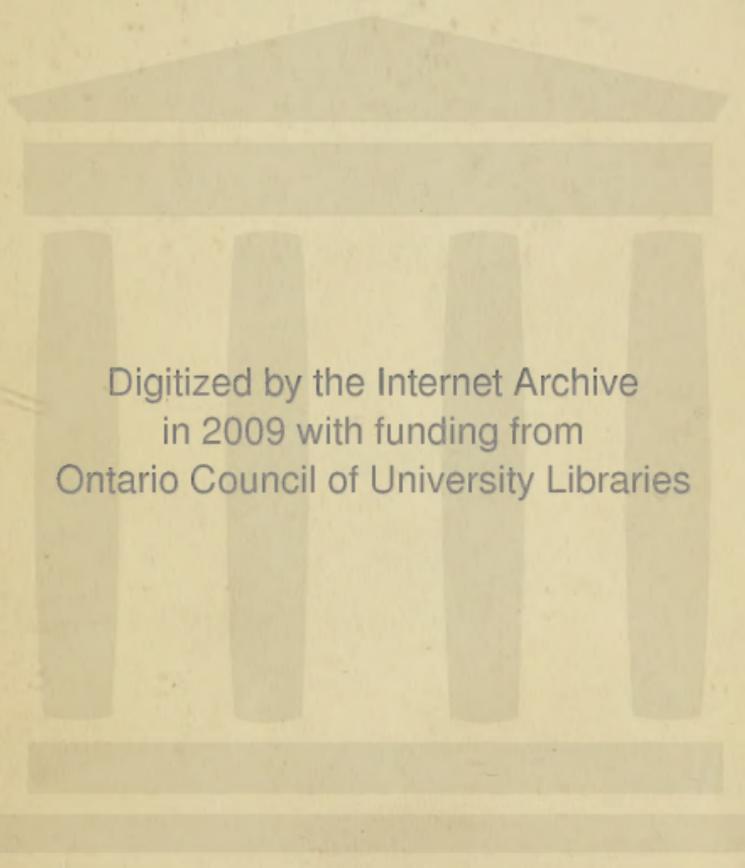


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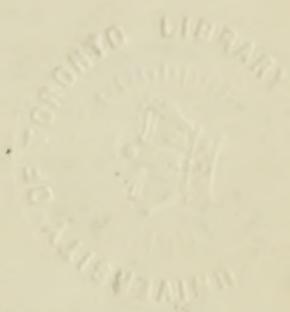
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ENDOCRINOLOGY

*The BULLETIN of the ASSOCIATION for
the STUDY of INTERNAL SECRETIONS*



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ENDOCRINOLOGY:

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STUDY of the INTERNAL SECRETIONS*

JANUARY—MARCH, 1918

ADRENALIN VASODILATOR MECHANISMS

By Frank A. Hartman

(From the Laboratory of Physiology, University of Toronto.)

It is well known that adrenalin causes constriction of arteries and that it does so by stimulation of myoneural junctional tissue. Moreover as a result of this constriction large doses of adrenalin produce a marked rise in blood pressure. Due to these facts the idea has prevailed that adrenalin vasomotor effects are essentially constrictor. Until lately we have been led to believe that adrenalin acts thus on all of the vessels except those without constrictor innervation. Even though it has been shown by a number of investigators recently that adrenalin causes active vasodilatation in the blood vessels of certain areas, the opinion is still held in many quarters that this reaction is exceptional. We will attempt to show that vasodilatation is the usual response in certain areas of the body when moderate doses of adrenalin are administered, and that this may be due to stimulation of certain structures located neither in the central nervous system nor at the extreme periphery.

Cannon and Lyman (1) demonstrated that cats respond to small doses of adrenalin (intravenous) by a fall in blood pressure in a majority of cases. To be sure other more or less isolated observations of this sort had been made previously, but the credit belongs to them for establishing the fact. Because this was opposed to the generally accepted idea of adrenalin action it appeared attractive for further research. An attempt was made by me to account for the fall in blood pressure. By tying off the arteries of the splanchnic area or of the head and limb area and then determining the blood pressure response to adrenalin, I was led to the discovery that there was a shifting of the blood from the splanchnic area to the outlying skeletal muscles (2). This was accomplished by active dilatation of skeletal muscle areas attended simultaneously by active constriction of the splanchnic area. At the same time it was observed by use of the nasal plethysmograph that the nasal mucosa constricted.

Later, Hoskins, Gunning and Berry (3) using the plethysmographic method, confirmed my observation that there was active dilatation in the "peripheral" regions, but they went further and demonstrated that the skin constricts while the muscle dilates. Hoskins and Gunning (4) and ourselves (5) working independently made a study of the spleen, kidney and intestine by the use of oncometers. On the whole the observations of both of us agreed with the first observations on the differential action of adrenalin (2) i.e. depressor doses of adrenalin cause constriction of the splanchnic area. However we did differ from each other to a certain extent in our findings on the intestine. While Hoskins and Gunning

frequently obtained dilatation of the intestine with small doses we found constriction to be the more common and that dilatation usually resulted from larger doses and was preceded by constriction.

It is now well established that the blood vessels of certain areas of the body do actively dilate with the intravenous injection of moderate doses of adrenalin. The question next arose as to the place of action of the adrenalin in causing this dilatation. Was it due to stimulation of possible sympathetic vasodilator endings? Our first evidence opposed to this view was obtained in the study of vasodilatation in the intestine. Destruction of the semilunar and superior mesenteric ganglia usually prevented the dilatation (5). This indicated that the seat of stimulation must be either in these ganglia or else at some place in the central nervous system. We next studied the effect on the adrenalin response of cutting the nerves to a limb. Gruber (6) has shown that dilatation does not occur in a limb freshly cut off from the central nervous system. We found that this prevented active dilatation from adrenalin. This evidence appeared to indicate some central nervous effect or at least that the mechanism for adrenalin dilatation was not located in the nerve endings.

We proved in another way that the dilatation was not the result of stimulating "sympathetic vasodilator nerve endings" (7). In the case of the intestine, a short loop in a large dog was prepared for the oncometer and then carefully dissecting out the vein and artery supplying this loop so as to avoid injury to the nerves, these were tied off and cannulae inserted for perfusion. This loop was now kept alive by perfusion with oxygenated Ringer's solution at a

temperature of 37° to 38° C. Its only functional connection with the rest of the animal was by the nerves. Placed in an oncometer any changes in volume could be observed and recorded by means of a Brodie's bellows. We found that suitable doses of adrenalin injected into the jugular vein caused dilatation in the perfused loop. These doses were often large enough to cause a rise in blood pressure.

In a similar manner the active adrenalin vasodilatation of the limb was proved to be due to some mechanism far removed from the vessels affected. A hind limb placed in a plethysmograph had its circulation cut off by clamping the abdominal aorta well above the bifurcation. The part was immediately perfused with warm oxygenated Ringer's solution through a cannula inserted into the common iliac artery, the outlet being the corresponding vein. Small doses of adrenalin injected into the jugular vein were able to cause dilatation of the perfused limb. It seemed from these experiments that some central nervous mechanism must be involved in the vasodilatation from adrenalin.

Absence of the Mechanisms in the Central Nervous System

We attempted to locate these mechanisms in the central nervous system by destroying various portions, testing for the presence of the mechanism in each case by the plethysmographic method.

Decerebration did not interfere with either the intestinal or limb mechanism, nor did it prevent the fall in blood pressure from adrenalin. However, just as soon as the medulla was injured or destroyed there was a reversal in the blood pressure response. In spite of this both the hind limb mechanism and

the intestinal mechanism were active. Where there was any doubt as to this, the limb and intestine were tested by the perfusion method.

We destroyed more and more of the spinal cord and still obtained action from the mechanisms. If the intestinal mechanism were located in the central nervous system, it would have to be in the region where the splanchnic nerves left the spinal cord, as destruction of the brain and cord above did not prevent action. However complete destruction of the brain and spinal cord did not prevent intestinal vasodilatation from adrenalin as determined by the perfusion method. Therefore we were mistaken in presuming the location of the intestinal mechanism to be in the central nervous system.

Investigating in a similar manner we found that the adrenalin vasodilator mechanism for the hind limb is not located in the central nervous system. Active dilatation of a perfused hind limb with intact nervous connection could be obtained when adrenalin was injected into the jugular vein even after complete destruction of the sacral, lumbar and lower half of the thoracic cord.

Location of the Intestinal Mechanism*

If the intestinal mechanism is not located in the central nervous system it might be in the sympathetic ganglia, for it was by destruction of these that intestinal vasodilator effects were either prevented or considerably reduced. We were able to demonstrate after the following manner that this is one location of the mechanism for the intestine. To eliminate peripheral effects, perfused loops of intestine

*The original work included in this and the following section was done in collaboration with L. G. Kilborn and L. McP. Fraser.

were used as already described. All splanchnic nerve fibres were cut and in some cases the vagi. Six dogs were studied by this method. In every animal adrenalin injected into the jugular vein caused dilatation of the perfused loop of intestine. Cutting the nerves between the ganglia and the loop prevented these effects.

Nicotine should reduce the adrenalin vasodilatation in the intestine, if the sympathetic ganglia control such action. Nicotine was used for this purpose in four cats. In three, the drug was administered intravenously. Two of these had the dilatation reduced, while in the third it was prevented. Painting the superior mesenteric ganglion of a fourth cat prevented the dilatation of the intestine. We believe that we have proven that the mechanism causing vasodilatation in the intestine, when adrenalin is injected into the general circulation, is located in the collateral sympathetic ganglia, probably in the superior mesenteric ganglion.

Location of the Limb Mechanism

If the adrenalin vasodilator mechanism for the hind limb is not located in the brain or spinal cord, it must be located in some structure situated between the cord and the peripheral nerve trunk, either the ganglia of the sympathetic chain or else the ganglia of the dorsal roots. Judging from the location of the intestinal mechanism it would seem more logical that the sympathetic ganglia were the structures sought.

The right hind limb of a dog (26.0 kgm.) was placed in a plethysmograph. The last five lumbar and the first sacral sympathetic ganglia were destroyed on the right side. The limb was next com-

pletely shut off from the circulation and perfused with warm oxygenated Ringer's solution. Injection of 1.5 cc. of 1:20,000, adrenalin into the jugular vein caused slight dilatation of the perfused limb, while double the dose caused a marked dilatation.

A second animal was studied after destruction of the last five lumbar and the first two sacral sympathetic ganglia. The dilatation from adrenalin was very marked.

In a third dog both sympathetic chains were completely destroyed on both sides from the third lumbar ganglion downward. The perfused limb dilated as in the other experiments when adrenalin was injected into the general circulation.

The animals were always examined at the completion of the experiments to ascertain the limit of gangliar destruction.

We were first inclined to believe that the mechanism for the limb was not located in the sympathetic ganglia, but that it must be in the dorsal root ganglia. However this appeared to be wrong, as the following experiments indicate.

In two dogs we were able to obtain dilatation, in a perfused limb, from adrenalin injected into the jugular vein after all dorsal root ganglia to that limb had been destroyed.

In another experiment we destroyed the sympathetic ganglia on both sides beyond any region which might supply the limb used for perfusion. Good dilatations were obtained in the perfused limb. Then the spinal nerves were cut distal to the dorsal root ganglia. No response could be obtained. Therefore we were forced to the tentative conclusion that either

the dorsal root ganglia or the central nervous system was the seat of action after sympathetic destruction. But other experiments described above have shown that the central nervous system is not involved. Moreover we obtained dilatation in the perfused limb of a dog after the sympathetic ganglia and the dorsal and ventral roots central to the ganglia had been destroyed.

Thus far our work indicates that the limb mechanism is located in both the dorsal root ganglia and the sympathetic ganglia.

Comparison of the Two Mechanisms

Obviously, if there is to be a shifting of blood from the splanchnic area to the muscles the dilator mechanisms for the intestine and the limb must behave somewhat differently because the intestine contains a large share of the "splanchnic" blood. The two mechanisms do behave differently. While small doses of adrenalin produce constriction in the intestine and dilatation in the limb, larger doses cause constriction and dilatation in the intestine and constriction in the limb. Greatly increasing the dose above that causing intestinal dilatation does not cause predominant constriction in the intestine unless the mechanism has been fatigued by huge doses. In addition to these differences we have evidence that the limb mechanism is developed earlier than the intestinal mechanism.

Occurrence of Adrenalin Vasodilator Mechanisms

It might be said that these mechanisms may be of little importance because of the possibility of their being limited to the carnivora. We have been mak-

ing a survey of the vertebrates for this reason. Although it is not completed it will be of interest to note some of our results.

The mechanisms seem to be absent in the Reptiles (turtle), Birds (fowl) and at least one order of Mammals, viz., the Rodents (rat and rabbit). In view of their absence in the Rodents we were much surprised to find them present in a lower mammal, one of the Marsupials (opossum). It seems that they are found in all of the carnivores, at least those tried (cat, dog, ferret). We have shown, therefore, that these mechanisms are not limited to the carnivora.

Discussion

It begins to appear that both the dorsal root ganglia and the sympathetic ganglia contain vasodilator mechanisms which are susceptible to adrenalin. These mechanisms cause dilatation in the vessels of the limb and probably in the vessels of all skeletal muscle. The collateral sympathetic ganglia contain vasodilator mechanisms for the intestine, but whether the dorsal root ganglia contain similar mechanisms for the intestine we cannot say.

Of the two types, the skeletal muscle mechanism may be the more important because it causes shifting of the blood to parts that need it most in times of action. We can suggest no good reason for the existence of the intestinal mechanism unless it be to prepare a ready reservoir for the blood when the pressure increases, from too great a constriction of the vessels of other regions. Even though intestinal dilatation may begin with doses which are not pressor in their action, it might be preparing the

way for the return of the blood from the muscles with greater amounts of adrenalin. The very fact that the intestines continue to dilate with increasing doses of adrenalin although the muscle vessels reverse and begin to constrict lends color to this suggestion.

The picture which we have at present in regard to the action of adrenalin on the blood vessels is this:

A mammal at birth (excepting the rodents), responds to adrenalin by constriction of the vessels pretty generally over the body, i.e. both in the intestine and skeletal muscle, no matter how large or how small the dose if it is effective, so that only a rise in blood pressure can be obtained. After a few weeks, about eleven in the cat, the skeletal muscle mechanism begins to appear; adrenalin now causes a shifting of the blood to the muscles when entering the circulation in small quantities and a fall in blood pressure may result because of a predominance of dilatation over constriction. But it is somewhat later that increasing the dose of adrenalin will cause dilatation of the intestine although the limb vessels will reverse and constrict. And then finally we find developing the intestinal mechanism which can be brought into play with the larger amounts of adrenalin.

Recapitulating,—in the adult, adrenalin poured into the blood in small quantities, causes by its peripheral effects, constriction of the vessels in the skin, mucous membranes, and abdominal organs, driving the blood into the vessels supplying the skeletal muscles which are actively dilated for its reception through the effect on the sympathetic and dorsal root gangliar mechanisms. But as the quantity of adrena-

lin liberated increases, the peripheral effect begins to overcome the gangliar effect in skeletal muscle, the intestinal vessels by action on the sympathetic ganglia begin to dilate and the blood is reversed in its path.

Although the effect of adrenalin on blood pressure, a fall with small doses and a rise with larger doses—is the more evident, the differential effect is after all the more important.

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A NOTE ON THE USE OF CORPUS LUTEUM TO PREVENT THE PAINFUL BREASTS OF MENSTRUATION

By H. Lisser, A.B., M.D.

Instructor in Medicine, University of California Medical School

Coincident with the increasing interest in endocrinopathies there has come widespread development of organotherapy. Much has been accomplished; far more remains to be unraveled and properly evaluated. Probably we have barely scratched the surface in this promising sphere of therapeutics, but unfortunately a great deal of indiscriminate use of ductless gland extracts has ensued, much of which will be deservedly discarded.

At present, Corpus Luteum, is receiving much attention and many remarkable results have been claimed for it. It would seem to be of considerable value in ameliorating or even eliminating the disagreeable symptoms of the menopause; especially the artificial menopause. It has been recommended by one eminent authority as very useful in combating the vomiting of pregnancy, although some dispute this. It has been advocated in sterility, and in an occasional selected case may prove successful. Some authors have found it beneficial in functional amenorrhea; and also in dysmenorrhea. It has been tried in many other conditions, and in the course of time it will find its proper place in our therapeutic armamentarium.

All clinical experimentation on human beings is in the nature of things inaccurate, since it is difficult to control and is influenced by prejudice. The report of an isolated instance is of course, valueless,

but it would seem that the following case embodies a new observation, to which it may be worth while calling attention. So far as I am aware, *Corpus Luteum* has not been used to influence the painful breasts so common during menstruation or just previous to it. However, in the extensive literature bearing upon the ductless glands which has accumulated in recent years, I may have very well overlooked a report similar to my own. In most women the breasts are somewhat tender at this time, but in a small minority they become so acutely painful as to constitute a really distressing symptom, the relief of which is quite welcome.

The patient was a young married woman, aged 24, and came to me in January, 1916, with two complaints—obesity and very painful breasts at the menstrual period.

Family history. Her father died when patient was very young; he was not fat. Her mother has always been stout, but of late years very fat indeed, up to 260 pounds. She is slightly taller than the patient, who is five feet 2 inches. Patient is the only child living and the only child that came to term. There were premature twins born dead. The mother has three sisters and one brother; none of them are stout except the sister, who is very stout. The mother of the patient has taken Thyroid Extract and lost 80 pounds in three months. There is therefore, a family tendency to ductless gland disturbances.

History. Patient has been married $3\frac{1}{2}$ years; never pregnant. Patient has always been well except for occasional tonsillitis (she has recently had tonsils removed). She is rather thirsty, drinks more water than normal and voids rather frequently. She perspires neither more nor less than normal. She is normally bright and active and is definitely not stupid or sleepy. Sexual intercourse is not gratifying.

Menstrual history. Regular every 28 days; flows profusely; lasts 6 to 9 days; suffers considerable pain so that frequently she remains away from work (school teacher) for a day or two. Breasts are very painful 5-6 days before her periods, so painful that she can barely touch them or have her clothes come in contact with them.

Examination. Short stout girl, excellent complexion, color good; 5 ft. 2 inches; weight $21\frac{1}{2}$ years ago, 160 pounds; average

weight, 145 pounds; weight on first visit to me, 140 pounds. Patient has a little more hair on lips, chin, and cheeks than normal, otherwise no abnormal distribution. Hands are short, wrists thick; relatively short forearm; round, fat face; fat, somewhat pendulous abdomen; thick, heavy hips; fat pads on upper chests, and large pendulous breasts. This abnormal fat is not painful. Tongue is not thick. Patient shows no signs of hyperthyroidism. Tonsils are enlarged. Eyes normal, mouth normal, thyroid normal, heart normal, lungs normal, abdomen normal, reflexes normal. Pelvis, normal (confirmed by competent gynecologist). Blood pressure, 125/95.

Treatment. From January, 1916 to June, 1916, patient was given thyroid extract (B. & W.) up to 15 grains per day without any ill effects. Her weight was reduced from 140-130 lbs., no success resulted from attempting to reduce it further by thyroid treatment.

During this time, as heretofore, she complained regularly of dysmenorrhoea and very painful breasts. Beginning with August, 1916, she was given Lutein tablets (H. W. & D.) 5 grain tablet t.i.d. The effect was prompt and remarkable. She was completely relieved of her painful periods and her breasts were perfectly comfortable; in fact, not tender at all; the periods did not last so long and the bleeding was not so profuse.

During the following months, sometimes by accident and sometimes purposely, Lutein Tablets were omitted and on each occasion she experienced a return of her painful periods and very tender breasts. Apparently, then, Lutein Tablets were not in any sense curative, but whenever taken prevented the disagreeable disturbances associated with menstruation. This is summarized as follows:

January, 1916—No Lutein. Much pain with periods. Very painful breasts.

February, 1916—No Lutein. Much pain with periods. Very painful breasts.

March, 1916—No Lutein. Much pain with periods. Very painful breasts.

April, 1916—No Lutein. Much pain with period. Very painful breasts.

June, 1916—No Lutein. Much pain with periods. Very painful breasts.

July, 1916—No Lutein. Much pain with periods. Very painful breasts.

August, 1916—Took Lutein. No pain with periods. No pain in breasts.

September, 1916—Took Lutein. No pain with periods. No pain in breasts.

October, 1916—Took Lutein. No pain with periods. No pain in breasts.

November, 1916—Took Lutein. No pain with periods. No pain in breasts.

December, 1916—No Lutein. Much pain with periods. Very painful breasts.

January, 1917—Took Lutein. No pain with periods. No pain in breasts.

February, 1917—Took Lutein. No pain with periods. No pain in breasts.

March, 1917—Took Lutein. No pain with periods. No pain in breasts.

April, 1917—No Lutein. Much pain with periods. Very painful breasts.

May, 1917—No Lutein. Much pain with periods. Very painful breasts.

June, 1917—No Lutein. Much pain with periods. Very painful breasts.

July, 1917—Took Lutein. No pain with periods. No pain in breasts.

August, 1917—No Lutein. Some pain with periods. Breasts very sore.

September, 1917—No Lutein. Some pain with periods. Breasts very sore.

October, 1917—Took Lutein. No pain with periods. No pain in breasts.

November, 1917—Took Lutein. No pain with periods. No pain in breasts.

Conclusion. Case is reported in which Corpus Luteum entirely relieved unusually painful breasts associated with menstruation. This would seem to be a new observation.

A favorable effect was had as well upon the dysmenorrhea and menorrhagia.

A STUDY OF THE SYMPTOMS OF EXOPHTHALMIC GOITRE

By Francis M. Pottenger, A.M., M.D., LL.D.,
Monrovia, Cal.

In my work as a specialist in tuberculosis, I have been impressed with the frequency with which we find enlargement of the thyroid gland in the early active stage of the pulmonary form of this disease. In fact, it is not infrequently that the diagnosis of exophthalmic goitre instead of tuberculosis, is made in these cases on the three symptoms: enlargement of the thyroid, acceleration of the heart beat, and loss of weight. Although the eye symptoms are not present, it is explained on the basis of the diagnosis being made before the complete syndrome has manifested itself.

Since becoming interested in the subject of visceral neurology, I have been impressed with the unsatisfactory explanations which have been offered to account for the clinical phenomena which accompany this disease. While many phases of this clinical picture must, with present knowledge, continue to remain doubtful, there are certain physiological and anatomical relationships whose discussion may serve to clarify some of the troublesome points. In this paper I do not desire to express dogmatic opinions, but rather to discuss relationships which may be suggestive and helpful, approaching the subject mainly from the interesting viewpoint of visceral neurology.

Graves' Disease presents a picture, the complexity of which has not been sufficiently appreciated, partly because the subject has been approached

from too narrow a standpoint. Attention has been centered too much on the prominent symptoms and not enough upon the other phases of the disease. Among the various standpoints from which it will bear discussion, are:

1. The vegetative nervous system.
 - (a) sympathetic.
 - (b) parasympathetic.
2. The central nervous system.
3. The various glands of internal secretion.

THE RELATIONSHIP TO THE VEGETATIVE NERVOUS SYSTEM

I.

Sympathetic Nervous System

It is important to note that three of the cardinal symptoms of this disease: exophthalmos, increased thyroid secretion and rapid heart, are manifestations of irritation of sympathetic fibres. The rapid heart, and possibly the thyroid secretion and the eye symptoms, may be caused by general sympathetic stimulation; but all could be accounted for by a stimulation of the *cervical* sympathetics without a general sympathetic stimulation. It is important then to determine whether or not there is an irritation in the *cervical* ganglia of the sympathetics in cases of Graves' Disease, or whether the motor cells in these ganglia are unduly sensitive to stimuli.

In recent studies by Wilson and Durante¹ and Wilson², important references to the literature on this subject are discussed in connection with their own valuable contribution to the subject. In the former paper they say:

"It would appear from our examination by the method detailed, that definite histologic changes do occur in the *cervical* sympathetic ganglia in hyperplastic toxic (exophthalmic) goitre."

and further:

“These histologic changes consist of various states of degeneration, viz (a) hyperchromatization, (b) hyperpigmentation, (c) chromatolysis, and (d) atrophy, or (e) granular degeneration of the nerve cells. All of these are but successive steps in degeneration, which, if uninterrupted, proceed to the complete destruction of the ganglion cells affected. Not all of the ganglion cells in any of the ganglia examined were so completely destroyed as to render improbable their return to normal under favorable conditions. There is some evidence that in ganglia from cases clinically improved some of the cells have partially or wholly recovered.”

A stimulation which would be sufficient to cause degeneration of nerve cells, in all probability, would be preceded by a preliminary period in which the cells would be only in a state of increased excitability.

This calls for an examination into the relationship which the cervical sympathetic ganglia bear to the eye, the thyroid and the heart; and an especial discussion of the question whether the changes in the cervical ganglia produce the thyroid stimulation or whether the changes in the thyroid cause the irritation and, later, degeneration in the ganglia and are indirectly responsible for the heart and eye symptoms.

Anatomical Consideration. The cervical ganglia send off the following branches of particular interest in our discussion:

1. *Eye.* Motor fibres to the Müllerian muscle and dilator fibres to the pupil. Found only in the superior cervical ganglion.
2. *Thyroid.* Efferent cells to this gland are found in both the superior and medium cervical ganglia.
3. *Heart.* The motor cells which send accelerator fibres to the heart are found in the superior, medium and inferior cervical ganglia, the latter being the chief source.

From anatomical considerations then, an irritation of the superior cervical ganglion might stimulate efferent cells which would, reflexly:

1. Cause a shortening of the muscle of Müller which pushes the eyeball forward, causing exophthalmos.

2. Stimulate the thyroid gland to increased secretion and, if excessive, produce hyperthyroidism.

3. Stimulate the accelerator fibres going to the heart, causing the rapid heart found in this disease. (There are also other causes operative in Graves' Disease which tend to cause rapidity of the heart as will be mentioned later).

The experiments of Cannon, Binger and Fitz³ support the foregoing conclusions.

Stimulation of motor cells in the medium ganglion might affect fibres going to the thyroid and the heart; and stimulation of the cells of the inferior ganglion would affect the heart alone, but very strongly.

Physiological Considerations. In order to discuss the question of the relationship of the changes in the cervical ganglia to the thyroid gland, we must discuss one of the fundamental and most important principles involved in studying the vegetative nervous system, viz: *When the various ganglia of the sympathetic system migrated from the central nervous system, did they carry with them the powers of the cells in the gray matter of the central system to mediate reflex acts?*

This is a most important question from the standpoint of physiology. Such able students of physiology of the vegetative nervous system as Langley⁴ and Gaskell⁵ believe that reflexes do not take place through sympathetic afferent neurons and efferent motor neurons except as contact is had in the cord. They thus deny the possibility of a reflex taking place from one viscus to another, the synapse occurring in sympathetic ganglia. On the other hand, Bechterew⁶ quotes approvingly the work of Ramon Y. Cajal, who believes that a reflex may be formed between sensory sympathetic and motor sympathetic

neurons in sympathetic ganglia; the cells of the ganglia having the same function as to the production of reflexes as those of the central nervous system from which they migrated.

Thus it will be seen that if the view held by the English physiologists is correct, it is impossible for afferent impulses traveling centralward from a toxic goitre to produce histological changes in the cells of the cervical sympathetic ganglia, such as have been described by Wilson and Durante, because the nutrient cells of the afferent neuron lie in the ganglion of the posterior root. On the other hand, if the view of the continental physiologists is correct, this is possible, for nutrient cells of the sensory neurons would also be found in the cervical ganglia. We are now face to face with a situation in which clinical pathology may be able to settle the discussion upon this important physiological principle. *If it can be shown that the pathological changes in the cervical sympathetic ganglia are secondary to the prolonged irritating afferent impulses which come from a pathological thyroid, and that exophthalmos and rapid heart are reflexly caused by the ganglionic changes, then it is established as a fact that the cells in the sympathetic ganglia possess the power to mediate reflexes.* Further investigation along this line is most desirable. The important experiments carried out in Cannon's laboratory do not throw light on this question, because the union is with the preganglionic fibres.

Three Views of Graves' Disease from Its Relationship to the Sympathetic Nervous System

From our discussion so far and that which follows, we are led to see that as far as the cardinal symptoms, exophthalmos, hyperthyroidism and

tachycardia, are concerned, Graves' Disease might be any one of the following:

1. *A disease produced by certain pathological conditions in the sympathetic nervous system, which show as increased excitability with lowering of the threshold of response in selective portions of the system, affecting particularly neurons which go to the eye, thyroid and heart.*

2. *A disease of the sympathetic ganglia, in which a chronic irritation, affecting the ganglion cells which give origin to fibres supplying the muscle of Mueller, the thyroid gland and the heart, is present.* This, in the superior cervical ganglion, could affect the motor cells to all of these organs; if in the medium, to the thyroid and heart; and if in the inferior, to the heart alone.

3. *A disease of the thyroid gland which causes afferent impulses to travel centralwards to the cells in the cervical sympathetic ganglia, and on account of their persistency produce chronic stimulation which later results in histologic change.* Resulting from this stimulation there takes place a persistent activation of the motor cells which innervate the muscle of Müller, resulting in protrusion of the eyeball; and of those which innervate the heart, resulting in tachycardia. (This can only occur if sympathetic ganglion cells have the power of mediating reflexes).

Aside from the cardinal symptoms above mentioned, which are distinctly of sympathetic origin, there are a few cases in which the entire disease picture is that of a lessened vagus or a positive sympathetic irritation, as mentioned by Eppinger and Hess⁷. Such cases have excessive tachycardia; no sweating; no marked gastrointestinal symptoms;

slight rise of temperature; no eosinophilia; and at times, alimentary glycosuria. Such cases must not necessarily be considered as being due alone to the action of the thyroid secretion upon the sympathetic nerves. In this connection we must consider that the sympathetics and parasympathetics in their opposition to each other do not always exert an equal force. It seems to me possible that some of these cases are those in which the stimulation of the parasympathetics is not wholly able to overcome the normally high (for the individual) sympathetic tonus. This will be discussed in relation to "vago-tonia" later. Owing to the reciprocal relationship generally admitted to exist between the thyroid and adrenals, the sympathicotropic action of adrenalin must play a part in every clinical picture.

Circulatory Phenomena. The circulatory phenomena are intensely interesting. The heart beat is accelerated, and strong, often so strong that it causes an uncomfortable pulsation in the larger vessels, such as the aorta and carotids. This at times causes a shaking of the head and marked pulsation of the abdominal aorta. Contrary to the increased muscular tonus of the heart and large arteries, the walls of the peripheral vessels are relaxed, as is shown in the flushing of such peripheral structures as the face, ear and fingers.

This condition in the vascular system argues in favor of the cause of the tachycardia, being in the sympathetic ganglia which give off motor fibres to the heart. The blood vessels of the head, neck and upper extremities receive their constricting sympathetic fibres from connector neurons originating from the I to the X, particularly the II, III and IV thoracic

segments of the cord (Gaskell) and the motor cells supplying the vessels are found in all of the ganglia connected with this part of the cord. The heart itself receives accelerator fibres from motor cells in the superior, medium and inferior cervical ganglia; and an irritation of the motor cells in these ganglia for the heart, might take place without causing general stimulation of the motor fibres going to the vessels supplied by neurons which are connected with the same thoracic segments.

We can not, however, look upon the tachycardia which accompanies this disease as being so simple in explanation as that of a stimulation of some of the accelerator neurons in the cervical ganglia. Much of it must be accounted for by the stimulation of the adrenals and the general increase in metabolic activity, while part of it is of central origin. Neither must the psychological state of the patient be omitted from consideration in accounting for it.

II.

Parasympathetic Nervous System

While the cardinal symptoms above described are manifestations of increased stimulation on the part of the sympathetic nervous system, there are many other symptoms which show distinct evidence of parasympathetic stimulation. When we consider the full symptomatology of this disease, we are forced to the conclusion that it is of such a nature that its symptoms are not due to effects exerted on the vegetative system alone, nor on one division to the exclusion of the other, but to many causes, including disturbances in the central nervous system, in psychological equilibrium, and in the equilibrium of the endocrine glands.

Many of the common symptoms, however, belong to the group which represents stimulation of the parasympathetics, thus:

1. *Von Graefe's Sign.* When eyes are lowered the upper lids do not follow the cornea readily, because of the high tonus in the musculus levator palpebrae, innervated by the III nerve.

2. *Dalrymple's Sign.* Widening of the lid slits, giving the expression of fright is due to the same high tonus in the musculus levator palpebrae.

3. *Epiphora.* Increase in flow of tears, due to stimulation of the vegetative fibers of the VII nerve.

4. *Excessive Sweating.* Sweating from the manner in which it is influenced by pilocarpin, atropin, and adrenalin, seems to be due to parasympathetic stimulation. This, however, is not certain.

5. *Diarrhoea.* Diarrhoea is produced by an excessive stimulation of the glands and longitudinal muscles of the gut; and since all of the muscles of the gastrointestinal tract are activated by the parasympathetic (vagus and pelvic) nerves, this must be considered as parasympathetic stimulation.

6. *Hyperacidity.* This is evidence of an increased action on the part of the secreting glands of the gastric mucosa which are innervated by the vagus.

7. *Eosinophilia.* This blood picture seems to predominate in states which accompany a predominant stimulation of the parasympathetic system.

With reference to the non-cardinal symptoms, it must be remembered that they are not constant. Some of them, like diarrhoea, are found in 30 per cent of cases (Sattler), vomiting in 15 per cent; while the metabolic disturbances which must be looked

upon as the most important pathological change in this disease, were found, according to Kocher, in 88 per cent of all cases examined by him.

Considering the vegetative system alone, it is evident that Graves' Disease is accompanied by both sympathetic and parasympathetic symptoms; and if we account for all as being due to thyroid secretion, it must be a complex polyvalent substance (Biedl.⁸) It seems to me equally plausible that thyroid secretion, in its sensitizing role, lowers the threshold of response, and that the group of symptoms which presents depends: (1) upon the constitutional underlying tonus (sympathicotonia or vagotonia); and (2) upon the tonus of individual organs in the same individual, and the manner in which the nerve cells respond to stimuli.

RELATIONSHIP TO THE CENTRAL NERVOUS SYSTEM

Neurasthenia, and mental disturbances, are common in this disease.

Tremor is exceedingly common, and is thought by many to be of central origin. It is most marked in the upper extremities. It is to be looked upon as being evidence of increased irritability of motor centers.

There seems to be a general disturbance in the equilibrium of nerve cells of such a nature that the threshold of response for stimulation is lowered. This manifests itself in a general unsteadiness of many body functions.

In many cases, such centers as the vasomotor, respiratory and vomiting are disturbed.

Psychical disturbances of all grades are found during the course of the disease.

RELATIONSHIP TO OTHER ENDOCRINE GLANDS

The secretion of the thyroid gland is one of the most important chemical regulators of the body, and one without which the patient can not long exist. Further, because of its action upon other important structures, and its interrelation with other glands of internal secretion, when produced in overabundance, it will disturb functions which depend on a normal balance of secretion from other important glands of internal secretion. The precise relationship which exists can not be stated no matter how essential to this present discussion. Suffice it to say that the entire equilibrium in the chemical, as in the nervous control of the body, is disturbed and often destroyed when the secretion of the thyroid gland is either markedly increased or decreased. Particularly is there reciprocal relationship supposed to exist between the thyroid and the adrenals, pancreas, thymus, and gonads. The relationship of the thyroid to these structures will be further discussed in this paper in relationship to Kendall's interesting reports.

Influence of Vagotonic and Sympathicotonic Dispositions Upon Symptomatology

The conception of an underlying vagotonic and sympathicotonic constitutional disposition, as suggested by Eppinger and Hess¹, is of great importance to clinicians in helping to explain the variability of symptoms as they exist in medical practice. All the smooth muscle and all secretory glands of the gastrointestinal tract and all the structures which have been formed embryologically from it, such as the respiratory and part of the genitourinary tract, and

the liver and pancreas as well as other glands of internal secretion, are supplied by fibres from both the sympathetic and parasympathetic systems. In each instance one system activates and the other inhibits; and equilibrium of action or normal function is maintained by the effects of the two systems balancing each other. This equilibrium under normal conditions is fairly stable. A considerable stimulation on the part of either system may be withstood by the opposing nerves without normal function being disturbed. There are some structures also which are innervated wholly by one of the systems alone. There are a great many individuals, however, in whom the tonus of one or the other of these systems is commonly above normal. If the tonus in the sympathetic system is stronger than normal, then a slight increase of sympathetic stimulation may cause marked sympathetic symptoms. Such a person is normally sympathicotonic. If the parasympathetic tonus under normal conditions is abnormally high, then a slight increased stimulation of parasympathetic fibres may produce marked parasympathetic symptoms. Such a person is normally vagotonic.

The natural underlying disposition is often sufficient to modify greatly or even determine the character of the symptoms; and it is well to bear this in mind in analyzing the symptoms of any disease, but particularly in one such as Graves' Disease, in which all nerve activity is heightened.

Eppinger and Hess divide Graves' Disease according to whether the symptoms are predominantly those of sympathetic or parasympathetic stimulation, into sympathicotonic and vagotonic types, thus:

Characteristics of the *Vagotonic Type* are: 1, relatively slight increase in pulse-rate; 2, subjective cardiac symptoms; 3, marked von Graefe's sign; 4, wide lid slits; 5, very moderate exophthalmos; 6, marked epiphora; 7, excessive sweating; 8, profuse diarrhoea; 9, gastric hyperacidity; 10, eosinophilia; 11, disturbance in respiratory rhythm, and 12, absence of alimentary glycosuria.

Characteristic of the *Sympathicotonic Type* are: 1, marked exophthalmos; 2, epinephrin mydriasis; 3, Moebius' sign; 4, frequently dry eye; 5, a high degree of tachycardia without subjective cardiac symptoms; 6, no sweating; 7, no diarrhoea; 8, falling out of hair; 9, rise in temperature; 10, absence of eosinophilia, and 11, alimentary glycosuria.

In these two types of Graves' Disease it should be noted that the *vagotonic* type shows a general widespread parasympathetic stimulation, while the *sympathicotonic* type shows most marked symptoms on that part of the sympathetic system whose motor cells lie in the cervical ganglia. The two noticeable exceptions to the last statement are, slight rise in temperature and alimentary glycosuria, which, if due to sympathetic stimulation or increased adrenal secretion, are a result of general and not local action. The adrenals are stimulated by thyroid secretion.

The rise of temperature can easily be accounted for by the increased metabolism which is present, especially if associated with vasomotor disturbances which interfere with heat dissipation. In this connection it has been estimated (Barker)⁹ that an individual at rest with a well marked hyperthyroidism utilizes as much oxygen as a man at hard work. Not only is nitrogenous metabolism accelerated, but car-

bohydrate and mineral as well. In severe cases CO_2 production and O_2 consumption may increase 70 per cent (Falta)¹⁰. Cannon's⁸ experimental animals increased as much as 150 per cent.

Alimentary glycosuria is supposed to be due to increased stimulation of the adrenals, caused by the increased thyroid secretion. Gley¹¹ does not accept this relationship with the adrenals as established. Kendall, however, believes it an essential part of thyroid activity. Since alimentary glycosuria is not regularly found in this disease, it might be looked upon as due to some peculiarity of the patient or to some general condition which exists, and not necessarily an integral part of the syndrome of hyperthyroidism.

DISCUSSION

In studies of visceral neurology and endocrinology, it is essential to be familiar with the tendency which such and such nerve stimulation or such and such chemical products from endocrine glands has to affect certain actions; but the analyst must not be unmindful of the fact that the physiological organism is exceedingly complex and that definite tendencies may be altered or wholly controverted; otherwise, the more independent physiological facts which are at his disposal, the greater his confusion.

In the light of the above analysis, it seems not improbable that we have been confusing several different conditions in our picture of Graves' Disease, thus:

1. A local sympathetic stimulation confined to the motor cells of the cervical ganglia, which may be primary and cause the sympathetic eye symptoms, being a factor in the production of tachycardia and causing

the hypersecretion of the thyroid, this gland being activated by the sympathetics, as shown by Camon and Cattell¹²; or a local stimulation of the cells of the cervical sympathetic ganglia which results from irritating afferent impulses from the pathological thyroid gland forming synapses in the cervical ganglia and reflexly influencing the eye and the heart.

2. Changes in metabolism and disturbances in physiological equilibrium throughout the organism which are directly and indirectly due to a hypersecretion of the thyroid gland, most of which changes seems to be of a vagotonic nature.

3. A variable symptomatology due to: (a) natural underlying constitutional tendencies, such as sympathicotonia and vagotonia; (b) to variability in tonus of the nerve supply to different organs in the same individual, and (c) to differences in secretion from various endocrine glands.

Both the local sympathetic stimulation and general parasympathetic (vagal) stimulation is well illustrated in the eye. The muscle of Müller, which is activated by the sympathetics and unopposed by vagal fibres, is contracted and causes protrusion of the eye ball. This is made permanent by a deposit of tissue posteriorly to the ball after it is forced forward by the muscle. The levator palpebrae which is activated by the III nerve (parasympathetic) and unopposed by the sympathetic, causes widening of the lid-slits, and Von Graefe's sign. These are sometimes present but often absent, depending on the strength of the vagal stimulation. The pupil which is dilated by the sympathetic and contracted by the parasympathetic fibres in the III nerve, sometimes shows the effect of stimulation of one system, some-

times of the other, depending on whether the tonus in the one or the other system predominates. Dilated pupil is not constant like the exophthalmos, although it results from stimulation affecting motor cells of the sympathetics in the same ganglion. The difference might be accounted for in that the sympathetic stimulation of the muscle of Müller is unopposed, while that of the pupil is opposed by the III nerve.

The very interesting experiments of Cannon³ must not be overlooked, for they show that a chronic irritation of the cervical sympathetics may produce an artificial condition not unlike exophthalmic goitre. He anastomosed the phrenic nerve in cats with the cervical sympathetics which supply the thyroid. After the animals had fully recovered from the operation and union of the nerves had taken place, a condition was present in which a stimulation of the cervical sympathetics occurred with each respiratory excursion. These animals developed exophthalmos, tachycardia, diarrhoea, greatly increased metabolic activity, and while in the dark a rhythmic contraction and dilatation of the pupil with each respiratory movement. Cannon believes that exophthalmic goitre may be of central origin and that it occurs in individuals in whom the threshold of response in the sympathetic nerve cells supplying the organs involved is lowered so as to allow impulses to pass with unusual ease.

It might add further light to our discussion to include cases of hyperthyroidism, which are not accompanied by exophthalmos. There seem to be two predominant etiological factors in hyperthyroidism: One, deep emotions, sexual excitement and fear; the other, such infections as those of the nasal sinuses

and tonsils, alveolar abscesses and pulmonary tuberculosis.

While chronic infections of other structures such as the digestive tract and urogenital tract, as mentioned by Barker may be etiological factors, it will be noticed that infections commonly recognized as producing hyperthyroidism are confined to structures of the head and chest, structures which receive their sympathetic innervation from the upper six thoracic segments of the cord and which further return their afferent impulses through the cervical sympathetic ganglia. It would be well to bear this in mind for future study in order to determine if possible whether reflexes are taking place in these ganglia which result in stimulation of thyroid activity. McCarrison¹³ claims that intestinal toxemia is most commonly followed by hyperthyroidism. Toxemias act particularly through the sympathetics, as do such emotional states as are instrumental in producing hyperthyroidism; but this action seems to be general and would probably require some particular underlying cause on the part of the thyroid gland itself, in order to have an increased secretion on its part dominate the sympathetic picture.

