posterior lobe pituitary extract, preferably 0.5 c.c. of surgical pituitrin twice daily; in two cases reported, he found the effect to be temporary and immediate, but not permanent, although one of the patients was apparently cured by removal of infected teeth and tonsils.—H. L.

ENDOCRINE alterations of syphilitic origin (Alteraciones endocrinas que tienen un origen sifilitico). Abadalejo Garcia (H.), Rev. españ. de urol. y dermatol. (Madrid), 1920, **2**, 262.

Among the infections that cause edocrinopathies, the author ascribes much importance to syphilis. The glands attacked by this disease are the **thyroid** and the **hypophysis.** The syphilitic origin can be determined from the history and the laboratory reactions. Opotherapy is combined with antiluetic treatment.—E. B.

The classical ENDOCRINE syndromes. Barker (L. F.), N. York M. J. (New York), 1921, **113**, 353-363.

A brief and clear presentation of some of the more common clinical syndromes referable to disturbances of the endocrine functions of the **thyroid, parathyroid, thymus, hypophysis and epiphysis, suprarenal, pancreas,** and the **sex glands.**—H. W.

(ENDOCRINOLOGY) La endocrinologia en relación con la patologia infantil. Cavengt (G. S.), Soc. Ginec. españ. (Madrid), 1920, **3**, 113-140; Pediat. españ. (Madrid), 1920, **9**, 45-49.

General review of the physiology of the glands of internal secretion in infancy, together with a detailed study and original classification of infantilism.—E. B.

Man and the ENDOCRINES. Dickinson (G. K.), Med. Rec. (New York), 1921, **99**, 307-309.

The development of man and woman from the primitive type of 50,000 years ago through the various changes wrought by civilization with the consequent changes in appearance, strength, shape, character and intelligence, and the relation of the sympathetic autonomic and endocrine systems to these changes is entertainingly depicted. The primitive big boned, muscular and hairy man is supposed to have been dominantly **hypophyseal**, while the modern visceroptotic, narrow, fragile woman is **adrenal** in type. The emotional features are of **thyroid** and **ovarian** origin. (If read as a speculative fantasy the article will be enjoyed).—H. L.

The importance of the connective tissue in defence against cancer and its position in the ENDOCRINE system (Die Bedeutung des Bindegewebes bei der Ca-Bekämpfung und seine Stellung im endokrinen System). Fraenkel (M.), Deutsch. Arch. f. klin. Med. (Leipz.), 1921, **136**, 192-206; Berlin. klin. Wchnschr., 1921, **58**, 536-538.

The author reviews the elementary physiology and pathology of the connective tissue. The information is added that it has an important function in the endocrine organs, for example, as the reticuloendothelial tissue of the spleen, the connective tissue of the **hypophysis, thymus, thyroid,** etc., and the interstitial cells of the **testes.** Then the conjecture is added that perhaps this tissue itself has an endocrine function. The following supportive data are adduced. Wounds heal more rapidly when radiated with x-rays or when covered with sheet lead and the thymus and thyroid radiated. Thymic atrophy and hypothyroidism of the elderly may bring about lessened resistance of the connective tissue to cancer. Therefore, in the treatment of malignant neoplasms with x-rays not only the tumors themselves but the endocrine organs should be systematically radiated. (No clinical data are given. The article is full of unproved and improbable statements.)—J. K.

Behavior of ENDOCRINE organs (Zum Wesen und Wirken der endokrinen Drüsen). Hart (C.), Berl. klin. Wchnschr., 1921, **58**, 533-536.

Hart brought about the metamorphosis of axolotl larvae by the administration of **thyroid.** Mice kept in a warm atmosphere showed a decrease in size of the thyroid and a disappearance of colloid. Low temperature produced an increased activity. High temperature produced degenerative changes in the **testicle** similar to those from x-rays. At low temperatures the spermatogenesis was normal or increased. The importance of the consideration of temperature and climate in endocrine activity is suggested.—J. K.

ENDOCRINOLOGY and its practical application. Kaplan (D. M.), N. York M. J. (New York), 1921, **113,** 593-601.

The paper covers practically the entire field of endocrinology, in an unscientific way. It is of such a general nature that it does not lend itself to abstracting.—H. W.

(ENDOCRINE) Hypertrichiasis in childhood: The so-called "dog faced boy." Knowles (F. C.), Penn. M. J. (Harrisburg), 1921, **24,** 401-404.

Remarkable case of a hairy curiosity, with pictures. No endocrine disturbances were noted.—H. L.

(ENDOCRINE GLANDS) The delicate, nervous and backward child as a medical problem. McCready (B. E.), Med. Rec. (New York), 1921, **99,** 85-91.

The author discusses many of the factors in heredity and disease responsible for backward children, among others endocrine disturbances; only the latter are herewith abstracted. Exophthalmic goiter and other forms of ductless gland disturbances occur, usually, in subjects who have shown in early life definite signs of constitutional inferiority relating to the endocrine system. Such anatomic, physiologic and psychic variations are found in these children as retardation in growth rate, bodily disproportion, underweight or obesity, hypotonicity of muscles and ligaments, hypertrichosis and abnormal distribution of hair, long slender bones, delayed epipyseal unions, high arched palate, maxillary or mandibular prognathism, widely spaced teeth, defective teeth, small or malformed sella turcica, enlarged or abnormally small thyroid, persistent thymus, underdeveloped genitalia, cold clammy skin and extremities, subnormal and unstable temperature, low blood pressure, undue dryness or sweating of skin, localized flushing and pallor, enuresis, constipation, variations in cardiac rhythm, delayed puberty, dysmenorrhoea, tremors, etc., etc. For prophylaxis the author advocates treatment of endocrine insufficiencies with ductless gland extracts in the mother during pregnancy. For direct treatment McCready urges removal of foci of infection because of their etiologic role in producing "hypoadrenia." He advises also the use of **adrenalin, suprarenal**

extract, **thyroid, pituitary** and **gonads.** Children that stutter should be given atropine and adrenalin, which often helps to relieve a perverted metabolism resulting in suboxidation and spasm of the respiratory organs. He does not believe that stammering is always purely a psychic manifestation, but is initiated by perverted physiology. Mild forms of hypopituitarism as well as the outspoken cases should be treated with pituitary (rich in phosphorus and nuclein) and **thymus.** To stimulate the formation of leucocytes in the spleen, splenic substance may be given with advantage.—H. L.

Fatigue-ENDOCRINE weariness. McNulty(J.), N. York M. J. (New York), 1921, **113,** 288-290.

"Fatigue, as we see it today, is an expression of under or exhausted functioning of the so-called endocrine chain of glands or tissues; and the rational treatment of psychophysical fatigue is the employment of associated ductless gland substances as they seem to be physiologically in the living normal organism. The correction of fatigue is the correction of the social and economic abnormality; but the therapy of fatigue-endocrine weariness is the role of the physician of inclusive understanding in the administration of associated gland substances bearing internal secretions and enzymes. These are given as catalysts to activate resident reactions, not to stimulate or spur already jaded functions."—H. W.

(ENDOCRINOLOGY) The biological or more inclusive sense of therapy. McNulty (J. J.), N. York M. J. (New York), 1921, **113,** 602-604.

"The study of differentials in disturbed physiology, to the exclusion of the consideration of the normal, is what has made pathology hang as a pall over the physician and his methods. Much of our failure to aid successfully in the restoration to the normal is largely due to our lack of biological concept of the organism—not seeing the whole—its interrelated and interdependent functionings." Physiological therapy consists in the aiding of the regulators of metabolism which normally maintain the body in a balanced or normal condition. Aids to these regulators consist of the endocrine products and foods which have not been devitalized.—H. W.

Successful surgery in cases with ENDOCRINE disturbances. Neumann (W.), N. York M. J. (New York), 1921, **113,** 280-282.

A report of two cases: (1) enucleation and excision of large cystic goiter for **hyperthyroidism;** (2) monocryptorchism with congenital hernia and **dyspituitarism.** The technique of the operation is given.—H. W.

ENDOCRINOPATHY (Considerationes a proposito de un caso de endocrinopatia). Rodrigo (D.), Arch. españ. de Pediat. (Madrid), 1921, **5**, 279-285.

Clinial history of a child of three years with **thyroid, suprarenal and hypophyseal** insufficiency, probably due to infection.—G. M.

The ENDOCRINES in gastric disease. Schnabel (T. G.), Penn. M. J. (Phila.), 1921, **24**, 229-233.

The author's conclusions follow. (1) With dysfunction of the ductless glands there are sometimes found dysfunction and pathological changes in the stomach (as for instance nausea and vomiting in some cases of Graves' disease). (2) The relationship of the ductless glands to the stomach by way of the autonomic system has some evidence in its favor from an experimental and clinical standpoint (experimental removal of adrenals has resulted in peptic ulcers). Perhaps internal secretions influence the stomach directly. (3) The influence of some center in the central nervous system as a regulator of the vegetative system is still to be considered. (4) Fatigue seems to be a factor in gastric disease. (5) A very small percentage of 350 stomach cases showed endocrine disturbances. (6) Organotherapy should be tried, either alone or in combination with other agencies, in gastric disease, especially of a functional type; it may be followed by some success in a small number of cases. Schnabel tried out the ideas of Rogers, prescribing thyroid to the hypotonic hyposecreting type and suprarenal to the hyperfunctioning, hypersecreting group, but without success.—H. L.

The relationship of psychopathology to the ENDOCRINES. Stragnell (G.), N. York M. J. (New York), 1921, **113**, 386-389.

An interesting presentation of the manner in which the "modern psychopathologist takes cognizance of the endocrine status of the patient and how he utilizes his findings in his analysis of a case." For instance, in **gonadal** deficiency somatic and psychic compensations occur. Psychically there is a sexual inferiority which will be manifest by a great variety of symbolic substitutes. The man will have a powerful tendency to remain in a fixed relationship to the mother. The fixation is due to the unconscious realization of the sexual inferiority and the youth makes no attempt to search outside of the family circle for a true libido object. This fixation in turn frequently enables him to adjust his sexual life on a nonadult basis and so we find at the outset many cases of homosexuality tied up in this complex situation. Gonadal inferiority in the female results in a compensatory **adrenal** drive. A common picture is the adjustment of sex life on an arrested homosexual basis; the owner of the impaired **ovaries** and forceful adrenals assuming the dominant or male part of the union. Primary **thyroidal** inferiority is associated

with or results in an unstable vascular response and this in turn leads to a general inferiority and fear. This fear in turn will call for an adrenal stimulation giving a certain amount of unconscious satisfaction to the patient for the adrenal stimulation in satisfying the craving, causing an outpouring of adrenal product into the tissues serves to compensate for the inferiority brought about by the original thyroid conditions.—H. W.

A survey of ENDOCRINOLOGY. Timme (W.), N. York M. J. (New York), 1921, **113**, 374-378.

A general survey of the relation of the endocrine glands to the various phases of life. Nothing new.—H. W.

Some practical points in ENDOCRINOLOGY, with illustrative cases. Torbett (J. W.), Med. Rec. (New York), 1921, **99**, 866-868.