Experimental attempts to produce exophthalmos by the use of thyroid feeding are interesting. The reports seem to be decidedly conflicting, and it can be said that true exophthalmos has so far not been readily produced. Falta¹⁰ quotes the experiments of Kiam and Friedental and Hönnicke, as being successful through the administration of large quantities of thyroidin. He says they induced both a widening of the palpebral fissure and an exophthalmos, although not of a very marked degree. This seems

to be a physiological paradox, for widening of the palpebral fissure is due to parasympathetic stimulation through the III cranial nerve, while exophthalmos is due to sympathetic stimulation. If both of these effects result from the thyroidin, it seems most probable that one may be a direct action, while the other must be indirect and probably produced by some other chemical substance resulting from the stimulation of other endocrine glands, or that the thyroidin contains more than one active substance.

The secretion of the thyroid gland stimulates the adrenal glands, which are sympathiotropic. It might do this either as a part of a general sympathetic stimulation, or as a selective chemical stimulation confined to the gland itself. It has also been stated that thyroid extracts sensitize the nerve terminations on which adrenalin acts (Levy¹⁴). Paton¹⁵ quotes the work of Asher and Rodt as showing the effect of blood containing the products of the thyroid gland when injected into animals. Inasmuch as the thyroid secretion stimulates the action of the adrenals, they treated the blood with formaldehyde, which destroys the adrenalin "and found that the serum injected in a series of cases caused increased vagus excitability, increased action of adrenalin and increased irritability of the splanchnic and of the depressor nerve."

Hoskins¹⁶, in an interesting editorial (*Endocrinology*, Vol. 1, 1917, p. 404) on this subject supplies the experimental proof from his own work as well as that of others to show that there is a strong inter-relationship between the secretion of the thyroid and adrenals.

It would thus look as though thyroid secretion is a sensitizer of nerve cells. This phase has been particularly emphasized by Crile¹⁷. It would further seem that it has the property of activating both the sympathetic and parasympathetic systems. This from the knowledge of other physiological substances, seems hardly probable as far as the same substance is concerned; for these two groups of neurons are antagonistic in action wherever found. Does it not seem more probable that the thyroid secretion lowers the threshold of response in nerve cells generally; and in its action upon nerve structures, acts either as sympathiotropic or vagotropic, more probably the latter; and that aside from those symptoms which might result from irritation in definite ganglia, such as the cervical, the sympatheticotonic symptoms which manifest themselves might result from the increased adrenal secretion, another thyroid product, or a particular sensitization of certain tissues acted upon by adrenin? This, if we accept thyroidin as being vagotropic (Gley¹¹), would lead us to consider a vagotropic substance as acting upon the adrenals, which otherwise are stimulated by sympathetic irritation; or, compel us to assume that there are other substances in the thyroid secretion than the thyroidin which acts upon the adrenals. We must remember, however, that the chemical control of the body is lower in the course of development than the nervous system, and it is possible that some such a reciprocal relationship was necessary in order to maintain equilibrium. As it is necessary to make flexor muscles taut in order to maintain an equilibrium when extensors are contracting, so it might be necessary for a gland which

secretes a vagotropic substance to stimulate another gland to secrete a sympathotropic substance in order to maintain an equilibrium in those functions presided over by hormones.

While the prominent symptoms, exophthalmos and tachycardia, may be results of sympathetic stimulation, we are not warranted in assuming that they necessarily result from the action of thyroid secretion upon the sympathetic cells which innervate them. These symptoms and the increased thyroid secretion itself may be due to common sympathetic stimulation.

The striking feature of thyroid hyperactivity is its influence upon metabolism; the speeding up of metabolic changes resulting in the rapid breaking down of protein and only a slightly lower destruction of carbohydrates. Since the musculature and secreting cells of the entire gastrointestinal canal and the organs derived from it are innervated by the parasympathetics, it would seem that the action of thyroid secretion upon metabolism must be vagotropic as far as it acts upon vegetative structures; but since the increase in metabolism extends likewise to voluntary structures, we must not take too narrow a view of its action. Kendall¹⁵ reports the function of the thyroid. He says:

“While it has not been proved beyond controversy, there is much evidence to support the hypothesis that the function of the thyroid is to furnish the animal organism with ammonia resulting from the diamination of amino-acids. The amino-group in amino-acids is unavailable for the formation of urea and other nitrogenous compounds until it has been split out of the amino-acid. This diamination seems to be the function of the thyroid.”

The other ductless glands, such as adrenals, pancreas, parathyroid and thymus, in the opinion of

Kendall, are also concerned in the conversion of nitrogen compounds into their proper end products. He says further:

“The thyroid hormone is involved in the first split of ammonia from the amino acids. The adrenal cortex secretion then converts this substance into some other and the secretions of the thymus, the parathyroids, and other ductless glands are involved in the further elaboration of the nitrogen constituents which finally appear in the urine. It, therefore, is evident that the administration of the thyroid hormone merely starts an increased rate of production of ammonia, which, in itself, does not produce hyperthyroid symptoms. It is only when the other ductless glands are stimulated that the reaction is carried on at a rate sufficient to change the basal metabolism, the irritability of the nerves, and the other effects produced by administration of the thyroid hormone. These reactions take place within the tissues and, in part, within the blood; and the speed with which they occur, and hence the equilibrium maintained, producing an increase or decrease in metabolism, depend on the stimulation of the various endocrine glands and the ability of the tissues to carry on the reactions which are made possible by the secretions from the various glands.”

The work of Kendall is of great importance and confirms the idea that we are attempting to account for too many of the conditions which manifest themselves in Graves' Disease, as being directly due to the thyroid secretion. The disease is extremely complex; and while the hypersecretion of the thyroid gland starts the picture, it does not end until other ductless glands, the voluntary and vegetative nervous systems, the circulatory and digestive systems, and the entire metabolism, are severely deranged.

SUMMARY

1. Exophthalmic goitre is an extremely complex picture in which the clinicians have emphasized too much the exophthalmos, tachycardia and enlarged thyroid; while the real picture is that of a rapidly destructive metabolism dependent apparently upon the thyroid hypersecretion and its influence on the

nervous system and on other endocrine glands.

2. The relationship of the three prominent symptoms, exophthalmos, tachycardia and thyroid hyperactivity is not clear. These may all be evidence of the same stimulation of the cervical sympathetics; or the thyroid gland may be diseased primarily and the afferent impulses from it so irritate the nerve cells of the cervical sympathetic ganglia as to cause the marked stimulation of those motor neurons which supply the muscle of Müller and the heart, and cause exophthalmos and tachycardia.

3. If exophthalmos and tachycardia result from stimuli which emanate from the diseased thyroid, the synapse in all probability occurs in the cervical sympathetic ganglia, and the reflex would be proof that sympathetic ganglion cells have the reflex properties of the cells of the central nervous system.

4. Omitting the three localized cervical sympathetic symptoms, exophthalmos, enlarged and functionally hyperactive thyroid, and tachycardia; and the increased activity of the adrenals; most of the common visceral symptoms of this disease seem to manifest themselves in parasympathetic rather than sympathetic stimulation.

5. The variability of the symptoms seems to depend on the sensitizing influence of thyroid secretion upon nerve cells, lowering the threshold of response to nerve stimulation on the one hand, and to the natural underlying, predisposing nerve tonus as described by the terms sympathicotonic and vagotonic by Eppinger and Hess, and the relative tonus of these two divisions of the vegetative system in different organs of the same individual.

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COMMENT ON DR. POTTENGER'S ARTICLE

Swale Vincent, M. D., University of Manitoba, Winnipeg: Dr. Pottenger's paper would form a good introduction to a discussion on the whole subject of Graves' Disease and the physiology and pathology of the thyroid gland. The reader will be impressed by the amount of thought and ingenuity which has been

expended upon the subject; although, it must be confessed, the amount of actual original observation seems to be very small, amounting in fact to the record of frequent thyroid enlargement in the early stages of pulmonary tuberculosis.

One of the most interesting questions from a general physiological standpoint raised by Dr. Pottenger is that which concerns reflex action from the sympathetic ganglia. Langley and Gaskell are quoted as representatives of English physiologists who are opposed to the view that such reflexes are possible. I imagine that the list of English physiologists who are of this opinion might be considerably extended. Moreover, it may be questioned whether it is permissible to quote the views of Bechterew on this point as typical of those of "continental physiologists." I have carried out no investigations on the subject, but for teaching purposes I have assumed for some years that the matter was practically settled and that the verdict was against the occurrence of sympathetic reflexes. Certainly Dr. Pottenger has not adduced sufficient fresh evidence to disturb my belief.

As for the share played by "vagotonia" and "sympathicotonia" in the symptom-complex of Graves' Disease, it would be well to exercise due caution in expressing any opinion until such time as a sufficient amount of clinical evidence has been accumulated. It is at any rate consoling that Dr. Pottenger says nothing about "Hormone X."

AN ENDOCRINE PROBLEM

Recent experimental evidence is concordant in indicating that the secretion of adrenin is neither essential to life nor, under ordinary conditions, particularly significant as a factor in the physiologic economy. On the other hand clinicians, and particularly, certain of the French, continue to maintain that as a therapeutic agent adrenin even in very small doses is often effective. Milian, for example, claims that it is almost a specific against the alarming symptoms that occasionally attend the use of salvarsan. Even allowing for the potency of therapeutic suggestion, the persistence of such claims stands as a challenge to those who believe in the relative inefficacy of adrenin.

No thoughtful experimentalist will maintain that current laboratory methods of endocrine research are sufficiently delicate for the satisfactory investigation of many problems. At best merely tentative conclusions can be drawn from various laboratory experiments in this field.

Much more delicate are the spontaneous experiments which come under the eyes of clinical observers. But unfortunately in such experiments the conditions are usually beyond control and the analysis of the phenomena observed highly difficult. Moreover, the mental attitude, the preconceptions and tendency to theorize, upon the part of many clinical endocrinologists militates against a proper objective treatment of such data.

In an article abstracted in this number of *Endocrinology* Tracy has stated that a few drops of

adrenin a day administered subcutaneously or even placed under the tongue cause a marked augmentation of the vasoconstrictor reaction to stroking the skin. The writer has observed a small dose of adrenin hypodermatically to cause a marked generalized itching in a patient with an unstable vasomotor system.

In view of the admitted inadequacy of the methods hitherto employed an attempt to develop a more delicate technique for the investigation of adrenin problems has been made in the physiological laboratory of the Northwestern University Medical School, using the vasomotor reactions in animals without anesthesia, the operating and recording being carried out under local narcosis. Allowing, however, for the sensitizing effect of cocaine employed in the earlier experiments, no significant differences were detected between the reactions of anesthetized and non-anesthetized dogs.

Possibly Tracy's observation could be made the basis of an experimental technique, using either human or animal subjects. Also Cannon's observation that the denervated heart of an otherwise normal animal is very sensitive to adrenin might possibly be utilized. Other methods might be evolved which would obviate the necessity for anesthesia or immediate trauma.

If so, the whole problem of the pharmacology of adrenin could profitably be re-investigated. Similarly the influence of many factors such as hyperthyroidism and hypothyroidism upon the adrenin reactions should be further studied. Thus various clinical findings and experimental observations might be brought into closer harmony.

ENDOCRINOLOGIA—PATOLOGIA E CLINICA.

By Professor N. Pende. 1916, Pp. 1034, with 147 illustrations. Milan, Vallardi. Lire 35.00.

Prof. Pende's book is much more than a learned compilation of what was known about Endocrinology at the time of its publication. It is a successful effort toward a well balanced systematization where his deep knowledge of the new science is rendered even more interesting by the author's many original and nearly always genial views. Moreover the development is well ordered and the attempt is made to avoid any conclusion not based on well established facts.

The author emphasizes the harmonic action of the endocrine system in the three fields, "neuro-regulator, chemo-regulator and morpho-regulator." Although he believes that the study should comprehend also certain non-endocrine glands Pende deems it necessary, owing to the uncertainties of the new science, to keep within the limits of the purely endocrine system.

Each gland is to be considered potentially able to produce hormones of different qualities, the action of which would not be simultaneous but determined by the needs of the tissues or of the organs. The action of the hormones may be either direct on the cells or mediated through the nervous system.

According to the author there is no such thing as an "anti-toxic action" of the endocrine glands,—understood as a neutralizing action of the hormones on endogenous or exogenous toxins. The effect is obtained through their influence on the metabolism, which may either evoke antibodies from other tissues (bone marrow, lymphoid organs) or stimulate the activity of eliminative organs (liver, kidneys, etc.).

As to direct antagonism between hormones of different glands and their occasional vicarious func-

tion the author is rather skeptical, as he thinks that their action is exclusively determined by the need of the tissues or of the organs. In this way every change of activity on the part of one forces the other endocrine glands to adapt their own activities to the new exigencies created in the organism.

The book includes an intricate diagram illustrating Pende's hypothesis of an endocrine-sympathetic balance, based on a distinction between the "vegetative" and the "animal" systems. There is a certain degree of independence between the two systems; moreover their growth is not simultaneous, but alternating in such a way that, while one grows, it seems to hinder the growth of the other. According as one or the other predominates there may be two distinct types of development: i.e. the *Microsplanic* for the animal life and the *Macrosplanic* when the vegetative life prevails. Some hormones belong either wholly or partially to the one and some to the other system. The functional harmony of the individual organism depends on the balanced functioning of the two hormonal categories.

Intraglandular Hormones—The plurality of different hormones in the same gland is demonstrated for many of them; and the author feels justified in assuming such plurality for all glands in explanation of the apparently contradictory effects which the same gland may produce in the organism.

Endocrine-Sympathetic Relations—Seeing that these two systems are related reciprocally and that their functions are perfectly analogous Pende makes one system of both and calls it the "Endocrine-sympathetic system." Their synergy is shown by the reciprocal action of diseased conditions of either one on the other, and by nervous heredity on the genesis of endocrine diseases, as well as by the influence of glandular heredity on the genesis of sympathetic diseases.

Physio-Pathology of the Genital Internal Secretion—The genital internal secretion is produced by the testis and the ovary; but very likely there is some endocrine activity in the prostate, the mamma and the uterus, also. Besides the endocrine activity of their epithelial elements it seems that the connective tissue may assume the appearance and function of secreting elements, as in case of the myometrial gland of the rabbit and by the interstitial cells of the testis and the ovary.

The interstitial glands appear early in the testis, before any differentiation of sex, and their greater development in the foetus is indicative of a future male development. There seems to be an inverse relation between the growth of the tubular and interstitial tissues, as one is hypoplastic when the other is in full activity.

As for the ovary, though the cells from the epithelial tissue as well as those derived from the connective tissue are both "luteinic cells," the lipoids and functions of the interstitial cells cannot substitute the lipoids and functions of the corpus luteum.

The action of the genital hormones is more decided in conditions of genital insufficiency than in normal conditions. This is to be understood as regards their general action. As for their action on the development of the genital organs they do not determine the sex which is a matter of heredity, but only help to accentuate the differentiation of the sexes. The other hormones (thyroid, hypophysis) do not have any such differentiating action.

Besides the action on the development of the sexual characters the genital hormones influence the development of the skeleton, stimulate the general metabolism and, partially, the nervous system.

Physio-Pathology of the Adrenal System and of the Para-Sympathetic Organs—Pende emphasizes the probable significance of the union of the cortex and the medulla of the Adrenals and claims that

there must be some necessary interrelation of action between the two systems. The connection of the two elements becomes closer the more perfected the organism.

The *carotid gland* is only partially of cromaffine tissue; the *coccigeal gland* does not belong to the cromaffine system.

The author does not admit that the phenomena of sympathetic stimulation, due to fear or anger, are effects alone of adrenal hypersecretion; other glands may concur in this (thyroid).

It is very difficult to judge the action of adrenin from the large doses used in experiments. As for the relation of adrenin to the genesis of atheroma Pende believes that in most of cases it is due to other causes, seeing that the type of the lesion is different. He believes that the accessory cortical tissue and the parasympathetic cromaffine tissue are not able to function adequately in place of the cortex and the medulla of the adrenals. The syndrome of medullary insufficiency is not due merely to deficiency of adrenin in the blood.

Hypophysis and Pineal Gland—The difference between the colloid substance of the prehypophysis and of the neuro-hypophysis is emphasized. The pharyngeal hypophysis is constant in man and is analogous but not identical in its structure with the anterior hypophysis. The lack of differentiation of its tissue and its lack of reaction to changes in the organism, while the anterior hypophysis reacts, demonstrate its minor importance.

The author found in pregnant cats signs of hyperfunction of the anterior hypophysis in the formation of the "gravidic cells" which are never found in the non-gravid hypophysis. They occupy a great part of the tissue of the gland. Pende noted also a hypertrophy of the paraneural layer during pregnancy.

The author considers the *Pineal* an endocrine gland. It is connected by means of medullated nerve

fibres with the diencephalon and with the mesencephalon. As for its secretion there has been found an amorphous transparent substance, grains of a yellow pigment and lipoid granules(?). Besides the hormone action on the organism, some local action through its nervous elements is regarded as probable. Pende calls it a "neuro-glandule," to be classified with the hypophysis and the para-sympathetic glands.

Thyroid.—The colloid substance passes into the lymphatics; this *mobilization* seems to be aided or inhibited by physiologic factors which would act, like those mobilizing the glycogen from the liver, according to the needs of the organism. The excessive accumulation of colloid in the vesicles while there are signs of atrophy or inaction of the epithelial cells shows inactivity and not hyperactivity of the gland. A hyperfunctioning thyroid may be poor in colloids since it is sending them promptly into the circulation. The presence of solid, undifferentiated thyroid epithelium shows hyperfunction. The foetal thyroid is active, though it does not show all the elements found in the thyroid. The thyroid has not only an action on catabolism but also on anabolism.

After removal of the thyroid the growth of the body is not so much hindered as is the growth of the limbs; i. e. the growth of the animal system is more retarded than that of the vegetative system. According to the author the influence of the thyroid is rather on the morphologic evolution of the organism than on the general growth.

The action of the autonomic system (Langley) on the thyroid is twofold. Activity of the para-sympathetic innervation leads to the accumulation of the secretion within the gland; if, on the other hand, the sympathetic is dominating there is more activity and more prompt mobilization of secretion.

Parathyroids.—The importance of the parathyroid lipoids is emphasized. The colloid is like that

of the hypophysis and is eliminated through the blood vessels. It has nothing in common with the thyroid colloid.

In cachexia parathyreopriva, when the removed glands have been grafted successfully so that the condition develops very slowly there is no spasmodophilia.

The removal of the parathyroids creates instability of the thyroid function.

The symptoms caused by the removal of the thymus may be like those of parathyroid deficiency owing to certain functions shared between the two glands, but the function of the one cannot replace the function of the other.

Thymus—We must admit as secreting elements: the lymphocytoid cells, the epithelioid cells of the medulla with their hypertrophic forms, the corpuscles of Hassall and, finally, some peculiar eosinophil elements always present in the periods of activity of the organ.

The pathologic synergy of the thymus with the hemo-lymphopoietic organs is explained by the presence of many more lympho-adenoid and myelo-adenoid elements than in any other endocrine gland.

Pancreas—The author believes that both the tissues, the acinar and the insular, concur in the pancreatic secretion, and that, in pathologic conditions, the one may take the place of the other.

CLINICAL ASPECTS OF THE ENDOCRINE ORGANS

After a thorough semeiologic introduction the author suggests the following diagrams for the puriglandular syndromes and for the monoglandular syndromes.

PLURIGLANDULAR ENDOCRINE SYNDROMES

I—Pluriglandular syndromes with dominating uniglandular syndrome (with form of myxoedema, exophthalmic goitre, acromegaly, etc.)

II—Pluriglandular syndromes given by association of various monoglandular syndromes (myxoedema plus acromegaly plus Addison's disease).

III—Attenuated pluriglandular syndromes, whose type cannot be defined (many of Lorain's infantilisms, some cases of feminism, of attenuated virilism, of neuro-arthritic syndromes, etc.)

IV—Endo-exocrine pluriglandular syndromes (association of hepatic or renal cirrhosis with endocrine syndromes as Basedow's, Addison's diseases).

SUGGESTED CLINICO-PATHOLOGIC CLASSIFICATION OF THE MONO-GLANDULAR ENDOCRINE SYNDROMES.

I—Thyroid—

Athyroidism—Complete myxoedema of adults, Bourneville's myxoedema.

Hypothyroidism—Incomplete myxoedema of adults, infantile incomplete myx-idiocy, paroxistic hypothyroidism, hypothyroidism minimus, mono-symptomatic hypothyroidism.

Hyperthyroidism	}	Harmonic (orthoplastic)—hyperthyroidism, pubertal crises, menstrual crises, temporary emotional hyperthyroidism.
		Disharmonic (metaplastic)—Basedow's syndrome (classic), partial Basedow syndromes, thyroid instability.

II—Parathyroid—

Aparathyroidism—Severe tetany, spontaneous or post-operative.

Hypoparathyroidism—Slight tetany, spasmodophilia.

III—Pituitary—

Apituitarism—Cachexia hypophyseopriva, pathologic lethargy.

Hypopituitarism—Froehlich's dystrophy adiposo-genitalis, nanism, hypophyseal infantilism, hypophyseal feminism.

Hyperpituitarism	}	Harmonic (orthoplastic)—eurythmic gigantism, hyperpituitarism of puberty and of pregnancy.
		Disharmonic (metaplastic)—acromegaly, hypophyseal gigantism and acromegalogigantism.

IV—Adrenal—

Asuprarenalism—Asuprarenalism acute, with sudden death, cholericiform, apoplecticiform, pseudo-peritonitic, myocardic, encephalitic.

Hyposuprarenalism—Syndrome of Addison, periodic asthenia, gravidic hyposuprarenalism, etc.

		Harmonic (orthoplastic)—athletic constitution, and hypertonia.
Hypersupra-renalism	}	cortex — pseudo-hermaphroditism, hermaphroditism of suprarenal origin, virilism, precocious macro-genitosomia.
		Disharmonic (metaplastic)
		medulla — hypertensive crises, temporary glycosurias, arterio-necroses.

V—Genital—

Agenitalism—Syndrome from early castration, syndrome from late castration.

Hypogenitalism—Eunucoidism (geroderma) eunucoid feminism, late hypogenitalism, virilism of ovarian origin, genital obesity.

Hypergenitalism	}	Disharmonic (metaplastic)—Precocious puberty of primitive genital origin with heterosexual symptoms. Chlorosis?
		Harmonic (orthoplastic)—hypergenital constitution, eunucoid precocious puberty, hypergenital nanism.

VI—Thymic—

Athymism—Severe congenital idiocy(?)

Hypothymism—Pedatropy with atrophy and softness of the bones and muscular atrophies(?)

Hyperthymism	}	Harmonic (orthoplastic) — Infantile macrosomia(?)
		Disharmonic (metaplastic) — Status thymicus of young and adults.

VII—Pancreatic—

Apancreatism—Severe lean diabetes.

Hypopancreatism—Slight fat diabetes, alimentary glycosuria, pancreatic obesity.

VIII—Pineal—

Apinealism—Macrogenitosomia precox of pineal origin
pineal cachexia, pineal obesity.

—Giuseppe Vercellini.

ABSTRACTS

1. **(ADRENAL) Capsules surrenales et allaitement. (Supra-renal capsules and lactation.)** Verdozzi. (C.) Arch. Ital. de Biol. (Pisa) 1917, **66**, 121.

The author has studied the changes in the adrenal glands during pregnancy and the following period of lactation in the guinea pig. Animals weighing between 400 and 600 gms. were used. As a basis for comparison, the adrenals of a series of adult virgin females were employed. In these the relation of adrenal to body-weight varied from 1:1000 to 1:1350.

The period of gestation was estimated by the weight and length of the foetus. Twenty-four animals constituted the series in this phase. There was a marked increase in the weight of the adrenals due to hypertrophy of the cortical substance. If, following birth, the guinea pig was hindered from suckling its young, the weight of the adrenal capsules, which, at the moment of birth, was generally higher than the normal weight, diminished rapidly and descended below the average normal figure. If, on the contrary, the guinea-pigs were permitted to suckle their young, the weight of the adrenals increased rapidly, attaining the maximum at the end of about fifteen days. In the latter case it was the cortex which hypertrophied, especially the fasciculated and reticulated zones, the lipoid and pigments increasing.

Because the cortical adrenal substance is developed early in the embryo and increases in volume and apparent activity after birth, especially in the state of gestation, and during nursing, Verdozzi believes that the adrenal cortex is an important factor in the development and general nutrition of the organism.—F. A. H.

2. **(ADRENALS) The function of the suprarenal glands.** Ticken (T.) Med. and Surg. (St. Louis) 1918, **2**, 18-25.
(From Rush Medical College, Chicago.)

A brief historical discussion of the subject with a summary of the author's views as to the present status of the adrenal problem.—R. G. H.

3. **(ADRENALS) A note on some obvious consequences of the high rate of blood flow through the adrenals.** Stewart (G. N.) Am. Jour. Physiol. (Balt.) 1917, **45**, 92.

“From the relatively great quantity of blood passing through the adrenals, it might be expected that the blood of the adrenal veins would differ less from arterial blood than does ordinary venous blood.” Calculation shows that the adrenal vein blood would contain only 1 cc of oxygen per 100 cc of blood less than arterial blood. “Yet a recent writer (Menten; abstracted in this Journal) thinks it worth while to demonstrate that the oxyhemoglobin bands in adrenal vein blood” are stronger than those in jugular vein blood from the same animal.

For the same reason the author takes exception to the statement of Menten and Crile that the increased alkalinity of the adrenal vein blood is due to its adrenalin content. The great flow through the adrenals results in a greater alkalinity than in mixed venous blood; it acquires less CO_2 and is nearer to arterial blood. “It is not easy to gather in what way these writers suppose that the changes in the reaction of the adrenal vein blood is produced by the adrenalin in it.”—T. C. B.

4. **(ADRENALS)** *Über die diagnostischen Verwendung von Adrenalin besonders bei Milztumoren.* Oehme (C) *Deutsches Arch. Klin. Med.* (Leipzig) 1917, **122**, 101.

The lymphocytosis caused by adrenin is not a reaction only of the lymphoid tissue in the spleen, but of the lymphoid system generally, especially in the abdomen; the action of vegetative nerves also plays a part, the contraction of smooth muscle forcing the cells into the blood stream. The diminution in size of the spleen which occurs after adrenin is of diagnostic value in tumors of left hypochondrium.—Physiol. Abst.

5. **(ADRENIN)** *Die Beziehung der Nebennieren zur Piqure.* Biberfeld (J) *Arch. exp. Path. Pharm.* (Leipzig) 1916, **70**, 164.

In rabbits diuresis occurred, but there was no effect on carbohydrate metabolism either on piqure or on injection of adrenin.—Physiol. Abst.

6. **(ADRENIN)** *Über den Adrenalinegehalt der Nebenniere des Menschen.* Lucksch (F.) *Virchow's Archiv.* (Berlin) 1917, **223**, 290.

The total amount of adrenin in both adrenals is about 8 mgs. or 4 mgs. per gram of gland. Various diseases lower this, especially infectious diseases; the smallest quantity found was in Addison's disease, the largest in nephritis.—Physiol. Abst.

7. **ADRENIN.** *Vasodilator mechanisms in the cat at different ages.* Hartman (F.) and Kilborn (L. G.) *Am. Jour. Physiol.* (Balt.), 1918, **45**, 111.

The authors accidentally discovered that adrenalin in any dose fails to cause a fall in blood pressure in kittens. The only reaction is a rise. "As the fall in blood pressure is controlled by a central nervous mechanism, the failure of this mechanism to develop at an early age might account for the reaction in young kittens."

The results of observations on young kittens may be summarized as follows: The smallest effective dose of adrenalin causes a rise of pressure in young kittens, and the threshold is high. The response by a fall of pressure begins at about eleven weeks, and the mechanism is gradually developed. The fall of blood pressure is due to vasodilatation in the museles. The intestinal dilator mechanism often develops later than the limb mechanism, thus supporting the view that the two mechanisms are different. (See also "Adrenalin Vasodilator Mechanisms." Hartman, in this issue.)—T. C. B.

8. ADRENIN, Some actions of, upon the liver. Bainbridge (F. A.) and Trevan (J. W.) *Jour. Physiol. (Lond.)*, 1917, **51**, 460.

The authors have already shown that a slowly continuous injection of adrenin causes obstruction of the blood flow through the liver, and if the obstruction is prolonged the animal passes into a condition of shock. The present paper gives the methods employed, and describes the immediate effects of adrenin upon the blood flow in the liver.

The partial pressure was recorded from the splenic vein and the vena cava pressure from the illiac vein. The recording manometer was filled with 3.5% solution of sodium citrate:

When adrenin is injected either into a systemic vein or into a radicle of the portal vein, there is a rise of portal pressure, increase of the volume of the liver, and an increased flow of lymph from the thoracic duct. There is little or no alteration in the vena cava pressure. These effects are due to some obstruction of the blood flow from the liver, caused by the adrenin.

From theoretical considerations, as well as from the results of injecting distilled water, the authors think the obstruction may be due to a "narrowing of the capillary channels by swelling of the columns of liver cells, although the evidence does not warrant a definite conclusion."—T. C. B.

9. (ADRENIN) Beiträge zur Physiologie der Drüsen, Leon Asher. XXVII. Untersuchungen über die Automatie des Schleiendarmes und deren Beeinflussung durch Adrenalin. Backman (E. L.) *Ztschr. f. Biol. (München)* (1917) **67**, 307.

In experiments with the isolated intestine of the fresh-water fish *Cyprinus tinca*, automatic movements were maintained for an hour in oxygenated Tyrode's solution of half the usual calcium content. Large slow contraction lasting several minutes and a smaller series were observed. Pure adrenin 1:20,000,000 had an inhibiting effect on the automatic movements. In the preparation hemostasin, however, weak concentrations stimulated the contractions owing to the presence of chloretone, inhibition occurring with higher concentrations. Pilocarpine augmented the tonus and contractions of the intestine. The fish intestine is presumably provided with a sympathetic inhibiting and parasympathetic augmenting, nervous mechanism. Adrenin does not affect the muscular contractions produced by direct electrical stimulation.—*Physiol. Abst.*

10. (ADRENIN) Neosalvarsanexanthem und Adrenalinwirkung. (Exanthema caused by neosalvarsan and the influence of adrenin.) Nageli (O.) *Cor.-Bl. f. schweiz. Aertze (Basel)*, 1917, **47**, 1291.

A very remarkable case is described. A patient, fifteen minutes after an injection of 150 mgs. of neosalvarsan developed an exanthema. Twenty minutes later this exanthema had disappeared. Each time after injection of neosalvarsan the exanthema reappeared.

If, however, adrenin was injected first and some minutes later the injection of neosalvarsan was given, no cutaneous reaction was observed. The dose of adrenin required to prevent the reaction depended upon the dose of neosalvarsan; 0.5 mgs. adrenin was enough to prevent it when 300 mgs. neosalvarsan was injected. When, however, 600 mgs. neosalvarsan was injected it was necessary to inject one mg. of adrenin to avoid the exanthema.—*J. K.*

11 (ADRENIN) The alleged relation of the epinephrin secretion of the adrenals to certain experimental hyperglycemias. Stewart (G. N.) and Rogoff (J. M.) *Am. Jour. Physiol. (Balt.)* 1917, **44**, 543.

The view has been expressed that perhaps most of the forms of experimental hyperglycemia (asphyxia, pique, etc.) are dependent primarily upon excitation of the adrenals to increased secretion of epinephrin, thereby mobilizing the sugar, as does adrenalin when artificially introduced. The fact that subcutaneous injections are more effective is against this idea, and the experimental basis for these conclusions is quite unsatisfactory, for they are made on dying animals (practically) due to the removal of the adrenals, or on animals suffering from a major operation and anesthesia.

The relation of epinephrin secretion to hyperglycemia can be better investigated by the method of removing one adrenal and sectioning the nerves of the other. In this way the secretion is abolished, while the animals remain indefinitely in good health.

Using this method it is found that hyperglycemia associated with asphyxia or anesthesia can be obtained just as well as in cats that have not undergone the operation. There seems to be no essential difference between operated and control animals.

Observations on "emotional hyperglycemia" do not support the view that this condition is a constant or even a common phenomenon in cats.—T. C. B.

12. (ADRENIN) Studien über antagonistische Nerven. XIII. Die Wirkung des Adrenalins auf die Gefäße der Niere des Frosches und die Veränderungsfähigkeit dieser Wirkung. Zuckerstein (S.) Ztschr. f. Biol. (München) (1917) 67, 293.

In eleven experiments in which the glomerular capillaries of the frog's kidneys were perfused by methods used in Asher's laboratory, via one of the aortic arches, with hemostasin and Ringer's solution, the drop number diminished from 74 to 45 per cent. By the substitution of physiological salt for Ringer's solution, i.e., in the absence of calcium—the constricting effect of adrenin was abolished or much diminished. A repetition of these experiments on the tubular capillaries of the kidney perfused via the posterior vena cava was entirely negative, although the vessels responded to barium chloride by vigorous contraction. The failure of these vessels to react with adrenin points to the absence of sympathetic innervation. After complete section of all the visceral nerves in three frogs, adrenin caused dilatation of the glomerular vessels, although barium chloride still caused constriction. Presumably adrenin acts on the neuroplastic end organs, which exhibit unusual conditions of excitation in early nerve degeneration. The results confirm the findings of Roy Pearce in another vascular area of the frog.—Physiol. Abst.

13. (ADRENIN) L'hyperglycémie et la glycosuri adrénaliques. (Hyperglycaemia and adrenalin glycosuria.) Phocas (A.) C. R. Soc. de Biol. (Paris) 1917, 80, 938.

Adrenalin hyperglycaemia can be produced in rabbits deprived of their glycogen by fasting. Phocas suggests as an explanation of this the action of hepatic diastases upon substances other than glycogen (lipoids, glycoproteids) resulting in the formation of glucose. He assumes that adrenalin increases the quantity of hepatic diastases.

He determined the urea and phosphates of the urine of two starving rabbits before and after adrenalin injection. He found these notably increased on the second day after the injection, when the sugar disappeared from the urine. He believes that the glucose came from a large molecule, the nitrogen and phosphorus of which was excreted only after a final elaboration.—F. A. H.

believes that the glucose came from a large molecule, the nitrogen and phosphorus of which was excreted only after a final

14. **(CORPUS LUTEUM)** The existence of a typical oestrus cycle in the guinea pig with a study of its histological and physiological changes. Stockard (C. R.) and Papanicolaou (G. N.) *Am. Jour. Anat. (Phila.)* 1917, **22**, 225.

The authors have found from daily examination of the vagina of living animals and from microscopical studies that the guinea-pig has a regular dioestrus cycle lasting twenty-four hours and occurring every sixteen days. They conclude that the corpus luteum has a protective influence over the mucosa of the uterus and vagina since there is a parallel degeneration and development in all three organs. Ovulation was found to occur during every heat period. Absence of corpora lutea permits degeneration of the uterine epithelium.—E. R. H.

15. **DIABETES INSIPIDUS**, Maranon (G.) *Siglo Médico (Madrid)* 1917, **64**, 36.

The study of three cases confirms the modern view of the importance of the pituitary body in the genesis of diabetes insipidus. In one boy of three years of age, diabetes insipidus developed a few days after he had been shot in the head, the bullet lodging in the sella turcica and blocking the egress of the pituitary secretion. Treatment with pituitary extract alone relieved the symptoms.—Physiol. Abst.

16. **DIABETES INSIPIDUS. Neue Theorie des Diabetes Insipidus (A new theory of diabetes insipidus.)** Grundmann. *Berl. klin. Wehnsehr. (Berlin)* 1917, **No. 31**.

The cause of diabetes insipidus is, according to Grundmann, very complicated. The author found symptoms of vagotonia and of a paralyzed sympathetic system. To understand the whole complex of symptoms it is necessary to believe in an abnormality of the endocrine system. The function of the hypophysis is increased, as is also the internal secretion of the pancreas. These hormones produce an increase of the function of the adrenals and of the thyroid gland. Therefore a therapeutic agent consisting of hypophysis extract alone cannot relieve these cases.

The theory of Grundmann, "increased adrenal function with a paralyzed sympathetic system," sounds a little bit too theoretical. If this theory were right hypophysis extract alone would increase the symptoms; clinical experience has led to an opposite conclusion.—J. K.

17. **ENDOCRINE GLANDS**, Studies on. I. The relation between the pancreas and thyroid and parathyroid glands. II. The relation of the pituitary body with the thyroid and parathyroid and certain other endocrine organs in the rat. III. The effects on the thyroid and parathyroid of the rat of administering thyroid extract and certain other autacoids and salts. IV. The effects in the dog upon the remainder of the thyroid and parathyroid of partial removal of those organs. V. Effects upon metabolism of castration, of thyroidectomy, of parathyroidectomy, and of thyroid and parathyroid feeding. Kojima (M.) Quart. Jour. Exp. Physiol. (Lond.) 1917, 11, 255-351.

A series of papers dealing with the effects of extracts of certain endocrine glands upon other organs. The point of view is largely histological.

The first paper deals with changes produced in the pancreas by feeding thyroid and parathyroid. After a week of thyroid feeding the pancreas of the rat shows typical changes; the alveoli are smaller, the alveolar cells are smaller, the nuclei vary in size and staining capacity, the cytoplasm of the cells contain comparative little zymogen, and there are many mitotic figures, indicating rapid multiplication. After an intermission in the thyroid feeding these changes disappear.

The addition of small ox-parathyroid to the daily diet causes no marked changes in the pancreas. In all the experiments the islets of Langerhans were unaltered. There are no differences due to sex.

A second thyroid feeding following the first after an interval seems to have less effect than the first.

After feeding for some time (about a month), mitoses are no longer seen, and the zymogen granules are again plentiful. The cells are still vacuolated.

The effects produced by feeding thyroid gland are also observed after administering water-extracts, both unboiled and boiled, and after giving the residue from these extracts. Alcohol and ether extracts have no effect, but the residue causes changes similar to those obtained by feeding thyroid.

Castration appears to have no effect upon the structure of the pancreas nor to influence the effect of feeding thyroid.

An artificial combination of iodine with protein has no effect. Of the various salts of iodine, the sodium salts seem

to produce the most marked effect, the most interesting change being the production of mitosis in the alveolar cells. This effect is not obtained when the rats have been previously thyroidectomised: the effect is probably an excitation of the gland. The effects due to pilocarpine, adrenalin, pituitary body, known to be glandular excitants are different. The original paper should be consulted.

The mouse gives similar results to the rat, but in the cat, dog, rabbit, guinea pig and bird, mitoses have not been seen. There is, however, a disappearance of zymogen granules from the alveolar cells.

The second paper deals with the effects on the pituitary of thyroidectomy, parathyroidectomy both complete and partial, and of castration.

Thyroidectomy causes the appearance of a number of large swollen cells in the pars anterior. To a less extent this is true of parathyroidectomy. Castration also has the same effect. The paper should be read for detailed descriptions of the histological appearances.

The third paper discusses the effects on the thyroid and parathyroids of administering thyroid extract and other autoids* and salts. Administration of thyroid and of sodium and potassium iodides causes an accumulation of colloid in the vesicles of the thyroid of the rat. The cells of the parathyroids are generally swollen. Posterior lobe of the pituitary causes a swollen, barrel-like appearance of the epithelial cells of the thyroid. The structure of the parathyroids becomes loose. The cells are swollen and the nuclei shrunken. Adrenalin causes somewhat similar changes.

The fourth paper gives the microscopic appearances of the thyroid and parathyroids after partial thyroid and parathyroidectomy. The remaining portion of the thyroid undergoes proliferation of its epithelial cells, and the vesicles show marked polymorphism. There is little or no change in the parathyroids.

The effects of the thyroid and parathyroids, and of castration upon metabolism, are described in the fifth paper. Thyroidectomy in rats produces a diminution of both nitrogen and calcium output.

After parathyroidectomy in rats there seems to be an increase of calcium in the urine, and less is retained in the body, but nitrogenous metabolism shows no definite change.

Thyroid feeding produces a decrease in body weight and a diminution of nitrogen and gaseous metabolism in all animals, whether normal, thyroidectomised, or parathyroidectomised.

*Schaefer's term for stimulating hormones.

Castration is attended in male rats by diminution of CO_2 output.—T. C. B.

18. **ENDOCRINE organs in dementia praecox.** Kojima (M.) Proc. Roy. Soc. Med. (Lond.) 1917, 10, 88.

The thyroid tends to hypofunction in the male and to hyperfunction in the female. The sexual glands and adrenals are small in the female. The testes show only slight spermatogenesis. In the male the parathyroids contain clear watery cells and a few eosinophil cells; in the female the latter are abundant.—Physiol. Abst.

19. **(ENDOCRINE ORGANS) Beziehungen zwischen endokrinem System und Konstitution.** (Relation between the endocrine organs and constitution.) Hart (C.) Berl. klin. Wehnschr. (Berlin) 1917, 54, 1077.

Contains nothing new.—J. K.

20. **(ENDOCRINE GLANDS) Le alterazioni delle ghiandole endocrine (specie del timo) e del sangue in seguito alla vagotomia.** (The alteration in the endocrine glands [especially the thymus] and in the blood following vagotomy.) Pighini (C.) Patologica (Genova) n. 180, 1916.

The author of this experimental work comes to the following conclusions:

1. Chickens may live four-five days or more after the vagotomy; guinea pigs no more than four hours.

2. Among the effects of the vagotomy we must distinguish those due to the alterations of the respiration and of the circulation from those due to the lack of influence of such nerve on certain glands or systems.

Hypophysis, thyroid, the cromaffin tissue show hyperfunction. The thymus and spleen show atrophic conditions (especially the thymus of the chicken, which undergoes lipid degeneration, seen also in the cortex of adrenals, ovary and testis and marrow of long bones).

There is also to be found a greater number of neutrophiles and lymphocytes, while the eosinophils are diminished.

3. The thymus, spleen, cortex of adrenals, interstitial cells of the testis and ovary and bone marrow have their internal secretion under the control of the vagus.

4. Hence by suppressing the vagi there is a predominance of the sympathetic system, demonstrated by the hyperactivity of the cromaffin tissue, thyroid and hypophysis and by increase of adrenalin in the blood. (S. Maggiore in La Pediatria, Jan., 1917.)—G. V.

21. **ENDOCRINOLOGY, clinical, in general practice.** Harrower (H. R.) *Med. and Surg. (St. Louis)* 1918, **2**, 41.

This article presents two outstanding features—an emphasis of the importance of endocrine disorders in every-day practice, and some dubious endocrine theorizing. As examples of such may be mentioned the statements that the adrenals control the action of the sympathetic system, that a continued state of “hyperadrenia” is possible (it would involve intestinal paralysis) and that adrenal exhaustion is frequently the final cause of death in severe infections. The article as a whole, in common with much of the endocrine literature, includes an amount of “explaining,” which engenders a distrust of the subject matter itself.—R. G. H.

22. **GAUCHER'S DISEASE. A report of two cases in infants.**

Knox (J. H. M., Jr.), Wahl (H. R.) and Schmeisser (H.C.) *Bull. Johns Hop. Hosp. (Balt.)*, 1916, **27**, 1.