After a brief introduction in which some of the syndromes of endocrine dysfunction are mentioned, four cases are reported in which organotherapy, together with hygienic and dietetic measures, gave gratifying improvement.—H. L.

(GENERAL) The clinical application of blood chemistry. Stier (F. E.) & Hollister (G.), Northwest Med. (Seattle), 1921, **20**, 148-152.

The author states the value of estimating blood urea, uric acid and creatinine in nephritis. Blood sugar estimations in helping to differentiate renal **diabetes** from true diabetes, **thyroid** disturbances and **hypophyseal** disease, is then discussed. A few other points follow, not of endocrine interest.—H. L.

(GONADS) Pseudohermaphroditism and the question of surgical interference (Ueber Pseudohermaphroditismus und zur Frage des künstlichen Scheidenersatzes). Frank (M.), Monats. f. Gebs. u. Gyn. (Berlin), 1921, **53**, 5-15.

Of surgical interest.—F. S. H.

(GONADS) Experiments with the rejuvenation hypothesis of Steinach (Untersuchungen zur Verjüngungshypothese Steinachs). Romeis (B.), München. med. Wchnschr., 1921, **68**, 600-603.

The author compared the histological picture of the testicles before and after ligation of the vas deferens. No increase in interstitial cells was found. The sexual desire was not increased. The hypertrophy of the vesiculi seminalis and prostate as described by Steinach seems to be a pseudohypertrophy caused by stasis of the secretions.—J. K.

(GONADS) Pathology of the colliculus seminales (Zur Pathologie des Colliculus seminalis). Schmincke, Berl. klin. Wchnschr., 1921, **58**, 555; Deutsche med. Wchnschr. (Berl. & Leipz.), 1921, **47**, 665.

A short note on a case of pseudohermaphroditism masculinus internus. Instead of the colliculus seminalis a vagina was found. —J. K.

(GONADS) Germ cells of Anurans. Swingle (W. W.), J. Exper. Zool. (Phila.), 1921, **32**, 235.

A cytological study of the male sexual cycle of Rana catesbiana larvae. In these larvae there is a precocious sexual cycle, in which the germ cells develop normally to the first maturation division. During the first maturation division the spermatocytes degenerate. The normal sex cells develop at a later period, shortly before the metamorphosis of the larva, arising from the few spermatogonia which did not go through the precocious cycle.—M. M. H.

(GONADS) Steinach's puberty-gland (Over de z. g. puberteitsklier van Steinach). Woerdeman (M. W.), Nederl. Tijdschr. v. Geneesk. (Amst.), 1921, **65**, (ii), 343-347.

A critical (incomplete) review on the basis of which the author concludes that an endocrine, sexual function has not been proved for the interstitial cells.—J. K.

(GONADS) On the changes in the reproductive organs in heterosexual parabiosis of albino rats. Yatsu (N.), Anat. Record (Phila.), 1921, **21**, 217-228.

With the object of obtaining evidence regarding the effects of male and female hormones in mixed condition upon united individuals, Yatsu joined male and female white rats in parabiotic union. Normal males were joined to normal females, normal females to castrated males, and normal males to spayed females. In male-female parabiosis some Graafian follicles undergo the normal course of growth and the corpora lutea are formed, while a large majority of follicles undergo regressive changes. None of the changes are peculiar to this kind of parabiosis. The uterus is not modified very greatly, although sometimes hyperplasia of the subserosa is noticed. In the ovary of the castrated male-female parabiosis none of the follicles develops normally. No corpora lutea are formed. Follicular cysts are abundant and noticeable growth of the interstitial cells takes place. The uterus is greatly modified in this type of union, hydrometra being present to a marked degree. The testis is not affected at all by the union with either normal or spayed females. —W. J. A.

Correlation hormonica de las manifestations fisiopatologicas de la emotion. Luelmo (A.), Méd. Ibera (Madrid), 1921, **14**, 43-53.

A detailed study of the humoral theory of emotion, with discussion of various cases of emotion of adrenal origin in hyperthyroidism.—G. M.

HORMONES and emotions. Naccarati (S.), Med. Rec. (New York), 1921, **99**, 910-915.

Naccarati discusses the work of Crile and Cannon in relating the endocrine organs to the emotions and finds many suggestive confirmations clinically. He believes that the **thyroid** and **adrenal** are definitely disturbed in hysteria, anxiety neurosis, and in all the so-called emotional pschyoneuroses. The nervous symptoms associated with adolescence, menstruation, pregnancy and the menopause depend on the thyroid and the **gonads**. After the thyroid has been removed apathetic states often follow, directly dependent on lack of thyroid hormone rather than myxedematous infiltration of the brain. The author agrees with Von Monakow in the conception that moral traumata, severe psychic conflicts, and unsatisfied strong instinctive tendencies produce functional disorders in the endocrine glands through the sympathetic system. The sudden exhaustion of so-called "enfants prodiges" is explained by a physiological hyperactivity of the hormones at an immature age followed by marked hypoactivity with resulting mediocrity. Successes obtained through phychoanalysis or through other psychotherapeutic procedures are explained as due to the re-establishment of the endocrine equilibrium and of the normal sympathetic function by means of psychic stimuli.—H. L.

An anatomical consideration of the HYPOPHYSIS CEREBRI. Atwell (W. J.), N. York M. J. (New York), 1921, **113**, 366-370.

A comprehensive enumeration of the parts of the hypophysis must include the neural lobe and the three epithelial lobes. The latter are: (1) the pars anterior proprior, constituting the main bulk of the gland; (2) the pars intermedia, the thin strip investing and invading the neural lobe; and (3) the pars tuberalis, a thin layer closely applied to the infundibulum and the tuber cinereum, often completely surrounding the infundibular neck and extending upward to the optic chiasma. The pars tuberalis is incapable of producing the effects on the uterus, intestine, and blood vessels characteristic of the posterior lobe complex, nor does it produce growth effects of the anterior lobe group.—H. W.

(HYPOPHYSIS) Adiposo-genital syndrome and experimental DIABETES INSIPIDUS. Exhibition of a dog (Syndrome adiposo-génital et diabète insipide expérimental. Presentation d'un chien). Camus (J.) & Roussy (G.), Compt, rend Soc. de biol. (Paris), 1921, **85**, 296-297.

Exhibition of a dog with an experimental lesion at the base of the brain, made at the close of 1919. The animal has a permanent diabetes insipidus, and has developed a typical adiposo-genital syndrome. At the time of operation the dog weighed 15 kilos; his present weight is 26 kilos.—T. C. B.

Relation of the cerebro-spinal fluid to the HYPOPHYSIS (Die Beziehungen zwischen dem Liquor cerebrospinalis und der Hypophyse). Fleischmann (O.), Ztschr. f. d. ges. Neurol. u. Psychiat. (Berlin), 1920, **62**, 171-193.

Injection of extract of the posterior lobe of the pituitary leads, after a preliminary fall, to a long continued rise of arterial pressure, and so to increase of cerebro-spinal fluid. Hydrocephalus seems to be connected with damage to the pituitary.—Physiol. Abst., **6**, 308.

Action of extracts of HYPOPHYSIS on gastric contraction (Action des extracts d'hypophyse sur la motricité gastrique). Galan (J. C.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 32-33.

Hypophyseal extract always has an exciting action upon the tonus and contractions of the stomach, both isolated and in situ. The contradictory results obtained by others may be due to alteration caused by the method of preparation; to the acidity of the stomach; to preservatives, such as chloretone.—T. C. B.

(HYPOPHYSIS) Abnormal growth in diabetes insipidus (Wachstumsstörungen bei Diabetes insipidus). Gayler, Monatschr. f. Kinderh. (Leipz. & Wien), 1921, **21**, 356-366.

In common with other observers the author notes that children with **diabetes insipidus** may show retarded growth. This may be due to an endocrine disturbance producing both symptoms, but it is also possible that the enormous quantities of water taken by mouth and excreted may wash away substances of vital importance for normal growth. In view of this possibility the author determined the metabolism in a child with diabetes insipidus and found that when large quantities of water were given the excretion of nitrogen and calcium was greatly increased.—J. K.

Experimental radiation of the HYPOPHYSIS (Experimentelle Hypophysenbestrahlungen). Geller, Deutsche med. Wchnschr. (Berl.), 1921, **47**, 644.

The hypophysis of young animals (kind?) was repeatedly exposed to x-ray. Each animal was killed 4 months after the last treatment. It was less developed than the control. The hypophysis adhered to its surroundings. The cells in the pars glandularis were less clear than normally, the nuclei being irregular and staining badly. The uterus, ovaries and fallopian tubes were atrophied. Interstitial tissue in the gonads was difficult to find. Symptoms appeared to be the same as those produced by Aschner by extirpation of the hypophysis. (See also abstract from Berl. klin. Wchnschr., 1921, **58**, 565.)—J. K.

X-ray treatment of the HYPOPHYSIS and OVARIAN activity (Hypophysenbestrahlung und Eierstockstätitgkeit). Fraenkel (L.) & Geller (F. C.), Berl. klin. Wchnschr., 1921, **58**, 565-570.

Exposure of the hypophysis of rabbits to x-rays appeared to decrease the size of the hypophysis. The pars posterior was unchanged. There were pycnosis of the nuclei and the formation of vacuoles in the cells of the pars anterior and pars intermedia. The gland was held to the bone by adhesions and could be removed only with difficulty. The uterus was atrophied and the ovaries were reduced to half the size of those in the controls. The animals were less developed and fatter than were controls. The author offers various speculative considerations, suggesting radiating of the hypophysis as a possible means of forestalling such bodily changes in pregnancy as depend upon over action of the hypophysis.—J. K.

(HYPOPHYSIS) A case of dwarfism (Ein Fall von Zwergwuchs). Haas (O.), Berl. klin. Wchnschr., 1921, **58**, 681.

The patient was 32 years old and 123 cm. tall. During the preceding three years he had become very stout. There was poor development of the pubic and no development of axillary hair. The testicles were normal and the penis large. The skiagram showed changes in the sella turcica. There was no goiter. The intelligence was good. The metabolism was low. The diagnosis was hypophyseal dwarfism.—J. K.

Contradictions in the studies of the action of extracts of HYPOPHYSIS (Les contradictions dans les études sur les actions des extraits hypophysaires). Houssay (B. A.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 33-34.

The discordance in the results of various observers is due to the method of preparation of the extract, preservatives, dosage, the species of animal used, and experimental conditions, such as the depth of anesthesia, and traumatic shock. Also, the extract has a complex composition not sufficiently known, and many effects may be due to "substances banales." Even the specific substances have never been demonstrated as actual physiological secretions.—T. C. B.

Normal and artificial diuresis in HYPOPHYSECTOMIZED dogs (La diurése normale et provoquée des chiens sans hypophyse). Houssay (B. A.) & Hug (E.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 315-317.