The paper opens with an analysis of the symptoms and findings in 16 cases of Gaucher's disease reported up to 1916. This is followed by a report of the cases of two infants, sisters, who did not thrive from birth and died, one at 11 months, the other at 15 months of age, from gradually increasing weakness. The striking clinical feature was the great enlargement of the spleen and liver. The blood picture showed moderate anemia. The leucocytes were rarely increased, and for the most part were markedly reduced in number. The skin in both cases had a peculiar yellowish-brown hue, more marked on the exposed surfaces. Microscopically, in both cases nearly all the organs were found to contain large, pale, granular or finely vacuolated cells, in which there was a peculiar refractive substance having the chemical and staining properties of lipid material. Because of these findings the authors conclude that their two cases represent true specimens of Gaucher's disease.

The author's cases demonstrated a unique implication of the medulla of the adrenal glands, that the Peyer's patches and thymus were equally involved and that there was a general and diffuse distribution of the characteristic large cells; probably a manifestation of one and the same process, which in infancy is apt to be more rapid and widespread.

The conclusion is drawn that there is no evidence that the large pale cells characteristic of the disease are derived from any one particular tissue cell, but rather that different tissues may produce the same type of cell. It is primarily the endothelial cells lining the small lymph sinuses and the cells of the reticulum that become transformed into these characteristic large vacuolated cells, and of these (author's cases) the rec-

ticular cells of the lymph-adenoid tissue appeared the most susceptible. Hence it would appear that Gaucher's disease is not primarily a disease of the spleen or of any other organ or set of organs, but is a generalized process due to a disturbance in fat metabolism, manifesting itself by a more or less diffuse accumulation of lipid material in many cells, especially those of the hematopoietic system, with the formation of characteristic large pale cells.—H. W.

- 23. GAUCHER'S DISEASE, the cases of.** Reported by Drs. Knox, Wahl and Schmeisser. Mandelbaum (F. S.) and Downey (H). Bull. Johns Hopkins Hosp. (Balt.), 1916, **27**, 109.

The article is a critical review of the two cases reported by Drs. Knox, Wahl and Schmeisser in the Johns Hopkins Hospital Bulletin, 1916, **27**, 1—abstracted elsewhere. From a careful consideration of the report and a thorough study of materials sent them by Dr. Wahl they conclude that the cells found and described by Drs. Knox, Wahl and Schmeisser are not the characteristic cells of Gaucher's disease, either as to their origin, structures or staining powers but rather represented typical cells found in cases of lipoidemia. After giving the origin, structure and staining power of characteristic cells found in cases of Gaucher's disease and comparing them with the two cases under consideration and certain other cases they state: "That a widespread cellular hyperplasia associated with degenerative changes in many organs, exists, is not denied, but we do insist that the cases are not to be classified with a well recognized disease, definite in its clinical manifestations and always accompanied by characteristic changes in a specific group of cells."—H. W.

- 24. (GOITER). Warnung vor Thymol bei Kropfkranken** (Warning against Thymol in cases of goitre). Edens (E) Med. Klinik (Berlin), 1917, **13**, 807.

Edens saw two cases in which there was a goiter, which became toxic after the administration of thymol. In the first case the patient died, in the second one the patient recovered when she discontinued the use of a mouth water containing thymol.

Both patients were very nervous and lost weight as long as thymol was used.

Edens points out that the influence of thymol on experimental goiter was previously noted by McCarrison (Quart. Jour. Med., 1909).—J. K.

- 25. GROWTH. Patologia della crescita** (Pathology of growth). Marotta (A.). Libreria Detken (Napoli), 1914.

1. Diseases and abnormalities of the growing period are more numerous than is apparent.

2. They almost always occur between the ages of 2 and 16 years.

3. As predisposing conditions, heredity, urban life, insufficient food and unhygienic surrounding are important.

4. A very great influence is exerted by the endocrine glands.

5. The critical period is puberty. (S. DeStefano in *La Pediatria*, Feb., 1917.)—G. V.

26. (**HORMONES**). A bit of hormonology, with practical applications. Tracy (E. A.). *Med. and Surg.* (St. Louis), 1918, 2, 35.

The article opens with the statement that "Epinephrin is a normal constituent of the blood." This is followed by a page of quotations from Falta of statements of various degrees of credibility which the author believes "clinicians will accept as presenting succinctly most of what is known of epinephrin activities." This belief the reviewer does not share.

Then follows an elaboration of a theory that the functioning of the autonomic nervous system is dependent upon and mediated through the presence of adrenin and pituitrin on the one hand and of thyroid, thymus and lymphoid tissue hormones on the other. For a discussion of the chief objections to this theory the reader is referred to Vincent's Critique on "Vagotonia" in the preceding number of "Endocrinology." One outstanding fallacy is the assumption that all vasoconstrictor fibers are sympathetic and all vasodilators, parasympathetic. The single fact that adrenin causes the capillaries of skeletal muscle to dilate serves to render the whole theory untenable.

The article further records some interesting observations upon the pharmacology of adrenin. It is stated that 1 to 3 drops of this substance placed under the tongue two or three times a day is sufficient materially to augment the cutaneous vasoconstrictor reflex to stroking.

The suggestion is offered that the sublingual route would be much more satisfactory for the administration of pituitrin in obstretrical practice than is the hypodermic route, since much better control would be possible.—R. G. H.

27. **HYPERTHYROIDISM in the recruit.** Brooks (H.) *Jour. Am. Med. Assn.* (Chgo.) 1918, 70, 728.

(From Camp Upton Base Hospital.)

The author expresses surprise at the high incidence of hyperthyroidism among young male adults in the recruiting camps. The most prominent symptom is tachycardia, rarely

accompanied by arrhythmia. The rate is nearly always increased by exercise. Throbbing of superficial arteries is common, as is other evidence of cardio-vascular perturbation. The blood pressure is very low except in hypersensitive patients. Adrenin causes augmentation of the symptoms and there is an apparent hypersensitiveness to thyroid. Emotional instability is a very common manifestation.

In about two-thirds of the cases a definite hypertrophy or prominence of the thyroid is seen. Heredity plays a certain part in the syndrome. A considerable proportion of the subjects report a family history of goitre—usually maternal—and in most instances there is a family history of hysteria, insanity, perversions or genius. Exophthalmos is seen in the long-standing cases. In short, all the cardinal symptoms of exophthalmic goitre are present.

Many of the patients recover under the healthful and normal routine of camp life. Recreation and freedom from mental distress are important factors in recovery.—R. G. H.

28. (HYPOPHYSIS) The cell-changes in the hypophysis of the albino rat after castration. Addison (W. F. H.) *Anat. Rec. (Phila.)* 1917, **28**, 441.

Castration in the male rat is followed shortly by permanent alterations in the glandular portion of the hypophysis. There results a hypertrophy of the gland, an increase in the blood supply of the ventral lobe and an increase in the production of colloid. The basophiles and acidophiles of the ventral lobe which apparently are continually being differentiated from a common type of cell (reserve cell) that persists throughout life, are seriously affected, the former increasing in number and size, and undergoing vacuolar degeneration; the latter seemingly "de-differentiating" into reserve cells. The author regards the changes in the hypophysis as due to loss of the interstitial cells of the testis.—E. R. H.

29. (HYPOPHYSIS) Aus Hypophysengewebebestehender retropharyngealen Tumor. (A retropharyngeal tumor consisting of tissue showing the same structure as the pituitary body.) Leegaard (F.) *Arch. f. Laryngol. (Berlin)* 1917, **31**, No. 2.

Description of a case. The tumor was examined microscopically, and showed itself an adenoma. The author suggests the idea that these tumors can take their origin from little isles of tissue showing a pituitary structure. Normally such islands are always to be found in the wall of the pharynx.

—J. K.

30. (**HYPOPHYSIS**) Case of dyspituuitarism in a girl aged 15. Stephenson (S.) Brit. Jour. Chil. Dis. (Lond.) May, 1916.

A girl of fifteen offers simple bilateral optic atrophy, diminished power of vision of the left eye (5/36), sella turcica much greater than normal, absence of menstruation and of hair on the pubis. Given thyroidic therapy from 2 to 4 grm. a day, but without result. (From Abst. in *La Pediatria*, Feb. 1918.)—G. V.

31. (**HYPOPHYSIS-DIABETES**) Diabetes mellitus und acromegalie. Steiger. Ztschr. f. klin. Med. (Berlin) v. 74, 324.

Steiger has observed five cases of acromegaly in two of which he found symptoms of diabetes. The combination of acromegaly and diabetes is not very rare. One of Steiger's patients died in diabetic coma; at the post mortem examination a tumor of the hypophysis and an increase of the connective tissue of the pancreas were found. The adrenals and the thymus were enlarged; there was a goitre and atrophy of the genitals.

Contrary to this there have been described cases of acromegaly and diabetes in which the pancreas showed a normal aspect. Therefore, Steiger concludes that it is incorrect to believe that the only cause of diabetes is an abnormality of the pancreas. Every disease he states, which disturbs the equilibrium of the endocrine system, may cause diabetes mellitus.—J. K.

32. (**HYPOPHYSIS**) The active principle of hypophyseal extracts. Houssay (B. A.) *La Prensa Med.* (Buenos Aires) 1915, No. 5, p. 82. Correction, *Endocrin.* 1917, 1, 393.

The active principle of the hypophysis is not by any known method obtainable pure and unaltered. The pharmacodynamic substance of hypophyseal extract is not the actual potent secretion.—B. A. H.

33. (**INTERNAL SECRETION**) A further contribution to the metamorphosis of Amphibian organs. The metamorphosis of grafted skin and eyes of *Amblystoma punctatum*. Uhlenhuth (E.) *Jour. Exp. Zool.* (Phila.) 1917, 24, 237.

The author shows conclusively that two organs at least (skin and eye) are dependent for their full development upon some non-specific internal secretion which may be an agent like thyroid substance. In the experiments performed, pieces of skin and eyes of *Amblystoma* larvae were grafted onto larvae of the same and of other species. These grafts developed their own color markings but did this only if and when

the host metamorphosed, whether the host were younger or older than the animal from which the organs were taken.—E. R. H.

- 34. (INTERNAL SECRETIONS) Uremia and the internal secretions.** Remond and Minvielle. Bull. Acad. Med. (Paris) 1917, 77, 105.

Extracts of liver and thyroid were injected into animals; these bore the subsequent injection of human uremic serum better than controls did. The extracts also afforded a certain degree of protection against cantharides nephritis.—Physiol. Abst.

- 35. ORGAN EXTRACTS, effects of, on the contraction of voluntary muscle.** Rogers (J.), Coombs (Helen C.) and Rahe (Jessie M.) Am. Jour. Physiol. (Balt.) 1918, 45, 97.

A continuation of studies, some of which have been previously abstracted in this journal. This paper deals with the effect of the "residue" of various endocrine glands on striated muscle.

Residues from the thyroid, parathyroid and adrenal glands have the power of re-energizing fatigued muscle. Liver, spleen, ovary and pancreas do not have this effect, nor does the "coagulable" portion of the extracts of any of the glands.

Hypofunctioning of the thyroid and adrenals (and probably other endocrine organs) is accompanied by muscular weakness, and the authors think their results are significant from this point of view.

Excision of the thyroid seems to have no immediate effect upon the fatigability of striped muscle.—T. C. B.

- 36. (OVARY) Treatment of certain forms of asthma with ovarian substance and corpus luteum.** Fishberg (M.) Med. and Surg. (St. Louis) 1918, 2, 26.

(University and Bellevue Hospital Medical College.)

The article is an admirable variant from what we have learned to expect under such captions. After a brief discussion of possible endocrine factors in asthma, the author engagingly emphasizes the fact that in only a minority of his cases were favorable results obtained and that no adequate basis for theorizing is afforded.

Several illustrative cases are described.

The article concludes with a resumé: "Some cases of asthma in women are favorably influenced by ovarian therapy. In most of these cases there may be observed some relation between the asthmatic paroxysms and the generative functions. In some the attacks are ameliorated during preg-

nancy or menstruation; in others the paroxysms are more apt to occur, or are more severe when the patient is menstruating. In many cases of asthma occurring during the menopause, natural or artificial, the administration of ovarian substance relieves the dyspnea along with other symptoms of the menopause. Ovarian substance, or corpus luteum, in moderate doses may, in these cases, act specifically, ameliorating the attacks or preventing their recurrence. Most of these patients seem to have a peculiar intolerance to the derivatives of opium which aggravate the asthmatic attacks and make them sick otherwise."

From the showing made in Fishberg's cases the treatment of asthma by ovarian substance would seem to be deserving of further critical study.—R. G. H.

37. (PARATHYROIDS) Tetany and the parathyroid glands.

Koch (W. F.) *Med. and Surg.* (St. Louis) 1918, 2, 9.

(From the Detroit College of Medicine and Surgery.)

This article is a discussion of the physiology of the parathyroid glands from a physico-chemical point of view. It begins with a section devoted to theoretical considerations which appeal to the reviewer as being, like many other physico-chemical discussions of biological topics, mostly an expanded paraphrase of admitted facts couched in an obtruse terminology.

Theoretical considerations aside, however, the article affords an admirable discussion of the present-day status of the parathyroid problem. It develops particularly a claim first put forward by Koch in 1913 that the essential feature of parathyroid deficiency is an intoxication due to the accumulation in the body of guanidin bases. Koch's findings have since been confirmed by Paton and his collaborators. On the basis of all available evidence it is maintained that the cause of parathyroid tetany is a guanidin intoxication of the central nervous system and the myoneural junctions.

A mother substance from which the guanidin may be formed is cyanamide, a body which may be recovered in methylated form from the urine of parathyroidectomized dogs. The cyanamide can readily take up ammonia to form guanidin. If not so converted to guanidin the cyanamide is readily hydrated to form innocuous urea.

Ammonia is normally excreted in combination with various acid radicals. According to Koch's view it is the route of disposal of ammonia, which is the determining feature in the causation of tetany. Anything which increases the acid content of the body would serve to deplete ammonia and hence decrease guanidin formation. The actual occurrence of tetany itself, by liberating lactic acid would thus tend to

check guanidin formation, and for the time being serve as a detoxicating mechanism. A full development of this conception would involve a consideration of the whole complicated matter of acid-base equilibrium of the body. One interesting feature of the hypothesis is its explanation of the mechanism whereby augmented protein metabolism, by increasing ammonia production, aggravates parathyroid tetany.

The fact that calcium salts alleviate tetany is explained on the ground that they decrease the permeability of the body cells and hence the taking up by them of guanidin.

On the other hand an increased excretion of lipoids by augmenting cell permeability increases guanidin intoxication.

The least convincing feature of the paper is a hypothesis that the body cells normally produce methyl cyanamide as a "hook," which they are able to dispatch to the parathyroids to obtain a supply of hormone necessary to their welfare.

The following therapeutic deductions are offered: Neither parathyroid grafts nor the administration of parathyroid substance are of much promise. Palliative methods are, therefore, alone generally possible. These are the administration of calcium—which has a limited usefulness—and administration of sufficient acid to depress the level of available ammonia below that necessary in the formation of guanidin. Only enough acid should be used to maintain "electric neutrality" of the blood.

The article is difficult to abstract and the original deserves the careful consideration of those who are interested from any point of view in the parathyroid glands.—R. G. H.

38. (PINEAL) The development of the paraphysis and pineal region in mammalia. Warren (J.) *Jour. Comp. Neurol.* (Phila.) 1917, 28, 75.

A technical account of the development of the paraphysis and pineal body in man and other mammals.—E. R. H.

39. (PINEAL GLAND) Die Glandula Pinealis. (The Pineal Gland.) Uremura. *Frankfurt. Ztschr. f. Path.* (Wiesbaden) 1917, 20, No. 3.

A very complete study on the histology of the pineal of the pineal gland (nothing new).

The author believes that there is a relation between the gland and the anterior lobe of the pituitary.

On some cases of adiposity the pineal gland and the anterior lobe of the pituitary were very large. In one case of gland. The author found brain sand in this gland in a child as young as four years. Description of three cases of tumor atrophy of the pineal gland there was also atrophy of the anterior lobe.—J. K.

40. (SEX) Sex studies. IX. Interstitial cells in the reproductive organs of the chicken. Boring (A. M.) and Pearl (R.) Anat. Rec. (Phila.) 1917, 13, 253.

Interstitial cells were found in ovaries of adult chickens, but not in those newly hatched. They were found in testes of male chickens just hatched, but not in adults. The authors point out that absence of interstitial cells of the testis has been noted in many different mammals. They do not consider the testicular interstitial cells necessary for the male domestic fowl. They question the theory of the relationship between such cells and sex characters.—E. R. H.

41. (SEX) The early history of the germ cells in the armadillo, *Tatsuia novemcincta*. Vanneman (A. S.) Am. Jour. Anat. (Phila.) 1917, 22, 341.

The germ cells in this form arise in the blastocyst close to the endodermic wall probably from the cells of this endoderm and then push in the endoderm of the future fore gut. In the 4 m.m. stage they leave the endoderm, and migrate along the mesentery and then enter the gonad. Germ cells were never found within the blood vessels.—E. R. H.

42. (SEX GLANDS) Ein Fall von Kongenitaler Anorchie. (A case of congenital anorchidism.) Wildholz (H.) Cor.-Bl. f. schweiz. Aertze (Basel) 1917, 47, 1307.

There have been described seven cases in which people were born without testes. Wildholz publishes the eighth case of congenital anorchidism. The patient, a man of twenty years, showed a great development of the subcutaneous fat. The secondary sexual characteristics were not developed; the penis had the dimensions of that of a boy of 6-7 years. There was no prostate to be found. The X-ray photograph of the hand showed still detached epiphyses. The X-ray photograph of the skull showed an enlargement of the sella tursica.—J. K.

43. (SEX GLANDS) Die Steinachschen Forschungen über Pubertätsdrüsen und Geschlechtsmerkmale I, II. (The experiments of Steinach on the transplantation of the sex glands.) Boruttan (H.) Deutsche med. Wehnschr. (Berlin) 1917, 43, 1454, 1484.

In this paper Boruttan describes the experiments of Steinach. Steinach transplanted ovaries in castrated males and testes in castrated females. The effect was that the animals changed their character; the male developed a female type, the females behaved like males. Steinach observed these animals for more than three years and saw that the males with ovaries were still smaller and had thinner bones than their

sisters. The females with testicles were much larger and had much heavier bones than the normal males. Steinach calls this "hyperfeminirung" and "hypermaskulirung."

Following Steinach's work transplantation of testicles into men who had lost these organs was attempted. The results have been brilliant; the psychical symptoms disappeared, the potency returned. (Lespinasse has made a similar observation.—R. G. H.)

Another very important experiment was carried out by Steinach. He exposed young animals to very small doses of Röntgen-rays; these worked as a stimulant; the mammary glands, the uterus and the fallopian tubes showed an enormous hypertrophy. The Graeffian follicles had disappeared and the connective tissue between them showed hypertrophy.

In a case of sexual precocity in a rat it was found that the hypophysis and the pineal gland were absolutely normal.

The experiments carried out by Steinach have proved that the hormones of the testis and ovaries have an antagonistic action. Steinach has castrated very young guinea pigs and then transplanted the testis and the ovaries in the abdominal muscles of one guinea pig. These animals were in most cases true hermaphrodites; they have testes and at the same time normal female mammary glands.

Immediately after this operation the guinea pig behaves like a male, but after some weeks he first becomes sexually indifferent and at last his behavior is perfectly female. This is followed again by indifference. About three months after the operation the masculine sexual characters return. These alternating sexual periods go on during the life of the animal.—J. K.

44. (SPLEEN) The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. **XIV. Changes in the blood following diversion of the splenic blood from the liver. A control study of the effects of splenectomy.** Krumbhaar (E. B.), Musser (J. H.) and Peet (M.M.) *Jour. Exp. Med.* (N. Y.) 1916, **23**, 87.

Dogs whose splenic veins have been ligated or transplanted into the inferior vena cava, or in which an Eek fistula had been made, develop: (1) an anemia which resembles that following splenectomy; (2) a rapid increase in the resistance of the red cells to hypotonic salt solutions preceding or coincident with the anemia. Resistance usually returns to normal at about the same time that anemia disappears. (3) an initial leukocytosis, involving at first the polymorphonuclear leucocytes and transitional cells.

Ligation of the splenic vein caused considerable atrophy of the spleen, but not necrosis or thrombosis. The other opera-

tions caused little or no change in the spleen.

The disturbances following these operations may be due to a loss of a certain volume of blood to the liver, or to the loss of a splenic hormone. As the authors suggest, "if the former is true, the method of production of the anemia still remains unexplained. It is evident, furthermore, that the latter theory has also no value unless it is assumed that this hormone must be activated by passage through the liver."

—H. W.

45. (SPLEEN) Blood dyscrasias associated with splenomegaly.

Weis (J. D.) New Orleans M. & S. J., 1916, 69, 9.

(General clinical consideration.)

46. (SPLEEN) Blood dyscrasias associated with splenomegaly.

Parham (F. W.) New Orleans M. & S. J., 1916, 69, 13.

(Etiology of splenomegaly.)

47. (SPLEEN) Observations on splenomegaly. Weis (J. D.)

New Orleans M. & S. J., 1916, 69, 135.

Of no endocrine interest.

48. (SPLEEN) The etiology and pathology of blood dyscrasias associated with splenomegaly. Lanford (J. A.) New Orleans M. & S. J., 1916, 69, 3.

Clinical consideration; nothing new.

49. (SPLEEN) Atypical form of splenic diseases. Kanavel

(A. B.) Ill. Med. Jour. 1916, 30, 110.

Discussion of general clinical and operative conditions relative to disorders of the spleen.

50. (SPLEEN) The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. XV. The resistance to hemolytic agents of dogs in which the splenic blood has been diverted from the liver. Krumbhaar (E. B.)

and Musser (J. H.) J. Exp. Med. (N. Y.) 1916, 23, 97.

Ligation of the splenic veins, or transplantation of the splenic veins or portal vein (Eck fistula) into the inferior vena cava in dogs results in a lessened tendency to jaundice following injections of toluenediamin or hemolytic immune serum. Splenectomized animals exhibit similar reactions. The anemia and increased resistance of the red blood cells following these operations are probable factors acting against the hemolytic agents used. The lessened tendency to jaundice is also due, according to the authors, in part at least, to a mechanical factor dependent on the course of the blood supply to the liver.—H. W.

51. **SPLENITIS**, report of a case. Wilson (T.) U. S. Nav. M. Bull., 1916, 10, 674.

Reports a fatal case of splenic abscess.

52. (**TESTIS**) The internal secretion of the testes. Wheelon (H.) Interstate Med. J. (St. Louis) 1917, 24, 1089.

The article is a "collective abstract" relative to the seat of origin of the internal secretion of the testes. From a consideration of the effects of pathological processes, castration, vasectomy, the action of the X-rays, testicular transplants and observations upon cryptorchid animals and men it is concluded that the testicular hormone has its origin in the interstitial cells or cells of Leydig present in the testes.—H. W.

53. (**TESTIS**) Seasonal changes in the interstitial cells of the testis in the wood chuck (*Marmota morax*). Rasmussen (A. T.) Am. Jour. Anat. (Phila.) 27, 475.

The paper contains a good discussion of the general significance of the relationship between hibernation and interstitial cells. In the woodchuck the author finds that spermatogenesis progresses slowly during hibernation, increases suddenly for a month at the termination of this period, then drops nearly to zero after the period in which the female bears her young, after which time spermatogenesis increases again slowly until the following year. The development of interstitial cells on the other hand does not occur except during the spring and early summer. They reach their greatest size only after spermatogenesis has begun to lessen. The interstitial cells are smallest in late summer and autumn. The cytoplasm contains much pigment and some lipid. In the spring the cells increase in size (especially the cytoplasm) and there is an increase in the amount of lipoids and fat.—E. R. H.

54. (**THYMUS**) Beiträge zur Kenntnis des thymotoxischen Serums. Ogata (M.) Acta. Schol. Med. (Kioto) 1917, 1, 449.

Ten cc. of thymotoxic serum, obtained from rabbits immunized with dog's thymus were injected subcutaneously within fifteen days into nine dogs ten to sixty days old. Six control animals received a similar injection of normal rabbit serum. Growth was retarded in the animals treated with thymotoxic serum and the thymus was atrophied, with increase of the interstitial connective tissue. In nearly all the animals the bones were smaller and less dense and contained relatively more water and a smaller absolute amount of calcium oxide, magnesium oxide and phosphoric oxide. The percentage of total ash was somewhat smaller in five cases only. The injection of serum from rabbits previously treated with ovarian

tissue from the dog produced no effect on the thymus, indicating the specific nature of the thymotoxic serum.—Physiol. Abst.

55. **THYMUS Menschliche Hungerthymus.** (Thymus in a case of starvation.) Hart (C.) Virchow's Arch. f. path. Anat. und Physiol. (Berlin) 1917, 224, No. 1.

A child of three days which died of starvation, showed an atrophy of the thymus; the weight of the gland was 5 grm. There was a fatty degeneration of the cells. The author believes that during fasting toxins are formed which have an influence on the thymus. In experiments on dogs he came to the same conclusion. (Previous observers have noted that the thymus is especially subject to atrophy in inanition.)—J. K.

56. **THYMUS.** Ist der postoperative Basedowtod ein Thy-mustod? (Is the postoperative death in Graves' disease caused by the thymus?) Melchior (E.) Berl. klin. Wochenschr. (Berlin) 1917, 54, 35.

A very long article, to prove that the thymus plays no part in causing death after operation in Graves' disease. In 75-85 per cent of Graves' disease the thymus is large, but the cases in which there is no large thymus are very severe. The patients who die after operation never show the symptoms of a status thymicus but simply show a rapid increase of the symptoms of Graves' disease. The prognosis of operation is much worse in cases with a small thymus than with a large one.

—J. K.

57. **THYROID, action of, upon the growth of the body and organs of the white rat.** Herring (P. T.) Quart. Jour. Exp. Physiol. (Lond.) 1917, 11, 231.

The results are in general agreement with those of Hoskins (Jour. Exp. Zool. 1916, 21, 295). Larger doses were employed, and it is interesting to note that there was a greater degree of hypertrophy of some of the organs than was obtained by Hoskins.

Small doses fed daily have but little effect on the body growth as measured in length, but tend to diminished growth as estimated by body weight. Thyroid feeding causes enlargement of the suprarenals, heart, liver, spleen, testes and ovaries. There are no constant changes in the thymus. There is a decrease in the size of the pituitary in females. Kojima's statement (see abstract in this number of Endocrinology), that the pancreas is hypertrophied, is confirmed.

The uterus of the young rat appears to be checked in its growth, and as there is a similar check in the growth of the pituitary, the author thinks there may be a close correlation between these two organs.—T. C. B.

58. (THYROID) Studien über die Schilddrüse. XXX. Die Wirkungen auf den Darm. Eiger (M.) Ztschr. f. Biol. (Muncheu) 1917, 67, 372.

In connection with the diarrhoea accompanying Basedow's disease the effect of Burroughs Wellcome thyroid tablets was tested on the surviving rabbit intestine by the method of Magnus. Weak doses distinctly increased muscle tonus, stronger doses increased the strength of the contractions, while stand-still followed the use of very strong doses.—Physiol. Abst.

59. (THYROID) Influence of thyreodin on standard metabolism. Krogh (M.) Ugesk. f. Laeger (Kobenhavn) 1916, 52, 4.

Determinations of the oxygen consumption have been made on urethanized frogs before and after administration of thyreodin and with and without division of the four nerve trunks for the limbs. From the fact that thyreodin causes a much smaller rise in metabolism after cutting of the nerves, it is provisionally concluded that it acts chiefly by increasing the tone of striated muscle.—Physiol. Abst.

60. (THYROID) Ueber die Wirkung der Schilddrüse auf den Blutkreislauf, II. Oswald (A.) Pflüger's Archiv. (Bonn) 1916, 166, 169.

Further experiments to prove that iodothyroglobulin is the really active agent of the thyroid secretion. Its methylene derivative has similar actions; removal of the iodine weakens the effect, but if the iodine is added to it artificially the effect is not strengthened. Other iodine-holding natural products (gorgonin, spongin) act on autonomic nerves in the same way as the thyroid globulin, but not so markedly; the nucleoprotein of the organ or protein-free extracts have no effect.—Physiol. Abst.

61. (THYROID SPLEEN) Physiologie der Drüsen. L. Asher. XXXI. Ueber das Zusammenwirken von Milz, Schilddrüse, und Knochenmark. Du Bois (M.) Biochem. Ztschr. (Berlin) 1917, 72, 141.

In some rabbits, the spleen, in others the thyroid, in others, still, both organs were extirpated; full details of the resulting blood picture are given in reference to colored corpuscles, leucocytes, lymphocytes, hemoglobin, etc., and of the response of such animals to oxygen want (injection of HCN). The general conclusion drawn is that both organs affect the bone marrow, the spleen being inhibitory and the thyroid stimulating it.—Physiol. Abst.

62. (THYROID) The treatment of goitre with quinine and urea injections. Watson (L. F.) *Med. and Surg. (St. Louis)* 1918, 2, 49.

The quinine and urea injection has limitations the same as any other treatment for goitre and must be employed only in selected cases. It will not benefit the symptoms in those patients in whom the circulatory and nervous system have been permanently damaged. The treatment is contraindicated in fibrous and calcareous types of goitre; partial thyroidectomy is the only measure that will remove the tumor in these cases. The treatment of the exophthalmic type in young adults, especially in men, is difficult and should be attempted only under the most favorable circumstances. The treatment is surrounded by certain dangers, immediate and remote. One inexperienced is liable to puncture the trachea or one of the large blood-vessels, or to make the injection into the soft tissues of the neck. Injections that are too extensive will produce the same signs of myxedema that follow the removal of too much thyroid by operation. The necessity of minimizing the slight pain of any injection by means of local anesthesia cannot be too strongly emphasized. If the quinine and urea treatment is administered without preliminary injections of a few minims of sterile salt solution, followed by injections of sterile water, attacks of acute hyperthyroidism which might result disastrously, are liable to follow.

The gradual improvement of the exophthalmos in certain cases following the quinine and urea treatments points to a nerve control exerted by the thyroid on the exophthalmos.

Exophthalmic and non-exophthalmic goitre occur later in life in non-goitrous localities than in sections where the disease is prevalent.

The number of patients cured is highest in the group of those who came for treatment early in the disease; the benefit received by those who came later, was in proportion to the degree of damage done the circulatory and nervous systems. A goitre that has once disappeared has never recurred. A majority of the patients in this group have been under observation for two to five years.—Author's Summary.

63. (THYROID) Desquamation und Secretion in der Glandula thyroidea. (Desquamation and secretion in the thyroid gland.) Guillebeau, *Virehow's Arch. (Berlin)* 1917, 224, 217.

Small pieces of the thyroid gland from different animals were kept during one or two days in an incubator. They always showed an increase of the follicular epithelial cells. The author was able to observe the production of colloid by the cells.—J. K.

64. (THYROID) Blood picture in a case of Basedow's disease with parathyroid tetany. Sandelin (T.) *Finska Läk. Handlingar* (Helsingfors) 1917, 59, 90.

In this case there were two operations; the second produced tetany and death. During tetany there was an increase of neutrophile leucocytes, and a fall in lymphocytes and eosinophiles. The coagulation time was delayed. The picture is that of sympathetic stimulation.—*Physiol. Abst.*

65. (THYROID) Beiträge zur Physiologie der Drüsen. Leon Asher. XXIX. Nachweis der Stoffwechselwirkung der Schilddrüse mit Hilfe eines eiweissfreien oder jodarmen Schilddrüsenpräparates. Abelin (J.) *Ztschr. f. Biochem.* (Oldenburg) 1917, 70, 259.

"Thyreoglandol-Roche" is a derivative of thyroid gland which is soluble in water, free from protein and contains little iodine. When added to a nitrogen-poor diet, it caused a rise in the nitrogen output of a bitch. A similar increase occurred after its administration to the fasting animal. After thyroidectomy (parathyroids intact) a precisely similar rise in the nitrogen output followed the ingestion of thyreoglandol by the fasting animal and this result was confirmed on a thyroidectomized dog. The reaction is not constant in the normal animal, and was absent in a control bitch. Identical effects were produced by the similar administration of Burroughs and Welleome's thyroid tablets. It is evident that the stimulation of metabolism which is the characteristic feature of the thyroid is not associated with protein, and is not dependent on the amount of iodine present.—*Physiol. Abst.*

66. (THYROID) Beiträge zur Physiologie der Drüsen. Leon Asher. XXX. Untersuchungen zur Frage ob nach extirpation von Schilddrüse und Nebenschilddrüsen biologisch nachweisbare toxische Stoffe im Blute auftreten. Backman (E. L.) *Ztschr. f. Biolog.* (München) 1917, 67, 353.

Thyroidectomy or parathyroidectomy was performed on six rabbits, and after the development of the typical symptoms the animals were killed and the action of their serum and plasma were tested on the isolated intestine of the normal and operated rabbit. In neither case was there a specific effect on the automatic movements of the bowel; the presence of proteinogenic amines and alkaloids in the blood in thyropriva tetania is thereby excluded. The intestinal movements and reaction to adrenin of the operated animals resembled the normal. Normal oxalated plasma is without effect on the isolated bowel; there is a late secondary increase of tonus due to sodium oxalate and to coagulation of the plasma. Blood

serum, on the other hand, with or without oxalate, causes an immediate increase in the tonus and height of the contractions.—Physiol. Abst.

67. (THYROID) Experimentelle Studien über die Schilddrüse: (1) Der biologische Nachweis der inneren Sekretion der Schilddrüse im Blute der mit Schilddrüsenextracten gefütterten weissen Ratten; (2) Der biologische Nachweis der inneren Sekretion der Schilddrüse im Blute der Schilddrüsenvene sowie auch in der Blutbahn der Basedow-Kranken. Eiger (M.) Ztschr. f. Biol. (München) 1917, 67, 253, 265.

The augmenting action of thyroid secretion on adrenin can be demonstrated on the Laewen-Trendelenburg frog by first determining the subminimal dose of adrenin. The subsequent injection of the latter with a diluted and inactive extract of thyroid gland or preparation causes a marked constriction of blood vessels.

Ordinary plasma (oxygenated three to five hours) from dogs, normal and goitrous men, has no activating action on the subminimal dose of adrenin, unless it be obtained from the inferior thyroid vein, when it gives a positive reaction. The plasma of rats fed on thyroid for considerable periods, and plasma obtained from seven patients suffering from Basedow's disease had a well-marked activating action on adrenin, thereby demonstrating the presence of thyroid secretion in the blood in these conditions.—Physiol. Abst.

68. (THYROID and PITUITARY) Beiträge zur Physiologie der Drüsen. Leon Asher. XXVIII. Die Einwirkung von Thyroidea und Hypophysisextrakten auf die Nierengefäße, Baekman (E. L.) Ztschr. f. Biol. (München) 1917, 67, 327.

The effect of intravenous injections of thyroid and pituitary extracts on the general blood-pressure and volume of the kidney were studied in four rabbits narcotized with urethane. The vagi were cut to obviate shock and two of the animals were eviscerated. The blood pressure in every case was unaffected by thyroid tabloids; an occasional rise was noted with "thyroglandol." In the eviscerated animal (exhibiting the primary effect of thyroid extract) the renal vessels were always dilated, but dilatation or no change were observed in the intact animal. Single and repeated doses of "pituglandol" and "pituitrin" caused a considerable slow and lasting rise in blood-pressure. Constriction of the renal vessels was the constant result in the eviscerated animal, but it alternated with dilatation in the intact animal. Neither extract had any demonstrable effect on artificial splanchnic stimulation.—Physiol. Abst.

69. (THYROID) Changes in the central nervous system in hypothyroidism, Mott, (F. W.) Proc. Roy. Soc. Med. (Lond.) 1917, 10, 51.

There is a universal chromatolytic change in the cells of the central nervous system. A marked case of myxedema is described in which the changes are figured. In the pituitary, the pars intermedia showed excess of colloid, but this is not regarded as evidence of vicarious relationship. The lipoids in the suprarenal cortex were diminished.—Physiol. Abst.

70. (THYROID) Anabolic action of the thyroid gland, Janney, (N. W.) Proc. Amer. Soc. Biol. Chem. Jour. Biol. Chem. (N. Y.) 1917, 29, 6.

Thyroid in large doses exerts a catabolic action characterized by toxic symptoms and by a great increase of all the urinary nitrogenous constituents except creatine. The anabolic action of small doses of thyroid administered to cretins and exophthalmics over extended periods was accompanied by an added retention of nitrogen and an improvement in the symptoms.—Physiol. Abst.

71. (THYROID) Three children with sporadic cretinism, in one family. Herrman, (C). Arch. Pediat. (N. Y.) 1917, 34, 831.

This is the second series of three cases of sporadic cretinism occurring in one family to be reported by Herrman, the first appearing in N. Y. State Jour. Med. Aug. 1914.

He gives a good clinical description of the three patients who were 22 (female), 20 (male), and 18 (female) years old respectively. They were all backward in physical and mental development, and gave a history of having been under intermittent treatment since three years of age. They were all breast fed from eight to sixteen months and showed signs of deficiency early, these being manifested by delay in teething, sitting and walking. He placed them on a combination of thyroid, pituitary and suprarenal extracts, obtaining marked improvement in 2½ months.

The parents were not related in this series, but they were in the first. Herrman found consanguinity in only five cases out of 50 which have come under his observation. He thinks that anomalies of the so-called ductless glands can be best explained on the basis of heredity and that there is probably some defect in the function of the endocrine system in the ancestry of these children.—M. B. G.

72. THYROID extract in hydrocephalus. Elsberg (C. A.) Arch. Pediat. (N. Y.) 1917, 34, 851.

In a paper on "Chronic Internal Hydrocephalus, the Newer Methods for Its Recognition and Treatment," read before the Section on Pediatrics of the New York Academy of Medicine, Elsberg stated that there are three definite types of hydrocephalus: that due to obstruction, that due to diminished absorption and that due to hypersecretion. For the differentiation of these types, he used phenolsulphonaphthalein as an indicator. He advised that in cases of hydrocephalus due to hypersecretion, a lumbar puncture should be done every few days, and the patient should be given thyroid extract in doses up to the physiological limit. A certain number of satisfactory results could be obtained by this combination of thyroid feeding and repeated lumbar punctures in this type, but very little improvement had been seen with this treatment in hydrocephalus due to diminished absorption.—M. B. G.

73. THYROID. Studies of the changes in, caused by pituitary extract. Pardi, (U) *Lo Sperim.*, Jan. 1916. *Abstr. Arch. Pediat* (N. Y.) 1917, **34**, 802.

The object in view was to determine whether modifications of the structure of the thyroid could be caused by pituitary extract alone or by other organic extracts as well. Halion and Alquier investigated the matter some time before. Pardi had under observation four groups of rabbits, 31 in all. They were treated with intramuscular injections of extracts of spleen, pituitary body and liver. The daily dose was 2 cc. injected in the gluteal region. Twenty-four hours after the last dose the animals were killed. Results: (a) Changes of structure in thyroid were practically the same following the injections of the various extracts. (b) Changes indicate colloid hypersecretion and not hyposecretion. (c) The action of the extracts employed caused vasomotor symptoms by stimulating either directly or indirectly the secretion of colloid substance.—M. B. G.

74. (THYROID) Attempts to produce experimental thyroid hyperplasia. Burget (G. E.) *Am. Jour. Physiol.* (Balt.) 1917, **44**, 492.

The experiments were undertaken to determine certain factors that have been reported to induce thyroid hyperplasia in men and experimental animals.

The author finds that a high protein diet develops hyperplasia of the thyroid in rats. If kept under unhygienic conditions, rats develop hyperplasia of the thyroid on a standard diet of bread and milk; and a combination of high protein diet with unhygienic conditions gives a greater degree of hyperplasia than either method alone. Young growing rats on a high protein diet do not develop hyperplasia.

The influence of feces from goitre patients and from goitre dogs was tried out on cats, since these animals seldom have goitre when brought to the laboratory, or develop it when kept under laboratory conditions. About 100 cc. of a solution of feces from a goitrous dog, and from a case of exophthalmic goitre, seemed to have no effect.

Suturing the right phrenic with the right cervical sympathetic after the method of Cannon, Binger and Fritz gave negative results, as far as hyperplasia of the thyroid was concerned. The same is true for the removal of a portion of the cervical sympathetic.—T. C. B.

75. (THYROID) Cretinism and Chagas' disease. (Second communication) Kraus (R.) and Rosenbush (T.) *La Prensa Med.* (Buenos Aires) 1916, No. 17. Correction, *Endocrin.* 1917, 1, 376.

The authors show that the goitre occurring in Argentine is not produced by *Trypanosoma Cruzi*.—B. A. H.

76. (THYROID) Tuberkulose der Schilddrüse mit besonderer Berücksichtigung der Tuberkulose in Basedow-Schilddrüsen (Tuberculosis of the thyroid and exophthalmic goitre.) Urmara (S.) *Deutsche Ztschr. f. Chir.* (Leipzig) 1917, 140, 324.

Urmara has observed some cases in which a tuberculous infection was followed by Graves' disease. The author believes that the toxin of the tubercle bacillus can stimulate the secretory activity of the thyroid gland. If a patient with Graves' disease is infected with tuberculosis the symptoms increase rapidly.—J. K.

77. (THYROID) Die Erfolge ausgiebiger Schilddrüsenresektion bei Morbus Basedow. (The surgical treatment of exophthalmic goitre.) Lick (E.) *Deutsche Med. Wehnschr.* (Berlin), 1917, 43, No. 42.

The author maintains that surgical extirpation is always the treatment of choice in exophthalmic goitre. Upon the appearance of exophthalmos most of the thyroid gland should be removed at once without waiting for the appearance of any other symptoms. X-ray treatment has little effect. Splendid results have been observed when extirpation has been followed by injections of quinine and urea into the part of the gland not removed.—J. K.

78. (THYROID-SEX GLANDS) Über das Verhalten der genitalen Funktionen beim Myxoedem des Weibes. (The sexual functions in women suffering from myxoedema.) Veil (W. H.) *Arch. f. Gyn.* (Berlin) 1917, 107, 199.

Description of two cases of women with normal sexual functions in whom a strumectomy was performed. In both cases too much of the gland was taken away and the symptoms of myxoedema developed. The menstruation became irregular, both women showed all symptoms of a true menopause, the uterus became smaller and at last menstruation ceased. In both cases a perfect recovery was observed after administration of thyroid gland.—J. K.

79. (THYROID) Kohlehydratstoffwechsel bei Erkrankungen der Drüsen mit inneren Sekretion. (Carbohydrate metabolism and diseases of the endocrine organs.) Ritter (F.) and Weiland (W.) *Ztschr. f. exper. Path. u. Therap.* (Berlin) 1917, 19, 118.

It was the intention of the authors to study the carbohydrate metabolism in different cases of disease of the endocrine organs. Because of the war they could not continue their experiments. Therefore they now publish only their experiments with patients suffering from diseases of the thyroid gland. In myxoedema they found a high amount of blood sugar; in one case even 0.198 per cent. In Graves' disease they found it very low and glycosuria was never observed to occur after administration of 100 gms. of glucose or laevulose by mouth. In all cases of myxoedema 300 gms. of glucose were enough to cause glycosuria. They observed once more the well known fact that after intravenous injections of sugar in cases of myxoedema, it took a greater time for all of the sugar to be excreted in the urine than in cases with normal or hypertrophic thyroids.—J. K.