Contradictory opinions as to the rôle of the hypophysis in diuresis led to the examination of 45 dogs with ablation of the hypophysis, or with lesions in the neighboring region. The authors conclude that dogs deprived of the hypophysis excrete the same amount of urine as the controls. Post-operative polyuria and oliguria are

transitory phenomena. Diuresis ("Hydrique") was less and progressed more slowly in hypophysectomized animals than in the controls. Extract of the gland produces a feebler diuresis in animals with the hypophysis removed, than in the controls.—T. C. B.

Does the PITUITARY secretion influence the development of the PROSTATE? Lisser (H.), N. York M. J. (New York), 1921, **113**, 391-393.

A presentation of five cases of preadolescent hypopituitary infantilism, two of the Fröhlich, and three of the Levi-Lorain types—all boys; the ages were ten to eighteen, but the mental age three to nine. Three showed complete absence of the prostate so far as could be determined by rectal examination. The other two revealed a very diminutive prostate.—H. W.

Is there a HYPOPHYSEAL form of adiposis dolorosa (¿Adiposidad dolorosa existe una forma hipofisaria de este proceso)? Lopez Albo (W.), Arch. de Neurobiol. (Madrid), 1920, **4**, 339-404.

Detailed history of this subject and exposition of a case of typical Dercum's disease with marked hypophyseal manifestations. The sella turcica was very small as determined radiographically and notable improvement followed opotherapeutic treatment.—E. B.

(HYPOPHYSIS) A case of hyperpituitarism. Mills (A. E.), M. J. Australia (Sydney), 1921, **ii**, 64.

A somewhat typical case in a man of 42 is reported. In addition to acromegalic manifestations, there were signs of osteoarthritis.—R. G. H.

Pathology of the HYPOPHYSIS. v. Monakow (P.), Schweizer Arch. f. Neurol. u. Psych. (Zurich), 1921, **8**, 200-207.

Monakow's illustration shows the almost completely shriveled hypophysis in a man of 58 with obesity, of the pituitary insufficiency type, and tuberculosis, with extreme apathy and oliguria. Necropsy revealed further degeneration of the convoluted tubules in the kidney, the findings exactly similar to those in a previous case of injury of the pituitary. This confirms the relation between the pituitary and the kidneys.—J. Am. M. Ass., **77**, 821.

The influence of HYPOPHYSIS preparations on peristalsis (Zur Frage der darmperistallischen Wirkung der Hypophysenpräparate). Pirig (W.), München. med. Wchnschr., 1921, **68**, 553.

The injection of extract of whole hypophysis resulted in relief in a patient with constipation in whom drastic treatment with cathartics had been unavailing.—J. K.

Visual disturbances of perihypophyseal origin (Trastornos visuales de origen perihipofisirias). Poyales (F.), Progresos de la Clinica (Madrid), 1920, **8**, 621-625.

A detailed study of the visual disturbances in a case of dystrophia adiposo-genitalis. From an opthalmic examination, one is often able to make, according to the author, early diagnosis of a lesion of the hypophysis before the endocrine symptoms, proper. appear.—E. B.

INFANTILISM and DWARFISM (Zur Kenntnis des Infantilismus und Zwergwuchses). Brandis (G.), Deutsch. Arch. f. klin. Med. (Leipz.), 1921, **136**, 323-346.

Three cases of infantilism are described. A woman of 27 had been a small infant. Her height was 133 cm. She had never menstruated. There was no body hair and the genitalia resembled those of a girl of 10. The epiphyseal lines corresponded to those of an eighteen-year-old girl. The intelligence was normal. There was no alimentary or adrenalin glycosuria. Treatment with hypophysis and ovary gave negative results. The second subject was a boy of 12, whose growth had been normal to the age of six, when it had ceased. He was very intelligent. There was no evidence of myxedema. The gonads showed about normal development. Injections of adrenalin evoked glycosuria. The metabolism and the sella turcica were normal. The third case was that of a feeble-minded woman of 28. She had normal menstruation, augmented sexual libido, but somewhat sparse genital hair. The genitalia appeared normal. The sella turcica was perhaps less than average size. The carbohydrate tolerance was normal. The article closes with a good review of the evidence bearing on the pathogeny of infantilism.—J. K.

A case of intestinal intoxication (Herter's intestinal INFANTILISM). Orgel (S.), Med. Rec. (New York), 1921, **99**, 268-270.

A case of dwarfism in a female child 1 year old is recorded. Various types of deformity, dwarfism and infantilism are briefly mentioned—such as **thyroid, pituitary, thymic,** renal, cardiac and angioplastic, **pancreatic** and intestinal. The patient described was thought to correspond to the Herter intestinal type. Cod liver oil and phosphorus was given and in 7½ months the child grew 4½ inches in height and gained 7 lbs. 12 oz.—H. L.

(INTERNAL SECRETIONS) Variations in chloride metabolism during menstruation (Schwankungen im Chlorid-Stoffwechsel unter dem Einflusz der menstruellen Vorgänge). Eisenhardt (W.) & Schaefer (K.), Biochem. Ztschr. (Berl.), 1921, **118**, 34-38.

Studies of the chloride content of blood before, during and after the menstrual period demonstrate that marked changes occur.

One or two days before the onset of menstruation or in the first two days of the period there is generally an absolute and relative hyperchloremia. When menstruation ceases the blood chloride falls back to the normal value. These phenomena were observed in two cases of transitory amenorrhea at the menstrual period. It is considered that the reaction is factored by endocrine disturbances, possibly of the **thyroid** and **ovary**, as well as by the loss of blood.—F. S. H.

Disorders of the INTERNAL SECRETIONS in children. THYROID, THYMUS and PINEAL glands. Gordon (M. B.), N. York M. J. (New York), 1921, **113**, 239-243.

Hypothyroidism does not predominate in either sex; heredity plays but a slight part; breast feeding does not prevent its development and lues as an etiological factor is of slight importance. In the hypothyroid child mental defects may range from a slight dullness to a marked aberration resembling that present in cretinism. Physical defects, backwardness in development of the power of holding up the head, sitting, standing, walking and talking, teething, and changes in the skin and appendages are common accompaniments of hypothyroid states. The so-called "hypoplastic type of child" is often an undernourished individual readily cured by a liberal increase in diet and improved environment.—H. W.

(INTERNAL SECRETIONS) Pathological conditions of the organs of reproduction in the female causing and stimulating gastroenteric disturbance. (Katz (J.), Med. Rec. (New York), 1921, **99**, 228-229.

The author believes that abnormal coitus, abortion, retroversion or retroflexion uteri, partly involuted uterus, prolapsus uteri, tears of the perineum, tumors of the uterus or adnexae, inflammations of the uterus and adnexae, erosions and inflammation of the cervix are all capable of causing symptoms of gastric or intestinal disease, sometimes simulating gastric or duodenal ulcer or appendicitis. He suggests that this occurs by throwing the nervous balance into disharmony for a time, altering the internal secretions. Three illustrative cases are recorded.—H. L.

Mechanical influence of the nutritive vitellus in ovular segmentation (Influencia mechanica del vitelus nutritivo en la segmentación ovular). Lasura (S. A.), Actas del Congreso de Bilboa para el Progreso de los Sciences, 1920, **4**, 75-83.

The author reviews several interesting teratological cases observed in trout in which he relates the displacement of the vitellus to the development of the female trout, influencing in it the development of one or more of the glands of **internal secretion.** The functional alteration of these glands, he assumes, gives rise to the teratological phenomena. These are grouped in three orders: (a)

malformations of the vertebral column; (b) malformations of the ventral wall; (c) malformations of the head.—G. M.

INTERNAL SECRETION and the nervous system. Löffler (W.). Schweizer Arch. f. Neurol. u. Psych. (Zurich), 1921, **8**, 163-184.

Löffler comments on the way in which study of the internal secretions has thrown light on the reciprocal dynamic relations between the nervous system and metabolism, and between the nervous system and the cardiovascular system. Even mental processes are conditioned in part by processes of internal secretion, and these in turn reflect the influence of psychic processes. The great unifying principle of the internal secretions, he says, forms a band uniting the various branches of medicine, and it is impossible to overestimate the value of such a band in these days when everything seems to tend to drive the various disciplines farther apart. One of the most convincing data cited is that stimulation of the splanchnic nerves in animals does not have much effect on blood pressure if the efferent veins from the suprarenals are clamped, while the blood pressure rapidly rises if the veins are left open. Puncture of the fourth ventricle has no action likewise if the efferent suprarenal veins are clamped. This hormone secreted by the suprarenal, he remarks, is the only organ-specific endocrine substance chemically isolated as yet. The low pressure common in Addison's disease and the extreme sensitiveness to epinephrin of patients with this disease are well established facts, as also the disappearance of the lipoids in the suprarenals in affections with much muscular strain, as in clonic convulsions, psychomotor agitation and in certain infections. Steinach's experiments have confirmed with even stronger testimony Brown-Séquard's assertions in regard to the potency of the internal secretion of the testicles. As Steinach ligates the vasa deferentia, or as a testicle is transplanted, the retention of the products of the secretion allows more of it to get into the blood and thus act on the nervous system. The sensation of rejuvenation is thus evoked by this erotization of the central nervous system.

—J. Am. M. Ass., **77**, 821.

(INTERNAL SECRETIONS) The role played by the emotions in the etiology of functional nervous diseases and dementia praecox. Owensby (N. M.). J. Med. Ass. Georgia (Augusta), 1920, **10**, 56.

From the observations indicating that endocrine discharge may occur during emotional outbreaks the author tentatively assumes that such psychoses as result from perturbed emotions are due to continued influence upon the cerebrum of the hormones so liberated. The **thyroid, gonads** and **adrenal** glands are regarded as most significant in this regard. It is suggested that endocrine gland ablation might be advisable as a therapeutic measure. As specific evi-

dence the clearing up of a case of dementia precox following partial thyroidectomy is adduced.—R. G. H.

Hemopathies and the glands of INTERNAL SECRETION (Hemopatias y glándulas de secretión interna). Pittaluga (G.), Arch. de Cardiol. y de Hematol. (Madrid), 1920, **1**, 350-368.

The author insists that among the hemopathies there exists a group of hemodystrophies to which belong the hemorhagic diatheses (purpura hemophilia, Barlow's scurvy, paroxysmal hemoglobinuria and hemolytic icterus), the polycythemias, chlorosis, and the diathesis eosinophilica. The hemodystrophies are characterized by: (1) predominance of the anatomopathological alterations; (2) the intervention of neuropathic and endocrine disturbances; (3) hereditary predisposition. Chlorosis is the most characteristic of these forms of hemopathy, being intimately related to ovarian and occasionally adrenal dysfunction. The hematic alteration most typical in chlorosis is a lack of constancy of the relation between hemoglobinuria and hematin. Pittaluga emphasizes the observations of Naegal that the blood in the premenstrual period in almost all women is found in a chlorotic state. In hemoragic diathesis, aside from the external factors (avitaminosis) there may be constitutional perturbations of the endocrine organs. Aside from the hemodystrophies in other diseases of the blood, we find also disturbances of the glands of internal secretion; thus, in pernicious anemia, says the author, in spite of the cachexia, the panniculus adiposis does not disappear, presenting in its distribution certain characters of a myxedematous or unuchoid type. This indicates a dysfunction of the regulatory glands of fat metabolism, especially the thyroid and the genitals, but to some extent, also, the suprarenals and the spleen. —G. M.

Relation of vitamines to the glands of INTERNAL SECRETION (Vitamines. Su relacion con las glandulas de secrecion interna). Solanillo (J.), Méd. Ibera (Madrid), 1921, **14**, 226-239.

A critique.—G. M.

Un caso de LIPODISTROFIA PROGRESSIVA, con curiosas alteraciones endocrines. Marañon (G.), Arch. de Neurobiol. (Madrid), 1920, **1**, 15-25.

The author reports a case of typical lipodystrophy observed in a young woman of twenty, who presented at the same time numerous endocrine symptoms: brilliant eyes, irregular pulse, a tendency to sexual inversion indicating a hypertrophic reaction of the suprarenal cortex, very abundant menstruation and irregular melanoderma and mild mononeucleosis. From the frequency of the endocrine disturbances in this case and in those of other authors,

Marañon believes that the glands of internal secretion intervene in the production of lipodystrophia progressiva.—E. B.

(MENOPAUSE) Epilepsia climaterica. Sanchis Benús (J.), Arch. Neurobiol. (Madrid), 1920, **3**, 1-15.

The author treats of three cases of women suffering epileptic crisis at the commencement of the disturbances of the menopause. He believes that this group of patients may be diagnosed as "climacteric epileptics," although this term eliminates all idea of pathogeny. In effect he treats essentially of patients with stigmas of degeneration; i. e., women previously epileptic in whom the climacteric takes no other part than to precipitate the attacks. The article contains also an extensive critique on the etiology of epilepsy.

—G. M.

Disturbances of the MENOPAUSE and dermapathies (Trastornos menopausicos y dermopathias). Sicilia (E.), Arch. dermosifil. (Madrid), 1921, **1**, 26-27.

Cases of eczema appearing during the menopause.—G. M.

Precocious MENSTRUATION (Menstratio praecox). Krasemann (E.), Monatschr. f. Kinderh. (Berlin), 1921, **19**, 317-321.

This girl developed very rapidly as an infant. Vaginal bleeding was observed at the age of 6 months. This was irregular at first, but later appeared for 3-4 day periods at intervals of 4 weeks. The child was first examined at the age of 3. At this time she had the build of a girl of 6 or 7, with pubic hair and partially developed breasts. When 6 years old she appeared to be 12-13. The feminine characters were more marked than at the first examination and the breasts were better developed. X-ray examination of the skeleton and a general physical examination showed a physical development comparable to that usually found at 14. The mental age on the other hand was that of 6. The condition seemed to be associated with an early development of the whole body. No cause was found, though there was a possible cyst of the right ovary present. There was no hypophyseal tumor. Krasemann considers the condition of probable endocrine origin, though this later is not proven.—C. H. G.

MONGOLISM (Contribución al estudio del mongolismo). Cavengt (S.), Pediat. españ. (Madrid), 1921, **4**, 100.

Almost all authors include mongolism among the endocrinopathies. Cavengt considers this classification dubious. He reports three typical cases. The cause in one case seems to be syphilis and in the other two organic exhaustion of the parents. The immediate cause is unknown. The diagnosis is easy. The treatment recommended is hygienic regimen, general tonics, and in case of probable syphilitic origin, antiluetic measures.—E. B.

(ORGANOTHERAPY) Some illustrative cases of ductless gland therapy in the insane. Bentley (J.), M. J. Australia (Sydney), 1921, **i**, 399-401.

Five psychopathic patients improved and one deteriorated while taking a proprietary pluriglandular preparation. Two subjects of acute senile mania were apparently made more excitable by desiccated **pineal** gland.—R. G. H.

The nature of the luteal and interstitial cells of the OVARY (Sulla natura della cellula luteinica e della cellula interstiziale dell' ovario). Brugnatelli (F.), Folia Gynaec., 1920, **13**, 111-120.

In a culture in vitro of a resting ovary only indifferent cells developed, whereas similar cultures of ovary from animals in heat showed the development of luteal cells.—Physiol. Abst., **6**, 301.

PANCREAS and HYPOPHYSIS. Kraus (E. J.), München. med. Wchnschr., 1921, **68**, 794.

After removal of the pancreas in cats, the eosinophile cells of the hypophysis disappear. These cells also disappear in juvenile **diabetes.** After this operation, the **thyroid** at first hypertrophies and then becomes smaller. Lipoids disappear from the cortex of the **adrenal** while the medulla stains more deeply with chromate. The **gonads** and the **pineal** body become smaller. The **parathyroids** show little change.—J. K.

PARATHYROID glands of thyroidless Bufo larvae. Allen (B. M.), J. Exper. Zool. (Phila.), 1920, **30**, 201.

If the thyroids are removed from larvae of Bufo, the parathyroids undergo a marked hypertrophy. There is no change in the character of the parathyroid tissue, and no evidence that the hypertrophy is compensatory.—M. M. H.

Macrogenitosomia precox—PINEAL tumor (Makrogenitosomia praecox—Zirbeltumor). Baar (H.), Ztschr. f. Kinderh. (Berlin), 1920, **27**, 143-152.

Reports a 5 year old girl who developed normally up to the age of 3. She then began to grow rapidly, pubic hair appeared, and enlargement of the clitoris was noted. The external genitalia were very well developed, but menstruation did not appear and no others of the secondary female characteristics were present. The general appearance was that of an 8-9 year old child. The bones of the hand were well ossified. Neurological examination showed a slight reflex hyperexcitability with patellar clonus. The Romberg sign was positive and a cerebellar ataxia was present so that the child could walk only with a support. The eye grounds showed no evidences of increased intracranial pressure. The early puberty and the neuro-

logical symptoms lead Baar to classify this case as one of probable pineal tumor.—C. H. G.

Studies in the physiology of vitamins: Is water soluble vitamin identical with SECRETIN? Cowgill (G. R.). Proc. Soc. Exper. Biol. & M. (New York), 1921, **18**, 148-149.

Several vitamin-containing products were tested. All except one, tomato juice, gave negative results. The test animals (dogs) were proved to be sensitive to secretin as ordinarily prepared.
—R. G. H.

The interstitial cells of the TESTICLE (Ueber die Zwischenzellen des Hodens). Berblinger (W.), Berl. klin. Wchnschr., 1921, **58**, 556; Deutsche med. Wchnschr. (Berl. & Leipz.), 1921, **47**, 665.

The author concludes that the sexual hormones are formed in the cells which produce the sperms and that the interstitial cells have only a nutritive function.—J. K.

Undescended TESTICLE in inguinal canal. Gilbride (J. J.), N. York M. J. (New York), 1921, **113**, 659-657.

Report of case.—H. W.

(TESTICLE) Relations between the interstitial gland and the course of tuberculosis (Beziehungen der Pubertätsdrüse zum Verlauf der Tuberculose). Hautner (H.), Wien. klin. Wchnschr., 1921, **34**, 300.

Of 13 guinea pigs the author castrated 4, ligated the vas deferens on both sides in 5, and on one side in 1. The 3 remaining animals were kept as controls. All were injected with tubercle bacilli. The ligated animals died quickly, but no difference was noted between the castrated and control animals. The author concluded that the operation of Steinach is contraindicated in patients with acute tuberculosis.—J. K.

Transplantation of TESTICLE. Lichtenstein (R.), Ztschr, f. urol. Chir. (Berlin), 1921, **6**, 305-314.

Lichtenstein relates that the implanted testicle was cast off or absorbed in four cases in which he implanted a testicle in the scrotum after resection of the tuberculous testicle. In another case both testicles had been destroyed by a shell wound, and the man presented the typical symptoms of total castration. Lichtenstein slit a testicle and implanted each half separately on scarified muscle tissue in the inguinal region, under ether, and kept the man in bed for twelve days. The results in this and in twenty-one other cases since 1915 confirm the therapeutic effect of free testicle transplantation, and that this technic offers favorable conditions for survival, and for

the continued functioning for years of the implanted testicle. He adds that Lydston's high percentage of cases in which it was cast off is due to his method of implantation in the scrotum. Conditions here are far from being as favorable for vascularization as in a bed cut for it in the fascia over the oblique muscle in the inguinal region, slightly scarifying the muscle. The implant can be a retained testicle from another person who has one normal testicle. The father or brother will sometimes give a testicle for transplantation, especially when it is explained that only a half or third of the testicle is required. In one of his cases the testicle was derived from an operation elsewhere, and had been kept on ice for several hours. The results were faultless, as also in a case in which he implanted a testicle taken from a ram.—J. Am. M. Ass., **77**, 743.

(TESTICLE) The interstitial gland—what it is and its supposed function. Morley (W. H.), N. York M. J. (New York), 1921, **113**, 393-394.

A review of several recent articles.—H. W.

(TESTICLE) The closure of the vas deferens by the formation of a cicatrix (Ueber das Verhalten des menschlichen Hodens bei narbigem Samenleiterverschluss). Simmonds, Berl. klin. Wchnschr., 1921, **58**, 556; Deutsche med. Wchnschr. (Berl. & Leipz.), 1921, **47**, 665.

The testicles were examined in 40 cases in which one or both of the vasa deferentia had been closed by cicatrix formation. In 30 cases spermatogenesis was normal, but in 2 the interstitial cells showed granulation. The author believes that experiments on animals are not applicable to the human subject and that the internal secretory function is due to the epithelium preparing the sperms. —J. K.

(TESTICLE) The interstitial gland (Zur Frage der Zwischenzelle). Sternberg, Berl. klin. Wchnschr., 1921, **58**, 556; Deutsche med. Wchnschr. (Berl. & Leipz.), 1921, **47**, 665.

The author examined the testicles of hermaphroditic and homosexual patients. From his work (of which no details are given), he concludes that while we do not know the function of the interstitial cells, it is certain that they do not produce the secondary sexual characters.—J. K.

Interstitial gland of the embryonic TESTIS in mammalia (Sur la glande interstitielle du testicule embryonnaire chez les mammifères). Aron (M.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 107-110.

Embryology of the interstitial gland. It probably develops in two periods the first before birth, regresses and gives place to the adult gland. The two phases are morphologically different.—T. C. B.

The supporting tissues of the interstitial gland of the TESTIS in the wild boar and in the domestic boar (Le tissu de soutian de la glande interstitielle du testicule chez le sanglier et chez le verrat). La Coste (A.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 66-68.

Histological.—T. C. B.

On the histological modifications undergone by the inferior pole of the TESTIS in partial castration (Sur des modifications histologiques subie par des restes du pole inférieur du testicule dans la castration partielle). Lipschütz (A.), Ottow (B.) & Wagner (Ch.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 86-87.

Histological description of the testicular tissue remaining after partial castration as described previously, showing degeneration of the germinal tissue.—T. C. B.

Inferior and superior poles of the TESTIS in partial castration (Du pole inférieur du testicule dans la castration partielle. Pole supérieur du testicule dans la castration partielle). Lipschütz (A.), Ottow (B.) & Wagner (Ch.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 88-89.