This issue has been prepared with the collaboration of M. B. Gordon, T. C. Burnett, F. A. Hartman, B. A. Houssay, J. Koopman, E. R. Hoskins, G. Verecellini, Homer Wheelon and various writers who have submitted author's abstracts. With the permission of the editors certain abstracts have been quoted from "Physiological Abstracts" and "Chemical Abstracts."

ENDOCRINOLOGY:

*The BULLETIN of the ASSOCIATION for the
STUDY of INTERNAL SECRETIONS*

APRIL—JUNE, 1918

THE THYROID HORMONE AND ITS RELATION TO THE OTHER DUCTLESS GLANDS*

E. C. Kendall, Ph.D., The Mayo Foundation,
Rochester, Minnesota

Much of the research work concerning the ductless glands has been from the viewpoint of relating some one gland to some particular portion or restricted function of the body. Thus, the pituitary has been associated with the growth of the bones and certain skeletal formations, the thyroid has been associated with the nerves, and some writers have satisfied themselves that the activity of certain ductless glands is explained by clinical syndromes wherein only portions of the body show abnormalities. There have been relations suggested which were based on embryologic grounds. Organs and tissues derived from some common source have been supposed to be more or less related in function. Some of the most elaborate relationships of the ductless glands are based on histologic findings. The vast

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amount of research work that has been done with this object in view has indeed told us a great deal concerning the relationships of the ductless glands to certain bodily functions, but beyond this knowledge one cannot penetrate without new tools, and without applying quantitative determinations to the physiologic processes involved.

Before the chemical balance came into existence, the alchemist held sway over the theories of matter and the relationships existing between chemical substances. The phlogiston theory was unassailable on any ground other than quantitative analysis. From a survey of the literature today concerning the ductless glands we cannot boast of being very far out of the alchemist's age, and as yet very few investigators have approached the subject in a quantitative manner, with a realization of the actual problems existing.

For a complete analysis of the exact chemical reactions produced by this or that gland, nothing short of the actual isolation of the products in question can really solve the problem, and even after the chemical substances responsible for the activity of the various glands have been isolated, the interpretation of their physiologic functions requires, not only the microscope, the kymograph and the chemical laboratory, but most of all the application of physics, chemistry, hydrolics and mechanics. Too much emphasis has been laid in the past on clinical and experimental conditions that are only partial expressions of a fundamental reaction which in almost every case has so far escaped detection. In the meantime these minor details have been stretched

to the utmost in order that they may fit the theory of the supposed function of the gland in question.

Realizing that the function of the thyroid must be based on simple chemical reactions, and trusting in the probability that the substance producing these reactions would be stable enough to be separated, the isolation of the iodine compound occurring in the thyroid was begun by me eight years ago. During this investigation a very large amount of fresh thyroid glands has been used, and the work has been pushed in several directions so that now not only has the isolation of the substance been accomplished but it has been analyzed, its empirical and structural formulae have been determined, and its synthesis has been completed.* The physiologic action has been studied, and a large number of patients have been treated in the Clinic.

All this work has emphasized the necessity of viewing the function of any endocrine gland on the very broadest possible grounds. For example, in cretinism there is a certain characteristic expression of the face, the long bones do not grow normally, the skin is dry and scaly, the hair is scant and brittle, there is no ambition, and mental activity is very much below normal. Shall one then say that the thyroid controls the length of the long bones, the skin, the hair and the nerves? This is all true, but it does not deal with the actual function of the gland and the chemical processes involved. It is following only so far as the eye can see. In this instance quantitative studies have been directed to anatomic changes and not to physiologic processes. A change

*Mr. Osterberg, working in our laboratory, succeeded in synthesizing a small amount of thyroxin in December, 1917.. Further work is in progress.

in the physiologic function is being interpreted in terms of the end result produced by the change. One almost loses sight of the fact that the thyroid is just as vitally concerned in normal conditions. To the majority of those most interested the function of the thyroid does not mean a physiologic process based on chemical reactions, but the word brings to mind a disturbance defined in clinical terms.

According to the older view the active constituent of the thyroid functions within the gland itself. The blood passing through the gland is purified; before it enters the gland it is toxic to the organism, and after leaving the gland it is not toxic. Others have held that the location of the activity of the substance was in and through the nervous system, that through the nerves the various thyroid manifestations were brought about and that the secretion was carried from the gland to the nerves by the blood stream.

During the past ten years Plummer has been making a very detailed study of the function of the thyroid, and he has been led to believe that the location of the active constituent of the thyroid, when it functions, is within the cells not of any particular set of organs or portion of the body, but that it is a constituent of cellular life and activity. Plummer states that the active constituent of the thyroid determines the rate at which any particular cell can produce energy, that is, it establishes the quantum of energy which any cell can produce when it is stimulated either from within itself or from without, so that the thyroid is directly related to the production of energy within the body. He has shown that one-third of one milligram of the active constituent of the thyroid increases the basal metabolic

rate one per cent in an adult weighing approximately 150 pounds. Here we have not only a definition of the function of the thyroid, but it is expressed in mathematical terms with such exactness that the number of milligrams of the substance functioning within the entire body can be estimated. It is between 23 and 50 milligrams, that is, between one-third and two-thirds of one grain.

We are still confronted with the problem of the exact chemical reactions involved, but here again a great deal of light is thrown on the problem by the chemical constitution of the active constituent of the thyroid. For reasons given hereinafter the substance has been named "Thyroxin."

When thyroxin is given to a myxedematous patient all the symptoms due to myxedema are promptly relieved. When it is given in too large amounts hyperthyroid symptoms are produced. This has been known now for more than three years, and on these grounds it has been stated that thyroxin is the active constituent of the thyroid. But the fact that a physiologic response is produced by the administration of a substance is not an explanation of the physiologic function of that substance, and it was not until a quantitative value was placed on thyroxin that the real physiologic processes involved could be demonstrated. It seems that one of the most important results of this work has been the furnishing of the material with which quantitative values could be determined.

The moment we know that in a myxedematous patient the administration of 10 mg. of thyroxin increases the basal metabolic rate 30 per cent, we have the key to the explanation of the relief of a very com-

plex clinical syndrome. The edema is relieved. The sluggish mentality is relieved. The dry scaly skin becomes moist. The hair ceases to fall out and becomes soft. The voice that has been very slow, returns to its normal tone and character. The mentality which has been befogged becomes clear, and the individual expresses his normal personality. In short, every cell in the body responds with its own expression of activity. It seems impossible that all this can be done with a single crystalline substance, and because our knowledge has been limited as to just what and how much was going on, we have let visible changes lead away into theories that are narrow and which obscure rather than enlighten. But, when we know that simultaneously with the clinical improvement the basal metabolic rate has been increased 30 per cent, it follows axiomatically, from laws of mechanics, hydrolics and physics, that very fundamental changes have occurred throughout the entire body. It has long been known that the thyroid influences basal metabolic rate in the body. It is a present-day conception that it is through metabolic processes that the thyroid produces its physiologic effect, but the scope of this action and the chemical processes involved have not been emphasized or established.

In order to explain the action of thyroxin, when 10 milligrams of the substance increases the metabolic rate 30 per cent, as Plummer puts it, it would take a discussion as broad as biology itself. This aspect of the question must receive greater attention in order to bring out the physiologic processes involved in the function of the thyroid, and with it, the other ductless glands. The scope of the problem

is so broad that several investigators viewing it from entirely different standpoints can each obtain results satisfactorily conforming to their conclusions, but no one of which forms a fundamental physiologic process. For instance, investigating the question of resistance to infection, the removal of the thyroid establishes the fact that in thyroidless animals infection is much more prevalent. This is of interest to the bacteriologist, serologist, immunologist, etc. The fact that the growth of bones is retarded is an entirely different phase of the subject, and so, a long list of investigations concerning the thyroid which have been carried on with positive results leading to various conclusions concerning its activity, could be cited.

Until it was shown that the confusing clinical syndrome found in myxedema could be entirely relieved by a single substance, the problem as to how many active constituents occurred in the thyroid could not be settled. In fact, the fundamental reaction underlying all expressions of thyroid activity could not be made as long as clinical symptoms alone were used as a criterion of physiologic activity. But, establishing the relation of thyroxin to the basal rate of metabolism in mathematical exactness furnishes the first clew to the physiologic processes involved, and it is evident that physiologic response to an injection of thyroxin is found in a summation of the activity of all the cells in the body. If anyone chooses to investigate any one particular process he will find that process altered, for a change in metabolic rate is accompanied by fundamental changes in every aspect of the reactions going on within the body. This is where the application of physics, mechanics,

hydrolysis and chemistry must be made in order to understand, not only the changes produced by the administration of thyroxin, but what the effect of a second factor would be.

The injection of adrenalin into an animal with a normal basal metabolic rate will necessarily be different from the injection of adrenalin into an animal with a metabolic rate 30 per cent above normal, if viewed purely from a consideration of the physics involved. As Plummer has pointed out, it is possible to explain the supposed relation between thyroid and adrenalin on grounds involving the rate of flow of the blood, entirely apart from any other action.

When it comes to establishing relations between the other ductless glands and the thyroid, progress can only be made when the various activities of the glands are viewed in as broad an aspect as Plummer has suggested for the action of thyroxin. Disturbances of the pituitary lead to changes in basal metabolic rate which are marked but are less than those found in thyroid disturbances. Changes in the pancreas and what we know of the adrenal also lead to changes which are smaller than that produced by thyroxin. We can at least tentatively assign to the thyroid the supplying of an agent which is of fundamental importance in the production of energy. This can be carried one step further in a chemical sense, and we may assume that thyroxin is involved in the production of carbon dioxide. The other ductless glands then assume positions of secondary importance to the thyroid, in carrying out these chemical reactions, and may be assigned the role of preparing the various metabolites for their final action with

thyroxin. No definite hypothesis can at this time be given beyond the fact that the various clinical syndromes produced by hyper- or hypo-action of the various glands, are syndromes resulting from the effects of these substances throughout all the cells of the body, through their action in maintaining the rate of energy production going on within the cells.

It is perfectly possible to explain the apparent selective action of various internal secretions to restricted portion of the body on these grounds, and in fact selective action vanishes when the action of the gland is placed on this broader basis.

Beside the action suggested for certain of the ductless glands of preparing metabolites for their final interaction with thyroxin with the production of energy, we must also assign to some agents within the body the task of taking care of bi-products and of elaborating other substances. Nitrogen compounds include toxic substances among their number. For the proper elaboration of these compounds, which assume fundamental importance in normal physiology, some very substantial mechanism must exist. That certain of the ductless glands should be given the power to affect the rate at which the body can prepare and care for nitrogenous compounds seems highly probable, and of late the parathyroid assumes great importance as one of the glands thus involved. That others of the glands are also concerned also seems to be indicated.

It was therefore of great interest to determine the chemical nature of this iodine containing compound which occurs in the thyroid and is so fundamentally involved in normal physiology. Analysis has shown that it contains an indol group with the

iodins undoubtedly attached to the benzene ring, and that on the carbon atom adjacent to the imino group of the indol ring there is an oxygen atom. (Fig. 1.)

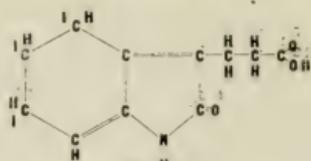


Figure 1

The structural formula of the active constituent of the thyroid.

For reasons given hereinafter, it appeared desirable to emphasize the presence of the oxy-indol nucleus and it appeared equally desirable not to emphasize the presence of iodine. The substance was therefore named "Thyro-oxy-indol," which has been shortened to "thyroxin" for every-day reference to the substance. At first we attempted to show that the activity of thyroxin was due to the oxygen condensing with the amino group of an amino acid and the carboxyl group of the amino acid reacting with the imino group of thyroxin. It has been shown, however, that this does not occur; but that the physiologic activity of the substance is produced by the CO-NH groups has been demonstrated as follows:

The injection of pure thyroxin is followed by a very definite and marked physiologic response. When the hydrogen on the imino has been replaced with acetyl the substance loses its physiologic activity and the injection of the substance is without demonstrable effect. Investigation of the acetyl showed that, in alkaline solution, the indol form of the compound no longer exists, but that there is hydrolysis of the CO and NH groups resulting in the opening of the ring and the formation of COOH and NH₂ (Fig. 2). Further investigation showed

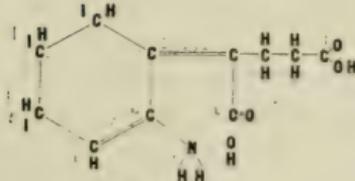


Figure 2

The open ring form of thyroxin as it exists in the body.

that thyroxin behaves in this same way, and that it exists within the body, not in the closed ring form such as is present in indol, but in the form COOH NH_2 . The ability of the indol ring to thus open, furnishes the first concrete conception of how the substance behaves chemically within the body. The fact that both thyroxin and the acetyl derivative exists in open form, suggests that the reason for the inactivity of the acetyl is because of interference with the chemical reaction associated with the NH_2 group of thyroxin. One is at once struck with the fact that the open and closed forms of thyroxin bear to each other the same relation as does creatin to creatinin, and that the same relation exists between amino acids and the form in which amino acids are united in protein. Establishing these active groups emphasizes the importance of the chemical nucleus CO NH and COOH NH_2 within the body, which appears to be a necessary structure for the carrying out of chemical changes leading to the production of energy.

Patients with complete atrophy of the thyroid have basal metabolic rates approximately 40 per cent below normal. It has been shown that administration of thyroxin alone can bring back and maintain the normal metabolic rate in such patients. But in complete atrophy of the thyroid, the complete or

nearly complete absence of thyroxin may be assumed. The question arises as to what maintains energy output from 100 per cent below normal, which would be death, up to 40 per cent below normal, the point to which basal metabolism sinks in the absence of thyroxin. May it not be the other chemical substances in the body possessing the same grouping that occurs in thyroxin? These are amino acids and proteins, creatin and creatinin, and a few other less well-known compounds. It seems probable that on the administration of thyroxin a reaction which has been carried on within the body by other compounds is merely increased in rate, but that there is no difference or disturbance of the reactions that have been going on.

In regard to the relation of iodin to the activity of thyroxin, the presence of iodin in the compound must exert some influence, and it seems not improbable that the presence of iodin renders the active groups more reactive. In the absence of iodin it would take a greater working pressure to bring about its reaction. The substitution of the iodin by hydrogen or chlorine or bromine would undoubtedly be followed by an alteration in the degree of reactivity of the substance, but its gross chemical nature and properties would not be altered thereby. That the iodin breaks off from the molecule and is used as iodin per se for any purpose, seems absolutely impossible because Plummer has shown that this substance functions for as long as from 15 to 21 days after being administered, and that it acts as a true catalyist, being used over and over, hour after hour, without destruction except at a very low rate. It is finally removed from the body either by actual de-

struction, or by slow loss in an undestroyed form. Our knowledge of other catalytic agents shows that poisoning of catalysts is common if not universal, so that its slow destruction is to be expected.

The exact chemical reactions involved when this substance functions are still unknown, but that the substance possesses the formula as shown above is established by the ultimate chemical analysis of its derivatives. That the active groups present in thyroxin are a necessary mechanism for the production of energy within the body seems highly probable, and it is of great interest and significance that there exists a close analogy between this substance, whose exact effect on metabolism we know, and other substances, creatin, creatinin, amino acids and proteins, which are also intimately associated with reactions occurring within the animal organism. Are these substances also concerned in the maintenance of the basal metabolic rate?

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THE PITUITARY BODY AND POLYURIA

B. A. Houssay, Buenos Aires

The following article comprises a summary of various of our observations previously published or reported before the Asociación Médica Argentina (May 3, 1915) and abstracted in *La Prensa Médica* (1915, p. 451). A concluding report of the entire investigation is shortly to appear.

Different immediate effects occur when pituitary extracts are administered to dogs intravenously. The chemical composition of the gland is very constant, as are the physiological effects of the gland extracts, but these effects vary qualitatively according to the methods of preparation. Extracts of the fresh glands produce brief vasodepression followed by augmented arterial pressure; during the depressor phase of the reaction the kidney volume is diminished and oliguria occurs, but when the pressure rises a renodilation accompanied by more or less marked diuresis is noted. Sometimes we have noted an initial renodilation with or without general hypotension which persists for a short time into the hypertensive phase; this may or may not be followed by renodilatation. In other instances, in case of the more strongly hypertensive extracts, kidney dilation and diuresis, together with augmented blood pressure, occur as the primary reaction without initial hypotension. This effect is observed generally in case of extracts prepared by the aid of metallic salts, of decoctions of powder of the posterior lobe desiccated at 37-45° and of preparations from glands extracted with alcohol. It would appear, then, that there occur in pituitary

extracts both rencontractor and renodilator substances, one or the other predominating according to circumstances. The diuretic effects run parallel with the renovascular effects.

When we observe the diuresis of twenty-four hours, the effects are not the same and they vary according to the animals. In rabbits there is constantly noted a strong oliguria, but in dogs and in the human beings the effects are extremely variable, and sometimes can be contradictory. In man it is common to observe diuresis, especially in oligurics, although this action is less than in case of other diuretic substances. In polyuric men the effect is almost constantly a depression of urine secretion. In the rabbits a tolerance to the drug develops and the initial diuresis returns at the end of a few weeks, in spite of daily injections.

We conclude from the pharmacologic action of pituitary extract that it is not permissible to deduce an insufficiency of the pituitary body from the successful use of the extracts in polyuria.

We cannot agree that the cerebro-spinal fluid has, as Cushing has claimed, the same effects as pituitary extracts. We have demonstrated, with Giusti in 1911, that the latter retains its actions, in spite of being treated with subacetate of lead, while in case of former the action is lost. In 1913 we proved, as Mackenzie has proved (*Quart. Jour. Exp. Physiol.*, 1911, p. 305), that the cerebro-spinal fluid had not the diuretic action and not even the galactagogue action, which are the most specific tests of pituitary material. For this reason we cannot concur in the opinion that the active components of pituitary extracts pass to the cerebro-spinal fluid. This does

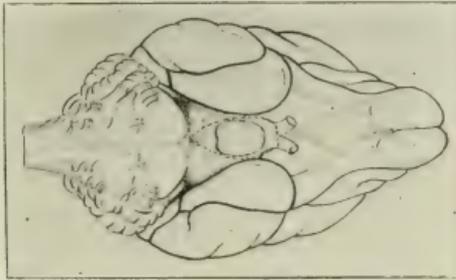
not signify that we deny that the pituitary body has some secretions that pour into the third ventricle (as Hering affirms), but it is not proved that it is the diuretic or hypertensive substance.

The operations made for the removal of the pituitary gland produce different results in adult dogs and in puppies. In the adults it is very often oliguria, while in puppies it is polyuria that occurs during the first few succeeding days. These results are in agreement with those of Cushing and his co-workers. These effects are due merely to the trauma, and it is possible to observe them in animals operated upon without actually removing the gland, or even touching it. The intervention of the pituitary in the polyuria can be excluded, because we have obtained this reaction in cases in which we have removed the whole gland, proved by a series of sections of this region, studied histologically.

As we were not able to study directly the injuries of the cerebral basal zone, because the operation to disclose it produced oliguria (adult dogs) or polyuria (puppies), we employed a method similar to that of Camus and Roussy (*Presse Médicale*, 1914, p. 517). Pricking through the sphenoid with a hot needle or utilizing iron filings (in which manner it is possible to observe the dogs a very long time, while with the pricking it is necessary to kill them a few days after the puncture because the injury disappears quickly), we obtained in all cases identical results. If the pricking had been in a determined cerebral zone we observed polyuria, and if the pricking had been outside of this zone the polyuria did not occur. In one case the puncture encountered the pituitary stalk

and penetrated into the third ventricle, without injuring the brain and no polyuria developed.

The zone able to generate polyuria in our experiments was limited behind, by the peduncle protuberance; before, by a line near the anterior limit of the optic chiasma and laterally, as shown in the accompanying drawing.



Ventral surface of brain of dog showing zone injury of which produces changes in kidney secretion. Zone outlined by dash line.

Finally, we consider that the cerebral basal zone can generate polyuria. We do not deem it probable that the pituitary constitutes a part of this zone, although it is possible that the posterior lobe of the gland participâtes.

It cannot be accepted, now, that polyuria is due to a diuretic hypersecretion of the pituitary gland.

ON THE SEASONAL VARIATION IN THE IODINE CONTENT OF THE THYROID GLAND.

Frederic Fenger

Research Laboratory in Organotherapeutics, Armour & Company,
Chicago, Ill.

In previous communications on this subject it was shown that a marked seasonal variation exists in the iodine content of the thyroid gland of cattle, hogs and sheep. There is in general from two to three times as much iodine present in the glands in the months between June and November as in the months between December and May. (1) A more or less regular seasonal change in the size of the fresh gland exists in the case of cattle and sheep, but not in hogs. A consideration of the several causes for the fluctuations leads to the conclusion that the temperature is perhaps the most important of all. (2)

These investigations were conducted from September, 1911, to December, 1913, during which time samples of fresh glands were collected twice a week and stored at freezing temperature. The glands were trimmed, prepared and analyzed twice a week. The bi-monthly samples represented about ten pounds of fresh glands.

During the past four years, 1914-1917, data have been accumulated on more than one hundred lots of desiccated thyroids from cattle, hogs and sheep which furnish the raw material for medicinal thyroid preparations. The samples were supplied by the factory and analyzed in this laboratory for control purposes.

Each of these lots represent many thousand glands and the collection time covered periods of several weeks. The animals furnishing the raw material came from all parts of the United States, with the exception of a few of the Eastern and Southeastern States. It is evident, therefore, that such factors as locality, feed, water, and particularly the considerable individual variation which is known to exist, have been satisfactorily eliminated. The fundamental causes for the fluctuations in the iodine content of the thyroid gland consequently must be temperature and weather conditions.

In the tabulation below are given the maximum and minimum iodine content of the thyroid glands collected during the two periods mentioned above and the yearly averages for the entire six years. All figures are calculated to a dry fat-free basis.

Time	Percent of Iodine in desiccated fat-free glands		
	1911-1913	1914-1917	Entire Period 1911-1917
Cattle:			
Maximum	0.43%	0.43%	
Minimum	0.04	0.04	
Yearly average	0.205%
Hogs:			
Maximum	0.47	0.38	
Minimum	0.17	0.15	
Yearly average	0.300
Sheep:			
Maximum	0.28	0.26	
Minimum	0.06	0.04	
Yearly average	0.150

It will be seen that the figures obtained during the last four years are almost identical with the earlier findings, as far as cattle and sheep are concerned. In case of the hog, the differences are more marked. This is in all probability due to the decreased number of hogs slaughtered during hot weather and the extended collection time.

The average iodine content of the hog thyroid,

taken year by year, is considerably above that of cattle and sheep. This may be of some significance, since the former is an omnivorous animal, while the latter are strictly herbivorous.

The seasonal variation in the size of the thyroid gland of cattle and sheep has been referred to above. Of these, the beef gland particularly is influenced by cold temperatures. It has been noticed year after year that the onset of severe cold weather is followed in a week or two by a noticeable enlargement of the cattle glands and consequent lowering of iodine content. This enlargement is less prominent or occurs later in mild winters than in severe ones. The glands of sheep are also quite sensitive to temperature changes, but not to the same degree as those of cattle.

Fluctuations in the yearly average iodine content of the thyroid gland also exists. These are naturally small and vary but a few hundredths of one per cent from year to year. They are undoubtedly due to weather conditions generally.

Where due allowances are made for climatic fluctuations and the differences in the time periods of collection, the last four years' results, when plotted out on paper, follow closely the curves published in previous reports.

SUMMARY

Additional evidence has been furnished to show that a distinct seasonal variation exists in the iodine content of the thyroid gland from cattle, hogs and sheep. The temperature factor is the most important of all in producing these fluctuations.

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CONFUSIONAL INSANITY AND THE OVARIES: A CASE HISTORY

George Howard Hoxie, A. M., M. D.,
Kansas City, Mo.

In the 1898 Edition of his *Psychiatrie*, Kraepelin states (1) that there is a close relation between menstruation and psychic disturbance, but that he inclined to the view that the relation was not causal.

In a symposium on the subject of the relationship between gynecologic and neurologic conditions before the Michigan State Society last spring, Reuben Peterson (2) held that there are four classes of patients to be considered, viz.:

1. Women with neurologic symptoms whose pelvic organs are anatomically and physiologically normal.

2. Women with neurologic symptoms whose genital organs are anatomically normal but whose functions are abnormal.

3. Women with derangements of the nervous system whose pelvic organs are unquestionably diseased and where the disease may aggravate but does not necessarily cause the nervous manifestations.

4. Women of naturally good nervous organizations whose nervous manifestations have followed upon and hence apparently are due to true pelvic lesions."

This analysis is very useable, for it puts the crux where it belongs,—namely, in the antecedent condition of the nervous system. And in our study we should make this point our first determination.

Bandler (3) outlines a very comprehensive theory

as to the interaction of the ductless glands in gynecology. He lays great stress on the influence of the ovary on the pituitary, and seems to believe that definite psychological manifestations may result from ovarian insufficiency.

Auer (4) in 1915 expressed the opinion: "that the occurrence of insanity at puberty and adolescence after severe physical and mental strain and at the time of menopause,—all periods when the metabolic changes of the body are intense,—and the occurrence in syndromes unquestionably the result of disease of the glands of internal secretion of idiocy, imbecility, depression, mania and dementia suggest strongly that the true etiology of the effective psychoses lies in a junctional disturbance of the glands of internal secretion."

The best statistical study is perhaps that of Carey McCord (5), which he summarizes thus: "At the Michigan Home and Training School a survey has been made of 1,134 feeble-minded inmates for evidences of involvement of the internal secretory system in the defects of growth and development in the feeble-minded. Of the number examined, 240, or 21.16 per cent, presented the characteristics of various glandular syndromes. From our investigation the following inferences appear justified:

"1. Of the glandular cases seen in the feeble-minded, heredity stands out as the foremost factor in the etiology.

"2. The demonstration of syndromes in the feeble-minded does not in itself allow any inference that the feeble-mindedness is attributable to the glandular dysfunction. The glandular disease may determine the increasing defect, but more often the co-existing feeble-mindedness and glandular defect are both the outcome of a common cause.

"3. Promiscuous treatment of the feeble-minded with glandular derivatives is unprofitable and unwarranted. In established glandular types among the feeble-minded, more often glandular treatment is of no distinct and lasting value.

"4. In borderline cases of glandular disease with trivial mental inadequacy, glandular therapy may prove of special value. More often in these cases no true mental deficiency exists, and all manifestations of mental inadequacy are referable to the glandular mal-function. In such cases glandular treatment persistently carried out may be the factor deciding between normality and increasing defects."

In the following case we have some data not usually encountered, and they are given in the hope of making more definite our concept of the relation between ovarian secretion and neurologic condition. The psychic perturbations are well brought out in the transcription of the patient's own words.

Female, age 25, single, high school teacher.

Family History, without definite stigmata.

Personal History. Normal childhood. Menses at 12; since 14, painful. The pain is in the left side and begins before flow and lasts into second day. At 19 cured and lay in hospital for three weeks. She had taken normal, college and university work, graduating with high honors. She had done special work in biologic research and won high commendation from the head of the department. She had taught in a high school two years with general satisfaction. Her statement of her scholastic life follows: "I was graduated from advanced course at the normal when I was seventeen. I did teach school in our little country school and stayed at home while teaching. When I entered

the university I was given junior credit plus ten hours. I completed both degrees B. A. and M. A. in two and a half years, graduating in nineteen-ten. The year following my entrance to the university I taught school at ———. While here I stayed with my sister, who was married when I was a mere child. When I was graduated from the normal Miss ——— told me to write, but not to attempt anything for publication until I was 35, but to write, write. She gave me a beautiful picture for having made the best average in the class. Prof. ——— told me to study sculpturing, Mrs. ——— wanted me to specialize in music. When I entered the university the zoology people wanted me to specialize in their department. Dr. ——— suggested that I try for the Bryn Mawr scholarship and said he would help me. The spring term of 1910 I assisted in zoology and was invited to join the zoology faculty meetings. That same spring I modeled chromosomes in clay with which to make candy chromosomes for the Sigma X banquet.”

Her present complaint is of pains in the back of her neck and through the heart, and a backache, duration four or five weeks, but the patient is too confused to state her condition clearly. An aunt's letter follows:

“Nov. 29, 1913. ——— was engaged to be married and the date was set several times, but each time there was some excuse; once it was that she must help her brothers, by teaching school, to a profession of some kind. Then her poor health had been a reason. The young man has been very patient and I do not suppose realized that her mind had anything to do with putting the date off so many times. But he came to the conclusion it must be she did not love him

sufficiently and wrote to that effect and we think the engagement is broken. In those spells she says she is 'broken-hearted,' and nothing can take the 'pain out of her heart,' that 'no one cares or understands,' that 'no one belongs to her,' till it is very distressing, but she never mentions his name or tells us her trouble, but wants to make us think her worry is all about the boys' failure in life. My sister can see now that ———'s mind has not been entirely right for several years at times. And I suppose she has been suffering from this trouble since about fifteen or sixteen years of age. She has always been a great student, graduated from the ——— Normal and the State University; has taught school for several years and her pupils love her so much they always want her to come back. She tried it one week this fall but had to resign."

Status: 12. VII. 1913. Weight 132 (last year 130 $\frac{1}{2}$). Nocturia and dysuria present. Neck shows enlarged thyroid (circumference 31.5 and 34 cm). Slight rotary nystagmus. BP, 85-109. Pulse, 108. Heart and chest negative. Right hypochondrium slightly tender. Left groin very tender. Pushing on left leg causes pain in back. Uterus retroflexed, not tender. Bladder very tender. Tongue serrated. Urine: acid, 1028, indicanuria, many bacteria in fresh specimen, much epithelium. Blood: Hb. 80; Rbc. 5,600,000; Wbc., 15,300; polys. 64; monos. 25; eosin. 7. (amphophiles 22).

24. VII. 13. Entered hospital for treatment. T. 97.6, 98.4; P. 80-96; R. 20-24. BP. 80-100-110. Dysuria. Sleep poor. Has been weeping much at home. Twitches arrhythmically.

25. VII. 13. Under ether, uterus dilated, Naboth-

ian cysts opened, erosions curetted, etc. Left hospital after 10 days.

5. IX. 13. Office consultation. Still nervous. Nocturia. Pain in left hypochondrium. Neck 31 and 33 cm. Weight 131.

21. IX. 13. Patient's statement of condition:

"Pulse varies from 120 to 130. Pain in side—two distinct and separate pains, one a dull ache, the other sharper and feels as if part of my anatomy were contracting—brings me up with a start at times. Pain under ribs part of time. Pain in back nearly all the time. Pain in stomach has been very severe for some seven days. The sharp pains extend further down into the abdomen than formerly. My throat bothers me a very great deal—feels as if something were choking me. Red pimples occur all over my body. The slightest blow makes an ugly black spot. My skin is rough and dry and scales off constantly. * * * I have no ambition or enthusiasm—don't seem to care about living. It is horrible to feel this way. I am sure I don't understand why I do."

6. X. 13. From patient's statement:

"Condition of tongue—not as badly coated but more highly decorated around the edge. Appetite—none at all, but eat from sense of duty. Digestion is fairly good. Sleep—very restless and am forced usually to resort to sleeping tablets. Bowels act three or four times during day. Kidneys either act very frequently or rarely. In either case, the amount is small. There is always an action during the night and frequently three or four. Pain—not as much in stomach and under ribs. Pain in back and side is much the same. Opposite the heavy pain over my heart, there is a dull pain under the left shoulder

blade. I have been having a heavy dull ache in my head and when I stand it becomes a throbbing pain accompanied by dizziness. When I was ill last week I suffered very much with pains in my side and back. There was no flow but a discharge."

4. XI. 13. Daily weeping—sobbing—nightmares. Weight 127. Pain in left sacral region most of the time. Coarse tremor of hands and tongue. Pain in left groin when defecating. Neck 30.5 and 32.5. Urine full of bacilli (motile) with pus.

12. XI. 13. From patient's statement:

"I was so tired and weak when I arrived in ——— that I sank almost at once into a comatose state. The last thing I remembered was vigorously and emphatically protesting with the girls not to send for you—I knew I would be all right in the morning. I felt this manifestation of coma enveloping me when I was in your office—I think it was this condition of mind that made me so stupid. Uncle (fictitious—G. H. H.) says you understand why I always exhibit my very worst self when I get nervous and that I must not worry about it, that it will come out all right, when I get less nervous and stronger. He's such a comforting Uncle. I have been having a little fever each day since coming home. Since beginning the medicine and enemas I have suffered with severe burning pains very low down in the abdomen. The pains are more severe when the kidneys act. They act six or seven times during the night."

30. XI. 13. Mental condition worse rather than better—confused. Visions of father who had died two years before. Indicanuria persists with bacilluria. Re-enters hospital.

2. XII. 13. Endometritis with profuse secretion.

Rectum still inflamed. Renal excretion of phthalein 28% in 1 hr., 56% in 2 hrs.

Blood: Hb. 90, Wbc. 7500, polys. 80, eosin. 5, monos. 22 (amphophiles 22%). Urine culture, staphylococcus.

8. XII. 13. Hysterical delirium caused by mother's visit.

17. XII. 13. Tenderness in left hip persists; it seems to include both muscles and bones.

29. XII. 13. Cervix practically normal.

1. I. 14. Tenderness in left groin very slight. Patient cannot bring her fore fingers together with eyes shut.

10. I. 14. Still indicanuria. Earthy phosphates.

22. I. 14. Better but cannot collect thoughts or remember recent events. Still visits her father in her dreams. Still has far-away look in her eyes. Pain in side and headache after exercise.

14. III. 14. Just returned from spending a month in a sanatorium for mental disease. The contact with the really insane has brought about self-control. She still feels a "hurt inside" which she cannot explain and thinks that it has been there since father's death. No memory of her last few years.

A letter about April 28, 1914, gives her own statement of her symptoms thus:

"At night I am afraid to go to sleep and afraid to remain awake. My heart and soul are so hurt that I don't feel I can endure it much longer. When I do sleep I dream Miss ——, mother and you stand around my bed exclaiming in derision, 'You are not a truthful person; we don't trust you; you are not good like your friends,' and oh! the scorn in your voices. Then, often I plead with you to believe in me and

show me what to do, you all refuse and desert me. At this point I find myself screaming or sobbing.

"I was beginning to feel so much better the last few days I was in Colorado. But nothing seems to help the weight in my head now. I am out doors nearly all day working in my garden. I work until I can endure the feeling of wrong doing no longer, then I have to cry it out and begin over again. I never have a moment's peace. I am beginning to think I shall never be a normal person again. I have forgotten how to smile or be able to bring joy to anyone. I am so wretchedly unhappy—I find myself imagining all kinds of things about myself that would make me different from good people.

"The last time I menstruated I began to menstruate four or five days too soon. The nature of the discharge indicated I had taken cold some way. I am so dizzy-headed, have a bad taste in my mouth and have very sluggish bowel action and bad stomach."

10. IX. 14. Her mythical uncle still "writes" to her.

4. XII. 14. Menses accompanied by a delirium. Relieved by corpus luteum. Urine negative. Is a pupil nurse in a hospital.

9. IV. 15. Has lost 25 pounds. Now has sore throat and grip.

4. VIII. 15. Pain in left kidney, with frequency and painful micturition.

2. IX. 15. Laparotomy—Hertzler—A fibroma of the round ligament 3.5 cm. in diameter removed. Left ovary senile. Right only slightly better—neither removed.

5. IX. 15. Culture of urine shows a Gram negative bacillus still present.

25. IX. 15. Constant back and left side ache. Wob-
bly on her feet. Troubled by dreams.

10. XII. 15. Left kidney and ureter still tender.

23. II. 16. Patient requires corpus luteum at every
menstrual season. Mental confusion present but can
be controlled by this remedy.

30. I. 17. Weight 144½. Still shows nervous
weakness at menstrual season, but can do her work.
Backache and left side ache.

18. IV. 17. Frequent micturition. Sore throat
Tired out. Mentally clear.

13. IX. 17. Blood: Hb. 100; Rbc. 4,600,000; Wbc.
9000; polys. 71; eosin. 3; monos 25. Vaccinia with
infected arm. Mentally clear.

SUMMARY

A young, university-bred woman who has always
suffered from dysmenorrhea, practically since the
onset of puberty, after teaching in a high school for
two years, alarms her friends on account of her men-
tal imbalance. Her own account of her condition
would place it among the melancholias. But her
physical condition is also bad on account of neglected
pyelitis and cervicitis and constipation. Treatment
for her physical condition, with rest in a convalescent
home, slowly brought her out of her melancholia.
But not until corpus luteum was given at the men-
strual season did she clear up sufficiently to make
herself practically useful. The monthly attacks are
of the confusional nature—melancholy because con-
fused. The young woman is now successfully carry-
ing on her chosen work.

DISCUSSION

In this case the connection between the ovarian
dysfunction and the mental confusion was incontro-

vertible. The other physical conditions—the back-ache, the pyelitis, the vaccinia, etc.—came and went without disturbing the patient's mental condition. But the ovarian dysfunction produced regularly the mental confusion. The mental confusion seemed to disappear as regularly upon the administration of corpus luteum (either H. W. & D.'s "lutein," or P. D. & Co.'s ampoules of soluble extract). The patient grew steadily stronger and the attacks of confusion more fleeting, so that at the end of the story she was not incapacitated for work at any time during the menstrual cycle. We were rather slow in arriving at this conclusion, and worked first on the hypothesis of its being a base hyperthyroidism. Then, as this syndrome disappeared, we thought of Freud's theories; and then, as the mind became clearer, of simple hysteria. But in the end when all the complicating symptoms subsided it seemed clear that the disease was of the confusional type and due to atrophic ovaries.

The interesting finding of the very rare fibroma of the round ligament, and its removal, seemed to have very little bearing or influence on the mental condition, although the operation relieved some of the dysmenorrhea.

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DIABETES INSIPIDUS

Ketil Motzfeldt, M. D., University Clinic,
Christiania, Norway.

Diabetes insipidus has for centuries been recognized as a distinct clinical entity, the main symptom of which is polyuria without pathological content in the urine. The etiology, however, has been obscure.

Older writers have distinguished between an "idiopathic" and a "symptomatic" form, while more recent authors have sought by the functional kidney tests to establish a distinct division between primary polyuria and primary polydipsia. It has also been suggested to reserve the term diabetes insipidus for the "true" cases, that is for the primary polyurias due to an insufficient ability of the kidneys to produce a concentrated urine.

During recent years new viewpoints have been advanced of far reaching significance for the conception of the etiology and pathology of this disease, — views that have been reflected in the therapy, which at present seems to be more promising than has previously been the case. Although many obscure questions remain to be solved, it now appears justifiable to classify the disease as a disorder of the pituitary body. There are many cases in which this cause is beyond doubt, and probably the majority of the "true" diabetes insipidus cases will turn out to be of pituitary origin.

It has long been known that polyuria often occurs after traumatic lesions of the skull, and that it is a frequent symptom of certain nervous diseases, organic as well as functional.

Claude Bernard's celebrated piqure (1854) threw some light upon these facts, and he believed that he had discovered a "centre" for diabetes insipidus. Later investigations, however, have shown that polyuria will result from lesions of many other parts of the nervous system.

These observations gained in importance, as Magnus and Schäfer (1901) showed that the pituitary extracts had certain diuretic properties. This statement has led to considerable confusion and it has but recently been recognized that the effect really is antidiuretic.

Clinically the direct relationship between diabetes insipidus and the pituitary body was first pointed out by Frank (1912), and during the few years that have elapsed since, similar cases have been reported where this relationship is unquestionable.

As far as our present, limited knowledge goes, the most frequent pathological findings are tumors, syphilis and tuberculosis.

The pituitary adenomas, which are the most frequent causes of acromegaly, only exceptionally lead to polyuria, and little is known about the effect of the pituitary cysts. In most of the cases there have been found malignant tumors, either of the neighborhood, secondarily involving the pituitary, or in the gland itself. Metastases from cancer are especially prone to locate in the hypophysis.

The frequency of a syphilitic history in these cases has long been known. Anatomically the usual finding is syphilitic basal meningitis. This probably in some way interferes with the functional activity of the hypophysis. In a few instances there were syphilitic lesions of the gland proper.

In many of the cases of diabetes insipidus on record the patients have been suffering from pulmonary tuberculosis, but this fact has not attracted much attention. Of recent years careful anatomical investigations, however, have shown actual tuberculosis of the pituitary body, sometimes with total destruction of the gland.

These changes are easily overlooked, and in some cases the lesion has not been discovered until the microscope has revealed it. Negative findings, where the hypophysis has not been specially examined, therefore, amount to little.

There are, furthermore, as I have reason to believe, a certain number of cases due to atrophy or congenital hypoplasia of the gland. It is well known that polyuria often sets in during or after acute infectious diseases, and also how apt the ductless glands in general are to be damaged by infections. It is a common experience, gained in experimental as well as in clinical surgery of the hypophysis, that polyuria often occurs after removal or injury to the gland.

Most writers on this subject have supported the theory that these conditions have acted as stimuli for the pituitary, in accordance with the views of Magnus and Schäfer. But as there are some cases where the entire gland has been destroyed, we are obliged to drop this hypothesis and assume a hypo-function of the gland. Some cases have shown a total destruction of the posterior lobe, while the anterior has remained intact.

During the past four years, or since attention has been directed to the pituitary body as concerned in this disease, there has not been reported a single

autopsy finding in which this gland has not been in some way involved.

These cases are not numerous and they are scattered in the literature of many countries, and a presentation of the features common to them has not yet been given. By making retrospective diagnosis in the older diabetes insipidus literature I have been able to add a number of cases where the pituitary origin can be regarded as pretty well established. On this basis I will now outline some features of the clinical picture. It has been surprising to see how relatively clear-cut and uniform this condition is, when facts which were previously considered of minor importance are taken into account. The picture is in general agreement with what the textbooks give as the symptoms of diabetes insipidus, without any regard to the pituitary origin. Adiposity is frequently mentioned, but it seldom reaches any extreme degree. In the few cases where it has been tested, there has been found a high carbohydrate tolerance. Almost as common as adiposity is sexual underdevelopment, the degree of which will be dependent as well upon the seriousness of the disease as upon the age at the onset. If the polyuria sets in during childhood, puberty will very likely be delayed or entirely lacking and the patient remain in a more or less pronounced infantile state. When the onset has come in adult age, regressive changes in the sexual organs have sometimes been noted. Impotency and amenorrhoea are among the most constant symptoms, and usually set in simultaneously with the polyuria which in most instances starts quite suddenly. The secondary sex characteristics show the same changes. The growth of hair in the

armpits and on the pubes is scanty, and even marked loss of hair may come on shortly after the onset, though this is comparatively rare. The growth of the beard is apt to be scanty and slow, while there are usually no changes in the hair on the head, and the eyebrows are also intact. This last mentioned fact is in distinction from hypothyroidism, where the "eyebrow sign" is said to be of value.

These patients usually suffer from constant fatigue and are troubled with a never-ceasing lassitude; in other words there is a more or less marked asthenia. In many cases psychic alterations also take place, such as somnolence and apathy, sometimes accompanied by depression and melancholia.