Histological, pointing out certain differences between the two poles.—T. C. B.

Evolution of the TESTIS after ligature or resection of the vas deferens and after ligature of the testicular vessels (Evolution du testicule après ligature ou résection du canal déférent et après ligature des vaisseaux testiculaire). Retterer (E.) & Voronoff (S.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 153-156.

Histological.—T. C. B.

(TESTES) On the functional significance of the secretions of the epididymus and vas deferens (Sur la signification functionelle des sécretion épididymaire, et déférentielle). Benoit (J.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 951-952.

Not of endocrine interest.—T. C. B.

(TESTES) On the involution of the spermatogenic processes provoked by experimental alcoholism (Sur l'involution du processus spermatogénétique provoquée par l'alcoholisme expérimental). Kostitch (A.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 674-676.

Histological.—T. C. B.

(TESTES) New observations on partial castration (Nouvelles observations sur la castration partielle). Lipschütz (A.), Ottow (B.) & Wagner (Ch.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 42-43.

A continuation of work previously reported, in which it is shown that the testicular mass may be still further reduced (to about one per cent) and masculinization proceed normally.—T. C. B.

(TESTES) Alteration of secondary sex characters in a tuberculous cock (Sur les altérations des charactères sexuels secondaires chez un coq tuberculeux). Milojevic (B. D.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 89-91.

The bird had been mistaken for a hen. Autopsy showed it to be of the male sex. Examination of the testes showed no decisive departure from the normal in regard to the interstitial tissue. There was a general tuberculosis and the author is inclined to think that a pathological condition may alter the secondary sex characters without morphological changes in the sex glands.—T. C. B.

Changes in the TESTES after ligation of the vas deferens especially in relation to the interstitial tissue (Unterbindungsfunde am Hoden unter besonderer Berücksichtigung der Pubertätsdrüsenfrage). Tiedje, Berl. klin. Wchnschr., 1921, **58**, 556.

Data reported elsewhere.—J. K.

The results of earliest removal of the THYMUS glands in Rana pipiens tadpoles. Allen (B. M.), J. Exper. Zool. (Phila.), 1920, **30**, 189-200.

The thymus glands were removed from larvae of Rana pipiens at a very early stage (larvae of 8 to 8.5 mm.). The operation had no effect on growth, metamorphosis, or general metabolism of the larvae. The gonads and thyroids were studied particularly, but showed no changes.—M. M. H.

Pathology of the THYMUS. Bircher (E.), Schweizer Arch. f. Neurol. u. Psych. (Zurich), 1921, **8**, 208-215.

Bircher describes eight cases in children in which thymectomy was followed by disturbances in growth. The ossification centers and the growth in height showed abnormal conditions. These experiences warn against thymectomy in children, and also against roentgen-ray treatment of the entire gland.—J. Am. M. Ass., **77**, 821.

(THYMUS, PARATHYROIDS) A special form of galvanic hyperirritability in fragilitas ossium (Über eine spezielle Form galvanischer Überempfindlichkeit bei "Fragilitas ossium"). Bolten (G. C.), Monats. f. Psych. u. Neurol. (Berlin), 1921, **49**, 144-153.

The author reports four cases of fragilitas ossium with special regard to the galvanic nervous irritability and the calcium metabolism. From a (one-sided) review of the literature he concludes that the thymus, parathyroids and thyroid, possibly, are involved in the etiology of the condition. Especial weight is given to the thymus, despite the growing opinion that this organ is concerned only in immunity mechanisms.—R. G. H.

Study of the histology of the THYMUS of the anurans under normal and experimental conditions (Recherches d'histologie normale et expérimentale sur les thumus des amphibiens anoures). Dustin (A. P.), Arch. de biol. (Liége), 1920, **30**, 601.

The author has made a histological study of the thymus of Rana fusca at various stages of development under normal conditions, and also after fasting and thyroid feeding. His conclusion with regard to the histogenesis of the organ is that the small cells are derived from the epithelial cells of the anlage. They are transformed by a series of "diminishing" divisions from the large epithelial cells to the small cells which resemble lymphocytes, a process which can be traced through its successive stages. At no period can an invasion of the anlage by lymphocytes be demonstrated. The myo-epithelial cells, on the other hand, are exogenous mesodermal elements. The process by which the small thymic cells arise is subject to a critical study under varying conditions, since the author regards it as the most important process in the organ. He believes that the function of the thymus is to regulate the metabolism of nucleins. Nucleins brought into the body in excess of its immediate needs are stored in the thymus. The changes to be seen in the cells of the epithelial anlage, which end in pycnosis, represent a process of giving up nucleins to the body as they are needed. The diminishing divisions are seen to occur more slowly in thyroid-fed animals in which the supply of nucleins from food is particularly good, and in which there is consequently less demand on those stored in the thymus. Conversely, in fasting animals, the diminishing divisions and the final pycnosis advance more rapidly than under normal conditions. Dustin, therefore, regards the thymus as neither endocrine nor hemotopoietic, and offers an entirely different theory of its function.

—M. M. H.

(THYMUS) A case of status thymico-lymphaticus accompanied by rachitis (Su di un caso di stato timico-linfatico accompagnato a rachitismo). Jemma (G.), Pediatria (Naples), 1921, **29**, 126-130.

Description of a girl of 20 months in whom an enlarged thymus and lymphatic hypertrophy were found at autopsy. The thymus weighed 11 grams. The child had florid rachitis and apparently

died from respiratory embarrassment resulting from the chest deformity. In view of the more recent studies on rachitis the abstractor doubts if there was any etiological relationship between the status thymico-lymphaticus and the other changes as was suggested by Jemma.—C. H. G.

(THYMUS) So-called status thymico-lymphaticus as an independent disease (Der sogenannte Status thymico-lymphaticus als selbständige Krankheit). Löwenthal (K.), Jahrb. f. Kinderheilk. (Berlin), 1920, **93**, 1-15.

Löwenthal reports a case of status thymico-lymphaticus in a 16 months old baby. At autopsy he found a generalized lymphatic hyperplasia with dilatation and hypertrophy of the heart. The posterior wall of the left ventricle showed an aneurysmal swelling. Histological examination showed marked lymphocytic infiltration of the cardiac wall with atrophy of the muscle fibers. The child had an unexplained fever and examination showed a lymphocytic infiltration of the corpus striatum in the region of the supposed heat center. The author believes that the lymphatic hyperplasia found in children with the so-called status thymico-lymphaticus falls within the limits of the normal and that the changes are quantitative rather than qualitative. It is only in those cases in which there is an unusual localization of the lymphocytic development as in the heart or brain, that one can claim a true departure from the normal as an independent disease.—C. H. G.

The relation of the THYMUS to criminality. Morris (S. J.), Med. Rec. (New York), 1921, **99**, 438-439.

Of 192 bodies sent to the anatomical laboratory of the West Virginia University Medical School, 52 came from the insane hospitals, 10 from the tuberculosis sanitarium, 74 from the poorhouses, 20 from the State penitentiary and 36 from undertakers. In this number 22 persistent thymuses were found, 20 of which were from the 20 criminals. All were first or second degree murderers with the exception of one, who was a rapist. Morris feels justified in concluding that the persistent thymus is in some way accountable for the mental state that caused these men to be criminals.—H. L.

Pathology of the THYMUS in the accidents of anesthesia (Pathologia del timo en los accidentes de la anestesia). Mozota (R.), La Especialidad Practica, 1919, **2**, 36-39.

Mozota considers that the thymus may play a part in the accidents of anesthesia in the following ways. The gland may hypertrophy and exert undue pressure on the mediastinal tissues when the body is relaxed by anesthesia. Tuberculous thymitis may lead to sudden death either by compression or by intoxication from thymic

hypersecretion and adrenal hyposecretion that always is found in this condition.—E. B.

THYMIC disease. Siegel (A. E.), N. York M. J. (New York), 1921, **113**, 290-292.

Thymic disease is of more frequent occurrence than is generally supposed. Thymic disease and status lymphaticus are closely allied and differ principally in the extent of the involvement. Thymic enlargement may be a misnomer because the symptoms may arise with little or no enlargement. While there may be hypertrophy or hyperplasia, difficulty seems to be caused more by hypersecretion or hypertoxicity of the secretion. The thymic secretion exercises a selective depressant influence on cerebral respiratory centers. Exposure to x-rays is the best method of treatment.—H. W.

The relation of carbon dioxide and water excretion in THYROIDECTOMIZED and SPLENECTOMIZED rabbits in relation to variations in the external temperature (Das Verhalten der Kohlensaüre- und Wasserausscheidung des schilddrüsen- und milzlosen Kaninchens bei normaler und erhöhter Aussentemperatur). Asher (L.) & Hauri (O.), Biochem. Zeitschr. (Berl.), 1919, **98**, 1-34.

Working with rabbits and using the Haldane apparatus for determining the respiratory exchange, the authors report modifications in the CO_2 and water excretion in thyroidectomized and splenectomized animals as dependent upon variations in the external temperature. Thyroidectomized rabbits react in two ways. (1) In the first period after thyroidectomy there is a rise in the CO_2 and water excretion if the external temperature is normal (20°C.), while if the external temperature is raised to 33° C. the heat polypnoea so characteristic of normal rabbits is absent and the water excretion is markedly reduced while the CO_2 excretion is only slightly raised. The authors believe that the absence of heat polypnoea in thyroidectomized rabbits is a new symptom of thyroid insufficiency in this animal. (2) In the second period after thyroidectomy there is a fall in the CO_2 and water excretion when the external temperature is normal, but when the external temperature is raised heat polypnoea occurs, but the decrease in the CO_2 and water excretion remains. Splenectomized rabbits show an increased CO_2 and water excretion with the external temperature normal and also when the external temperature is raised. No noteworthy change in the rate or depth of respiration results from changing the temperature. They further show that when the spleen is removed from a previously thyroidectomized rabbit a rise in the CO_2 and water excretion occurs. This confirms the work of Danoff, who showed that splenectomy causes a distinct rise in the respiratory exchange in rats. The data of four rabbits only are given.—D. M.

Roentgen ray therapy in HYPERTHYROIDISM. Barker (W. C.), N. York M. J. (New York), 1921, **113**, 273-275.

The reduction of the size of the thyroid for cosmetic purposes, for the relief of pressure or for the removal of tumors, whether benign or malignant, is a problem for the surgeon and should never be attempted by x-ray therapy. The use of the x-rays in the treatment of the thyroid is only to inhibit cell action. Technique is given. —H. W.

Treatment with iodothyrin and THYROID of infantile myxedema caused by congenital athyroidism (Ueber Behandlung von infantilem Myxödem infolge angeborener Schilddrüsenmangel mit Jodothyrin und Hammelschilddrüse). Baümler (Ch.), München. med. Wchnschr., 1921, **68**, 600-601.

Baümler reports his observations on a patient whom he had observed for twenty years and who had been born without a thyroid gland. He found that iodothyrin tablets produced in general much better effects than fresh gland material. This latter tended to produce insomnia and giddiness, while the effect of the former was uniformly satisfactory.—J. K.

(THYROID) Exophthalmic goiter and surgery. Bram (I.), N. York M. J. (New York), 1921, **113**, 266-273; 330-332. .

Surgery is indicated in Graves' disease when there are symptoms of pressure, malignant degeneration of the thyroid, or local points of infection which are found to have an etiological bearing on the syndrome. Surgery is contraindicated in the vast majority of cases when the pathogenesis of the disease points to the thyroid as playing but a small part in the causation of the syndrome, and when the symptomatology of the affection is widespread. "Physiology indicates that, in the human being, it is almost as dangerous to attack surgically an overactive vital organ, such as the thyroid, as to attack surgically an overactive heart. On empirical grounds, Graves' disease belongs strictly in the field of the internist who, having made endocrinology his field of special endeavor, is capable of demonstrating complete and permanent non-surgical cure of every case of the disease in which the vital structures are not badly damaged and a reasonable degree of cooperation is obtainable.—H. W.

(THYROID) Surgical treatment of goiter (Algunas consideraciones sobre el tratamiento quirugico del bocio). Calderon (C.), Méd. Ibera (Madrid), 1921, **14**, 236-237.

A casual exposition tending to demonstrate the necessity of operating upon all voluminous goitres although they may be well tolerated.—G. M.

THYROID deficiency in oto-laryngology. Callison (J. G.), N. York M. J. (New York), 1921, **113**, 283-288; 326-329.

The ear, nose and throat manifestations of thyroid deficiency are as follows: large tongue, bearing the indentition of the teeth; hard, elastic condition of the inferior turbinates, the so-called primary atrophic rhinitis; infiltration of the submucosa of the bronchi and bronchioles, with narrowing of their lumen, with difficulty in breathing, cyanosis, and asthma-like attacks; infiltration of the larynx, including the vocal cords, with loss of the singing voice; hypertrophied tonsils and adenoids; hacking cough for which there is no apparent reason; nasal hydrorrhea, usually of a paroxysmal type; infiltration and thickening of the tympanic membrane, middle ear and Eustachian tube, with tinnitus aurium and deafness; the oozing hemorrhages sometimes seen in tonsil operations; lengthening of the bleeding and coagulation time; frequency of infection, i. e., lowered resistance. The article ends with a consideration of the treatment of thyroid deficiency.—H. W.

The effect of THYROXIN on growth in white rats. Cameron (A. T.) & Carmichael (J.), J. Physiol. (Lond.), 1921, **55**, v.

Details to be published shortly.—T. C. B.

(THYROID) A schizotrypanum in the bats (Vesperugo pipistrellus) of lower Alsace. Schizotrypanosis and endemic goiter [Un schizotrypanum chez les chauves-souris (Vesperugo pipestrellus) eu Basse-Alsace. Schizotrypanose et goitre endémique]. Chatton (E.) & Courrier (R.), Compt. rend Soc. le biol. (Paris), 1921, **84**, 943-946.

Description of a trypanosome found in the blood of bats, and possibly having an etiological relation to endemic goiter.—T. C. B.

Syndromes of THYROID insufficiency (Sindromes de insuficiencia tiroidea). Collar y Jimenez (J.), Plus Ultra (Madrid), 1920, **14**, 10-24.

The author makes a study of thyroid insufficiency in all its details and describes three clinical cases of infantile myxedema. —E. B.

The surgical aspect of HYPERTHYROIDISM. Deaver (J. B.), N. York M. J. (New York), 1921, **113**, 265-273.

A general review.—H. W.

Action of canine THYROID on the isolated heart of normal rabbits and of rabbits sensitized against canine thyroid (Action de la thyroïde de chien sur la coeur isolé du lapin neuf et du lapin sensibilisé vis-a-vis de la thyroïde de chien). Demoor (J.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 235-237.

Observations were made on the isolated hearts of young rabbits, perfused with Locke's solution to which was added fresh dog's thyroid extract in the proportion of one lobe to four hundred cubic centimeters of solution. Normal Locke's solution was used alternately. When the normal heart was perfused with "thyroid Locke's" solution, there was a phase of excitation of short duration (sometimes absent), characterized by exaggerated rapidity and amplitude of the systole; this was followed by a phase of exhaustion (fléchissement) in which the rapidity and amplitude became diminished, and finally the heart stopped. In some cases the arrest was not complete and the heart continued to beat feebly and irregularly. Upon substituting normal Locke's solution the heart recovered. Rabbits were immunized against dog's thyroid by intraperitoneal injections of thyroid extract, either one-half lobe at intervals of five days, or in a single massive dose of one lobe. The hearts of the immunized rabbits when perfused with "thyroid Locke's" solution failed to show the cardiac "fléchissement" but the phase of excitement was more intense and persistent.—T. C. B.

(THYROID) The interpretation of the basal metabolic rate in toxic goiter. Else (J. E.), Northwest Med. (Seattle), 1921, **20**, 118-121.

The following are a few of the author's conclusions: The rise in the basal metabolic rate is the first evidence of hyperthyroidism. As the disease increases in intensity the rise in the basal metabolic rate precedes the clinical manifestations. The more severe the onset and the more severe the course the higher the rate will be in proportion to the symptoms. In severe cases the variation will be great, while in mild cases the rate and the symptoms will run almost parallel. When the disease reaches its height there comes a time when the rate runs about parallel with the symptoms. As the disease begins to improve, the rate drops more rapidly than the symptoms. In cases having frequent exacerbation the rate may be normal or below normal in the interval, although the symptoms are present continuously. If permanent lesions have developed, symptoms may persist indefinitely even though the disease has run its course and the rate be normal or even subnormal. Rates can be grouped into: up to 25 per cent plus, mild; 25 to 50 per cent plus, moderate; 50 to 75 per cent, severe; 75 to 100 per cent, very severe; over 100 per cent, exceedingly grave. The basal metabolic rate is the most accurate index to the activity of the thyroid gland, but it must be considered in conjunction with the clinical history and symptoms in order that the proper interpretations may be made. Several tests are frequently necessary for accurate conclusions. One is not justified in treating the more severe cases of thyrotoxicosis without studying the basal metabolic rate and governing the treatment thereby. Whether a single artery should be ligated or more than one at the

same operation, or thyroidectomy should be the method used, depends in great part upon the metabolic rate.—H. L.

(THYROID) The heart in goiter and in status thymolymphaticus (Zur Frage des Kropfherzens und der Veränderungen beim Status thymolymphaticus). Fahr, Berlin. klin. Wchnschr., 1921, **58**, 555; Deutsche med. Wchnschr. (Berlin), 1921, **47**, 665.

Subjects having goiter may have normal hearts. Changes in the heart are observed particularly in Graves' disease and in diffuse colloid goiter. The author denies the existence of a relationship between exophthalmic goiter and status thymolymphaticus. This latter is of toxic, not thyreogenic origin.—J. K.

HYPERTHYROIDISM in a child. Report of case. Frantz (M. H.), N. York M. J. (New York), 1921, **113**, 275-277.

A report of a case which demonstrated a symptom complex of hyperthyroidism dating from the age of 1½ years. The mother suffered from the same ailment and lived in a goiter district. The appearance of the disease in the child is considered as possibly congenital.—H. W.

(THYROID) A goitrous region in High Maestrazgo (Un foco estrumoso del alto Maestrazgo). Garcia Guijarro (F.), Méd. Ibera (Madrid), 1921, **14**, 113-117.

This article is a study of the pathogenic theories of endemic goiter which describes a point of convergence encountered by the author in the village of Putell (alto Maestrazgo) numbering some 500 inhabitants. There are found numerous adults with goiter or cretinous degeneration. Among the children 25 per cent of the boys and 35 per cent of the girls suffer from thyroid affections, some lacking in intelligence as compared with those children of neighboring villages.—E. B.

(THYROID) A case of Meige's chronic trophedema in a hypothyroid subject (Un caso di trofoedema cronico acquisito del Meige in soggetto ipotiroideo). Garin (G.), Riv. crit. di clin. med. (Firenze), 1920, **21**, 313-332.

This is a detailed report of a case of a patient who had been normal until 1913 (February), when he had his first attack of edema accompanied with fever (39°). The spells came about at several months' intervals, lasting over one week, then disappearing but for a slight swelling at the ankles, noticeable towards evening. Characteristic of this case was the low blood pressure (90/50), which under thyroid treatment rose to 120/75; at the same time the renal output increased. Notwithstanding large doses of thyroid (endothyroidina, 45 to 60 cgm. twice a day plus ten drops adrenalin, one per thou-

sand) for several months his pulse never went above 78 and he always showed a positive oculo-cardiac reflex. But finally the patient improved under the thyroid treatment even to being absolutely well for a period of over five months. The author is disposed to classify this form of edema with myxedema. In his opinion it is hard to distinguish from one another the syndrome of Quinke, the syndrome of Meige and the nervous and pseudo-nervous edemas. He would designate as nervous edema only that due to abnormal function of that part of the nervous system, which controls the circulation and the formation of the interstitial fluid in the tissues.—G. V.

The diagnosis and treatment of HYPERTHYROIDISM. Goetsch (E.), N. York M. J. (New York), 1921, **113**, 378-383.

A further discussion of toxic adenoma of the thyroid gland and the usefulness of the Goetsch adrenalin test in the diagnosis of this condition.—H. W.

(THYROID) Irritability of the involuntary nervous system in Graves' disease and hyperthyreosis and its alteration after surgical treatment (Ueber den Erregbarkeitszustand des vegetative Nervensystems beim Morbus Basedowi und den Hyperthyreosen und seine Beeinflussung durch die operative Behandlung). Grunenberg (K.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 648-649.

Patients with hyperthyreosis or exophthalmic goiter generally show the sympathicotonic type of adrenalin blood-pressure curve (See Dresel, Endocrin., 1920, **4**, 107.) After operative treatment the irritability of the involuntary nervous system falls. The adrenalin curve becomes normal or even vagotonic. Hyperthyroidism selectively affects the sympathetic apparatus.—J. K.

Studies of the THYROID apparatus. II. The changes in the amount of intestine-contracting substances of the thyroid of the albino rat according to age. III. The action of THYROXIN on the isolated intestinal segment. Hammett (F. S.) & Tokuda (K.), Am. J. Physiol. (Balt.), 1921, **56**, 380-389.

The data indicated in the captions are reported in two short papers. Apparently there is an increase in intestine-contracting substances in the thyroid at birth, at weaning, at puberty, and at the time rapid growth is completed. Each of these periods is followed by a period in which the extract is less active. The opinion is expressed that these changes are expressions of general changes in the organism in which the thyroid participates. Solutions of thyroxin in sodium hydroxide cause no more contraction of intestinal segments than sodium hydroxide alone. It is evident that thyroxin is not the constituent of the thyroid causing the contractions.—T. C. B.

Clinical and laboratory tests in HYPERTHYROIDISM. Harrower (H. R.), Med. Rec. (New York), 1921, **99**, 645-648.