The skin is usually dry and these patients perspire very little. Another valuable sign is the slightly subnormal temperature. Apart from these general manifestations there are certain symptoms which are directly pointing to the hypophysis, such as enlargement of the sella turcica and bitemporal hemianopsia. Neither of these findings are very frequent, and negative results do not speak against the pituitary diagnosis. The combination of polyuria and hemianopsia has long been known, and the visual disturbance is often of a peculiarly short duration, the *hemianopsia fugax*. All the distressing symptoms of an intracranial tumor may of course be seen in some cases.

It could not be expected to find all or even the majority of the above mentioned symptoms and manifestations in each case. However, I believe it will be very rare, in cases of primary polyuria, not to find anything pointing towards the pituitary body. There seem to be two fairly distinct types: the obese,

indolent; and the lean, infantile type. The family history does not give definite information, although some instances have shown a pronounced hereditary tendency. The complaint, which causes the patient to consult the doctor, is almost invariably polyuria, but when the degree is only slight the most distressing feature has been weakness or headache, and very rarely, eye troubles.

This varying picture will naturally suggest a disease of different ductless glands, but space will not permit me here to enter into a discussion of the intimate relationship between these glands. However, all of these signs can, with apparent probability, be referred to the hypophysis.

As mentioned, pathological experience has shown that it is no longer permissible to assume an excess of pituitary secretion. It will therefore be of interest to see how the disease compares with the hypofunction of the gland. The picture of this condition has of late been brought out in an admirably clear way,—by Cushing's work especially. It is sufficient to point out what he regards as the four cardinal symptoms:

1. High carbohydrate tolerance.
2. Subnormal temperature, slow pulse, low blood pressure.
3. Drowsiness and sleepiness.
4. Asthenia.

Anhidrosis, scanty growth of hair, sexual hypoplasia, impotency and amenorrhoea also belong to the picture, and it is now pretty well established that Froehlich's syndrome, the dystrophia adiposo-genitalis, is due to hypopituitarism.

The correspondence is so striking and obvious indeed, that further comment is unnecessary. Here I..

wish, however, to emphasize that it is not unusual to see very marked cases of adiposo-genital dystrophy or other cases of hypopituitarism with a normal output of urine. The functional activity of the posterior lobe seems to be well specialized.

Usually the diagnosis is easy when the conditions just emphasized are taken into consideration.

It is doubtful whether a subcutaneous injection with some pituitary extract is of diagnostic value, as the antidiuretic effect seems to be a general physiological action, not limited to the cases of pituitary insufficiency.

Psychic treatment or forced restriction of water, sometimes valuable in primary polydipsia, has not proven efficacious in "true" cases. A diet poor in chlorides and nitrogen has been the main treatment and has been able to lower the output to a certain extent. On the whole, however, the treatment has been rather unsatisfactory; none of the drugs recommended is of special value. Opium will sometimes decrease the thirst and in that way lower the output without exerting any influence on the concentration. The only remedy which has power to check polyuria and concentrate the urine is the extract of the posterior lobe of the hypophysis. A subcutaneous injection with an ampoule of some of the usual commercial preparations will probably be sufficient to exert a very marked influence on the output. This effect will usually show in a few hours and reach its maximum in 4-5 hours. Unfortunately the effect is not lasting and the output will probably be high again the next day. There are, however, cases on record where the diuresis has been checked for weeks afterwards. The injections are well borne; paleness,

slight headache and ringing in the ears may occur, but only last for a few hours.

Intravenous injections are not advisable as they may lead to collapse.

As this treatment cannot be kept up for a long period, it would be a great advantage if treatment by mouth might prove of some value. This mode of administration is far less efficacious, but is without discomfort and, as far as our present knowledge goes, is free from danger, even in large doses. Such treatment, therefore, can be carried on indefinitely.

The sufficient dose has to be tried out in each case, and as a rule very large doses are required, the amount of active material absorbed from the intestinal tract being evidently very small. The commercial dry preparations will very likely prove inefficient. Wherever possible the treatment should be tried with fresh material from the abattoir, as well for economical reasons as for the fact that the dried preparations are less potent. As it is very difficult, at least in pronounced cases, to check the 24 hour amount of urine in this way, it will probably be the best plan to confine the therapeutic aims to securing a normal output during the night and thus relieve the patient of one of the most distressing features—the restless nights.

One patient who has been under my care for the past two years has been very much improved by an intermittent pituitary feeding. She has taken from two to seven fresh pituitary bodies from cattle every evening. The output has hereby been checked during the night,—usually decreasing from nearly 2500 cc. to approximately 300 cc. At the same time the general state of health has improved consider-

ably, adiposity and drowsiness having disappeared, and menses have been re-established. Feeding the anterior lobe alone does not lead to this effect. This patient also shows another interesting feature. At present one hypophysis will have the same effect as, two years ago, could not be obtained by less than seven glands. The most satisfactory explanation of this fact will probably be that the hypophysis of the patient during the functional rest by the extraneous help has gained in secretory ability. This would be analogous to the explanation of the increased sugar tolerance in diabetes mellitus after alimentary rest, and is more in harmony with the laws of general physiology, than the usual assumption that the pituitary extracts stimulate the pituitary body.

This is an entirely new field for organotherapy, and only the future can tell how many cases will be benefited by treatment along these lines.

In the syphilitic cases an energetic antiluetic treatment will often prove of lasting value. The cases due to tumor have to be treated according to general surgical principles. In one case where the patient presented some evidence of brain tumor, the output was checked by a lumbar puncture.

As previously mentioned there has been confusion as to the effect of the pituitary extracts on the flow of urine. Recent clinical investigations, and among them my own work, have, however, shown quite definitely that the extracts from the posterior lobe physiologically serve to secure a normal concentration of the urine. I have gone more deeply into this question experimentally and my results indicate that this action is exerted on the sympathetic nervous system, especially on the vaso-motor nerves for

the renal vessels. These results may lead to a broader view of the polyurias. When the sympathetic system does not get its normal stimuli, as is the case in organic lesions with destruction of the posterior lobe of the pituitary body, polyuria will result. In functional disorders of the nervous system polyuria of varying degree and duration is frequently seen. The most satisfactory explanation in these cases seems to be to assume a temporary lack of tone of the vasomotor fibres in the sympathetic nervous system. The "urina spastica" of the old observers is probably rather a "urina atonica," indicating a lowered tone of the renal vaso-constrictors. Possibly these pathological polyurias of varying severity and of apparently different origin, ranging from the occasional polyuria of the neurotics to the polyurias of extreme degree in diabetes insipidus, can be linked together by the sympathetic nervous system.

Though this field is in urgent need of further investigation, it has become clear that diabetes insipidus is merely a symptomatic evidence of disordered pituitary function, and that it is due to a deficit of secretion. In consequence, administration of pituitary preparations will be the proper therapy.

VASCULAR CHANGES PRODUCED BY ADRENALIN IN VERTEBRATES

Frank A. Hartman, Leslie G. Kilborn and
Ross S. Lang.

(From the Laboratory of Physiology, University of Toronto.)

The majority of physiologists still teach that adrenalin is essentially constrictor in its effect upon the blood vessels, ignoring the fact that doses which are probably physiological in their magnitude cause dilatation in a large proportion of vessels. These teachings are founded upon the older experiments in which massive doses of the hormone were used. Such amounts of adrenalin are probably never secreted by the adrenal glands (1, 2, 3). Although in the last few years it has been conclusively proven that small quantities of adrenalin cause vasodilatation and a fall in blood pressure as a result (4, 5, 6, 10) the fact is still ignored. This situation may be easily explained, for, among the common laboratory mammals some give evidence of vasodilatation while others consistently fail to do so. These animals which have been found to give positive proof of dilatation belong to the carnivores, while those that do not belong to the rodents. In face of the experimental facts it was as easy to believe the response of cats and dogs exceptional, as that the effect in rabbits was different from that in other animals. In view of this disagreement, it was perfectly natural to assume that the action of adrenalin in cats and dogs was unusual, since it did not conform to other beliefs such as the absence of vasodilator fibers in the sympathetic nervous system.

This research was undertaken with the object of determining whether the dilator action of adrenalin was confined to the carnivores. It was conceivable that other groups might give a similar action, although none were known to do so; accordingly a survey was made of all the groups available. The results have been sufficient to remove all doubt as to the general occurrence of vasodilatation from adrenalin.

A brief sketch of our present knowledge concerning this dilatation is needed as a foundation for this research. The nature of the mechanism on which adrenalin acts was worked out largely by experiments upon cats and dogs. Those experiments have proven that a differential effect is produced—dilatation in skeletal muscle (5, 6) and intestine, (large doses)—constriction in skin (6), intestine (small doses), kidney (8, 10), bone (16), thyroid (15) and spleen (7, 10). With small doses, the vessels in skeletal muscle more than counteract the constriction in the skin and abdominal viscera, so that a fall in blood pressure results. When the amount of adrenalin is sufficiently large, the constriction of skin and visceral vessels (excepting intestine) becomes great enough to more than compensate for the dilatation in skeletal muscle, thus producing a rise in blood pressure.

The dilatation produced by adrenalin has been shown to be brought about by dilator mechanisms located in the sympathetic and dorsal root ganglia (12) as well as in a "terminal" receptive substance which has been called the myoneural junction (13, 14). The latter, a counterpart of the constrictor myoneural junction, is assumed to be associated with dilator fibers.

METHODS

The methods employed in this research were those already described in work from this laboratory (10, 11, 12).

All animals, unless otherwise stated, were anaesthetized with ether. Blood pressure was taken from the carotid artery, except in the fowl, in which case the sciatic artery was used. Injections were made into the jugular vein.

Solutions of adrenalin chloride were made up by diluting the 1:1,000 preparation of Parke, Davis & Co. Volume changes were registered by means of Brodie's bellows. The plethysmograph for the limb was either of the type which enclosed the paw, or else like a cuff, so that the paw might be excluded (13). It was necessary to use artificial respiration in the fowl when the abdomen was opened.

RESULTS

Reptilia (Chelydra)

A snapping turtle (5.3 kgm.) was employed as representative of the reptiles. Doses of adrenalin as small as 0.2 c.c., 1:1,000,000 were tried with no effect upon the blood pressure. Even 0.5 c.c., 1:100,000 had no effect. 1.0 c.c., of the latter concentration caused a rise from 46 mm. to 50 mm. 0.4 c.c. 1:10,000 caused a change from 44 to 54 mm. 1.0 c.c. of the same solution produced about the same effect. Indeed it was found that with large doses, sensitiveness to adrenalin was soon lost. 0.5 c.c., 1:1,000 following the above, increased the pressure only 6 mm. from 51 mm. Repetition of this had no effect, nor did twice the dose. Two months later, the blood pressure and intestinal effects were studied in the same animal. The blood pressure responses were similar. The in-

testine always gave constriction when there was any effect. This was observed with doses ranging from 0.5 c.c., 1:100,000 to 3.0 c.c., 1:10,000. After the latter dose, 1.0 c.c., 1:1,000 produced no intestinal change.

Although only tentative conclusions can be drawn from a single animal, they are at least valuable when considered in connection with other vertebrates low in the scale. We have found that the vascular system of the turtle is not very sensitive to adrenalin and that there is evidence of only a constrictor mechanism. The failure to obtain a fall in blood pressure or a dilatation of the intestine indicate an absence of the dilator mechanisms.

Aves (Gallus)

The fowl serves as an example of the warm blooded vertebrate other than the mammal. It is much more sensitive to adrenalin than are the cold-blooded vertebrates. Moreover it does not easily lose its power to respond to this hormone, even after numerous doses.

Constriction is the only effect produced by adrenalin in the fowl. Both the limb (Fig. 1) and the intes-

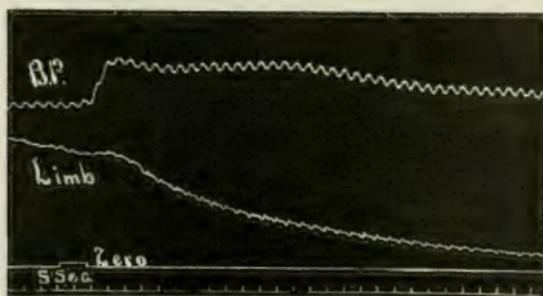


FIG. 1

Effect of 0.5 c.c., 1:100,000 adrenalin upon the limb in the fowl, 1.0 kgm. (Reduced %.)

tine (Fig. 2) respond in this way. From a study of

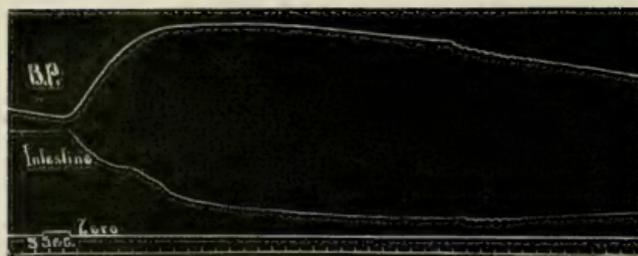


FIG. 2
Prolonged constriction of the intestine in the fowl. (0.92 kgm.)
Produced by 0.5 c.c., 1:10,000 adrenalin. (Reduced $\frac{2}{3}$).

seven animals no evidence of the existence of the adrenalin vasodilator mechanisms (Table 1) has been found.

TABLE I.
RESPONSE TO ADRENALIN IN THE FOWL

Weight in kgm.	Dose	Blood pressure change in mm. of mercury	Limb	Intestine
1.1	0.2 cc 1:1,000,000		Slight constriction	
	0.5 cc 1:100,000	109-138	Constriction	
	1.0 cc "	114-182	Marked constriction	
1.0	0.1 cc 1:100,000	118-130	Constriction	
	0.5 cc "	106-134	Marked constriction	
0.92	0.2 cc "	65-79	Constriction	Constriction
	0.5 cc "	95-175		Marked constriction
0.85	0.2 cc 1:1,000,000	52-54	Constriction	
	0.5 cc 1:100,000	55-65	Marked constriction	Constriction
	1.0 cc "	80-119		Constriction
0.95	0.5 cc 1:100,000			Constriction
	0.5 cc 1:10,000			Very marked constriction

MAMMALIA

Marsupialia (Didelphys)

A single opossum about two-thirds grown (weight 1.3 kgm.) was used in this research. A fall in blood

pressure (Fig. 3) was easily obtained from adrenalin.

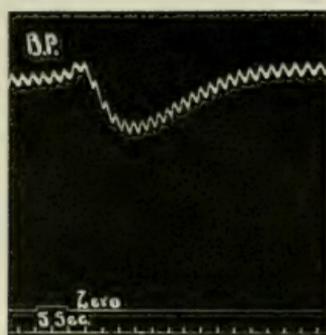


FIG. 3
Blood pressure fall in the opossum produced by 0.2 c.c.,
1:100,000 adrenalin. (Reduced %.)

This was usually preceded by a brief rise. With larger doses pure pressor effects resulted.

Although the limb included in the plethysmograph possessed a smaller proportion of muscle than that in most mammals it gave active dilatation (Fig. 4) ex-

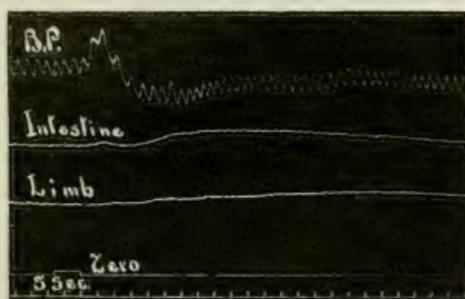


FIG. 4
Dilatation of limb and intestine in the opossum caused by a
depressor dose of adrenalin, 0.2 c.c., 1:10,000. (Reduced %.)

cept when large doses were used. The intestine dilated actively in response to adrenalin (Fig. 5), the dilatation becoming very marked with large doses (Table II).

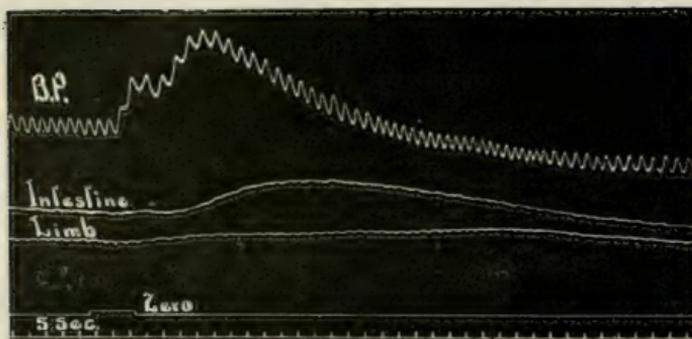


FIG. 5
Marked dilatation of the intestine in the opossum resulting from the injection of a pressor dose of adrenalin 0.5 c.c., 1:10,000. (Reduced $\frac{3}{5}$.)

TABLE II.
RESPONSE OF THE OPOSSUM TO ADRENALIN

Dose	Blood pressure change in mm. of mercury	Response of limb	Response of Intestine
0.05 cc 1:100,000	140-142-136		
0.1 cc "	138-144-128		Dilatation
0.2 cc "	144-151-135	Slight con- striction	Dilatation
0.5 cc "	118-125-106	Dilatation	Constriction and dilatation
0.5 cc 1:10,000	123-180	Small dilatation	Marked dilata- tion
1.0 cc "	98-215	Small dilatation	Marked dilata- tion

We may conclude then that the opossum and probably all marsupials possess adrenalin vasodilator mechanisms similar to those in the cat and dog.

UNGULATA

Perissodactyla (Equus)

Unfortunately the horse which we used was in such poor condition that it cannot be considered typical. It was anaesthetized with chloroform, and 1:1000 adrenalin was injected in every instance. In no case was there a fall in blood pressure. 5.0 c.c., adrenalin changed the pressure from 114 mm. to 162 mm.

10.0 c.c. increased the pressure from 80 to 260 mm.

Attempts to produce dilatation of the intestine were successful when 25.0 c.c. was injected, there being a strong constriction followed by a dilatation. 20.0 c.c. produced constriction only.

Intestinal dilatation was the only indication of the presence of an adrenalin vasodilator mechanism in the horse.

Artiodactyla (Capra)

In view of the unsatisfactory condition of the horse, it was imperative that another animal belonging to the ungulates be tried. An experiment with a goat (weight 13.0 kgm.) removed all doubt as to the existence of adrenalin vasodilator mechanisms in this order. A depressor effect (Fig. 6) as well as

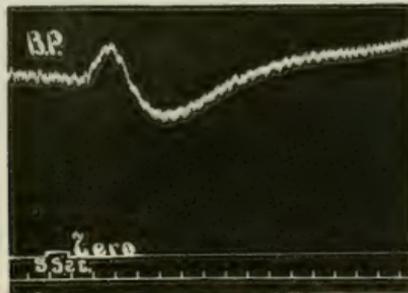


FIG. 6
Fall in blood pressure from 0.4 c.c., 1:100,000 adrenalin in the goat, 13.0 kgm. (Reduced $\frac{1}{2}$.)

active dilatation of the limb (Fig. 7) could be obtained from the injection of small amounts of adrenalin. However nothing but constriction in the intestine (Fig. 8) resulted from even large doses of adrenalin until perfusion was attempted. A loop of intestine, with nerves intact, but shut off from the general circulation and perfused with oxygenated Ringer's solution gave pronounced dilatation both when

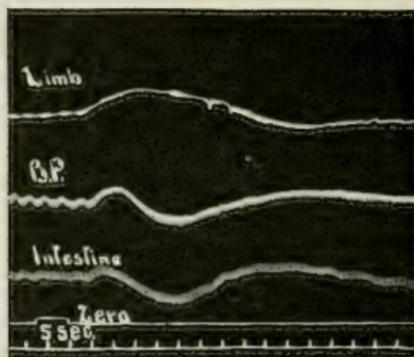


FIG. 7
Dilatation of the limb and constriction of the Intestine produced by 0.5 c.c., 1:100,000 adrenalin in the goat. (Reduced $\frac{1}{2}$.)

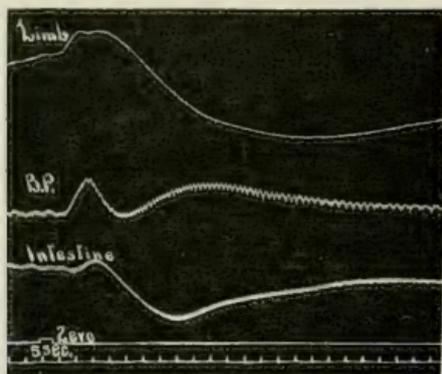


FIG. 8
Constriction in the limb and intestine caused by 1.0 c.c., 1:10,000 adrenalin, goat. (Reduced %.)

TABLE III.
RESPONSE OF THE GOAT TO ADRENALIN

Dose	Blood pressure, mm. of mercury	Change in Limb	Change in Intestine
0.4 cc 1:100,000	110-128-94	Dilatation	
0.5 cc "	62- 68-53	Dilatation	Constriction
0.7 cc "	72- 80-61	Dilatation and Constriction	Constriction
0.3 cc 1:20,000	80- 92-66	Constriction	Constriction
1.0 cc "	84-106	Constriction	Constriction
1.0 cc "	28- 26		Dilatation*
2.0 cc "			Dilatation*

*Intestine perfused.

1.0 c.c., and when 2.0 c.c., 1:20,000 adrenalin were injected into the jugular vein. (Table III).

Our experiments thus indicate that the mechanisms for dilatation from adrenalin are found in the ungulates.

CARNIVORA

Cats and dogs were the only Mammals known to possess adrenalin vasodilator mechanisms before this research was undertaken. We were interested in finding out whether all families in this order reacted to adrenalin in the same way. Two other families were therefore investigated, viz.—the *mustelidæ* and the *procyonidæ*.

Mustelidæ (Putorius)

Study of an old ferret (weight 0.6 kgm.) indicated the presence of the vasodilator mechanisms. This evidence was largely limited to depressor effects of adrenalin, 0.2 c.c., 1:1,000,000 causing a fall of 6 mm. from 152 mm. In one instance dilatation of the limb was obtained.

Procyonidæ (Procyon)

Typical adrenalin vasodilator effects were obtained in the raccoon. A marked fall in blood pressure was produced by small doses. (Fig. 9). Dilatation of

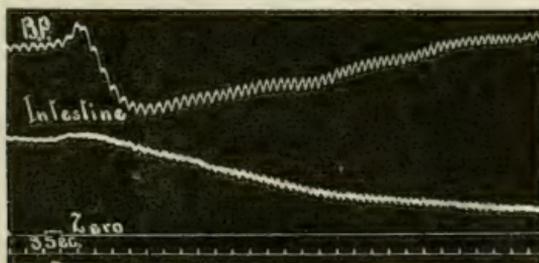


FIG. 9
Fall in blood pressure and constriction of the intestine produced by the injection of 0.2 c.c., 1:100,000 adrenalin. Raccoon. (Reduced %.)

the limb sometimes resulted from depressor doses. Constriction (Fig. 9) or constriction and dilatation (Fig. 10) occurred in the intestine depending upon

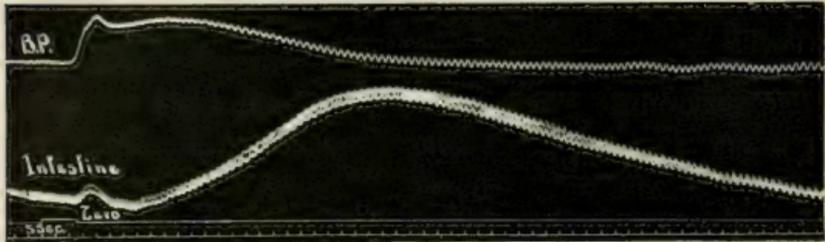


FIG. 10
Dilatation of the intestine produced by 0.3 c.c., 1:10,000 adrenalin, raccoon. (Reduced $\frac{2}{3}$.)

the amount of adrenalin injected, just as in cats and dogs.

RODENTIA

A reason already given that the cat and the dog have been considered possibly exceptions in their behavior toward adrenalin is the fact that the rabbit does not give the same results. We will show, however, judging from the rat and rabbit that rodents are an exception in their behavior toward adrenalin and that the reaction of the cat and dog is the typical one for most mammals.

Muridæ (Mus)

A fall in blood pressure could not be obtained in the white rat. In an animal weighing 0.23 kgm., 0.05 c.c., 1:100,000 adrenalin caused a pure rise from 69 to 83 mm. Smaller doses such as 0.3 c.c., 1:1,000,000 had no effect.

Leporidæ (Lepus)

We have never obtained evidence of the presence of adrenalin vasodilator mechanisms in the rabbit. At least twelve rabbits have been examined in this

connection. It has always been our experience that whenever a dose of adrenalin is large enough to produce any effect, nothing but a pure rise of blood pressure results.

There might, however, be a differential effect without a fall in blood pressure. In one experiment the coeliac, superior mesenteric, inferior mesenteric and renal arteries were tied (5) without changing the reaction to adrenalin.

The limb reaction was determined in four animals. With small doses a dilatation which appeared to be passive, sometimes occurred. When the amount of adrenalin was increased constriction was produced. (Fig. 11). The presence of active dilatation was

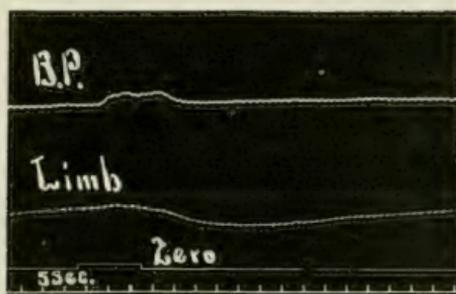


FIG. 11

Constriction of the hind limb of a rabbit (2.4 kgm.) from 0.4 c.c., 1:100,000 adrenalin. (Reduced $\frac{1}{2}$.)

then sought in another way. The hind limb of an animal was perfused with Ringer's solution, and adrenalin was injected into the jugular vein. If dilator mechanisms sensitive to adrenalin, exist in the sympathetic and dorsal root ganglia, the limb under these conditions should respond. The injection of even large doses of adrenalin into the jugular vein was without effect. Injection into the perfusion fluid as it entered the iliac artery was also without

effect in one animal, while in a second rabbit the first two doses (0.5 c.c. and 0.1 c.c., 1:100,000) caused constriction, but later doses had no effect.

In one experiment the sciatic and femoral nerves in one limb had been cut seventeen days before. However no evidence of a terminal dilator mechanism could be obtained. In the cat and dog this has been obtained easily by such a method (13, 14).

Very small passive dilatations were produced in the denervated limb of the rabbit when adrenalin was injected into the general circulation. This limb was perfused later, doses of adrenalin varying from 1:1,000,000 to 1:10,000 concentration being injected into the fluid, but without result.

The reaction of the intestine was observed in four animals. In one, there was small passive dilatation with small doses. The other three constricted with doses of this size. In all there was prolonged constriction with large doses (Fig. 12). As an illustra-

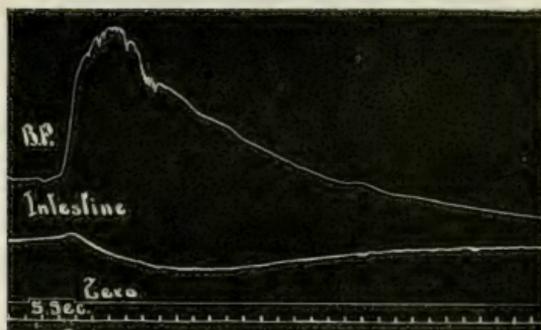


FIG. 12
Constriction of the intestine of a rabbit due to the injection
0.5 c.c., 1:10,000 adrenalin. (Reduced 3%.)

tion of the amount of constriction; a loop 37 c.c. in volume constricted .72 c.c. after the injection of 0.5 c.c., 1:10,000 into the general circulation.

In an unpublished research we have found that there is a dilator mechanism for the kidney located in the aortico-renal ganglion. One of the methods employed has been to apply adrenalin solutions to the ganglion, noting the volume change in the kidney. We did this in a rabbit, but obtained constriction in the kidney instead of dilatation.

We conclude from our results that rodents do not possess adrenalin vasodilator mechanisms.

PRIMATES

Monkey (*Pithecus*)

Adrenalin vasodilator mechanisms are present in the monkey (Table IV). Excellent dilatations of a

TABLE IV.
RESPONSE OF THE MONKEY TO ADRENALIN

Dose	Blood pressure change in mm. of Mercury	Limb	Intestine
0.1 cc 1:100,000	96-101-92	Dilatation	Constriction and slight dilatation
0.4 " "	94- 98-86	Dilatation	
1.0 " "	80- 98	Very marked dilatation	
0.3 " 1:10,000	86-124	Marked dilatation	Marked constriction and dilatation
1.3 " "	64-166	Marked dilatation	Marked constriction and dilatation
2.5 " "	64-177	Marked dilatation and constriction	Marked constriction and dilatation

leg were produced (Figs. 14 and 15) by doses of adrenalin ranging from 0.4 c.c., 1:100,000 to 0.7 c.c., 1:10,000 (weight of animal 5.2 kgm.) (The foot was not included in the plethysmograph). Indeed, a large dose of adrenalin was required to cause reversal in the limb (Fig. 16). By perfusing the limb and injecting adrenalin into the jugular vein we attempted to bring the gangliar mechanism into action, without

result. We thought this might be due to failure of the adrenalin to reach the ganglia on account of

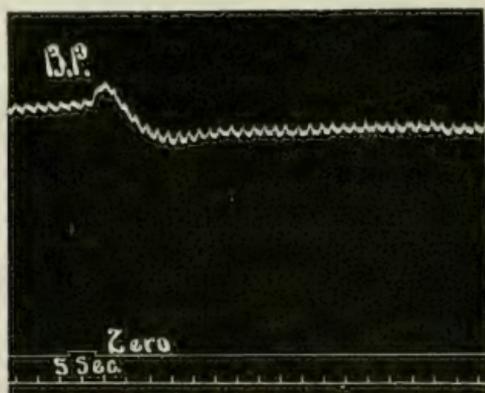


FIG. 13
Fall in blood pressure in the monkey (5.2 kgm.) resulting from 0.4 c.c., 1:100,000 adrenalin. (Reduced $\frac{1}{2}$.)

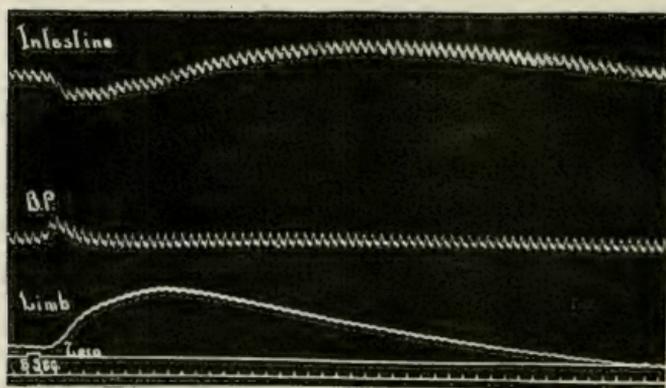


FIG. 14
Response to 0.5 c.c., 1:100,000 adrenalin in the monkey. Constriction followed by dilatation of the intestine. Marked dilatation of the limb. (Reduced $\frac{2}{3}$.)

clamping the aorta too high up, as that has frequently been the case in cats. On the other hand injection of the hormone into the perfusion fluid easily produced dilatation. The explanation, therefore, might be that the vasodilator myoneural junction and not the gan-

gliar mechanism was the source of the dilatation. We are inclined to doubt this as being typical, for there is no reason to believe that the monkey is different from the cat and dog in which the gangliar mechanism is an important source of adrenalin vasodilatation (13).

The intestinal mechanism in the monkey worked

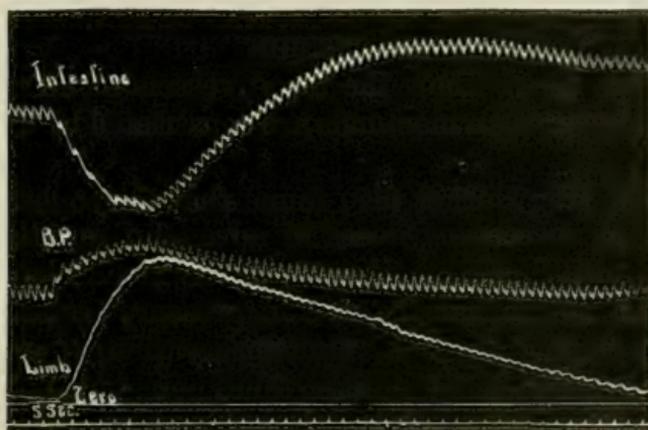


FIG. 15

Effect of a larger dose of adrenalin, 0.3 c.c., 1:10,000 in the monkey. (Reduced $\frac{2}{3}$.)

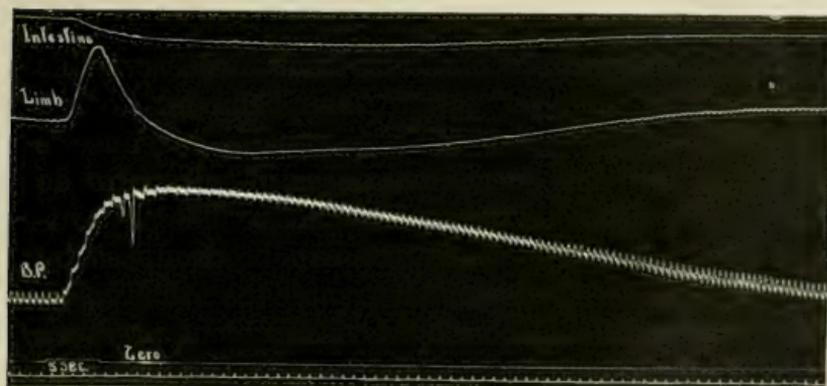


FIG. 16

Reversal in the limb produced by a large dose of adrenalin, 2.5 c.c., 1:10,000 in the monkey. (Reduced $\frac{3}{4}$.)

very well (Figs. 14 and 15) until large doses of adrenalin were used when constriction only was obtained (Fig. 16).

A fall in blood pressure was obtained from the injection of small doses of adrenalin (Fig. 13), but as sometimes happens in cats or dogs the fall became small or almost disappeared after a few doses had been injected (Fig. 14).

DISCUSSION

So far as we know the blood vessels of all vertebrates lower than mammals are constricted by adrenalin.

In the frog Burket (17) found that the constrictor effect of succeeding doses of adrenalin rapidly declines until there remains only a very small response. He also noted that the rise in pressure lasts much longer than in the cat. Our observations upon the turtle are somewhat similar, there being a rapid loss in sensitiveness to adrenalin and a prolonged effect when the rise is produced. In addition attention should be called to the fact that the threshold for a blood pressure response is much higher in the reptiles than in the mammals.

It is of interest to note also that birds resemble mammals in some respects in their behavior toward adrenalin. The threshold for adrenalin response is about as low and successive doses of adrenalin do not readily decrease the sensitiveness. The percentage rise in blood pressure that can be produced by adrenalin in the fowl is much greater than that possible in the reptile, although the rise in blood pressure is more prolonged in the fowl than in the mammal. It may be partly due to the absence of dilator mechanisms which could be affected by adrenalin and thus

tend to offset the constrictor effect. Dale (22) was able partially to paralyze the constrictor mechanism in the fowl, but he obtained no fall in blood pressure from adrenalin.

Besides the carnivores and rodents which have been extensively studied by different investigators, a few observations have been made upon the ungulates and primates. Barger and Dale (18) paralyzed the vaso-constrictor mechanism in the pig and the goat with ergotoxin, but failed to obtain a fall in blood pressure when adrenalin was injected. Barbour and Prince (19), in experiments with perfused hearts obtained dilatation of coronary vessels in the ox, sheep, pig, and rabbit, but constriction in the monkey.

Auer and Meltzer (20) obtained usually a rise, but sometimes also a fall in blood pressure from the intraspinal injection of large amounts of adrenalin in the monkey.

We have been able to show in all orders of mammals which we have studied, except the rodents, that both adrenalin vasodilator mechanisms (for skeletal muscle and intestine) are present. On the other hand, we have been unable to prove the presence of such mechanisms in the rodents. Moreover, no one else (21, 23) has ever been able to produce a fall in blood pressure by the injection of adrenalin in the rabbit. Dale (22) was unable to obtain a reversal by the use of ergot, although he abolished the pressor effect of adrenalin.

Dilatation from adrenalin had been observed in the rabbit. The Meltzers (24) obtained dilatation of the ear vessels of the rabbit from the subcutaneous injection of adrenalin. Ogawa (25) produced dilatation

of the perfused kidney, intestine and hind limbs of the rabbit by adrenalin. However, he usually obtained constriction of the kidney even with dilute solutions. He did not secure a primary dilatation in the limb. We are led to conclude as a result of our experiments that even though adrenalin vasodilatation may occur in the rabbit it is relatively unimportant.

In conclusion, we are justified in assuming that the usual vasomotor reaction in skeletal muscle is dilatation with moderate doses of adrenalin, rodents being exceptional; and because of the uniform occurrence in other mammalian orders as well as the presence in the monkey we have considerable reason for believing that these mechanisms are also present in man.

We wish to thank Lois McPhedran Fraser for assistance in a part of this research.

SUMMARY

1. Birds and reptiles possess no adrenalin vasodilator mechanisms.
2. A small amount of adrenalin produces a fall in blood pressure in marsupials, ungulates, carnivores and primates.
3. Adrenalin vasodilator mechanisms for the limb and intestine are present in marsupials, ungulates, carnivores and primates.
4. Rodents are exceptional in their reaction to adrenalin, vasodilator mechanisms sensitive to this hormone being absent.
5. Dilatation in the blood vessels of skeletal muscle is the usual response to adrenalin in mammals.

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SUPPURATION OF GOITROUS THYROID
FOLLOWING ADMINISTRATION OF
THYROID EXTRACT: A
CASE REPORT

Edward A. Tracy, M. D., Boston.

The patient was a widow, aged 51 years. When first seen she was melancholic and sleepy in the daytime. She had a moderate-sized goitre. Her melancholy was increased, if not caused, by the fact that her son was in prison. A half grain desiccated thyroid after each meal was prescribed.

After a week's administration of the material the right lobe of her thyroid became painful. The treatment was stopped. After two weeks the painful lobe reddened and a week later "broke," three days after the patient, on her own volition, had applied a bread and water poultice. It may be remarked here that the mental condition cleared up rapidly after the administration of the desiccated thyroid.

On seeing her after the poulticing had been done for several days, I was alarmed at the appearance of the sloughing lobe of thyroid. I had her apply a sulpho-naphthol poultice every three hours. After a few days I snipped off the dead thyroid tissue presenting—about the size of a dime—and had her continue antiseptic treatment until healing occurred—four months later. Healing was delayed because of the necessity of the patient to do household duties.

This case illustrates the care with which thyroid extract must be given in such cases. In goitre, with myxedema symptoms, I should commence with half a

grain of desiccated thyroid a day, and watch carefully for the least sign of trouble, such as slight pain in the thyroid. On its appearance omit the medication. Enough may have been given to awaken the dormant tissue to renewed activity. If not, we can carefully renew our medication, and watch again.

A CASE OF PARATHYROID INSUFFICIENCY

Arthur F. Hertz, M. A., M. D., Oxon., F. R. C. P.

(From the Neurological Department, Guy's Hospital, London)

The following case is remarkable in that it is the only one which I have seen in which the symptoms appeared to be due to a functional insufficiency of the parathyroid glands; and I have not found any record elsewhere of a similar case.

Opportunity was afforded to watch this case for over four years, and the result of suitable organo-therapy—the administration of desiccated parathyroid substance—was so decided that one can hardly believe that the symptoms which will be enumerated could have been produced in any other way.

Clinical History—A clerk, aged 47, came under my care late in 1910. When he was 30 years old he first noticed a slight enlargement of the thyroid gland. It gradually became larger and about two years previously—in 1908—it became necessary to remove the greater part of it. After this he remained perfectly well until four months ago, at which time quite suddenly he became greatly depressed and very nervous and restless. He suffered from an irresistible desire to keep moving, and instead of sleeping spent most of the night walking about. He began to be exceedingly tremulous and found that he had great difficulty in writing. There was a continuous fibrillary twitching of the eyelids, but no tetany was present at any time.

The general appearance was not unlike that of a severe case of Graves' disease, but his eyes were

sunken instead of being prominent and the thyroid gland could neither be seen nor felt. When he was taken ill in August (1910) he weighed 191 pounds, but now he weighed only 144 pounds, and despite an increasing appetite—he ate enormously and did not seem to suffer from this—he was losing weight rapidly.

At the time I first saw him with Sir Bertrand Dawson he complained of some difficulty in swallowing and said that the food seemed to stick in his throat. This was shown by a fluoroscopic examination to be the result of irregular spasmodic contractions of the esophagus. He also had some irregular intestinal pains which might be accounted for in a similar manner. While previously he had been accustomed to open his bowels once a day, he now passed three or four large, but otherwise seemingly normal, stools each day. The urine was somewhat reduced in quantity, but otherwise normal.

He was greatly troubled with palpitation and his pulse was constantly about 120. His face and neck were deeply flushed and the secretion of the sweat glands was unaffected. It was noticed that his hair had ceased to grow, though it did not fall out and become thinner. His beard was not growing so fast and while formerly he had his hair cut about every ten days, now six weeks had passed without any noticeable increase in its length. In addition to this he had become completely impotent.

It seemed obvious that the condition was of endocrinous origin, and it was thought possible that the condition resulted from injury to the parathyroid glands during the operation on the thyroid

gland which was performed more than two years previously.

A definite diagnosis was not made and the treatment here outlined was expectant.

Treatment—He was put to bed and beside the ordinary full hospital diet, he received four pints of milk a day. His pulse gradually became slower and the abdominal discomfort disappeared. However, his weight continued to fall until it reached $130\frac{1}{2}$ pounds ten days later. The restlessness was not modified and he found it extremely difficult to stay in bed. He was given large doses of opium and bromides, which had a favorable effect, and he gained slowly in weight until two months later he weighed 159 pounds. During this time desiccated thyroid gland and later Moebius's antithyroid serum were tried, but the former aggravated the symptoms and the latter made him sick.

In February though the pulse was somewhat slower and the restlessness and tremor less marked, his other symptoms were unaltered. He was allowed to get up and returned to his work.

His weight at once began to fall, and in spite of continuing the same diet and both opium and bromides, his weight on June 18th was lower than ever— $127\frac{1}{2}$ pounds. With difficulty he continued his work, but on that day he began to take one-tenth grain of dried ox parathyroid glands (Armour) four times daily, and four days later both the opium and the bromides were discontinued.

The gain in weight was most remarkable. During the first four days he gained $6\frac{1}{2}$ pounds, the next five days 12 pounds, five pounds the next four days

and the same amount during the next six days or a total of $28\frac{1}{2}$ pounds in nineteen days. Coincidentally he became stronger every day, his sleep was better and more refreshing and the restlessness, tremor and dysphagia disappeared, his hair began to grow, the pulse gradually was slowed until it was less than normal, the amount of feces was reduced and the urine increased.

After a month of parathyroid therapy he was almost well, though it was not until he had been taking parathyroid gland for six months that his sexual functions were restored. About seven months after this treatment was instituted—January 11, 1912—his weight was 161 pounds and during that year he gained an additional 14 pounds; and about Christmas, 1912, he discontinued taking the parathyroid gland.