The author reviews briefly the tests which have been advocated in the differential diagnosis of incipient cases of hyperthyroidism. —H. L.

Contribution to the physiology of the glands. 46. The action of the THYROID hormone in the disturbed carbohydrate metabolism of phlorizin diabetes (Beiträge zur Physiologie der Drüsen. XLVI. Mitt. Leon Asher. Die Wirkung des Schilddrüsenhormons bei gestörtem Kohlenhydratstoffwechsel durch Phlorrhizindiabetes). Horrisberger (W.), Biochem. Ztschr. (Berlin), 1921, **121**, 64-75.

Basal metabolism determinations were made on phlorizinized rats which had been fed thyroid. The experiments showed that metabolism is raised whether the carbohydrate depots have been depleted by phlorizin or not. Phlorizin produces glycosuria in the albino rat, which is marked, lasting and constant. When given alone it does not raise the basal metabolism; in fact this phase sinks a bit as does the respiratory quotient.—F. S. H.

The toxic THYROID. Howard (W. F.), Northwest Med. (Seattle), 1921, **20**, 110-112.

Brief resumé of the clinical picture of toxic goiter, and its treatment medically and surgically. Nothing new.—H. L.

(THYROID) The goiter problem. Irwin (H. C.), Northwest Med. (Seattle), 1921, **20**, 115-117.

A compact summary of many interesting and well known clinical observations on goiter—its relation to geological strata; iodine content; the etiological rôle of infections; intestinal toxemia, which has been emphasized by Arbuthnot Lane, etc.—H. L.

HYPOTHYROIDISM and tabes dorsalis. A preliminary statement. Jelliffe (S. E.), N. York M. J. (New York), 1921, **113**, 383-386.

A presentation of two cases diagnosed as tabes dorsalis, which were later shown to be hypothyroidism; the tabes cleared up on the administration of thyroid preparation. It appears that dysthyroid condition can bring about a typical vagotonic state which can give rise to the characteristic crises of tabes. Jelliffe considers that "in the tabetic pathology the vegetative sympathetic pathways becoming more seriously involved in certain patients permits the vagotonic reaction, and that it is possible that concomitant dysthyroid pathology is a factor in the constellation of the constitutional pathology to aid in the production of crises of many kinds. Hence it may be read that the syphilitic infiltration process in the incoming vegetative fibre pathways, plus the dysthyroid modification of the effector

pathways, plus other factors, results in the crippling crises of tabes."
—H. W.

(THYROID) Differential diagnosis between rudimentary myxedema and hypofunction of the OVARY (Ein Beitrag zur Differentialdiagnose zwischen rudimentärem Myxödem und Hypovarismus). Kuhlmann (B.), München. med. Wchnschr., 1921, **68**, 550-552.

Two cases are described. A woman of 44 developed rheumatism, cutaneous atrophy and thinning of the hair. The thyroid was not palpable. There were no cardiac symptoms of myxedema. Thyroid treatment resulted in marked improvement. The injection of one mgm. **adrenalin** caused no increase of blood pressure, glycosuria or erythrocytosis. The injection of one mgm. of pilocarpine also gave no reaction. Conjunctival application of homatrophine resulted in 36 hours mydriasis. Death resulted from an intercurrent disease. Autopsy disclosed a very small thyroid with very little colloid. The second case resembled the first. The subject was a fat woman of 27 in whom menstruation had ceased. The skin was dry and the facies myxedematous. The hairs on the pubes and in the axillae were sparse. The uterus was atrophic. Adrenalin injection caused a rise of blood pressure, glycosuria and erythrocytosis. Pilocarpine produced perspiration and salivation. Homatropin mydriasis passed within 24 hours. **Thyroidin** treatment produced no benefit. The author concludes that hypothyroidism and ovarian deficiency may resemble each other closely, but that they may be differentiated by pharmacological means.—J. K.

(THYROID) Opotherapy in Basedowism (Opothérapie et petit basedowisme). Marie (A.), Bull. gén. therap. (Paris), 1921, **172**, 439.

Pluriglandular therapy in Basedow's disease arising from the emotional disturbances of the war has been efficacious.—F. S. H.

(THYROID) The prevention of simple goiter in man. Marine (D.) & Kimball (O. P.), J. Am. M. Ass. (Chicago), 1921, **77**, 1068-1070.

Simple or endemic goiter in man may be prevented as cheaply and as simply as in the lower animals, by the administration of 3 to 5 mg. of iodin twice weekly, over a period of a month, and repeated twice yearly. Klinger in Switzerland has reported as striking, and nearly as extensive, results as those obtained by us in Akron. In young individuals, with goiter of recent development, the curative effects of exceedingly small amounts of iodin are as marked as one sees in the goiter of animals.

There are no dangers worthy of consideration associated with the administration of the quantities of iodin used by Klinger or by us. Simple or endemic goiter most commonly develops during (1) fetal life, (2) around the age of puberty, and (3) during pregnancy,

and we believe that any plan which provides for its control during these three periods of life will practically eliminate endemic goiter. Goiter in the mother and fetus can be prevented as simply as that of adolescence, but, practically, it would seem that it is a responsibility of individual physicians, supplemented by public education. The prevention of goiter of childhood and adolescence should be a public health measure, best administered through the schools in order to combine the important additional factor of education. Beginning with the period of puberty, goiter occurs approximately six times as frequently in females as in males. The question, therefore, whether general prophylaxis should include both males and females would depend to some extent on whether the particular district was mildly or severely goitrous; hence the need for accurate surveys. The age of beginning and stopping the use of iodin would depend to some extent on race and climate. In the United States, probably the maximum of prevention coupled with the minimum of effort would be obtained by giving iodin between the ages of 11 and 17 years.

The prevention of goiter means vastly more than eliminating cervical deformities. It means, in addition, the prevention of those forms of physical and mental degeneration, such as cretinism, mutism and idiocy, which are dependent on thyroid insufficiency. Further, it would prevent the development of thyroid adenomas, which are an integral and essential part of endemic goiter in man, and due to the same stimulus. These multiple, circumscribed benign growths have many of the attributes of tumor, one of which is that their growth once initiated is frequently not controlled by iodin, as are all simple hyperplasias. The terminal metamorphoses are far more serious than those of simple hyperplasia, since, in addition to hemorrhage, necroses, cyst formation, etc., probably 90 per cent of the malignant tumors of the thyroid arise from these adenomas.

If the prevention of goiter is good preventive medicine, it is better preventive surgery. With so simple, so rational and so cheap a means of prevention at our command, this human scourge, which has taken its toll in misery, suffering and death throughout all ages, can and should be controlled, if not eliminated.—Authors' summary.

(THYROID) The surgical aspect of goiter. Mason (J. T.), Northwest Med. (Seattle), 1921, **20**, 112-115.

A brief summary of the history of Graves' disease; the embryology of the thyroid, and its surgical pathology (adolescent, colloid, adenomata, exophthalmic and malignant). The clinical course of toxic adenomas as distinguished from the hyperplastic variety is discussed. The author concludes that all toxic adenomata and hyperplastic goiters are surgical cases, but should receive preliminary medical care. Operation should be performed before permanent degeneration of vital organs has occurred.—H. L.

The experimental production of THYROID hyperplasia in dogs. Mellanby (E.) & Mellanby (M.), J. Physiol. (Lond.), 1921, 55, vii.

Observations made in connection with work on rickets and the production of defective teeth in dogs. When puppies received cod liver oil as the only fat in the diet, the thyroids were small and normal. With other fats there was always some hyperplasia compared to those of the cod liver oil puppies. The thyroids were especially large when butter was fed. Increasing the fat in the diet intensified the hyperplasia. The size and appearance of the thyroids varied with the energy content of the food taken, and with the opportunity of the animals to get rid of this energy by mechanical effort, or living out of doors.—T. C. B.

The application of the results obtained in experiments on the hyperplasia of dog's THYROIDS to the treatment of exophthalmic goiter (Graves' disease). Mellanby (E.) & Mellanby (M.), J. Physiol. (Lond.), 1921, 55, x.

The hyperplasia of the thyroid produced by feeding fat appears similar to that of exophthalmic goiter. The results seem to show that the same physiological laws hold for dogs and human beings in the production of certain thyroid abnormalities, and there is hope of developing a curative treatment along these lines.—T. C. B.

HYPERTHYROIDISM. Morris (M. F.), Med. Rec. (New York), 1921, 99, 133-136.

Morris considers toxemia, either chemical or bacterial, as almost always the cause of hypersecretion of the thyroid. Acute febrile infections frequently initiate the malady. Likewise chronic foci of infection are often responsible. Another source of hyperthyroidism is the toxemia of psychoneurotic origin—fear, anger, deep grief, prolonged mental strain, etc. The author describes the many signs and symptoms of hyperthyroidism. He recommends determination of the basal metabolic rate, the epinephrin hypersensitiveness test and the blood sugar curve as laboratory aids in diagnosis, especially in the mild, early cases. The various non-surgical measures employed in treatment are reviewed and strongly endorsed. When other treatment has been carefully tried and failed, surgery is in order.—H. L.

Pathology of tuberculosis of the THYROID (Zur Pathologie der Schilddrüsentuberculose). Nather (K.), Mitt. a. d. Grenzgeb. Med. u. Chir. (Jena), 1921, 33, 375-404.

As a result of the study of five cases the author concludes that when hematogenous tuberculosis of the thyroid is not a part of general miliary tuberculosis it is a symptom of finished tuberculous septicemia. Formerly it was believed that the thyroid is immune to

tuberculosis and tubercular subjects were even sent to regions where goiter was endemic on the supposition that acquired goiter would have a beneficial effect on the tuberculosis. The author controverts this belief.—J. K.

Cancer of an accessory THYROID (Karzinom einer versprengten Schilddrüse). Nordmann (O.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 643.

A tumor developed in the right side of the neck of a girl of ten. It had no connection with the thyroid. Histological examination proved that the gland was unquestionably of thyroid structure, showing partly simple and partly toxic goiter with carcinomatous degeneration. The tumor undoubtedly arose from an accessory thyroid. The thyroid gland proper was found at operation to be normal.—J. K.

(THYROID) Goiter. Northrop (H. L.), N. York M. J. (New York), 1921, **113**, 277-280.

A general review with presentation of cases. The advisability of medical treatment prior to surgery is pointed out.—H. W.

Contribution to the physiology of the glands. 45. The reaction of THYROIDLESS and THYMECTOMIZED rabbits to heat puncture (Beiträge zur Physiologie der Drüsen. XLV. Mitt. Leon Asher. Die Reaktion von schilddrüsenlosen und thymuslosen Kanninchen auf den Wärmestich). Nyffenegger (W.), Biochem. Ztschr. (Berl.), 1921, **121**, 41-63.

A report of the effects of puncture of the medullary heat center in thyroidectomized, thymectomized and thyro-thymectomized rabbits. Studies of the temperature changes of the experimental animals lead to the conclusions that several punctures made on the same rabbit produce the same result in each case. The removal of the thyroid from an animal shortens the duration of the reaction to puncture as well as causes a definite lowering of temperature. The same effect is produced by simple thymectomy and by thyro-thymectomy. In those rabbits in which a temperature fall was caused by puncture before removal of the thyroid or thymus, there occurred a more marked depression after extirpation of the glands in question.—F. S. H.