In August, 1913, he was seen again and though his weight had increased 4 pounds (it was now 179 pounds), he was more restless and his pulse was faster, so he was advised to continue to take one-tenth of a grain of the parathyroid gland daily. This was continued for four months and discontinued in November as, peculiarly enough, his face had assumed a brick red color, his throat was somewhat full and the vessels in the neck throbbed. These symptoms, however, disappeared after omitting the parathyroid.

I heard from him in February, 1914, at which time his weight was 189 pounds and he felt perfectly well and strong with no trace of nervousness, although he was working quite hard.

THE RELATION OF THE ADRENAL GLANDS TO SUGAR METABOLISM

Striking effects can be produced by the injection of adrenin. The body contains certain organs, the adrenals, capable of forming adrenin. The actual physiological function of these glands has not been satisfactorily determined. These facts have proven an irresistible stimulus to speculation and theorizing, both upon the part of clinicians and of laboratory investigators. The mysterious etiology of diabetes mellitus has been another potent stimulus to imaginative activity. Under such conditions it was inevitable that the possibility of producing glycosuria by the injection of adrenin should have led to a theory that the adrenals play an important part in sugar metabolism. The hypothesis is intrinsically attractive and has had many adherents. As usual in such cases, when the theory had been formulated a considerable amount of evidence reveals in many instances a partisan attitude,—a conscious or unconscious tendency to make the experiments support the preconceived theory. The existence of this attitude should at once awaken suspicion. To be suspicious of a given theory, however, and to disprove it are two quite different matters. Attractive theories die hard.

Many years ago Claude Bernard discovered that an irritative lesion of the floor of the fourth ventricle could give rise to glycosuria. The lesion was produced by a simple puncture through the roof of the ventricle. This is the so-called "sugar puncture" or piqure.

When the adrenal glands began to receive practical attention at the hands of investigators an attempt was made to correlate the piqure glycosuria with that produced by adrenin. Soon the literature provided the definite "proof" that, in the absence of the adrenal glands, piqure glycosuria could not be produced and that they form, therefore, an essential link in the chain of causation. Without going into a discussion of the technical details of the researches suffice it to say that the experiments cited in proof of the thesis were made upon moribund animals after severe trauma and anesthesia, all of which factors profoundly effect sugar metabolism. Under such circumstances the presence or absence of glycosuria after piqure could not logically be regarded as either proving or disproving the thesis.

Attempts to determine directly the effect of piqure on adrenal discharge were also not lacking. Kahn (1) investigated the matter at some length and concluded that no augmented discharge of adrenin took place after this operation. Later (2) he reinvestigated the problem employing more adequate technique and concluded that, as a matter of fact, the puncture does cause adrenal discharge. However, as Stewart and Rogoff (3) point out Kahn's results are not conclusive because he used a colorimetric method not suited to quantitative work or, when he used the delicate frog-perfusion method, took no note of essential conditions in the donor of the blood tested. Moreover, the quantitative factor was ignored, so far as Kahn's results were regarded as applicable to the problem of glycosuria. Osgood, working in Cannon's laboratory, has shown that to produce glycosuria it is necessary to inject many

times the maximum quantity of adrenin that can be evoked by stimulation of the nerves to the adrenals.

Following Kahn's reports a number of other papers appeared which were mostly of negative tenor and of late years the conviction has been growing that piqure glycosuria is not dependent in any essential way upon adrenal discharge. However, before negative results can be regarded as conclusive it must be shown that all essential conditions of experimental technique have been met. As Stewart and Rogoff maintain this has not hitherto been done. In particular, it must always be proven that the liver contains an adequate supply of glycogen before a failure to produce glycosuria or, what is more significant, hyperglycemia, can have any value as evidence.

The most recent investigation of the problem has been made by Stewart and Rogoff (3) in the Laboratory of Experimental Medicine at Western Reserve University. Use has been made of the fact that a considerable number of rabbits will survive the skillful extirpation of both adrenals and will afterwards have livers well filled with glycogen. A similar fact can be demonstrated for cats from which one adrenal has been removed and adrenin discharge from the other prevented by cutting its nerve supply. In such animals hyperglycemia can readily be caused by asphyxia, a fact which shows that sugar mobilization is still possible. In such animals piqure results in many cases in marked hyperglycemia. In case of the rabbit, at any rate, adrenal discharge can clearly be excluded as playing an essential part in the phenomenon and the proof in case of cats is all but absolutely conclusive. It was further shown

that, under the conditions of the experiments, injected adrenin readily caused hyperglycemia.

It may now be definitely asserted that the adrenal glands do not play any essential role in the production of piqure glycosuria and added doubt is thrown upon the theory that they play an essential part in any type of glycosuria or hyperglycemia. Whatever may be the explanation of the fact that the adrenals have an important influence upon bodily functions the burden of proof now rests heavily upon those who postulate the importance of adrenin discharge. Until this proof is forthcoming the elaborate superstructures that have been erected upon the pharmacology of adrenin have but fragile foundations. The assumption that "hypoadrenia" has any significance as an etiologic factor now needs something more substantial than mere reiteration before it is worthy of the serious consideration of intelligent clinicians.

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THYROID AND THYMUS. André Crotti, M.D.,
F. A. C. S., LL. D. 558 pages. With ninety-six
illustrations and thirty-three plates in colors.
Lea and Febiger, Philadelphia, 1918.

From the general tenor of the book one gathers that the author has set out primarily to write a practical and readable book. If this was the purpose the book may be regarded as a success. The first 60 pages are devoted to the anatomy, physiology and chemistry of the thyroid gland. Of these sections that on physiology is perhaps the least satisfactory of any in the book. Two excellent chapters on pathology and inflammations occupy the next 60 pages. The next section,—the greater part of the book as a whole,—is devoted to the subject of thyroid diseases. A full discussion of classification, etiology, symptomatology and treatment of these is included. The last two chapters are devoted to the thymus gland.

A noteworthy feature of the book is the illustrating. Many of the colored plates by Marcel Guelin are beautiful examples of anatomical drawing. To a very considerable extent, however, they are superfluous for any but aesthetic reasons. Many of the points brought out could have been shown as well or better by clean cut line drawings. One can not commend the use of an expensive colored plate to illustrate so simple a matter, for instance, as the placing of a subcutaneous ligature (Plate 33.)

The book as a whole is one of outstanding excellences as well as defects. The subjects of symptomatology and treatment of goitre are especially satisfactory, as is also the discussion of the geographical distribution of endemic goitre. The treatment of the historical aspects of the goitre problem is the best with which the reviewer is familiar; a full account of the Kocher-Reverdin controversy is a case in point.

So much for the author's efforts as a practical surgeon dealing with matters of fact.

As a scientist, however, dealing with matters still open to investigation, he is less satisfactory. His attitude is indicated in the prefatory statement: "I have gathered all I consider of value from the enormous amount of French, Italian, German and English literature . . . and I have endeavored, in my recital of sources and authorities, to give credit where credit is due." One can but admire the courage of a writer assaying the role of dogmatically evaluating the literature of the difficult subject of speculative endocrinology. The author's lack of success is perhaps sufficiently indicated by a single quotation (page 333.) "We *know* that their (adrenal) cortical cells . . . are entrusted with the duty of neutralizing the muscular toxins, and that the medulary cells . . . produce adrenalin whose tonic action upon the circulatory and muscular systems is well *known*. . . . We *know*, too, that the thyroid secretion is antagonistic to that of the suprarenal bodies."* As a matter of fact none of these things is known. Such confusion of fact and theory is not uncommon throughout the book whenever the author gets outside the realm of his personal experience. He does not make sufficient distinction between the fanciful conclusions of credulous, amateur experimentalists and the critical conclusions of competent scientists. In several instances a high value is placed upon notably faulty researches. The obsolete viennese "Wechselwirkung" theories, for example, are quoted as of current worth.

The announced endeavor "to give credit where credit is due" is but poorly carried out. To a serious student the value of the book is greatly restricted by the almost constant failure to include proper bibliographic references. The few that are given are

*Italics mine. R. G. H.

mostly in slipshod form. What, with proper attention to this point might have been a valuable book of reference is, in this respect, practically useless. Neither can the attempt to "include all that is valuable" be regarded as an entire success. Several important recent papers have been missed. Among these are Bensley's and Goetsch's work on thyroid cytology, Cannon's work on the control of thyroid secretion, Marine's on iodine fixation and that of Norris on thyroid embryology.

The author's use of the English language is somewhat remarkable. Some paragraphs might be taken as models of graphic, artistic exposition, while a few might be selected to serve as models of what not to do. Colloquialisms are frequently employed. Occasional unfortunate verbal peculiarities are encountered. Some of these are: "aspirative needle," "metabolistic" for metabolic, "adipositas" for adiposity, and "catheterism" for catheterization; reference is also made to a "thyroidly insufficient patient." A lack of familiarity with English scientific idiom is betrayed by the use of such expressions as "products of refuse" for metabolites, "anorganic" for inorganic, "superficial" for *surface* tension, "albumin" for protein, "vasomotry" for vasomotor, "autonomous" for parasympathetic and "depoisoning" for detoxication.

The discussion of the etiology of goitre, and especially of Graves' disease is, as might be expected, full. The pertinent clinical evidence is skillfully assembled. The experimental evidence, however, is less satisfactorily treated. The author believes that experimental Graves' disease has been successfully produced both in man and animals by feeding thyroid substance. The only properly objective research upon the subject which is known to the reviewer, a research which McCarrison regards as the most fundamental on the goitre problem, is ignored. Carlson,

as a matter of fact, was quite unable to produce anything at all closely resembling the disease either in man or animal by thyroid feeding. The problem propounded for discussion is: "Is Graves' disease a true hyperthyroidism?" This problem is soon lost sight of, however, in the consideration of quite a different question,—namely, that of the thyrogenic origin of goitre. The final conclusion is that the malady is essentially a toxic thyroiditis. Throughout the book, as a matter of fact, "Graves' disease" and "hyperthyroidism" are used interchangeably, ignoring the possibility, if not the probability, that Graves' disease is a *dysthyroidism*.

The two sections that most appeal to the reviewer are those on hypothyroidism in the young and on the water transmission of goitre. The latter is especially to be commended as a full, well-balanced exposition of the topic.

The two final chapters, on the thymus gland, have in general the same excellences and defects as those on the thyroid. The diagnosis and treatment of thymus hyperplasia are delightfully treated. In the discussion of the experimental pathology of the thymus much stress is laid on the work of Klose and Vogt,—work which various competent scientists have been unable to confirm.

Altogether it may be said that the reader who is interested in the thyroid and thymus glands from a "practical" clinical standpoint will find Cotti's book a rich storehouse of usable and entertaining lore. The reader, on the other hand, who is interested primarily as an endocrine biologist will find it unsatisfactory. To such it can be most commended for its excellent illustrations and for its historical material.

R. G. H.

ABSTRACTS

80. (ADRENAL) Disparition des enclases, lipocholestériques de la surrénale humaine dans l'agitation motrice. (Disappearance of lipid-cholesterol bodies of the human adrenal in motor disturbance.) Laignel-Lavastine (M.) C. R. Soc. de Biol. (Paris) 1918, 81, 324-325.

The adrenals were examined from six cases, each of which had suffered from intense and prolonged motor disturbances before death. The author failed to find lipid-cholesterol bodies in the adrenal cortex.—F. A. H.

81. (ADRENAL) La teneur en cholestérine des surrénales aux différents stades de la vie foetale (Cholesterol content of the adrenals at different stages of foetal life.) Chauffard (A.), Laroche (G.) and Grigant (A.) C. R. Soc. de Biol. (Paris), 1918, 81, 87-89.

As the adrenals increase in size in the foetus the cholesterol content increases until at birth the average amount is 15 grams per kilogram. The cholesterol content of the liver and kidney is about 2.5 grams per kilogram at birth.—F. A. H.

82. (ADRENAL) On the liberation of epinephrin from the ardenal glands. Rogoff (J. M.). Jour. Lab. and Clin. Med. (St. Louis), 1918, 3, 209.

This article is a review and critique of recent work and theories on the discharge of the adrenal secretion into the blood stream. Nothing essentially new is offered save a tentative theory that certain discharges of adrenal secretion may be due to reflexes involving a definite center located in the spinal cord.

At the close of the article the author strongly emphasizes the fact that our present knowledge of the adrenals is not sufficient to warrant epinephrectomy as a measure of relief in conditions of arterial hypertonus associated with Bright's disease, as has been done, on the assumption that this condition is associated with hyperadremia.—H. W.

83. (ADRENAL) The relation of the adrenals to piqure hyperglycemia and to the glycogen content of the liver

Stewart (G. N.) and Rogoff (J. M.) *Am. Jour. Physiol.* (Balt.) 1918, **44**, 90-116.

In rabbits which have survived the removal of both adrenals, and whose livers are well filled with glycogen, piqure causes decided hyperglycemia just as in normal rabbits. This is not compatible with the theory that piqure hyperglycemia is caused in the same way as the hyperglycemia produced by injecting adrenalin, by an increased liberation of epinephrin from the adrenals into the blood. It was frequently noticed also that hyperglycemia was caused by asphyxia in adrenalectomized rabbits.

The failure of previous observers to obtain piqure hyperglycemia in rabbits after the extirpation of both adrenals is attributed to the fact that they performed the piqure immediately after the epinephrectomy, or if an interval was allowed to elapse it was too short to permit complete recovery from the adrenal operation and the liver was insufficiently stored with glycogen. Even when a considerable interval is allowed after the adrenal operation, the state of nutrition or the diet is sometimes unfavorable for glycogen accumulation and therefore a positive result cannot be expected. There is no real evidence that piqure increases the rate of liberation from the adrenals.

It is pointed out that the reactions of denervated vascular regions and of the denervated heart, which have been interpreted as showing that the rate of liberation of epinephrin is increased by stimulation of afferent nerves and by asphyxia, may have a different significance. The response of these organs may indicate merely an increased rate of blood flow through the denervated regions and therefore an increase in the total quantity of adrenalin reaching them, without any actual change in the rate of adrenalin liberation from the suprarenal glands.

The formation and storing of glycogen in the liver is not affected by removal of both adrenals in rabbits, or by removal of one adrenal and section of the nerves of the others in cats with consequent abolition or marked reduction in the rate of liberation of epinephrin. In rats, also, extirpation of the adrenals produces no essential change in the capacity of the liver to form and store glycogen.—L. G. K.

84. (ADRENAL) Sur le fonctionnement de la capsule surrénale humaine dans les gangrènes gazeuses. (On the functioning of the human adrenal capsule in gaseous gangrene). Goormagtigh (M.) *C. R. Soc. de Biol.* (Paris) 1918, **81**, 14-17.

In gaseous gangrene of rapid development the adrenal cortex pours into the blood stream a large proportion of cholesterol and its ethers. Judging from the histo-chemical characteristics these substances undergo important changes at the time of passing into the blood. The elimination of cholesterol is less in sub-acute cases while in chronic cases part of the cholesterol accumulates in the center of the gland.

There appeared to be hyperactivity of the medulla.—
F. A. H.

85. (ADRENAL) Sur l'origine de la capsule surrénale chez les chéiroptères (Upon the origin of the adrenal capsule in the chiropters). Costa (A. C. da) C. R. Soc. de Biol. (Paris) 1918, 81, 51-53.

Although it is generally admitted that the two portions of the adrenal have different origins, Colson thought that in chiropters the two parts had a common origin. The author attempted to verify the work of Colson, but found that chiropters agree with other vertebrates.—F. A. H.

86. (ADRENALS) Dos casos de hematoma suprarrenal. (Two cases of adrenal hematoma.) Deluea (F. A.) Semana Médica (Bs. Aires), 1918, 25, 93.

Two cases are discussed. The first was that of a baby who was born asphyxiated but was resuscitated and appeared normal for two days. On the third day the mother noted pallor; on the fourth, jaundice developed and the infant cried all day. He was quieted by a bath but later had an attack of clonic convulsions. This was repeated several times during the night and the child died the following morning. In the second case the baby was born dead. Autopsy in each case showed hemorrhages into the adrenal glands. The parents in both cases were syphilitic. Deluea thinks that syphilis as well as extensive burns can produce the condition of adrenal hematoma.

G. P. G.

87. (ADRENALS) Le rôle des Surrenales dans l'action du pneumogastrique sur le cœur. Roger (H.) Jour. de physiol. et de path. gen. (Paris), 1917, 17, 187.

Whereas in normal rabbits it is impossible to maintain a prolonged cessation of heart beats by stimulation of the vagus, this is possible after the suprarenals have been removed. The heart may be kept at rest so long that asphyxial convulsions occur. This state can be converted to the normal one by the in-

jection of adrenin. Accordingly, the so-called escape from the vagus inhibition is regarded as due to central stimulation of nerves to the suprarenals, probably owing to the low blood pressure.—Physiol. Abst.

88. (ADRENALS) Un caso de mal de Addison. (A case of Addison's disease.) Fonte (C.) *Brazil Médico* (Rio de Janeiro), 1918, 32, 50.

Addison's disease developed in a man fifty-eight years of age,—an alcoholic; nothing of particular interest.

G. P. G.

89. (ADRENALIN) Hemmung der Kochsalzausscheidung im Harn durch Adrenaline. (The influence of adrenalin on the secretion of sodium chloride in the urine.) Frey, Buleke and Wels. *Deutsches Arch. f. klin. Med.* (Leipzig) 1917, 123, 163.

After subcutaneous injections of adrenalin the rate of excretion of sodium chloride through the kidney becomes slower. It is the same with the excretion of nitrogen. Adrenalin acts on the tissue of the kidney; in Bright's disease the reaction of the body to adrenalin is the same as in health.—J. K.

90. (ADRENALIN) L'action de l'adrenaline sur le coeur, étudiée par la radioscopie (Action of adrenalin on the heart, studied by the radioscope). Loeper (M.), Dubois (H.) and Wagner (C.) *C. R. Soc. de Biol.* (Paris), 1918, 81, 85-86.

The authors studied the hearts of a large number of normal and pathological subjects by means of the radioscope before and after giving one milligram of adrenalin. The hearts of normal subjects were found to be unchanged in a majority of cases. There was dilatation in many pathological cases. This was thought to be due to the increased pressure from constriction of the arterioles and inability of the heart to recover quickly. This method is suggested as a test for cardiac defects.—F. A. H.

91. (ADRENALIN) Location of the adrenalin vasodilator mechanisms. Hartman (F. A.), Kilborn (L. G.) and Fraser (L.) *Am. Jour. Physiol.* (Balt.) 1918, 46, 168-185.

Adrenalin causes vasodilatation in the skeletal muscle of the hind limb by acting on structures located in the lower lumbar and sacral sympathetic ganglia and in the dorsal root gan-

glia of the nerves supplying the limb. Similarly dilatation of the intestine is brought about by adrenalin acting on structures ganglia of the lower thoracic region. It is not probable that in the superior mesenteric ganglion and in the dorsal root the antidromic vasodilator impulses caused by adrenalin are identical with those of Bayliss since there is no evidence that the blood vessels of the skin dilate with adrenalin. These results, however, tend to support the view that the sympathetic system contains vasodilator fibers to the intestine and to the hind limb.—Authers' Abstract.

92. (ADRENALIN) The combination of local and general anaesthetics and the use of adrenalin. Wishart (D. J.) *Can. Pract. and Rev.* (Toronto) 1916, 41, 1-4.

Includes a discussion of the use of adrenalin in local and general anaesthesia. Cites two cases in which death occurred presumably from the injection of a few drops of adrenalin solution during chloroform anaesthesia.—F. A. H.

93. (ADRENALIN) The regulation of renal activity. IV. Regulation of urea excretion by adrenalin. Addis (T.), Barnett (G. D.) and Shevky (A. E.) *Am. Jour. Physiol.* (Balt.) 1918, 46, 39-51.

Subcutaneous injection of adrenalin in the rabbit is followed by an increased urea excretion by the kidneys. There is a certain amount of adrenalin which produces the greatest increase in function, smaller amounts having less and less effect until there is no change from the normal. With larger amounts the augmenting effect on secretion also becomes less until, with relatively large doses, the reverse effect of a decrease in function is found. Except with these large amounts the rate of urea excretion is more rapid than in animals not given adrenalin, in spite of a lowering of the blood urea concentration.

The adrenalin is supposed to influence the secretory activity of the kidney cells through the medium of something in the termination of sympathetic nerve fibers analagous to the receptive substance in the end-plates of muscle fibers.—L. G. K.

94. (ADRENALIN) Untersuchungen über die Adrenalinwirkung auf die weissen Blutzellen. (The effect of adrenalin on the leucocytes.) Hatigan (J.) *Wein. klin. Wchenschr.* 1917, 30, 1541.

The subcutaneous injection of 0.001 gram adrenalin causes a leucocytosis. In the first hour after the injection there is a

marked increase of the lymphocytes. The second hour the lymphocytes diminish but there is an increase of the neutrophil leucocytes. It generally takes six hours before the number of leucocytes has become normal again. If a double dose of adrenalin is injected the period of lymphocytosis persists about twice the ordinary time. If atrophine or pilocarpine is previously injected the reaction to the adrenalin is not changed.—

J. K.

95. (ADRENALIN, PITUITRIN) The regulation of renal activity. VI. The effect of adrenalin and pituitrin on the action of the kidney under strain. Addis (T.), Foster (M. G.) and Barnett (G. D.) *Am. Jour. Physiol. (Balt.)* 1918, 46, 84-89.

The condition of "strain" was produced by giving 5 grams of urea at the beginning of the experiment.

At high blood urea concentrations the degree of change in the urea excreting activity of the rabbit's kidney produced by adrenalin and by pituitrin is less than at low blood urea concentrations.—L. G. K.

96. (ADRENIN) Action of adrenin in auriculo-ventricular dissociation. Hardoy (P. J.) and Houssay (B. A.) *Revista Assoc. Méd. (Buenos Aires)*, 1917, 27, 462.

In a dog with experimental dissociation and in two patients the injection of adrenin caused a different degree of acceleration of the rate of the auricles and of the ventricles. The normal rhythm was not re-established, although at a certain moment there was a false appearance of removal of the block.—B. A. H.

97. (ADRENIN) Adrenin content of the suprarenal glands of cadavers of patients dying from beriberi. Ono (S.) *Jikwa Zasshi*, 1916; —, 1014.

Nine acute cases of beriberi and two dying during pregnancy were examined as to the post-mortem adrenin content of the suprarenal capsules. The results of the first nine varied from 4.96 to 5.99 mgs. as compared with the normal of 2.82 mgs. and those of the fatal cases were 3.01 and 4.49 mgs. Microscopically the medullary area appeared more fatty than normal and microscopically it was thought to be the seat of a lymphatic infiltration of a mild grade.—Chem. Abst.

98. (ADRENIN) Azione del l'adrenalina sul l'utero isolato, in riposo e gravido. (Quagliarello (G.) Arch. di Ostetricia e Ginecologia (Napoli) Serie II, vol. V, parte I. Abst. La Pediatria. April, 1918.

According to the experiments of the author the adrenalin heightens the tone in the isolated pregnant uterus, while inhibiting the virgin or the non-pregnant uterus.—G. V.

99. (ADRENIN) Carbohydrate metabolism in the surviving dog liver. Abelin (J.) and de Corral (J. M.) Biochem. Ztschr., 1917, **83**, 62-73. (Physiol. Abst., 2, 597.)

Perfusion of rabbit liver with a peptone solution does not affect glycogen, but in the dog it is diminished. In both animals adrenin perfusion has no effect on the hepatic glycogen. Chem. Abst. **12**, 820.

100. (ADRENIN) Ergotoxin and adrenin hyperglycemia. Laurin (E.) Biochem. Ztschr., 1917, **82**, 87-95.

Stenstrom stated that the hyperglycemia and glycosuria produced by adrenin could not be prevented by injecting pituitrin. Miculicich reported the same results with ergotoxin. This remarkable similarity of action between an animal and a fungus product is confirmed. Chem. Abst. **12**, 501.

101. (ADRENIN) Location of adrenalin vasodilator mechanism. Hartman (F. A.). Proc. Am. Physiol. Soc., Am. Jour. Physiol. (Balt.), 1918, **45**, 555. See. Endocrin, 1918, **2**, 1.

102. (ADRENIN) Relation between chemical constitution and physiological action. Pyman (F. L.) Jour. Chem. Soc., 1917, **111**, 1103-28.

A lecture dealing principally with work of the past ten years on adrenin and various esters, anesthetics, etc. References are given and conclusions summarized.

Chem. Abst. **12**, 593.

- 103 (ADRENIN) The combined digitalis-adrenin therapy. Frey (W.) Deutsche med. Wehnschr. (Berlin), 1917, **43**, 872-3.

This combination method is not recommended. Chem. Abst. **12**, 951.

104. **ADRENIN**, the effects of on the urine flow of anesthetized and unanesthetized dogs. Gunning (R. E. L.). *Am. Jour. Physiol.* (Balt.), 1918, 45, 528.

Adrenin in all effective dosages administered intravenously inhibits the urine flow in both anesthetized and unanesthetized dogs. The threshold of the reaction is slightly lowered in unanesthetized animals. Small injections and infusions merely decrease the flow of urine while larger doses produce a complete cessation of flow. The inhibition usually persists until shortly after the blood pressure reaction is complete. Diuresis succeeding the inhibition was not observed.

The rapid return of the flow to normal after prolonged infusions suggest that the drug exercises its inhibition on the kidney function in a way other than by the ischemia produced.

During the administration of ether the urine flow is completely checked and recovery under the anesthetic takes place slowly.—T. C. B.

105. (**ADRENIN, VI**) Further studies on the effect of adrenalin upon the blood flow in muscles. Gruber (C. M.). *Am. Jour. Physiol.* (Balt.), 1918, 45, 302.

The present research was carried out to determine whether or not adrenalin acted centrally or peripherally in producing vasodilation in muscles.

The conclusion reached is, that "Vasodilation in muscles caused by small amounts of adrenalin is dependent upon the tonicity of the vessel wall."

Small doses of adrenalin (0.5 cc 1:100,000) bring about vasodilation by their action on the peripheral vasodilator mechanism.—T. C. B.

106. (**DIABETES**) Treatment of diabetes from the general practitioner's standpoint. Janney (N. W.) *Jour. A. M. A.* (Chgo.) 1918, 70, 1282-87.

Of no direct endocrine interest.—R. G. H.

107. (**ENDOCRINE GLANDS**) Changes in the relative weights of the various parts, systems and organs of young albino rats underfed for various periods. Stewart (C. A.) *Jour. Exp. Zool.* (Phila.) 1918, Vol. 25.

In rats underfed from birth to 3, 6, and 10 weeks, the spinal cord, eyeballs, liver, and stomach and intestines (empty) increase considerably in weight. A less marked increase occurs

in the brain (at three weeks especially), spleen and intestinal contents (at 6 and 10 weeks, loss earlier), suprarenals and heart (progressive increase), kidneys, testes, epididymi (at 3 and 6 weeks, loss later), ovaries and hypophysis. There is no marked change in the weights of the thyroid and pineal glands, whereas the lungs and especially the thymus lose markedly. In young rats underfed for very long periods (up to 428 days), the marked increase is maintained in the weight of the spinal cord, eyeballs, suprarenals (usually), and brain (slightly). There is but slight change in the weights of the intestinal contents, kidneys, ovaries, testes(?) and pineal body. The thyroid, thymus, heart, liver (variable), spleen (variable), alimentary canal (empty) epididymi, and hypophysis (in males) usually suffer a loss.—E. R. H.

108. (ENDOCRINE GLANDS) El sistema nervioso y las glandulas endocrinas en un caso de myopathia. (The nervous system and the endocrine glands in a case of myopathy.) Navarro (J. C.) and Correas (C. A.) Soc. Med. Argent., 1917 (June 29).

Histological examination of the nervous centers, peripheral nerves, thyroid, hypophysis, suprarenals, etc., disclosed no demonstrable lesions.—B. A. H.

109. (ENDOCRINE GLANDS) Excretion of uric acid in several cases of disease of the blood glands. Nowaczyński (J.) Deutsche med. Wehnschr. (Berlin), 1916, 42, 1478-80. (Physiol. Abst. 2, 132.)

Although purin metabolism is frequently upset in diseases of the blood glands the changes are most variable. The injection of extracts also causes varying results, though ovarin and pituitrin produce a rise in the excretion of exogenous uric acid. Chem. Abst. 12, 941.

110. (ENDOCRINE GLANDS) The glands of internal secretion. Crispin (A. M.) La Prensa méd. Argentina (Buenos Aires) 1917, 27, 279.

Nothing new.—B. A. H.

111. (ENDOCRINE GLANDS) The origin of progressive muscular dystrophy. Editorial, Jour. A. M. A. (Chgo.) 1918, 70, 1376.

Discusses late work on the subject, including the possible relation of the endocrine glands to that malady.—R. G. H.

112. (**ENDOCRINE GLANDS**) The effect of the administration of various substances on the blood diastase of rabbits. Watanabe (C. K.) *Am. Jour. Physiol.* (Balto.), 1917, **45**, 30-43.

The dextrose content of the blood was increased without any change in diastase content by the administration of adrenin. Pituitrin injections and thyroid feeding had no effect on either diastase or dextrose content.

113. (**ENDOCRINE GLANDS LACTATION**) Preliminary research on the effect of extracts of certain endocrine glands on the amount of milk produced by cows and goats. D'Alfonso (C.) *Ind. latt. e. zootec.*, 1916, **14**, 215-6, 234-5, 253-4, 268-9, 286-7, 302-5, 316, 350-1; 1917, **15**, 7-9.

This is a repetition of previous studies of the effect of the injection of extracts of ovaries, testes, adrenals, thyroids, hypophysis and mammary glands on milk production.

Chem. Abst. **12**, 592.

114. (**GASTRIN**) Gastric secretin. Maydell (E.) *Diss. Kiev*, 1917. (*Physiol. Abst.*, **2**, 415-6.)

Gastrin prepared from the mucous membrane of the pyloric part of the stomach with 0.4% HCl was injected into dogs with chronic gastric fistula and esophagotomy. A rather energetic secretion of gastric juice was obtained under such conditions; its acidity was equal to that of the juice obtained by means of sham feeding, but its digestive power was less. The immediate introduction of the gastrin into the blood acts more feebly than upon subcutaneous injection, and in the former case a decrease of blood pressure occurs, but not in the latter. If the gastrin is treated with alcohol and ether, it is possible to separate two component parts, one of which evokes secretion and the other dilates blood vessels. Gastrin is absorbed neither by the duodenum nor by the large or small intestine. The gastrin prepared from the fundic region is inactive. Atropine diminishes the secretory effect of gastrin.

Chem. Ast. **12**, 718.

115. **GLAND EXTRACTS**, the bacteriolytic action of, on tubercle bacilli. Porter (A. E.) *J. Hygiene (Lond.)*, 1917, **16**, 55-65.

The results obtained point to a consistent relationship between lipolytic activity and bacteriolytic power on tubercle

bacilli. The least bactericidal extract was lung extract and the most powerful was pancreatic extract. Liver, thymus and lymphatic glands were strongly bactericidal. Other organs, suprarenal glands, pig and cat spleen, human and cat kidney, human and ox brain, ox thyroid, cat lung, ox bone marrow, and ox pituitary glands were found to be bactericidal to a lesser degree. Human skin extract was fatty and cloudy in appearance and exceptionally rich in esterases. This sample of skin bears out the relationship between lipolysis and bacteriolysis of tubercle bacilli in a striking way, as it was extremely bactericidal. No difference was observed between human and bovine tubercle bacilli in susceptibility to any gland extract examined. Other acid-fast bacilli, though on the whole less susceptible to the influence of these extracts, were bacteriolized by them. They were also killed by one lung extract (pig) which contained an unusual amount of olein lipase and which had no effect on tubercle bacilli.—Chem. Abst.

116. (GONADS) Körpertemperatur und Pubertätsdrüsen.
(Bodily temperature and the sex glands.) Lipschütz (A.)
Arch. f. d. ges. Physiol. (Pflüger's) (Bonn) 1917, **168**, 177.

The temperature of female animals is about 0.6-0.7° C. higher than that of males. After castration the temperature becomes about 0.4 lower. When after this operation a testicle is implanted the temperature becomes still lower.

In male animals, however, castration has no influence on temperature. When after castration an ovary is implanted the temperature rises until it reaches that of normal female animals.—J. K.

117. (GONADS) Microrchie et gynecomastie consécutives à une orchite double. Laignel-Lavastine (M.) and Courbon (P.)
Presse Méd. (Paris) 1917, **25**, 492.

Before the Société Médicale des Hopitaux (July 20, 1917) the case of a soldier of 22 was presented, who after suffering from mumps last December, which was complicated by a double orchitis, began to present retrogressive evolution in the reproductive organs. Virility was lost and there was a remarkable transformation of the secondary sex characteristics and the establishment of those of the opposite sex. Little by little these changes were accentuated and the mammae attained a marked degree of hypertrophy with atrophy of the testes and penis. The authors consider this of the plastic type of hermaphroditism.—H. R. H.

118. (GONADS) Spontane Geschlechtswandlung beim Hunde in Verbindung mit Morbus Basedowii. (Spontaneous change of sexuality in a dog suffering from Graves' disease.) Heilborn. Deutsche med Wehnschr. (Berlin) 1918, 44, 213.

A very remarkable case is described. A male dog becomes very nervous and thin and shows an exophthalmos; there is a large goitre and tachycardia; in the last two years the testes have become atrophic and the mammary glands larger. The most typical symptom, however, was an absolute homosexuality. The author does not discuss whether the changes in the thyroid have anything to do with the homosexuality.—J. K.

119. (GONADS) The effects of inanition upon the development of the germ glands and germ cells of frog larvae. Swingle (W. W.) Jour. Exp. Zool. (Phila.) 1918, Vol. 24.

Immature frog larvae were starved from the time of their emergence from the egg capsule for over one hundred days. During this interval the tadpoles were fed a few filaments of algae at odd times to prolong the experiment. No growth occurred, nor were there any indications of metamorphic changes. The control animals developed normally and underwent metamorphosis at the usual time. Microscopic examination of the gonads and germ cells showed that in the starved animals growth and development of these structures had, like somatic development, been completely inhibited. In one or two of the oldest animals of the starved series, germ cells were observed which appeared to be in the early maturation stages.

Drawings and photographs are given illustrating these points.—E. R. H.

120. (GONADS) Vorherbestimmung der Geschlechts. (Is it possible to prophesy the sex of the child during pregnancy?) Königstein (R.) Zentralbl f. Gyn. (Leipsig) 1917, 41, 1097.

Theoretically it would be quite logical when if the child in pregnancy is a boy, the serum of the mother would contain "protective ferments" against testicle. The experiments by Königstein in this direction gave from time to time a positive result, but not regularly enough to be of clinical value. The results, however, were remarkably better when, instead of ordinary testicle, that of an embryo or a calf was used.

121. (HYPOPHYSIS ADRENAL) The relation of the glands of internal secretion to milk production. Hammond (J.) and Hawk (J. C.) Jour. Agr. Sci., 1917, 8, 147-53.

The flow of milk produced by an injection of pituitary extract varies with the state of nutrition of the injected animal. The ratio of morning yield to pituitary yield rises with the fall of nutrition and falls as the nutrition rises again. Therefore the yield obtained as a result of pituitary injections tends to be more constant than the morning or daily yield. The fat percentage of the pituitary milk is increased by the state of lowered nutrition in the same way as with normal milk. Injections of adrenin give results similar to those of pituitary extract in causing hyperglycemia, but different in having no immediate action on milk secretion. The secondary effect on milk secretion is a decrease in the amount of milk produced for a period of a day following the injection. The fat percentage in the milk from the period following an adrenin injection is above normal but the absolute amount obtained is decreased. The rate of blood flow is very susceptible to changes in the sugar metabolism of the animal. Chem. Abst. 12, 822.

122. (HYPOPHYSIS) **Acromegaly.** Castex (M. R.) La Presna méd. Argentina (Buenos Aires), 1918, Supplement 25 (Feb. 10).

Although the subject (evidently acromegalic) presented an appearance of the sella turcica on the X-ray plate of an advanced stage of the disease and showed certain visual disturbances, the author believes that the symptoms, even headache and vomiting, are due to syphilis. He thinks the symptoms could all be ascribed to a functional defect of the pituitary secretion and doubts the existence of a tumor.—B. A. H.

123. (HYPOPHYSIS) **Cirurgia da hypophyse. (Surgery of the hypophysis.)** Novaes (J.) Brazil Médico (Rio de Janeiro), 1917, 31, 431.

Novaes in a review of an article by Segura criticises the latter for leaving the accessory hypophysis. G. P. G.

124. (HYPOPHYSIS) **Control of polyuria in a case of diabetes insipidus by means of hypophyseal extract.** Rosenbloom (J.) Jour. A. M. A. (Chgo.), 1918, 70, 1292.

The case of a boy of 12½ years is described in which polyuria of 9 years' duration existed. Thyroid tablets, 6 grains a day, were without effect, as were also pituitary tablets. Pituitary solution, however, injected subcutaneously brought about an almost three-fold reduction of the urine. The effect lasted about 24 hours.—R. G. H.

125. (**HYPOPHYSIS**) Beiträge zur Pathologie der Hypophyse. (Pathology of the hypophysis.) Fahr (T.) Deutsche Med. Wehnsehr. (Berlin) 1918, 44, 206.

A woman of 50 years suffered from convulsions; the Argyll-Robertson symptom was positive; the Wassermann reaction negative; the blood pressure was normal and the skin showed a brown pigmentation as in Addison's disease. The postmortem examination showed atrophy of both suprarenal bodies; medulla and cortex were both affected. Macroscopically the pituitary body showed no changes; microscopically, however, nearly the whole organ was changed to a mass of connective tissues, except the pars posterior, which showed no pathological changes.—J. K.

126. (**HYPOPHYSIS**) Further studies upon amphibian larvae from which the anterior lobe of the hypophysis had been removed. Allen (B. M.) Anat. Rec. (Phila.) 1918, Vol. 14.

The anterior lobe of the hypophysis was removed from larvae of *Rana pipiens* and *Bufo lentiginosus* as described in an earlier paper. The observations previously published were verified and much extended because of greater success in rearing the operated tadpoles. Several are still alive.

Limb development in both species is greatly retarded, running parallel with the condition in tadpoles from which the thyroid gland has been extirpated. In *Bufo* there is a color change to a light yellow-brown, and contrary to the case in *Rana* there is little retardation of bodily growth. The pars nervosa of the hypophysis forms normally in tadpoles, both *Rana* and *Bufo*, from which the anlage of the anterior lobe has been removed. There is, of course, no pars intermedia formed.

Gonads of operated *Rana* tadpoles were compared with normal controls of the same size killed several months before. They showed the same features as to size, structure, and germ-cell development as seen in the controls. The same correspondence in the gonads was noted when comparison was made with some small thyroidless tadpoles of the same size killed at the same time.

The retardation of bodily growth in *Rana* prevented the gonads from reaching the size attained in the controls at metamorphosis three months before. In *Bufo*, however, the operated tadpoles reached a bulk double that at metamorphosis. Correspondingly, the gonads and germ cells developed far beyond the condition attained at the time of metamorphosis in the controls.—E. R. H.

127. (HYPOPHYSIS) Pituitary disturbance in its relation to the psychoses of adolescence. (Abstract.) Tucker (B. R.)

A general description of the functions of the pituitary gland and of its anterior and posterior lobes is given.

Remarks are made upon the period of adolescence and the physiological disturbances of the pituitary secretion occurring at this time. The pathological disturbances of the pituitary secretion causing the psychoses are then taken up.

Pituitary adolescent psychoses are divided into four groups:

1st—Those with a pre-adolescent history of hypersecretion, in which during adolescence the secretion is apparently still further increased;

2nd—Those in which there is a history of pre-adolescent hypersecretion, in which during adolescence this secretion is markedly diminished;

3-a—Apparently normal pre-adolescent cases in which the secretion during adolescence is increased.

3-b—Those with an approximately normal pre-adolescent pituitary history, in which during adolescence the secretion is diminished;

4th—Those cases with a history of pre-adolescent decreased secretion, in which during adolescence the secretion is apparently still further decreased.

Cases are cited with radiographic findings to illustrate these groups and a description of their psychoses given.

Author's abstract. Read before neurological section, American Medical Association, Chicago, June, 1918.

128. (HYPOPHYSIS) Poliuria no hipofisiaria en un cancer de la mama con metastasis. (Non-hypophyseal polyuria in mammary cancer with metastasis.) Houssay (B. A.) Reunion de Médicos del Hospital Alvear, 1917 (June 29).

The author remarked that according to his experimental studies the so-called hypophyseal polyuria does not depend upon the hypophysis. In a clinical case studied a polyuria of 3-4 litres was not influenced by injections of pituitary material. At autopsy metastases were found in the frontal and bacilar sinuses and in the meninges, but the hypophysis and adjacent cerebral zone were not affected.—B. A. H.

129. (HYPOPHYSIS) Sobre o tratamento dos tumores da hypophyse e, especialmente, da acromegalia. (Treatment of hypophyseal tumors and especially of acromegaly.) De

Castro (A.), Souza (O. de) and Novaes (J.) Brazil Médico (Rio de Janeiro), 1917, 31, 415.

De Castro reviewed favorably the work of Segura, who was the first in South America to undertake the surgical treatment of pituitary tumors. Souza agreed with de Castro that attention should be paid to the parhypophysis. Novaes reviewed the Austrian statistics and concluded that both the nasal and frontal approaches to the hypophysis are very dangerous.

G. P. G.

130. (HYPOPHYSIS) Sobre un caso de poliuria esencial, de aparición a los 3 años de edad. (A case of polyuria appearing at the age of three.) Deluca (F. A.) Semana Médica (Bs. Aires), 1918, 25, 422.

Deluca discusses the theories of polyuria including the hypophyseal variety. He reviews the experimental work of Camus and Roussy and of the Houssay, which indicates that the condition is produced by injuries of a certain basal zone rather than of the gland proper. (See Houssay, *Endocrin.*, 1918, 2, 94.) A complete review of the Argentine literature on the subject is included. A case is discussed of a boy three years of age who complained of marked thirst and who passed four litres of urine daily. A detailed study of the case was not permitted.

G. P. G.

131. (HYPOPHYSIS) Su un infermo con sindrome psichica e femminilismo hipofisario, guarito con l'asportazione di vegetazioni adenoidi. Caliceti (P.) La Pediatria (Napoli) 1918, 26, 233.

The author refers to one of three cases of hypophyseal feminism with psychic syndrome, caused by adenoids, according to Prof. Citelli's opinion and his own. The patient has been seen eight months after the removal of the adenoids and showed a wonderful change from his previous conditions.

Physically stronger, with a much better color, lively and quick, he was not showing dullness or apathy as before. His hair on the face and on the pubis is now practically normal; and the sleep as well as his psychic behavior do not now longer show any abnormality.

Such an effect hardly eight months after the removal of the adenoids points—1st, to the hypophyseal nature of his previous feminism, asthenia and psychic syndrome; 2nd, to the right surmise of Prof. Citelli, that the adenoids may be the cause and not the effect (according to Poppi's theory) of hypophyseal alterations; 3rd, to the efficacy of intervention, even

late, whenever the hypophyseal alterations are not grossly anatomical.—G. V.

132. (HYPOPHYSIS) The action of hypophysis extracts on gastric juice secretion and gland secretions in general. Pal (J.) Deutsche med. Wehnschr. (Berlin), 1916, 42, 1030.

This paper concerns the action of the extract of the infundibular portion of the hypophysis on gastric secretion, on the action of the kidneys and other exocrine glands, as well as on the thyroid. In summary, the extracts act inhibitingly on certain glands. This action is demonstrable in man in cases of hypersecretion (on the kidneys in diabetes insipidus, on the thyroid in hyperthyroidism, and on the stomach mucosa in hyperacidity). On the other hand, it promotes the secretion of the mammary gland and the excretion into the follicles of the thyroid, but only when there is hyperfunction of these glands. The secretion of the innervated glandular apparatus (stomach glands, kidneys, etc.) is not only dependent on the irritability of the secretory nerves, but also of the inhibitory nerves. The depressant action of the infundibular extract on the secretion depends on the action of the extract on the irritability of these nerves, which are located in the sympathetic. The stimulating action can be traced to a direct action on the cells.—Chem. Abst.

133. (HYPOPHYSIS) The arterial supply of the human hypophysis. Anat. Rec. (Phila.) 1918, Vol. 14.

Three methods are being used: (a) Injection with thin collodion and corrosion by artificial gastric juice—somewhat unsatisfactory because of difficulty of injecting finer vessels, and because relations of arteries to tissues are not preserved; (b) wax reconstructions of thick collodion sections of foetal specimens—sections not yet studied; (c) dissection under binocular of gelatin-injected vessels.

Brains for dissection are injected through the common carotid, with contra-lateral carotid, both vertebrals and external and internal jugular veins ligatured. Robin's Prussian blue and carmin have been used. The base of the brain in the region of the sella tursica and the underlying bone are removed and preserved in formalin. The brain and meninges are carefully freed from the underlying bone, dehydrated and cleared in cedar oil. They may then best be dissected under oil of wintergreen with a binocular.

The brains are dissected through their underlying meninges successively upon two planes: (1) an intradural

plane, comprising the internal carotids and their branches within the cavernous sinus; (2) a subdural plane comprising the circle of Willis and its branches. Four brains only in the intradural plane have thus far been dissected.

In each of these four brains there are found, arising from each internal carotid at its first and superiorly convex flexure in the cavernous sinus, an artery of approximately one to two millimeters in diameter which quickly breaks up into several somewhat variable branches. These branches, together with an inconstant artery which may arise from the carotid in the sinus cavernosus more anteriorly, supply the semilunar ganglion, the third, fourth, fifth and sixth nerves in this region and the contiguous dura mater. One of the branches on each side, ramifying, courses between the layers of the dura across the posterior lobe; twigs are sent also to the dura and may even be sent to the anterior lobe.

The branch described is probably sufficient to supply the posterior lobe, but apparently does not form a considerable element in the supply of the highly vascular anterior lobe.—

E. R. H.

134. (HYPOPHYSIS) The development of the pars tuberalis of the rabbit's hypophysis. Atwell (W. J.) *Anat. Rec.* (Phila.) 1918, Vol. 14.

For the rabbit it has been possible to trace the development of the paired anlagen of the pars tuberalis of the hypophysis from an earlier stage than that given by Tilney ('13) for the chick and the cat, or by Miller ('16) for the pig. From the thickened epithelium which early lies in front of Rathke's pocket two thickened ridges are developed. These ridge-like eminences may be called the lateral lobes, and are evident in embryos of 10 days. At 14 days these lobes have begun to grow out laterally and are more sharply constricted from the body of the hypophysis.

The lateral lobes are the anlagen of the pars tuberalis of the adult hypophysis. They begin to be in relation with the brain wall at 16 days of development, and by 19 days a considerable portion lies spread out under the diencephalic floor. There are present at this stage two blunt nasal horns extending toward the optic chiasm and two sharper caudal horns extending backward to surround the neck of the neural lobe. The caudal horns have completely surrounded the infundibulum, and have met in the mid-line by the end of the twenty-eighth day. The nasal horns fuse with each other a day or so later.

Since the lateral lobes of the mammalian hypophysis may be seen early in development, it is now easier to consider them

homologous with the lateral lobes of the reptilian hypophysis.

Because of its paired origin, the anterior part of the pars tuberalis cannot be homologized with the "Vorraum" of the reptiles, as is done by Woerdeman ('14).—E. R. H.

135. (**HYPOPHYSIS**) **Trastornos hipofisiarios en Ginecología.** (**Hypophyseal disorders in gynecology.**) Guardado (J.) *Revista de la Asociacion Medica Argentina* (Buenos Aires) 1918, p. 256, (March).

Certain cases of amenorrhœa in which ovarian ophotherapy had been unsuccessful were treated with posterior lobe pituitary extract with favorable results. In other cases the treatment failed. The author thinks that the pituitary extract stimulated the ovaries.—B. A. H.

136. (**HYPOPHYSIS**) **Veränderung in der Hypophysis cerebri bei Kretinismus und Myxoedem.** (**Changes in the pituitary body in cretinism and myxedema.**) Eichhorst. *Deutsches Arch. f. klin. Med.* (Leipzig) 1916, **124**, 207.

In cretinism and myxedema a hyperfunction of the pituitary body is observed. The organ becomes larger and shows an enormous hyperemia. Often hemorrhages are observed. The glandular cells grow; the chromophil cells degenerate and are replaced by cells which show the same structure as the pregnancy cells of Erdheim and Stumme. Later on a growth of the connective tissue is to be seen; then the glandular tissue becomes atrophic; in the connective tissue necrosis and the formation of cysts is observed. At the end of the disease the pituitary body becomes smaller and smaller.—J. K.

137. (**HYPOPHYSIS-SYMPATHETIC SYSTEM**) **Diabetes insipidus in pregnancy.** Novak (J.) *Berlin. klin. Wchnschr.* (Berlin), 1917, **54**, 107-9.

This condition is due to stimulation of the sympathetic system. A study of cases in which the hypophysis enlarges in pregnancy shows that the regulating centre is not altogether in the bulb but partly in the mid-brain. *Chem. Abst.* **12**, 914.

138. (**INTERNAL SECRETION**) **Adiposis dolorosa Der cumsche Krankheit mit Beteiligung der optischen Leitungsbahnen.** (**Dercum's disease with ocular symptoms.**) Behr. (C.) *Klin Monatsbl. f. Augenheilk.* (Berlin) 1917, **59**, No. 728.

A case of adiposis dolorosa with amblyopia was treated with thyroidine without success. Pituitary extract ("Hypophysin") raised the vision to 7/15.—J. K.

139. (INTERNAL SECRETION) Is the course of experimental cramp modified by disturbance of the internal secretions? Fischer (J.) Sitz. nat. Ges. Rostock, 1914, 6, 1-2.

Fischer believes that the course of experimental cramp is modified by disturbances of the internal secretions. The absence of the thyroid and epithelium increases the cramp-producing component of the amyl nitrate action, while the absence of the suprarenals decreases it.—Chem. Abst.

140. INTERNAL SECRETIONS. Collip (J. B.) J. Can. Med. Assn. (Toronto), 1916, 6, 1063-1069.

Nothing new.—F. A. H.

141. (INTERNAL SECRETIONS) Lidodystrophia Progressiva in a male. Weber (F. P.), Brit. J. Chil. Dis. (Lond.) 1917, 14, 179.

The author presents a table of all of the cases of this condition in males reported in the literature, and describes a case in a boy of 13 years. This boy was moderately fat in the face and body until the age of 8 years. He then began to look thinner in the face, although in all other respects he continued to appear and feel perfectly well. The loss of fat gradually progressed and for the last three years there has been practically no fat left on the face and neck, except in the orbits. The fat covering on the gluteal regions and on the lower extremities, however, is fairly normal.—M. B. G.

142. (INTERNAL SECRETIONS) Results observed in a further study of prenatal causes of dentofacial deformities. Weinberger (B. W.) Dental Items of Interest, 1918, 40, 6-31.

A discussion of the factors influencing the growth of the bones of the face and the teeth, with special stress on the role of the internal secretions. Chem. Abst. 12, 933.

143. (INTERNAL SECRETIONS) Sexual precocity in the male. Strauch (A.) Amer. J. Dis. Chil. (Chgo.) 1918, 15, 132.

The author makes an exhaustive study of the literature on this subject, quoting freely from several sources and attempts to sum up our present knowledge of the condition. In a few

observations premature sexual development has been ascribed to such early and excessive practices as masturbation and cohabitation due to seduction. Where such pathological factors are absent, what may be the cause of the prematurity of the impulses for the somatic changes remains a problem. Though the nature of the primary stimuli that control these changes is not known, it is established that the endocrine glands in their interlocked and mutually affecting functions are of the greatest importance for the normal growth of the body and for sexual maturity, among them especially the genital glands, the adrenals, the pituitary body, the thyroid and the so-called "puberty glands," the thymus and the pineal.

The author quotes several cases in the literature in which the etiological factor was a tumor of the generative glands. He thinks that these tumors suggest that the irritation of the gonads causes an excessive and premature increase of the function of the interstitial tissue of Leydig, hastening the development of the secondary sexual characteristics. Where the causes were tumors of the adrenals, he ascribes to these merely a hastening influence on the development of the secondary sexual characteristics, causing also an excessive growth of the body, since other recognizable sexual functions, such as menstruation or ejaculation, are not mentioned in the reported cases. The relation between genital hypertrophy and the pineal gland is perhaps to be interpreted as due to a premature decrease of the functioning glandular tissue, which otherwise under normal conditions undergoes degeneration, beginning with the seventh year of life. The trophic disturbances, that is, the premature development, may be considered as a manifestation of the insufficiency of the epiphyseal gland.—M. B. G.

144. (INTERNAL SECRETIONS) Studies of internal secretions in their relation to the development and condition of the teeth. V. Summary of miscellaneous findings. Gies (W. J.) Dental Cosmos, 1917, 59, 1238.

Thyro-parathyroidectomy has no influence on the dentition of young white rats. Parathyroidectomy, without material disturbance of the thyroid, almost invariably produces deficient calcification, but has no influence on the general conditions or dimensions of the teeth. "Possibly the thyroids normally tend to induce deficient (subnormal) calcification of the teeth and the parathyroids normally tend to induce correspondingly excessive (supernormal) dental calcification." Physiological variation in the composition of the teeth, in rats, is relatively slight. Chemical changes in developing enamel occur under the influence of substances that originate outside of, and enter

or superficially affect, the cells involved in the production of enamel.—Chem. Abst.

145. LYPODYSTROPHIA PROGRESSIVA. Spear (I. J.).
Arch. Int. Med. (Chgo.), 1918, **21**, 39.

Case report of lypodystrophia progressiva occurring in a school girl 15 years of age who otherwise showed no pathological findings. The case has progressed continuously for the past six years. Thyroid extract failed to retard the progress of the disease. The author does not accept the view that the condition is due to abnormal function of the endocrine glands, but considers it closely related to the muscular dystrophies; one factor having to do with dystrophy of fatty tissue, the other with muscular tissues. There were no indications of altered functioning of the ductless glands.—H. W.

146. (MENSTRUATION) Sindroma apendicular en la menstruación. (Appendiceal symptoms in menstruation.) Plat-
ero (H.) Rev. Méd. del Uruguay (Montevideo), 1918, **21**, 71.

Three cases are described in which virgins without evidence of genital injury or infection had pain at McBurney's point for three or four days preceding menstruation. At operation swelling of both appendix and ovaries was noted. In one case pus was found in the peritoneal cavity. G. P. G.

147. MONGOLISM associated with congenital cataract.
Weber (F. P.) Brit. J. Chil. Dis. (Lond.) 1917, **14**, 267.

According to Weber, the only other published case of association of mongolism with congenital cataract was that of W. B. Hill, reported a few years ago.

The author reports a case of a boy of 13 months with a typical mongolian facies, protruding tongue, rhacitis, and congenital cataract. The thumbs and little fingers were rather short in proportion to the other fingers, the little fingers presented a slight lateral curvature with the concavity of the curve toward the other finger.

The mother of the boy gave a negative Wasserman reaction.—M. B. G.

148. (MONGOLISM) Congenital heart disease in a mentally defective child with a negroid-mongoloid facies. Weber
(F. P.) Brit. J. Chil. Dis. (Lond.) 1917, **14**, 269.

The author reports a case of a girl of 4 years with a brachycephalic head, upward slant of palpebral fissure, broad nose with low flat bridge, lips and cheek and soft parts above eyes thick and coarse, hair scant and curly, no hair on eyebrows, no lower and hardly any upper eyelashes. The face was highly colored at times. The thyroid could be felt but was not enlarged. There was dry skin and xeroderma, but no signs of rickets. The heart showed a definite systolic murmur, was always present, especially well marked over the base to the left of the sternum (perhaps a congenital pulmonary stenosis); X-ray examination showed a shadow on that side. The Wassermann reaction of the mother was negative. W. B. Hill has stated that 10 to 20 per cent of all cases of Mongolian type have congenital heart disease.—M. B. G.

149. (MUSCULAR DYSTROPHY) Chemical changes in the blood and urine in progressive muscular dystrophy, progressive muscular atrophy and myasthenia gravis. McCrudden (F. H.), Sargent (C. S.). *Arch. Int. Med.*, 1918, **21**, 252.

In three cases of progressive muscular dystrophy were found muscular weakness, hypoglycemia, hypocholesterinemia, creatinuria and normal excretion of ammonia. Treated patients demonstrated a rise in blood sugar with a parallel increase in strength.

Blood sugar was found low in one case each of progressive muscular dystrophy and myasthenia gravis and normal in progressive muscular atrophy. Creatinuria was present in the cases of progressive muscular atrophy and dystrophy and absent in myasthenia gravis.—H. W.

150. MUSCULAR DYSTROPHY, the endocrine origin of. Janney (N. W.) and Goodhart (S. P.). *Arch. Int. Med.* (Chgo.), 1918, **21**, 189.

The authors discuss the clinical and laboratory findings in a representative series of cases (9) of muscular dystrophy in children and adults. Metabolism experiments on these cases gave the following results: marked decrease in preformed creatinin in the urine; abnormal presence of creatin in the urine; low percentage of creatinin in the blood; normal amounts of creatin in the blood; hypoglycemia; delayed utilization of glucose. Distinct osseous changes accompany muscular dystrophy in most cases which resemble closely those conditions found in cases of disturbed function of the organs of internal secretion. Other changes indicative of general endocrine disturbance found in these cases were dryness and abnormal

pigmentation of the skin, brittleness of the hair, hypertrichosis, trophic changes in the nails, unusual distribution of fat and both hypertrophy and underdevelopment of the genitalia. Retardation of growth, a symptom indicative of endocrine hypofunction, was characteristic also of several of these cases.

After an extensive comparison of conditions found in muscular dystrophy with altered endocrine function the authors point out the possibility of muscular dystrophy and perhaps other so-called myopathies being in reality nothing more than symptom complexes caused by deficient function, not of one, but of various endocrine organs affected separately or coincidentally.

This attitude appears reasonable in view of the fact that the symptoms which are known to represent dysfunction of one ductless gland are often very similar to or identical with manifestations of the affection of another. For instance, stoppage of growth, adiposity and defective bone formation are known to result from lesions of either the pituitary, the thyroid or the sex glands. Hence, if these symptoms are associated with such widely different organs, it seems probable that muscular dystrophy may likewise represent a symptom complex which may be caused by dysfunction of various ductless glands singly or collectively. Therefore, muscular dystrophy cannot be ascribed to hypothyroidism, as the results of former investigations might seem to indicate. The fact that the hypophysis was unquestionably affected in one case and possibly the pineal body in two others, illustrates how difficult it would be to explain the present series of cases on a basis of hypothyroidism or disturbances of the hypophysis.—H. W.

151. MUSCULAR DYSTROPHY, progressive. McCrudden (F. H.) *Jour. A. M. A. (Chgo.)* 1918, **70**, 1216.

“In progressive muscular dystrophy, we find low blood sugar, and, following treatment which increases the blood sugar, an improvement in muscular strength.

“Blood sugar is the source of energy for muscular contraction. Active muscle rapidly uses up glucose. As the supply becomes exhausted, muscular strength diminishes and can be restored only by glucose. Agencies such as Addison’s disease, diphtheria toxin, and phosphorus and hydrazin poisoning, which reduce the blood sugar, cause profound myasthenia, the severity of which is proportional to the fall in blood sugar. Hypoglycemia, then, sufficiently accounts for the myasthenia, the most striking symptom of progressive muscular dystrophy.

“As the glucose of the blood is used up by the muscles, the loss is rapidly and quantitatively made good from the store of

glycogen in the liver, the blood sugar being thereby maintained at a fixed level. Hypoglycemia can result only from a failure of replenishment to keep pace with the needs, that is, from a loss of balance between supply and demand. Greater needs, such as increased utilization of sugar, or loss through the kidneys, can be ruled out in progressive muscular dystrophy. There is no rise in heat formation such as would accompany increased sugar catabolism, and the urine is free from sugar. A rapid fall in blood sugar during the first twenty-four hours of starvation—in health, the normal blood sugar level is maintained during starvation—testifies that in progressive muscular dystrophy, as in all forms of experimental hypoglycemia, there is a decreased rate of replenishment resulting from a diminished reserve of glycogen.

“The diminished glycogen reserve in experimental hypoglycemia results from impaired glycogen formation. The carbohydrate ingested is not converted into glycogen, but remains a long time in the blood, after which it is probably changed to fat. The deposition of fat in the muscles points to a similar impairment of glycogenesis in progressive muscular dystrophy.

“Impaired glycogenesis may result from damage either to the liver or to the suprarenals, the organs that control the process or other endocrine glands. If the fault is with the suprarenals, administration of epinephrin restores normal glycogenesis. If the fault is with the liver, epinephrin has no effect. A prompt and marked rise in blood sugar following the administration of epinephrin in progressive muscular dystrophy testifies to the efficiency of the liver in this disease and points to a deficiency in epinephrin.”—Abbreviated from original.

152. (OVARIES) Hernias conjenitas tubo-ovaricas. (Congenital tubo-ovarian hernia.) Lugones (C.) Soc. Med. Argent., 1917 (June 29).

Among fifteen cases observed in little girls there were two in which the ovaries were removed on account of hemorrhagic cysts. Microscopic examination confirmed the presence of hemorrhagic cystic cavities.—B. A. H.

153. (OVARY) Effect of hysterectomy on ovarian function. Richardson (E. H.) Proc. Am. Gyn. Soc., Jour. A. M. A. (Chgo.) 1918, 70, 1885.

“The uterus is not essential to a continuation of ovarian function, except as regards menstruation and reproduction. The disturbances of ovarian function attributed to hysterectomy

tomy are partly those associated with normal menstruation and partly those arising from damage to the ovary through operative trauma or disease. The weight of evidence furnished by anatomic, experimental and clinical investigations is overwhelmingly in favor of retention of sound ovaries both before and after the menopause age."

- 154. (OVARY) End results of the conserved ovary.** Polak (J. O.) Proc. Am. Gyn. Soc., Jour. A. M. A. (Chgo.) 1918, 70, 1975.

"From a study of seventy-three reoperations on patients in whom one or both ovaries were conserved, we must draw the following conclusions: 1. Routine conservation without due consideration of the ovarian and contiguous pathologic condition as it exists in the individual case, is not good teaching. 2. Regeneration of the conserved ovary depends largely on the type and duration of the existing infection and the condition of the tunica of the individual ovary. 3. Even when the most detailed technic is observed, the ovarian circulation is impaired. 4. The retained ovary, without the uterus, is always a focus for possible trouble. 5. The life history of the retained ovary is of short duration, and the trophic influence of the diseased ovary has been overestimated. Finally, a cured patient has few nervous symptoms."

- 155. (OVARIES) Evidence of toxic action of ovaries of Gar.** Greene (C. W.), Nelson (E. W.) and Baskett (E. D.). Proc. Am. Physiol. Soc., Am. Jour. Physiol. (Balt.), 1918, 45, 558.

- 156. (OVARY) La función endocrínica del ovario y la secreción mamaria. (The endocrine function of the ovary and mammary secretion.)** Coni Bazan (F. A.) Semana Médica (Bs. Aires), 1918, 25, 570.

In 1915 Coni Bazan published with Berutti an article upon mammary deficiency in lactating women treated with ovarian ophotherapy, corroborating various observations first recorded by Goñalons in 1914. The latter reported the successful use of corpus luteum in the treatment of these cases, adducing numerous clinical and experimental observations. Goñalons has discussed the matter also in a paper in Surg. Gyn. and Obst.

In his earlier article Coni Bazan stated that all cases of mammary insufficiency are preceded by menstrual disorders of hypovarian origin. The later paper is based upon a more careful study of cases in which corpus luteum or ovarian treatment influenced favorably the scanty milk secretion. As the

latter condition improved other symptoms of ovarian deficiency decreased. It is stated that these cases, called by pediatricians "essential hypogalactia" are actually hypovarian hypogalactia.
G. P. G.

157. (OVARY) Oogenesis in the white mouse. Kingery (H. M.), *Jour. Morph. (Phila.)* 1917. Vol. 30.

In the development of the ovary of the mouse there are two proliferations of cells from the germinal epithelium. The first, occurring before birth, gives rise to "primitive germ cells" and their follicle cells; the second, extending from about birth, or a few days after nearly to sexual maturity, forms the "definite ova" and their follicle cells. The primitive oocytes undergo synizesis (contraction of the chromatin) and then pass through the stages pachytene, diplotene, and dictye (of v. Winiwarter), after which they all degenerate. In the definitive oocytes there is no evidence of synizesis nor of synapsis (conjugation of the chromosomes), but the chromatin network, very delicate at first, becomes heavier, and then becomes attenuated as the cell grows in size. The definitive ova develop after birth by a process of differentiation from the cells of the germinal epithelium. Stages were seen transitional between mesothelial cells and primary. These are fated to degenerate. The suggestion is repeated that this is a stage in degeneration in which the normal relations of nucleus and cytoplasm are disturbed. The fact that similar stages have been found in somatic cells militates against the attributing of any special genetic significance to this condition in the germ cells.—E. R. H.

158. (OVARY) Seniladad prematura y atrofia genital. (Premature senility and genital atrophy.) Tureme (A.) *Revista Médica del Uruguay (Montevideo)*, 1917, 20, 742.

Tureme reports a very interesting study of the pathogeny of some of the genital atrophies. He obtained in four cases a history of puerperal infection which was followed in a short time by amenorrhea, whiteness of the hair, senile appearance of the skin and loss of the teeth without caries. The patients were observed from two to three years after the puerperal infection. A characteristic genital atrophy developed. The uterus diminished in size,—in case of one 6-para having a length of but 6 cm.,—and the vagina and labia majora also showed atrophy. In one patient obesity preceded the genital atrophy and early senility appeared; the mammae, however, remained normal in appearance.
G. P. G.

159. (OVARY) Sex Studies. X. The corpus luteum in the ovary of the domestic fowl. Pearl (R.), and Boring (A. M.), *Am. Jour. Anat.* (Phila.) 1918, 23, 1.

Evidence is presented in this study which is believed sufficient to demonstrate that there is normally found in connection with the discharge or degeneration of the ovarian follicle in the domestic fowl a structure which is homologous to the corpus luteum of the mammalian ovary. The origin of this structure in the bird is plainly simply from the theca interna. The course of development of the bird's corpus luteum is an abbreviation of that in the mammal.—E. R. H.

160. (OVARY) Sex studies. XI. Hermaphrodite birds. Boring (A. M.) and Pearl (R.) *Jour. Exp. Zool.* (Phila.) 1918, Vol. 25.

This paper is a detailed study of the external characters, behavior, anatomy, and cytology of a series of hermaphroditic fowls and guinea-chicken hybrids. The more significant general results obtained are as follows: The eight hermaphroditic fowls studied were all basally females with ovaries in various stages of embryonic arrest of development or degeneration. Three of the lot were demonstrably changing from the female to the male condition in respect of the structure of the gonads, secondary characters, and behavior. The assumption of male behavior (treading) by an otherwise normal female has no demonstrable basis in changed structure of the gonad. The sex or degree of activity of the gonad has no direct causal relation to the development of comb, spurs, and wattles. Body shape and carriage have a general relation to the sex of the gonad. The interstitial cells have, in this material, no causal relation to the secondary sex characters. The amount of luteal cells or pigment is in precise correlation with the degree of external somatic femaleness exhibited by the individual.—

E. R. H.

161. (OVARY) The formation and structure of the zona pellucida in the ovarian eggs of turtles. Thing (Alice) *Am. Jour. Anat.* (Phila.), Vol. 23.

The ovarian eggs of the various forms studied are surrounded by a single layer of prismatic epithelial cells, which are separated from each other at the surface by a special cement, the terminal bars. The zona pellucida is to be looked upon as a cuticular formation, taking origin in large part from these terminal bars. It varies in thickness from 1 to 22 micra,

depending on the stage, and early (3 micra) may be divided into an outer denser and thicker and an inner thinner, clearer, and striated layer. Later growth and differentiation occur mainly in the outer layer. The zona is made up of a homogeneous fundamental substance traversed by numerous fine canals, in which are contained filaments or prolongations of the epithelial cells outside, connecting these cells with the surface of the yolk beneath the zona. These prolongations vary in length with the thickness of the zona and end in knob-like enlargements on the yolk. The fundamental substance of the zona arises in part from a delicate secondary network within the primary network of the terminal bars which is apparently produced by the superficial cytoplasm of the cells and which gives rise at its surface to a cuticular substance similar to that derived from the terminal bars. From these networks are derived, as the thickness of the zona increases, the fundamental substance and its enclosed canals, thus presenting a structure well adapted to the conveyance of nutritive material from the maternal blood to the growing yolk.—E. R. H.

162. (OVARY) The winter cycle of egg-production. Goodale (H. D.) *Anat. Rec. (Phila.)* 1918, Vol. 14.

Of no direct endocrine interest.

163. (OVARY) Tubal and ovarian hemorrhage; its etiologic relation to pelvic hematocele and extra-uterine pregnancy. Bovee (J. W.) *Proc. Am. Gyn. Soc., Jour. A. M. A. (Chgo.)* 1918, 70, 1975.

“Trauma plays a part in producing these hemorrhages. Hemorrhage from the fallopian tube may occur from general conditions that similarly affect other tissues. Venous stasis from circulatory disturbances or pressure from tumors may reasonably be included in a list of its causes. Ovarian hemorrhage may be confined within the ovary, constituting one or more hematomas, or it may take place into the peritoneal cavity, producing, if abundant, a hematocele. No other organ of the body is so frequently the seat of hemorrhage as is the ovary. Stromal hemorrhage is commonly preceded by infection of the ovary. In but few cases have correct diagnoses been made before operation or necropsy. As to treatment, in the milder forms of the condition rest and anodynes may meet all indications. In the severer forms the same rules apply as are employed in the treatment of ectopic pregnancy.”

164. (**PANCREAS**) **Pancreatic diabetes.** Hardoy (P. J.) *Revista Assoc. med. Argentina (Buenos Aires)*, 1917, **27**, 123.

A man 21 years of age with positive Wasserman, considerable glycosuria, marked polyuria and emaciation (20 kg. lost in 3 mos.) was considered to have pancreatic diabetes. Functional tests indicated that the external secretion of the pancreas was normal. The author believed that the condition was due to relative over-activity of the sympathetic nervous system, the vagus being depressed. Accordingly he administered pilocarpine and the glycosuria disappeared. Allowing the patient the use of carbohydrate caused a return of the glycosuria which again yielded to pilocarpine treatment.—B. A. H.

165. (**PANCREAS**) **Sugar absorption and the pancreas.** v. Korsky (K.) *Ztschr. F. physiol. Chem.*, 1916, **98**, 37-48.

Experiments on dogs are described which indicate that when the blood is prevented from circulating through the organs of the body, including the pancreas, the introduction of a large quantity of dextrose solution into the intestine leads to an increase in the amount of dextrose in the blood; while, if the pancreas is left in the circulation, under otherwise normal conditions, a decrease in the amount of dextrose in the blood is observed. Chem. Abst. **12**, 497.

166. (**PANCREAS**) **The site of formation of fibrinogen.** Wohlgenuth (J.) *Berlin, klin. Wchnschr. (Berlin)*, 1917, **54**, 87-90.

The influence of the pancreas on the liver is not limited to carbohydrate metabolism, but is also related to protein metabolism, one effect being the liberation of fibrinogen into the blood. Chem. Abst. **12**, 933.

167. (**PANCREAS**) **Morphine hyperglycemia in dogs with experimental pancreatic deficiency.** Auer (J.) and Kleiner (I. S.). *Jour. Exp. Med. (N. Y.)*, 1918, **27**, 49.

The authors contend that any factor causing hyperglycemia will probably call forth a greater response in animals with a pancreatic deficiency than in normal animals. This conclusion was substantiated by injecting morphine, 2 mg per kilo body weight, into the subcutaneous tissue of dogs that had previously sustained partial removal of the pancreas. In these animals it was found that morphine produced a rise in the glycemia about four times greater than the same amount of mor

phine calls forth in normal dogs. Animals with pancreatic deficiency may be considered to be in a prediabetic state, hence, inasmuch as morphine causes hyperglycemia in these experimental animals, the inference is drawn that this test should be of value in detecting a weakened carbohydrate metabolism in the human subject. The data presented afford additional corroboration of the view that the responses of a normal and of a pathologically altered organism to the same drug in the same dosage may show very large quantitative differences.—H. W.

- 168. (PARATHYROID) Action of the serum of normal dogs and of those in tetany on the muscles of toads and frogs.** Houssay (B. A.) *Revista Assoc. Méd. Argentina* (Buenos Aires), 1917, **27**, 641.

The muscles of the frog, *Leptodaectylus ocellatus*, were not influenced by the serum of either normal or tetanic dogs. The muscles of some toads, *Bufo marinus*, submerged in the serum of a dog in tetany showed contractions, but these were produced also by the serum of normal dogs.—B. A. H.

- 169. (PARATHYROID) The present day therapeutics of spasmophilia.** Cozzolino (O.) *La Pediatria* (Napoli) 1916, **24**, 292. *Abstr. Brit. J. Chil. Dis.* (Lond.) 1917, **14**, 233.

Parathyroid opotherapy is discussed and attention drawn to the probable divergence in therapeutic value of preparations from too old or too young animals as not containing sufficient quantity of the active principle. The author considers that opotherapy in spasmophilia may, in the future, tend toward a pluriglandular or at least a parathyroid-thymic opotherapy. He lays stress on the value of proper feeding and care of slight ailments which may favor the development of convulsive manifestations.—M. B. G.

- 170. (PINEAL) Calcification in the pineal gland.** Boas (E. P.) and Scholz (T.). *Arch. Int. Med.* (Chgo.), 1918, **21**, 66.

Case report of extensive calcification of the pineal gland in an individual 74 years of age. No symptoms referable to a diseased condition of the pineal body were demonstrable during the period of observation. At necropsy (death caused by a strangulated sliding hernia) areas of softening were found in the brain involving the external capsule and island of Reil on the right side, primary contracted kidneys, cholelithiasis, and extreme arteriosclerosis and calcification of the coronary arter-

ies, with calcification of a large part of the myocardium of the left ventricle. The pineal gland showed slight enlargement and marked calcification.

Pineal calcification is now known to be a not unusual finding in roentgenograms of the skull. In the majority of cases this calcification is only an exaggeration of the deposits of brain sand normally found in the glands of adults. Inasmuch as calcification occurs normally in the course of involution of the pineal gland such changes are insignificant save in pre-adolescent individuals. Calcification of the gland occurring at the period when the gland is normally physiologically active may result in symptoms due to insufficiency of pineal secretion.—H. W.

171. (PITUITARY) Effect of tethelin on experimental tuberculosis. Corper (H. J.) *J. Infect. Dis. (Chgo.)*, 1917, **21**, 269.

Tethelin, a substance precipitated from the anterior lobe of the ox pituitary, has been shown by Robertson to have a stimulating action on growth in mice and rats. Because of this action, Corper suggests that tethelin might be used in the indirect therapy of tuberculosis by stimulating the resistance of the host to tubercle bacilli. Guinea pigs were infected with virulent human tubercle bacilli and injected on alternate days subcutaneously with 25 mg. doses of tethelin for 18 days, before and during the infection. Such procedure had no appreciable effect on the progress of the tuberculosis or on the duration of life of these animals. Tethelin administered in 25 mg. doses daily to guinea pigs sensitized to tuberculosis by dead and living human tubercle bacilli had no appreciable effect on the development, recession or rupture of intracutaneous tubercles produced by dead human tubercle bacilli, nor on deep puncture wounds of the skin in these animals.—Chem. Abst.

172. (PITUITARY) The influence of pituitary extracts on the daily output of urine. Rees (M. H.). *Am. Jour. Physiol. (Balt.)*, 1918, **45**, 471.

An attempt to ascertain "whether the subcutaneous injection of pituitary extract will cause any quantitative variation in the daily output of urine" and "whether such injection will in any way affect the quantity of urine excreted, and, if so, to find out if possible, the factor involved."

The methods of Motzfeldt were followed, except that the

observations extended over longer periods of time. The conclusions reached are:

1. Subcutaneous injections of pituitary extract do not alter quantitatively the daily output of urine in cats and rabbits, nor do they cause any marked variation in the specific gravity of the urine.

2. The subcutaneous injection of pituitary extracts causes a delay of seven to eight hours before the beginning of the diuresis which follows the ingestion of large amounts of water.

3. The delay in diuresis which is produced by subcutaneous injection of pituitary extract is due in part at least to a delayed absorption from the alimentary canal.

4. The subcutaneous injection of pituitary extract has no influence on the diuresis induced by the continuous intravenous injection of isotonic salt solution.—T. C. B.

173. PITUITRIN, its value in post-operative treatment.

Davis (N.) and Owens (R.). *New Orleans Med. and Surg. Jour.*, 1918, **70**, 712.

The authors present an enthusiastic account of their experience with pituitrin in 126 laparotomies. Although they regard it as of little use in obstetrical practice, they believe that it has an important place in surgery. They conclude: "That pituitrin is a valuable drug in stimulating the muscular coats of the intestine after abdominal section in non-septic cases. It is of decided assistance in preventing post-operative shock. It has very little if any effect upon cases complicated with septic peritonitis, but our results are inconclusive on account of the small number of cases. It stimulates the secretory section of the kidneys in cases of eclampsia. It materially reduces the amount of post-operative suffering."—R. G. H.

174. (PITUITRIN) The regulation of renal activity. V.

Regulation of urea excretion by pituitrin. Addis (T.), Barnett (G. D.) and Shevsky (A. E.) *Am. Jour. Physiol. (Balt.)* 1918, **46**, 52-62.

The subcutaneous injection of pituitrin in the rabbit is followed in all effective amounts by a decrease in the urea excreting activity of the kidney. The rate of urea excretion is slower than in animals not given pituitrin, although the blood urea concentration is higher.—L. G. K.

175. (PITUITRIN) The value of pituitary extract in incomplete abortion and placenta previa. Lipkis (A.) *Northwest Med. (Seattle)*, 1918, **17**, 74.

Pituitary extract in 0.5 c.c. doses will do away with the curette or pack in most, if not all, cases of incomplete abortion. It controls hemorrhage, and the placenta usually comes away within three days. In some few cases it may take longer—6 or 7 days. As a rule the longer the pregnancy and the larger the placenta the less time it will take for the uterus to empty itself and the more likely the placenta will come away as one piece. The advantage of this treatment over the prevailing method of cureting or packing is that it is simple, and by avoiding local manipulations, lessens the danger of infection.

In one case the author succeeded in delivering a placenta previa marginalis with one-fourth c.c. doses of pituitary extract.—Author's Abstract.

176. REPRODUCTIVE GLANDS, internal secretion of. Steinaeh, Foges, and Lode, *Ztschr. f. Sexualwissensch.* (Leipzig), August, 1917.

It is stated that after castration the sexual disposition of young mammals may be reversed by implanting a testis into females, or an ovary into males. The reproductive hormones are regarded as antagonistic, and the erotising effect does not occur if castration has not been performed. The "Lancet" in an annotation from which this is taken maintains a cautious attitude in reference to these results.—*Physiol. Abst.*

177. (SECRETIN) A new plant secretin. Bickel (A.) *Berl. klin. Wehnshr.* (Berlin), 1917, 552-3; Eisenhardt (W.) *Ibid.*, 553-4; Djenab (K.) *Ibid.*, 24-5. (*Physiol. Abst.*, 2, 605.)

Spinach contains a secretin which acts both on the stomach and the pancreas. In the fresh vegetable it is firmly united, but can be boiled out by water or liberated by hydrolysis with HCl. It resists this action, but is destroyed at 140°. It is an organic substance with an activity about equal to that of pilocarpine. Its action is shown better by intravenous injection than by administration by mouth. The relation of secretins and vitamins is discussed. Confirmatory experiments by Eisenhardt on dogs with Pavlov stomachs are recorded. The stimulating substance is the arginine-histidine fraction. Its relation to vitamins is also considered. Djenab determined that when injected into a femoral vein it lowers blood pressure and causes secretion from the pancreas. Injected into the mesenteric vein, the fall of pressure is less and does not last as long; there is no effect upon the pancreas. The conclusion is drawn that it is neutralized in its passage through the liver,

and to some extent, through the muscular tissues. The same effect is produced on the true pancreatic secretin; examination of the various levels of the intestinal mucosa shows that secretin is most abundantly obtained in the deeper layers of the duodenal lining. Chem. Abst. 12, 1069.

178. (**SECRETIN, II**) Its influence on the number of white corpuscles in the circulating blood. Downs (A. W.) and Eddy (N. B.). *Am. Jour. Physiol. (Balt.)*, 1918, 45, 294.

It is possible to produce an increase in the number of white corpuscles per cubic millimeter of blood by the administration of secretin, even in small doses and by subcutaneous injection.

The most efficient dose is 1 cc. of secretin solution per kilogram of body weight.

It is suggested that the effects described are due to a direct stimulating action of secretin on both the bone marrow and the lymphatic tissues in general.—T. C. B.

179. (**SPLEEN**) The elimination of iron and its distribution in the liver and spleen in experimental anemia. Dubin (H.), Pearce (R. M.) *Jour. Exp. Med. (N. Y.)*, 1918, 27, 479.

No increased elimination of iron was observed in the feces of dogs showing an essentially chronic experimental anemia produced by infecting the animals with *Trypanosoma equiperdum*. The storage of iron in the liver and spleen was slightly increased in amount, but of the same general character as in transient experimental anemia. Splenectomy before and after infection influenced neither the elimination of iron in the feces nor its storage in the liver. Retardation of the course of the trypanosome infection likewise failed to affect iron storage. In the presence of a bile duct-ureter fistula the iron content of the mixture of urine and bile was not appreciably greater than that of normal urine alone. Therefore, the elimination of iron in the bile does not seem to be an important factor in the dog. However, when bile is excluded from the intestine an unusual storage of iron occurs in the spleen. No explanation of the latter condition is offered.—H. W.

180. (**SPLEEN LIVER**) Hematogenous icterus, hemoglobin and iron metabolism. Lepehne (G.) *Beitr. z. path. Anat.*, 1917, 64, 55-126. (*Physiol. Abst.*, 2, 25.)

Clinical work on jaundice and experiments on animals show that there is an inter-relationship of liver and spleen in reference to hemoglobin and iron metabolism. After the spleen

is extirpated in rats and mice the Kupffer cells of the liver become active, and phagocytosis and accumulation of iron occur in that organ. Differences in that respect occur in different animals: the guinea pig, for example, does not show the same effect as that manifested in rats and mice.

Chem. Abst. 12, 939.

181. SPLENOMEGALY, Familial, a clinical study. De Lange (C.) and Schippers (J. C.) Amer. J. Dis. Child. (Chgo.), 1918, 15, 249.

The authors report the clinical history of seven children in one family, at least two of whom, in their opinion, presented the clinical picture of Gaucher's type of splenomegaly. Case 1. The first child in the family died at the age of two years of "hepatitis." Case 2. The second child, 11 years old, had enlargement of both spleen and liver; skin was slightly yellow tinted; death occurred suddenly after a serious hematemesis. Case 3. The third child died at the age of 17 days from an umbilical infection. Case 4. The fourth child looked healthy: his spleen was palpable beneath the costal margin. Case 5. The fifth child did not show any enlargement of either spleen or liver.

Case 6. The sixth child, a girl of $7\frac{1}{2}$ years of age, had a distended abdomen. The spleen was felt one-half inch above the anterior superior spine; the right border was $2\frac{1}{2}$ inches from the median line. The liver extended 3 inches below the costal margin. The Wassermann reaction was negative, as in the previous cases, and the Von Pirquet, positive. The others were negative except Case 4. The blood showed leucopenia with increase, however, in the number of mononuclear lymphocytes. There was no marked anemia. Splenectomy was performed.

Case 7. The seventh child, a girl, $5\frac{1}{2}$ years old, showed a few pigmented spots on the abdomen, but no jaundice. The spleen extended 1 inch above the anterior iliac spine; the right border was $2\frac{1}{2}$ inches from the navel. Splenic dullness was heard in the axillary line at the ninth rib. The liver was enlarged, the Wassermann reaction negative, and Von Pirquet, positive. Blood examination showed a leucopenia varying from 4200 to 8500, hemoglobin in very large amount, and a high count of erythrocytes. Splenectomy was done. The mother said that the enlargement of the liver and spleen was already noticed in this case at the age of two and in Case 6, at the age of four.

Examination of the father did not show any abnormalities; no enlargement of the spleen or liver. While his blood examination was practically normal on three tests, there was a con-

glycogen in the liver, the blood sugar being thereby maintained relative lymphocytosis. The authors emphasize this latter point, although they do not venture to state that the disease in the children can be traced back to the father. Clinical and blood examinations of the mother, maternal and paternal grandmother and maternal grandfather were all negative.

After the operation the blood of both children showed an increase in leucocytes. The liver in one decreased somewhat in size and then remained stationary, while in the other, it increased slightly and then returned to the size preceding the operation. Both children were in good health a year after the operation.

Microscopic examinations did not show the accepted pathological picture of Gaucher's disease. The authors think, however, that they are dealing with a familiar progressive disease of the spleen which produces, sooner or later, an increasing cachexia and in the course of which a hemorrhagic diathesis occurs ante-mortem.—M. B. G.

182. SUGAR METABOLISM AND DIABETES. McGuigan (H.). *Jour. Lab. and Clin. Med. (St. Louis)*, 1918, **3**, 219.

An interesting paper dealing with the history of diabetes and the various chemical tests used in the determination of sugar.—H. W.

183. (TESTES) Cases showing remote results of testicle implantation. Lydston (G. F.) *Jour. A. M. A. (Chgo.)* 1918, **70**, 907-8.

Two cases are described in which testes of boys 14-15 were implanted in the scrota of men lacking these organs. A marked development of virility followed. The author concludes that when technic and material are right and the recipient is properly selected, continuity of hormone production by the implanted gland for at least a prolonged period is certain and that permanent beneficial results are probable.—R. G. H.

184. (TESTIS) Chondriosomes in the testicle cells of Fundulus. Duesberg (J.) *Am. Jour. Anat. (Phila.)* 1918, **23**, 133.