Treatment of goiters. Pauchet, Paris chirurg., 1921, **13**, —— (No. 2); Abst., Arch. de Méd. cirug. y espec. (Madrid), 1921, **3**, 420-423.

In studying the therapeutics of goiters the solution of the following problems ought to be sought: What dangers attend the conservation of a thyroid adenoma when the necessity for its treat-

ment exists? What is the therapeutic value of physical and medical means? What is the danger of surgical treatment and what are its end results? What anatomoclinical varieties do we encounter and what are their therapeutic indications? The author answers these questions from the experience gained in the treatment of 300 cases during twenty-four years' practice. A. Amongst the dangers of goiter is carcinomatous degeneration, an infrequent complication. More frequently are respiratory disturbances—bronchitis, emphysema, and asphyxial accidents, these latter constituting a constant danger in intrathoracic goiters. Myxedema is a very rare complication, at least in the north of France. Thyroid degeneration resulting in Basedow's syndrome is common. Graves' disease may not cause exophthalmos, but only simple circulatory alterations, cardiovascular irregularities, etc. These manifestations are perhaps the most frequent and the most overlooked, both by the patient and by the physician. Latent myocardial injury should always be taken into account, and all goiters ought to be treated. As to therapy, iodide and x-rays have no effect upon diffuse goiters; their action is always transitory, almost always followed by relapse. Surgical treatment gives excellent results, immediate as well as ultimate. Goiter may be diffuse or nodular. The symptoms exhibited by goiters may indicate either hyper- or hypo-function of the thyroid. Diffuse goiters may be treated medically, by radium therapy and by x-rays, but operation may be later required. Aberrant goiters ought always to be treated since they are apt to result in sudden asphyxia. Cervical goiters ought to be treated by irradiation and operated upon in case this treatment fails. Nodular goiters ought to be enucleated in all cases; there is no danger in this operation. Intrathoracic goiters also demand operative treatment whenever recognized. They should be brought into the field by traction upon the thyroid lobes proper.

—R. G. H.

(THYROID) A strumous region of Catalan (Una comarca catalana estrumoso). Ricart Portelle (R.), Boll. méd. de Querida, 1921, **20**, 43-44.

Detailed description of a strumous region in the province of Querida in Mount Xica near the Pyrenees.—G. M.

(THYROID) Tuberculosis y hipertiroidism. Sanchez Conira y Mejarano (J.), Méd. Ibera (Madrid), 1921, **14**, 89-90.

In many cases of cutaneous tuberculosis and of Raynaud's disease the authors have encountered signs of hyperthyroidism. They report a line of union between those afflicted with scrofula and other lesions considered as tuberculosis of obscure pathogeny and Raynaud's disease, this latter being an advanced grade of peripheral acroasphyxia. In the same group they include the angiokeratosis of Mibeli and many other vasomotor disturbances.—E. B.

(THYROID) A case of hypothyroid infantilism, Brissaud type (Sobre un caso de infantilismo hipotiroidea de tipo Brissaud). Sanchez Garcia (C.), Méd. Ibera (Madrid), 1920, **14**, 93-96.

Clinical history of a typical case that was much improved by treatment with pluriglandular opotherapy.—E. B.

The glucose mobilization rate in HYPERTHYROIDISM. Sanger (B. J.), Proc. Soc. Exper. Biol. & M. (New York), 1921, **18**, 117-120.

The author studied the basal metabolism and blood sugar curves in six normal subjects and in eight subjects of Graves' disease. Standard methods were used. The chief conclusion was that carbohydrate administered is burned much more promptly in exophthalmic goiter than under normal conditions. It is suggested that this may explain the ease with which acidosis is elicited. A considerable amount of theorizing anent the available evidence leads the author to the conception that in this disease "The liver has a decreased ability to demobilize carbohydrate from the blood stream or perhaps there is a hypermobilization rate."—R. G. H.

Syndrome of THYRO-OVARIAN insufficiency, hydrocephalus and hypertrophied THYMUS (Syndrome d'insuffisance thyro-ovarienne, d'hydrocéphalie et d'hyperthymie). Sabrazes (J.) & Duperié (R.), Compt. rend. Soc. de biol. (Paris), 1921, **84**, 881-882.

Resumé of an article previously abstracted. See Endocrin., 1921, **5**, 282.—T. C. B.

The sensitizing action of THYREOIDIN and of HYPOPHYSIN on the pressor activity of ADRENALIN in children (Über die sensibilisierende Wirkung von Thyreoidin und Hypophysin auf die pressorische Wirkung des Adrenalins bei Kindern mit verschiedener Pulsbeschaffenheit). Schiff (E.) & Balint (A.), Jahrb. f. Kinderh. (Berlin), 1921, **95**, 73-77.

Continuing their studies on the pharmacodynamics of childhood the authors found that feeding thyroid in 0.5 gram doses for periods of 3-7 days was without effect on the blood pressure response to adrenalin. Hypophysin alone caused a fall in the blood pressure and when given with the adrenalin inhibited the pressor response to the latter.—C. H. G.

Some suggestions for the treatment of HYPERTHYROIDISM. Utley (F. B.), Penn. M. J. (Phila.), 1921, **24**, 544-547.

The author stresses especially the etiological relation of foci of infection to thyrotoxicosis and urges the removal of infected teeth, tonsils, appendix, gall bladder, or the treatment of intestinal stasis or

infection of the genito-urinary tract as of prime importance and more significance than the removal of part of the thyroid itself. Cysts, adenomata, fibromata and calcification of the thyroid require surgery, but the hyperplastic type should not be removed unless it is necessary at once to save the patient from the drive of the overactive thyroid. He also emphasizes the involvement of the **pituitary** and **adrenal** in hyperthyroidism. If infected foci are properly removed, no surgery of the thyroid itself will be necessary in most cases.—H. L.

A study of THYROID-iodine distribution and mobilization. Van Dyke (H. B.), J. Pharmacol. & Exper. Therap. (Balt.), 1921, **17**, 335.

The author was unable to confirm Rahe et al. and Watts, who have maintained that three to four hours' stimulation of the cervical sympathetic nerve in the dog causes a diminution of the iodine content of the thyroid gland on the side of the stimulation.—F. A. H.

A study of the distribution of iodine between cells and colloid in the THYROID gland. III. The effect of stimulation of the vago-sympathetic nerve on the distribution of iodine in the dog's thyroid gland. Van Dyke (H. B.), Am. J. Physiol. (Balt.), 1921, **56**, 168-181.

In connection with his studies it became necessary for the author to repeat the experiments of Rahe and others. Dogs were used and the vago-sympathetic stimulated over long periods of time. Three hours following stimulation there was an apparent diminution in iodine in the stimulated, as compared with the unstimulated lobe, in 54.5 per cent, and an apparent increase in 45.5 per cent. These differences seem to be due to normal variations in the concentration of iodine in the two lobes of the dog's thyroid, and the conclusion is, that stimulation of the vago-sympathetic, if it has any effect, is less than the normal variation between the stimulated and the control lobes.—T. C. B.

Roentgen-ray therapy in HYPERTHYROIDISM. Vaughan (W. T.), J. Lab. & Clin. M. (St. Louis), 1921, **6**, 281-288.

Following an excellent review of the evidence the author concludes that the percentage of recovery following medical, surgical or x-ray treatment is about the same, but the latter are perhaps swifter. Often a combination of the three methods is best. Treatment is most successful when individualized. Further advancement is to be hoped for. Present methods, in our ignorance of the pathogenesis of the disease, are merely therapeutic patchwork.—R. G. H.

(THYROID) Spontaneous, infantile myxedema. Wendel, München. med. Wchnschr., 1921, **68**, 158.

Demonstration of a girl of 11, with myxedema, in whom thyroid treatment was beneficial.—J. K.

(THYROID) The determination of the basal metabolic rate and its value in diseases of the THYROID gland. Wilson (C. M.) & Wilson (D.), Lancet (London), 1920, **(ii)**, 1042-1045.

The authors state that periodic determinations of the basal metabolic rate enable us to determine which of several methods of treatment, in diseases of the thyroid gland, is likely to prove effective in any one case. The results of treatment can be checked by following its effect upon a curve representing the basal metabolism taken from time to time, until it is apparent from the stationary readings that this method has brought about the full measure of alleviation of which it is capable. According to the authors' experience "basal metabolic rate determinations bring out the value of rest and its limitations, define the rôle of drugs, separate the type of case that x-rays benefits from the larger group in which they are of no avail, and, with regard to surgery, lay down precise rules for our guidance." The technique for the determination of basal metabolism is given in detail, and it is promised that a subsequent paper will contain the results upon which the above conclusions rest.—L. G. K.

(THYROID) The biological effects of proteinogenous amines. A contribution to the question of the aceto-nitrile reaction (Ueber biologische Wirkungen proteinogener Amine. Zugleich ein Beitrag zur Frage der Acetonitrilreaktion). Wuth (O.), Biochem. Ztschr. (Berl.), 1921, **116**, 237-245.

Wuth found that tryamine and di-iodo-tryamine when administered to mice protected them from doses of acetonitrile ordinarily fatal, thus simulating thyroid in their action. Beta-imidazolyl-ethylamine was ineffective.—F. S. H.

(VAGOTONIA) Modern views on vagotonia and sympathicotonia (Ueber den Stand der Lehre von der Vagotonie und Sympathicotonie). Frank (E.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 159-161.

A good review. The author believes that though there may be something valid in the theories of Eppinger and Hess, the greatest part is sheer nonsense.—J. K.

The influence of the vegetative nervous system on the fatty tissues (Der Einflusz der vegetativen Nervensystems auf das Fettgewebe). Müller (L. R.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 580

It is possible that the growth of the fatty tissue is regulated from a centre in the inter-brain. This may be proved by cases of **dystrophia adiposogenitalis** without changes in the **hypophysis** and of **hemi-adiposity**. This centre must be situated in the third ventricle.—J. K.

The abstracts in this number have been prepared by the staff assisted by

C. H. Green, Baltimore.

INDEX

ERRATA

Vol. V, No. 2, March, 1921, page 218.

Line 5, read: mm. for cm.
Line 6, read: mm. for cm.
Line 15, read: 22.1 for 82.1.
Line 17, read: –100.0 for 100.0.
Line 21, read: –49.9 for 49.2.
Line 22, read: –16.7 for 16.7.
Line 23, read: –14.2 for 14.2.
Line 25, read: –19.3 for 19.3.
Line 26, read: –29.5 for 29.3.

Standard values obtained from; Donaldson, H. H.: The Rat. Memoirs of the Wistar Institute of Anatomy and Biology, Philadelphia. No. 6. 1915.

Corrections calculated according to; Donaldson, H. H.: A revision of the percentage of water in the brain and spinal cord of the albino rat. J. Comp. Neurol., Phila., 1916, **27**, 77-115.