In the cells lining the proximal part of the excretory ducts in the testicle of *Fundulus* the chondriosomes are represented by long chondrioconts, whose disposition reminds one of the Heidenhain's or of the Pflüger's rods. In the latter part of the excretory ducts the chondriosomes are replaced by granules of pigment. The connective tissue of the testicle holds a num

ber of cells with special characters (bacilli-shaped chondriocysts, secretion granules); these cells are probably interstitial cells. Chondriosomes are found in all generations of germ cells and transmitted during mitosis from one generation to the following one.—E. R. H.

185. (TESTIS) The influence of excessive sexual activity of male rabbits. I. On the nature of the seminal discharge. Lloyd-Jones (O.) and Hays (F. A.) Jour. Exp. Zool., (Phila.) 1918, Vol. 25.

Of no direct endocrine interest.

186. (TESTIS) II. The influence of excessive sexual activity of male rabbits on the nature of their offspring. Hays (F. A.) Jour. Exp. Zool. (Phila.) 1918, Vol. 25.

Of no direct endocrine interest.

187. (TESTIS) The relations between the interstitial gland of the testicle, seminiferous tubules and secondary sexual characters. Loeb (L.) Biol. Bull. (Woods Hole) 1918, Vol. 34.

The author found that a guinea pig with certain female secondary sex characters was an abnormal male. The testes were small, had not descended and were made up of interstitial cells, and typical tubules which lacked spermatogonia. The interstitial cells were abnormal containing vacuoles and eosinophilic bodies. The mammary gland was female in character.—

E. R. H.

188. THYMUS and dwarf growth. Krabbe (K. H.) Ugeskrift. f. Laeger (Kobenhavn), 1917, 79, 1329.

A case of pronounced dwarf growth is described and it is suggested that the thymus is responsible for the condition. There were no symptoms indicating abnormal functions of the thyroid, parathyroids, pituitary, suprarenals, ovaries or pancreas.—Physiol. Abst.

189. (THYMUS) Extirpation of the thymus gland in *Rana pipiens* larvae. Allen (B. M.) Anat. Rec. (Phila.) 1918, Vol. 14.

The thymus gland anlagen were removed at their very inception from 8 mm. to 9 mm. tadpoles. This was accomplished by cutting into each side of the head with a cataract

needle. Although the severity of the operation retarded development for a time, recovery was rapid and complete. Seven specimens were reared to the time of metamorphosis, attaining normal size and appearance. All died or were killed at this time. It is impossible from the material at hand to determine whether the high mortality at this time was due to the absence of the thymus gland or to other causes. It was in sharp contrast to the fate of the controls. Further experiments will be made upon this point next year. They appeared to be structurally normal in every regard. The characteristic features of metamorphosis occurred. A careful study of the thymus gland region of each specimen showed that the glands had in each case been successfully removed. Five out of the seven were males. Sexual differentiation was complete, and measurements showed the gonads to be altogether normal in size as compared with metamorphosed controls. A comparison of sections of the gonads of operated and control specimens showed those of both to be identical in structure and in the developmental stage reached by the germ cells.—E. R. H.

190. (THYMUS) Is the influence upon development, metamorphosis, and growth of thymus, when taken as food, due to a specific action of that gland? Uhlenhuth (E.) Jour. Exp. Zool. (Phila.) 1918, Vol. 25.

The differences in the rate of growth between thymus-fed and worm-fed larvae of *Amblystoma opacum* and *A. punctatum* are not the result of a specific growth-promoting influence of the thymus, but are due to the circumstance that animals which are better fed grow more rapidly. In order to make this point clear, quantitative feeding experiments were introduced in the study of the effect of the thymus. The meaning of the results regarding the effect of the thymus on development and metamorphosis will not become entirely clear before extensive experiments are available concerning the relation between size, rate of growth, differentiation, age, and metamorphosis in animals which have been fed on only one kind of food. When thymus-fed larvae of *A. opacum* and *punctatum* metamorphose, they are smaller than worm-fed animals at the time of metamorphosis. Larvae of *A. opacum* develop more rapidly when fed on thymus than do the controls; but only some thymus-fed individuals metamorphose earlier, while the development of others ceases (except development of the skin), when they reach the stage preceding metamorphosis, and either metamorphose only after a relatively long time or die as larvae after a certain period. Thymus-fed *A. punctatum* behave similarly. Two of these species, kept in low temperature, remained larvae

for about fifteen months, and died after they had commenced to metamorphose. Similar cases, however, are found even among worm-fed animals. It seems that the thymus does not interfere with those factors necessary for differentiation during the larval period: when metamorphosis begins, a new factor seems to become indispensable to further differentiation, and the thymus diet apparently often disturbs in some way the development of this factor. After a thymus-fed larva has once metamorphosed, it may live on exclusive thymus diet to at least eighteen months of age.—E. R. H.

191. (THYMUS) Klinische Bedeutung der Thymusdrüse. (The clinical significance of the thymus.) von Haberer (H.) Arch. f. klin. Chirurgie (Berlin) 1917, **109**, 193.

In every case of partial thyreodectomy in Graves' disease it is necessary to look for the thymus and to enucleate it. The results of this combined operation are much better than when only a part of the thyroid is removed. There are classical cases of Graves' disease in which the thyroid is small, the thymus, however, being very large. In these cases complete recovery is observed after resection of the thymus.

The author operated on 40 cases in this way; he never observed a relapse. In young children the growth continued perfectly normally after removal of the thymus—J. K.

192. (THYMUS) Physiologie der Drüsen. Asher (L.) XXXIII. Eine neue Funktion des inneren Sekretes der Thymusdrüse. Müller (H.) Ztschr. f. Biol. (München), 1917, **67**, 489.

In frogs narcotised with urethane the triceps was fatigued by the method of Kornecker. In eight experiments Thyroglandol (La Roche) and in fifteen experiments a fresh watery extract of thymus was injected into the abdominal cavity and the effect on the height of the successive contractions was noted. The normal muscle fatigue curve descends gradually in a straight line. Provided fatigue were not too pronounced, both preparations caused its temporary disappearance in spite of continued stimulation, the height of the contractions (1) remaining stationary or (2) showing a slight increase; eventually the typical curve of fatigue reappeared. The action of thyroglandol was characterised by a latent period of twenty minutes, and was less marked than that of the fresh extract. Nucleoprotein, Ringer's solution and pituglandol, had no effect on the fatigue curve, and the author concludes that the beneficial action of thymus is specific. The physiological and patho-

logical significance of this new function of the internal secretion of the thymus is evident. Rabbit serum had a distinctly beneficial action on muscle fatigue, whereas plasma was inactive.—*Physiol. Abst.*

193. (THYMUS) Transplantation of the thymus in rabbits. Relation of the thymus to sexual maturity. Marine (D.) and Manley (O. T.). *Jour. Lab. and Clin. Med.* (St. Louis), 1917, 3, 48.

Transplants of thymus tissue in the subcutaneous tissues of the abdomen survive in sexually immature rabbits. Only auto-transplants persisted. The present experiments conform with the result of others and demonstrate that removal of the thymus hastens sexual maturity. Utilization of rabbits for breeding purposes hastens not only normal involution of the thymus but also the auto-transplants as well. This condition suggests that a specific nerve influence is not essential for these involutory changes.—H. W.

194. (THYMUS) Report of nineteen cases of hyperphasia of the thymus gland, treated by the X-ray. Benjamin (J. E.) and Lange (S.) *Arch. Ped.* (N. Y.) 1918, 35, 70.

The authors found that out of 225 cases of all sorts seen in their children's clinic, 19, or 8.47 per cent, showed undisputed evidences of enlarged thymus.

The chief complaint is nearly always a history of a cough in a child who does not show the prodromal symptoms of a cold but is apparently well. The cough is generally present at night and may be accompanied by a choking sensation.

The "threshold method of percussion" was used to outline the thymus. The child is placed on the mother's lap on his back. Percussion is begun well out in the chest, with such light strokes that when the ear is within a few inches of the area percussed only faintest possible resonance is heard. When sound disappears, dullness begins. Some observers outline the border of dullness by the tactile sense of resistance rather than sound. The outer borders are determined more easily than the lower boundary; the latter may be obtained by auscultatory percussion and is relatively less important. The writers found that the percussion outlines determined in this way correspond remarkably closely to the Roentgenogram. A clinical diagnosis of thymic enlargement is never absolutely positive without X-ray confirmation.

X-ray diagnosis is based upon an enlargement (usually lateral) of the thymus shadow, which normally rests upon and

is continuous with the heart shadow, which may, however, be confused with the shadow of congenital heart enlargement. In all cases where the diagnosis by the X-ray was doubtful, a therapeutic test of an X-ray exposure was given and found to be very reliable. Many symptomless and supposedly healthy children may show an apparently enlarged thymus upon the X-ray plate. An enlarged thymus in an apparently healthy child may be abnormal although its ill effects may not be manifest until some added strain be put upon the heart or respiratory organs or until the resisting powers of the child be called upon to overcome an acute infection.

Three treatments were the usual number given at intervals of one week, unless the urgency of the symptoms suggested more frequent applications, when a second dose was given in a day or two. In the average case the improvement was noted in 24 to 48 hours after the treatment.

The X-ray therapy in these cases was carried out as follows: A Coolidge tube backing up a $9\frac{1}{2}$ inch spark was employed. The rays were filtered through $\frac{1}{4}$ millimeters of aluminum and a piece of thick leather. The target skin distance was approximately nine inches. The routine exposure was 25 milliamperes-minutes. In mild cases a single dose over the anterior surface of the chest proved sufficient. In more urgent cases 50 milliamperes-minutes were administered at the first treatment, 25 anteriorly and 25 posteriorly. During the treatment the child was kept quiet by four sandbags, one placed across each arm and one across each leg. In order to get results it is essential that the treatments be comparatively heavy and that they be repeated at sufficiently short intervals.

The exposure varied from one-sixtieth to one-thirtieth of a second.—M. B. G.

195. (THYROID) Akuter Morbus Basedowi. (Acute Graves' disease.) Boir (C.) *Klin. Monatsbl. f. Augenheilk.* (Berlin) 1917, **59**, No. 728.

Three cases are described, in which soldiers after a great fright, showed a classical picture of Graves' disease.—J. K.

196. (THYROID) Blutzuckerbestimmungen bei einem Fall von infantilen Myxödem. Nilsson (N.) *Deutsche med. Wehnschr.* (Berlin), 1917, **43**, 41.

Hypothyroidism is associated with a raising of the assimilation limit for glucose; hyperthyroidism with the opposite. In the present case (a boy aged seventeen) there was an increase of the blood sugar after giving either thyroid tablets or

adrenin. The effect on the blood picture is also described.—
Physiol. Abst.

197. (THYROID) Effects of the extirpation of the thyroid gland upon ossification in *Rana pipiens*. Terry (G. S.) Jour. Exp. Zool. (Phila.) 1918, Vol. 24.

Examination of the vertebral column of thyroidless and control tadpoles shows that the removal of the thyroid gland produces a marked retardation in the process of ossification which almost amounts to a cessation of the process. Up until the period when the hind legs begin to grow in length there is little difference in the process of ossification between the thyroidless and control specimens, but after this period the retardation becomes markedly noticeable in the thyroidless animals. In comparing the thyroidless and control specimens of the same age, calcification of the cartilage seems to take place at about the same time in both, but the erosion of calcified cartilage preliminary to ossification takes place very slowly in the thyroidless tadpoles. As a result of this, the vertebrae in older specimens appear more uniform than in the controls of the same age when studied from whole-mount preparations. The outline of the centrum is very regular and the calcification appears uniform in all specimens studied. There is a heavy deposition of calcium salts in the end of the rib, not present in control specimens. There is a complete absence of spinous processes upon the vertebrae of the largest thyroidless specimen (43 mm. body length from anterior tip of head to cloaca). Comparison of the hind legs of the control with much older thyroidless specimens with the same leg length shows that the removal of the thyroid gland has greatly retarded if not completely stopped both the processes of growth and ossification.—

E. R. H.

198. (THYROID) Effects of external temperature and certain drugs on thyroid activity. Mills (C. A.). Proc. Am. Physiol. Soc., Am. Jour. Physiol. (Balt.), 1918, 45, 557.

199. (THYROID) Forma congestiva del hipotiroidismo. (Congestive form of hypothyroidism.) Mussio Fournier (J. C.) La Prensa Medica Argent. (Buenos Aires) 1918, 4, 463.

A patient 53 years old had suffered from attacks of pulmonary congestion . . . anuria and hematuria and hemiplegia which had become ameliorated. The congestions had been treated repeatedly and the kidneys had twice been decapsu-

lated. As there were falling out of the hair, headache, insomnia, transitory edema of the limbs, etc., and the Wasserman reaction was negative and antiluetic treatment was always followed by symptoms of intoxication, it was decided to institute thyroid treatment. The results were gratifying; many of the symptoms gradually improved. Prof. Kocher introduced three thyroid grafts from a Basedow patient. An improvement of the symptoms, but also glycosuria, followed. Anginal attacks from which the patient had previously suffered reappeared, the arterial blood pressure reaching 220 mm. The author attributes these untoward results to the hyperthyroidism.—

B. A. H.

200. (THYROID) Influence of thyroidin on standard metabolism. Krogh (M.) Ugeskrift for Laeger, 1916, No. 52.

Determinations were made of the oxygen consumption by urethanized frogs before and after the administration of thyroidin; also with and without division of the nerve trunks for the four limbs. Thyroidin caused a much smaller rise in metabolism after the nerves were cut. It is accordingly provisionally concluded that thyroidin acts chiefly by increasing the tonus of striated muscle.

Chem. Abst. 12, 719.

201. (THYROID) Headache from thyroid deficiency. Giacobini (G.) Semana Médica (Bs. Aires.), 1918, 25, 516.

A short paper, containing nothing new.

G. P. G.

202. (THYROID) Sarcoma of the thyroid gland. Jorge (J. M.) and Arrillaga (F. C.) Revista Asoc. Méd. Argentina (Buenos Aires) (Dic.) 1917, 27, 932.

A malignant sarcoma was observed in a woman 24 years of age. The case came to autopsy. Of the metastases present one especially worthy of interest had penetrated the veins of the neck and was prolonged to the interior of the heart.—B. A. H.

203. (THYROID) The acceleration of metamorphosis in frog larvae by thyroid feeding, and the effects upon the alimentary tract and sex glands. Swingle (W. W.) Jour. Exp. Zool. (Phila.) 1918, Vol. 24.

Very great acceleration of metamorphosis occurs in frog larvae when they are fed extract of thyroid gland. It is possible by judicious administration of thyroid to stimulate very immature tadpoles to complete metamorphosis, assuming all of

the adult characteristics except size. Examination of the gonads and germ cells reveals no observable changes, either gross or histological, from those of the control larvae of the same age and size; this despite the fact that from the standpoint of somatic development the thyroid-fed animals are months ahead of the controls.

The alimentary tract of tadpoles is a long, cylindrical, much-coiled structure, with little or no differentiation into stomach, small and large intestine. When the animals are placed upon thyroid diet the alimentary tract undergoes an extremely rapid differentiation to a well-marked stomach, small and large intestine. These changes occur within a few days. By thyroid feeding differentiation of the alimentary tract into its three characteristic divisions can be brought about in starved larvae in which all growth and development have ceased for months.

Drawings and photographs are given illustrating these points.—E. R. H.

204. (THYROID) The effect of the extirpation of the thyroid upon the thymus and the pituitary glands of *Rana pipiens*. Rogers (J. B.) Jour. Exp. Zool. (Phila.) 1918. Vol. 24.

The pituitary gland continues to develop when the thyroid gland is extirpated, the anterior lobe reaching a larger size in proportion to body length than it does in the pituitary gland in normal specimens. This is true in all stages up to young sexually mature normal frogs. In most cases the pituitary gland of the thyroidless tadpole is larger than that of the corresponding control without reference to body length. The pituitary gland is largest in proportion to body length in thyroidless tadpoles of the same age as young sexually mature frogs. The thymus glands continue to develop when the thyroid is extirpated. In metamorphosing controls they are much larger than those from thyroidless tadpoles of the same age. The thymus glands of the thyroidless tadpoles do not suffer degeneration like those of normal controls, but continue to grow; consequently those of thyroidless tadpoles do not migrate to the position in which the glands are found in adult frogs. The thymus glands of the thyroidless tadpoles grow to large size in later stages, but in early stages do not undergo the sudden increase in size that the controls do at metamorphosis.—E. R. H.

205. (THYROID) The effects of thyroid secretin on the excitability of the endings of the cardiac vagus. Levy (L.). Arch. Int. Med. (Chgo.), 1918, 21, 263.

The author's experiments were designed to determine whether or not the secretion of the thyroid gland increases the responsiveness of the vagus nerve terminations to electrical stimulation. If it does, as certain investigators maintain, thyroid secretion must be regarded as having a sensitizing effect on true sympathetic as well as on parasympathetic (vagus) endings.

In cats pithed to the mid-thorax it was found that repeated stimulations of either vagus with a given strength of stimulus resulted in a uniform series of responses, both as to degree of depressor effect and duration of cardiac inhibition. After inducing secretory activity of the thyroid through faradic stimulations of the central end of the cut cervical sympathetic, even at a time when increased pressor responses to a given dose of adrenin gave evidence that there had been a pouring out of thyroid secretion, there was no significant alteration in the depressor effect or duration of cardiac inhibition following stimulation of the vagus nerves. Therefore, it appears evident that after the thyroid gland has liberated its secretion in sufficient quantity to sensitize the sympathetic structures acted upon by adrenin in raising arterial pressure, there is no demonstrable effect on the excitability of the endings of the cardiac vagus.—H. W.

206. (THYROID) The aetiology and treatment of exophthalmic goitre with special reference to the use of radium. Aikins (W. H. B.) Can. Pract. and Rev. (Toronto), 1916, 41, 323.

A review of the etiology of exophthalmic goitre followed by a brief account of the various forms of treatment.

A brief summary is given of the treatment by medicaments, organotherapy, and Roentgen rays, and hydro-therapy, but many cases do not respond to any of these. Seven cases are discussed in which radium treatment, usually combined with the administration of hydrobromate of quinine and ergotin and the application of ice-bags to the praecordia was very effective. In all cases a very great improvement or a complete cure was recorded.—L. G. K.

207. (THYROID) The fate of the ultimobranchial bodies in the pig (*Sus scrofa*). Badertscher (J. A.) Am. Jour. Anat. (Phila.), 1918, Vol. 22.

The ultimobranchial bodies in the pig participate in the formation of thyroid follicles. The portion of the gland in full term embryos that is derived from these structures is small in

comparison to the part derived from the median thyroid anlage. Colloid first appears in the follicles of the thyroid gland in embryos 75 m.m. long. Colloid first appears in the follicles of the ultimobranchial bodies in embryos 125 m.m. long.

The cephalo-caudal extent of the ultimobranchial bodies is equal to or nearly equal to that of the thyroid gland in embryos up to about 33 mm. long. In stages from about 50 mm. length to full term they usually lie in the posterior half of the thyroid gland, but may be found in the middle third or in the middle two-fourths of the gland. In the majority of late stages they are entirely imbedded. The ultimobranchial bodies in a thyroid gland may vary in size, in shape, in the degree of their transformation, and in their location in the lateral halves of the thyroid gland.

The developmental stages in which the ultimobranchial bodies can no longer be recognized structurally from the median thyroid anlage vary greatly. The transformation of their greater part may take place as early as in a 35 mm. embryo, but in the majority of stages examined it takes place in later stages. Even in full term embryos an entire ultimobranchial body may not be completely transformed.—E. R. H.

208. (THYROID) The influence of large doses of thyroid extract on the total metabolism and heart in a case of heart block. Aub (J. C.) and Stern (N. S.). *Arch. Int. Med. (Chgo.)*, 1918, **21**, 130.

A case report of a woman 24 years of age showing auriculoventricular dissociation together with a systolic murmur and slow heart. The thyroid gland was not palpable. Thyroid extract was administered in increasing doses over a period of four months during which time the patient ingested a total of over 2,000 grains. During the last month the doses amounted to 28 grains per day. The basal metabolism was increased 47 per cent above normal and a rapid auricular rate, 120 per minute, followed the administration of the large doses of extract. Within 12 days after withdrawal of the extract the basal metabolism dropped to normal and within 19 days the auricular rate dropped to 71, which rate was thereafter maintained. The administration of thyroid extract had apparently no effect on the respiratory quotient or the blood sugar. Because of the increase in auricular rate without alterations in the ventricular rate it is suggested that thyroid extract does not increase the heart beat by direct action on the muscles, but through nervous elements.—H. W.

209. (THYROID) The influence of the thyroid of anastomosis of the phrenic and cervical sympathetic nerves. Marine (D.), Rogoff (J. M.) and Stewart (G. N.). *Am. Jour. Physiol.* (Balt.), 1918, **45**, 268.

A repetition of the experiments of Cannon, Binger and Fitz. In none of the animals were there any symptoms of Graves' disease. No respiratory hippus, and no exophthalmos. No histological difference between the two sides of the thyroid. No study of the metabolism seems to have been made.—T. C. B.

210. (THYROID) The isolation and identification of the thyroid hormone, etc. Kendall (E. C.). *Proc. of Am. Physiol. Soc., Am. Jour. Physiol.* (Balt.), 1918, **45**, 540.

The iodine-containing compound of the thyroid has the empirical formula $C_{11}H_{10}O_3NI_3$ and is shown to be tri-hydro, tri-iodo oxy-indol proprionic acid. Physiological testing has shown that this substance will relieve all the symptoms of cretinism and myxedema to the same extent as desiccated thyroid.

(It is assumed that a full report will appear later.)—
T. C. B.

211. (THYROID) The physiological action of the thyroid secretion and a method for its demonstration. Asher (L.). *Deutsche med. Wehnschr.* (Berlin), 1916, **42**, 1028.

By stimulating the nerves of the thyroid, it is shown that certain biological reactions are obtained which occur when thyroid preparations are given. For practical purposes the most useful reaction to demonstrate the thyroid secretion is the strengthening of the adrenin action with the Laewen-Trendelenburg preparation. By this method it is possible to demonstrate the presence of an increased thyroid secretion in the blood of cases with Basedow's disease. It can further be shown that by feeding rats with thyroid tablets an increased formation of thyroid secretion occurs. The most important biological reaction is obtained not only by thyroid gland extract but also by the protein and iodine free "thyreo-glandol" prepared by Hoffman-LaRoche, Basel. It produces the same action on metabolism as the whole gland.—Chem. Abst.

212. (THYROID) The prevention of simple goiter in man. Marine (D.) and Kimball (O. P.). *Jour. Lab. and Clin. Med.* (St. Louis), 1917, **3**, 40.

From a complete census of the condition of the thyroid gland in 3872 girls from the 5th to the 12th grades of the school population of a large community in the Great Lakes goiter district, it was found that 1,688, or 43.59 per cent, had normal thyroids; 2,184, or 56.41 per cent, had enlarged thyroids; and 594, or 13.4 per cent, had well defined, persistent thyroglossal stalks.

From the results of experimental work and general conclusions a method of prophylaxis has been developed and put into practice. This consists of the administration of small doses of the iodides.—H. W.

213. (THYROID) The relation of normal thyroid-gland development to bodily growth and differentiation in *Rana*, *Bufo*, and *Amblystoma*. Allen (B. M.) Anat. Rec. (Phila.) 1918, Vol. 14.

In *Amblystoma* both fore and hind limbs begin to grow before any colloid is formed in the thyroid gland. In *Bufo* it appears almost immediately after limbs have begun to grow, while in *Rana pipiens* it appears practically simultaneously with anlage of the hind limbs.

In all three forms there is a rapid growth of the gland and this corresponds closely with limb development. In all three forms the thyroid gland is well developed and contains a large amount of colloid long before metamorphosis is completed.

In axolotls of 140-160 mm. length the thyroid gland was found to be approximately of equal size and structurally similar to that of adult *Amblystoma tigrinum*. Colloid was present in large amount in both, but the axolotls were not well enough preserved to enable one to judge of its density.

Although the thyroid gland of *Bufo* is actually smaller at metamorphosis than that of *Rana* or *Amblystoma* its proportion to body size is greater than in either *Amblystoma* or *Rana*. This is probably correlated with the shortness of its larval life and the greater rapidity of its metamorphosis.

There is a clear correspondence between the normal development of the thyroid gland and normal progress toward metamorphosis, although limb development may be partly independent of it.—E. R. H.

214. (THYROID) The relation of the thyroid gland to regeneration in *Rana pipiens*. Allen (B. M.) Anat. Rec. (Phila.) 1918. Vol. 14.

These experiments involved three classes of tadpoles:
1. Tadpoles from which the thyroid gland had been extirpated

—absence of thyroid secretion. 2. Normal control tadpoles. 3. Tadpoles to which thyroid extracts were fed—excess of thyroid materials.

In each case approximately the terminal half of the tail was removed. Regeneration proceeded normally in quantity and in quality in all three groups. There was a certain amount of individual variation in the degree of regeneration, dependent upon the amount of material removed, the age, and upon individual factors, but the range in amount of regeneration was proportional to that in corresponding controls, in spite of the total length from 16.7 mm. to 58 mm. Class 3 was composed of tadpoles of intermediate size, ranging from 32.8 mm. to 45.1 mm. The amount of regeneration in this group was nearly proportional to that in corresponding controls, in spite of the fact that the thyroid feeding had caused a marked shrinkage in body length and had caused one-half of the specimens to develop to the stage where one or both of the fore limbs had broken through the skin. We conclude from these experiments that the thyroid gland does not influence the process of regeneration.—E. R. H.

215. (THYROID) The results of thyroid removal in the larvae of *Rana pipiens*. Allen (B. M.) Jour. Exp. Zool. (Phila.) 1918. Vol. 24.

Removal of the thyroid gland anlage was accomplished when the tadpoles were from 6 to 7 mm. in length. Development proceeded normally until the hind limb buds appeared. From that time the tadpoles underwent structural development very slowly, but continued to increase in size until they attained a length of trunk of from 30 to 43 mm. measured from the anterior tip of the body to the cloaca. The hind legs reached a length of 5 mm. The fore limbs did not break through the skin. The controls underwent metamorphosis normally while kept under identical conditions. The brains of the thyroidless tadpoles remained approximately in the structural form found in normal tadpoles in a corresponding stage of development. In the length of the intestine, the character of the mouth, the persistence of the gills and in all other somatic features studied, the tadpoles retained the structural characteristics that had been attained at the time when metamorphosis was arrested.

The gonads behaved in sharp contrast to the soma in that they continued in the normal course of development to a condition far beyond that found at metamorphosis and comparable to that of normal young frogs killed at the same time (February following the operation). This was true of both ovary

and testis as regards form, structural development and relative size. In the thyroidless tadpoles ripe spermatozoa developed in large numbers and oocytes grew to twice the size found in young frogs at the time of metamorphosis.—E. R. H.

- 216. (THYROID) The thyroid gland and the oxidative ferments.** Goldenberg (L.) *La Semana Méd.* (Buenos Aires), 1917, No. 50.

Thyroid extract added to iodine decolorized by zinc in an alkaline medium restored its reddish color. Sodium citrate prevented the reaction.—B. A. H.

- 217. (THYROID) Tratamiento del bocio exoftálmico por inyecciones de agua hirviendo. (Treatment of exophthalmic goitre by injections of boiling water.)** Olivieri (E. M.), Ronchi (P.), Ceballos (A.) and Bacigalupo (G.) *Soc. Med. Argent.*, 1917, (June 29).

Olivieri and Ronchi presented four cases subjectively and objectively improved by the treatment. They had less tachycardia, increase in weight (2 to 13 and 4.5 to 6 kg.) and diarrhea and vomiting ceased. Ceballos and Bacigalupo reported six cases, some of which improved gradually and some rapidly with no treatment other than the boiling water injections.—

B. A. H.

- 218. (THYROID) Un caso de acondroplasia con antecedentes familiares de hipotiroidismo. (A case of achondroplasia with family history of hypothyroidism.)** Mussio (F.) *Rev. Méd. Uruguay* (Montevideo), 1917, 20, 768.

Describes the case of a boy 15 years old, three of whose uncles had shown symptoms of hypothyroidism. The boy early developed signs of sexual maturity, including hirsutism, adult genitalia and deep voice. Mussio thinks that the case is one of hypergenitalism associated with thyroid-pituitary insufficiency.

G. P. G.

- 219. (THYROID AND THYMUS) Pharyngeal derivatives of amblystoma.** Baldwin (F. M.) *Jour. Morph.* (Phila.) 1918, Vol. 30.

This paper deals with the morphogenesis of the thyroid and thymus glands, and postbranchial and epithelial bodies of *Amblystoma*, beginning with larvae 5 m.m. long, and including stages in a metamorphosis and adult. The thyroid gland

arises as a solid outgrowth from the pharyngeal floor and breaks up into scattered cells, which, by mitotic division, give rise to the thyroid follicles, in which colloid appears in late larvae. There is no evidence of the formation of accessory thyroids. Venous twigs form a rete mirabile around the follicles, but the jugular vein does not participate in this. There is no thyroid artery. The thymus gland arises from five pairs of anlagen, derived from the dorsal margins of the corresponding gill pouches. The anterior two degenerate, the other three form the definitive organ. There are no ectodermal contributions to the gland. The adult gland is three-lobed and is innervated by the ninth and tenth nerves. The postbranchial body arises from a thickening of the pharyngeal floor behind the last gill pouch. In all cases, with one exception, it was asymmetrical. In the adult it lies medial to the additus laryngeus muscle. It never contains colloid. The carotid gland has no connection with cells of the pharyngeal wall or those of the degenerating gill pouches. At the time of metamorphosis two pairs of epithelial bodies arise from the ventral parts of the last two gill pouches. In the adult they lie just below the thymus and are supplied with blood from the second afferent and external carotid arteries and are innervated by the vagus. They are the homologues of the parathyroids of the mammals.—E. R. H.

This issue has been prepared with the collaboration of:

G. P. Gonalons, Buenos Aires, Argentine.

F. A. Hartman, Toronto University.

E. R. Hoskins, University and Bellevue Medical College,
New York.

L. S. Kilborn, Toronto University.

H. Wheelon, St. Louis University Medical School.

ENDOCRINOLOGY:

*The BULLETIN of the ASSOCIATION for the
STUDY of INTERNAL SECRETIONS*

JULY—SEPTEMBER, 1918

A NEW PLURIGLANDULAR COMPEN- SATORY SYNDROME*

Walter Timme

Associate Physician, Neurological Institute, New York City, N. Y.

INTRODUCTION

For the past six years there have come to my notice in my service at the Neurological Institute, New York City, as well as in private work, a fairly large number of cases in early adolescence whose chief complaint was great muscular fatigability. Usually combined with this outstanding symptom was headache referred to the frontal region and midway between the temples. Included in the history was frequently a statement of recent or concurrent rapid growth in height as well as of the extremities. Frequent repetition of these complaints in various individuals led me to go deeply into their antecedent history, their family history, and to follow the cases as carefully as possible during their course. Their clinical examinations also showed many character-

*Read in abstract at the second annual meeting of the Association for the Study of the Internal Secretions, Chicago, June 10, 1918.

istics in common, as did their laboratory and X-ray findings. Finally, one case, observed for six years, went through various stages to recovery at the age of thirty-two years. From his early history we recognized symptoms that are presented by cases observed from time to time in the beginning stages of this syndrome, notably the fatigability, the headaches, and the skeletal growth. "Cross Sections" at various stages of his further progress also resembled clinical pictures in different patients that had heretofore been somewhat puzzling to analyze.

In the past three years so many cases of the kind have been observed that from our past experience we have been enabled to foretell, to a degree, the progress that such cases would undergo in the future. To add to this assurance, of late it has been my privilege to see many individuals admitted to hospital for divers complaints of middle age, in whom were recognized the final compensatory stages of the syndrome here to be presented. Upon close questioning, their antecedent history bore out to surprising detail the facts that our studied clinical types presented to us in various stages of the syndrome. They were completely compensated cases and their presence in the hospital was for some entirely adventitious cause. So that our observation has netted us: (1) clinical types presented by single cases at various ages and stages of the syndrome; (2) progressive cases, observed over periods of from one to six years, showing the changing and probably compensatory nature of the disturbance; (3) completed cases in which the disturbance had come to a definite stop, in which the antecedent history bore out the close relationship to our isolated cases which were still in active progress;

(4) uncompleted cases in which the condition, after going through the several preliminary stages, remained indefinitely progressive. Manifestly, to complete the chain, it is necessary to observe at least one case from the beginning to the end of the disorder—a period varying from ten to twenty years. Until this can be done, we must fill in the gaps as best we can.

GENERAL DESCRIPTION

The syndrome, pieced together as above presented, may be generally described as beginning in youth some years before puberty and going through its varying stages in about two decades. In its incipency (*first stage*) it presents largely the characteristics of the so-called status thymico-lymphaticus, or status hypoplasticus of Bartels. There is complaint of muscular fatigability as a subjective sign. Objectively the case presents frequently, though not invariably, (for exception see case Bryan, fig. 6) an insufficient genital development, with perhaps inversion of sex type with a penis that emerges from scrotal folds of labial type, or cryptorchism or both. In the female, the menses are usually delayed, the uterus and ovaries remain infantile and there is scarcity of pubic hair. Blood pressure is usually low, and blood sugar content low. Emuresis is common. There is usually present, the white line of adrenal insufficiency of Sergeant.

In the *second stage*, that beginning at puberty, we find a continuance of the muscular fatigability or even an increase. The genitals may remain backward in development, the pubic hair is sparse and has the distribution of the opposite sex, the male showing a horizontal demarcation. Axillary hair is absent

and chin and lip show no signs of hair in the boy. Blood sugar is low, usually below .070%, and blood pressure below the normal. The white adrenal line may be elicited, especially marked after fatiguing exercise. Roentgenograms of the skull usually show a sella turcica which is small or which may apparently be even enclosed by the clinoid processes. This is an important point to determine, for the later progress of the disorder presumably depends upon the capacity of the pituitary gland to become hyperplastic. This excessive function of the pituitary later on dominates the picture and is conducive to compensatory cure. The thymus gland frequently is seen in the X-ray quite enlarged. In some cases of extreme fatigability, I have also seen pineal shadows. During the second stage, rapid growth in length begins to become manifest,—not ordinary normal growth,—but rapid in the extreme so that 5 or 6 inches in height a year is frequent. With this growth, fatigability increases, and it is on this account that the case is first brought to our attention.

In the *third stage*, we begin to see the results of some of the compensatory activities. It is usually ushered in about the 20th year of life. Growth has continued until the patient is 6 feet high or over; his weakness, even though his musculature seems splendid, is his prominent symptom. He shaves rarely or never. Pubic and axillary hair remain as before. Now he begins to notice an enlargement of his hands and feet, and a frontal headache or rather an intra-temporal headache comes on. Blood pressure remains low (90 to 100 millimetres systolic), blood sugar usually remains low, but now frequently rises as compensation progresses. Our patient shows decided

vagotonic symptoms. An X-ray of the skull at this stage, or during this stage, if the case progresses favorably, shows a sella turcica which, while small, may show erosion of the clinoids and a deepening of the cavity. This tendency of the pituitary to become hyperactive produces the headache (if the sella is contracted), the increase in blood sugar content, the growth of hands and feet, and a gradually rising blood pressure.

The *fourth stage* now comes on, from three to ten years later. This is the stage in which either complete compensation is produced or else the untreated case takes on the varying and various attributes produced by an enlarged pituitary body engrafted upon the earlier manifestations of a thymic state. That is, we have in the completely compensated case, features of acromegaly, although the blood-pressure and blood sugar are normal and the headaches have gone. The sella on X-ray seems large. In the uncompensated cases we usually see a sella which is still small and bridged, with headaches of increasing severity, perhaps attacks of *petit* or *grand mal*, mental torpor, increase of weight with constantly increasing fatigue and a final lethal termination in intercurrent disease.

A brief resume of the characteristic symptoms and findings in the different stages is here succinctly put forth:

First Stage. The bony structure shows various endocrine anomalies and defects; disproportion of various skeletal units; teeth late and epiphyses slow in joining shafts of bones; hyperextension of joints; hair growth late and sparse, distribution of invert type; cramps in muscles; tendency to hemophilia

and spasmophilia; enlarged thymus; tonsils large and adenoids; low blood pressure; low sugar content of blood; epistaxis; cyanosis of extremities; fatigability; small sella turcica; enuresis; low CO_2 coefficient of blood.

Second Stage. At about age of puberty; rapid skeletal growth begins; late menses and small or infantile uterus; great fatigability with all evidences of low adrenal supply—low blood sugar; low carbon dioxide combining power of the blood; white line of adrenal insufficiency; pubic hair of invert type; lack of hair on face and chin and axilla; smooth soft skin of child; genitals of invert type or else retarded; vagotonia; symptoms of hyperacidity and gastric ulcer; enuresis; undue length of long bones; low blood pressure; little stamina.

Third Stage. 20th to 30th year; beginning giantism; headaches pituitary in character; drowsiness; acromegalic beginnings or other pituitary stigmata; fatigability may continue or improve; mental confusion and hebétude; epileptiform attacks—uncinate in type; sella turcica enlarges or else erosion of sella or clinoids takes place; blood sugar gradually increases if cure established. In uncompensated cases mental symptoms, moral and intellectual deficiencies and delinquencies arise.

Fourth Stage. Either complete compensation—so that patient may live comfortably within limits of exertion or else progress to end of life as pituitary case. The various external manifestations of the pituitary disturbance remain even if physiological cure is complete. Blood pressure rises; headaches cease; fatigability vanishes.

DISCUSSION OF SYMPTOMATOLOGY

The bony structure in the first and second stages usually shows anomalies in proportionate skeletal growth, i. e., legs too long for thorax or vice versa; the joints usually are hyperextensible and frequently

the ligaments are so relaxed that dislocations are easily produced. The extremities can be thrown about like flails; while the teeth are usually delayed in their appearance they also show certain characteristics. The lateral incisors, especially in girls, are frequently greatly underdeveloped. The canines, likewise, are either underdeveloped or else take on the flat appearance of incisors, losing their fang-like appearance. With the cyanosis of the extremities we occasionally get a pustular-like eruption about the nails. The symptoms during the second stage may need some elucidation. The so-called "white line" of adrenal insufficiency was first described by Sergent. It has not been proven to be due to the deficiency, but in my experience it invariably accompanies low blood pressures, and may be made to disappear very quickly after a hypodermatic injection of adrenalin. Previous emotional disturbance, even so slight as that produced by standing before a camera to be photographed, will make its appearance impossible to obtain. It is obtained best by having the patient lying quietly in bed for a short while and then stroking the skin, preferably of the abdomen or thigh, lightly, with the palmar surface of the index finger. In 10 to 20 seconds, there will be a blanching of the skin thus stimulated. (See Sergent's article, *Endocrinology*, 1917, **1**, 18, for the explanation of this phenomenon.) The low carbon dioxide combining power of the blood plasma diminishes the so-called "buffer" property of the blood and leads to acidosis on slight provocation. The smooth soft skin of these cases, even in the third decade of life, with little or no secondary hair on the face, a faint suspicion of lanugo on the lip and chin, and a "peaches and cream" com-

plexion, frequently stamps these cases at sight. The headaches, produced as will be discussed in the pathogenesis, are of a specific type. They are invariably stated to be between the temples, the patient indicating the locality by putting one index finger on each temple, directed mesially. We have come to call them "pituitary headaches." The vagotonia present in many of the cases frequently takes on the character of hyperacidity of the gastric juice with frequently symptoms of gastric ulcer, spastic constipation and eosinophilia. In the third stage, the symptoms of great interest are the mental ones. In many years' observation of pituitary disorders, we have been frequently struck with the mental quips of the hypopituitarie. He exhibits lack of inhibition of the emotions, becomes highly excitable on little cause, alternating with sluggishness; frequently has phobias and compulsions—(one case was a true kleptomaniac)—shows frequently moral and sexual obliquities; and exhibition of pituitary feeding often modifies these characteristics. The symptoms of the uncompensated cases usually merge into those of a frankly dyspituitary syndrome which it is not my province to discuss here.

AETIOLOGY

In practically all our cases, there have been family histories of importance as regards endocrinopathies. Frequently, parents or grandparents have shown such disturbances as diabetes, goitre or acromegaly. A very common complaint is gigantism. Collateral branches, too, show similar disturbances. Thus, W. W. (fig. 10) the fully compensated case, has four cousins all afflicted with Graves' disease. There appeared in our cases no particular antecedent

disabling disease or injury. One case, now in the second stage, had two brothers, both dying suddenly after exertion without known cause, in youth—possibly a so-called thymic death.

DISCUSSION OF PATHOGENESIS

During the first stage, we see a clinical picture which is dominated by the characteristics of the status hypoplasticus of Bartels. The anomalies have been variously credited to hypofunction of the individual endocrine glands, excepting the thymus, which is supposedly hyperactive. Thus, Tandler and Gross and Tandler have described many of the features of such a condition due to deficiency of the gonads. Wiesel, Schur, and Schmors and Ingiers have given both clinical descriptions and histological and pathological findings in such hypoplastic conditions referable to underactive or inhibited adrenal glands. Many observers have described the smallness of the sella turcica. My own observations agree with these. All of our cases show the smallness of the sella turcica in the early stages and in addition many of them have the bridging over by the clinoid processes, evident on X-ray examination. With these deficiencies of glandular structure and their diminished physiological activity *ab initio*, the organism would of necessity come to early grief if some corrective were not forthcoming. Many cases do succumb early. Undue exercise, sudden excitement, narcosis, are all critical moments for such organizations, many of which cannot survive them. After puberty should have been reached (the second stage) the deficiency of the gonadal inhibition to growth (Tandler and Gross) is responsible for the extreme height rapidly reached

by our cases. One of our cases (Private B.) however rather opposes this theory in that the gonadal system early became hyperplastic and still the growth in body took place. This excessive genital development may be due in his case to an early involution of the pineal gland, for in the X-ray, calcification of the pineal is seen. (Some authors hold that the overactive thymus with disturbed calcium metabolism is the cause of such "thymic giantism.") The deficient adrenal-chromaffin system is to be credited with the great fatigability, the low blood sugar content, the low blood pressure and the white line. Now comes the third stage, the all-important one. It is in this period that the outcome of the syndrome is determined. In our judgment it is the pituitary gland which is here the critical factor. As we have seen, it is invariably enclosed in a small sella turcica and possibly even hemmed in by the clinoids. Among its functions we have as all important, a blood pressor principle and a sugar mobilization factor. Both of these are deficient in our patient. If the pituitary possibly could become hyperplastic and hyperactive with an intensification of these important properties, compensation might be accomplished. Such tendency to hyperplasia in a small cavity would of necessity through pressure produce headaches—an invariable symptom in the third stage of the compensated cases. And such headache would continue until the enlarged gland through erosion of its bony capsule or through pushing apart the clinoids made sufficient room for itself. As will be seen, these headaches continued for two to three years in some of our cases. Synchronously with these headaches, other incidental features of an enlarged pituitary gland became manifest;—(a)

acromegaly—lasting until the headaches ceased and the process then likewise ceasing; (b) a higher blood sugar content; (c) a higher blood pressure; (d) a diminished sugar tolerance. To make this view of the nature of the process of compensation more tenable, many of the sellae turcicae of our patients in the second and third stages show erosion of anterior or posterior clinoid processes; and in the final stage, an enlarged sella with practically no clinoid processes left at all. In the cases in which no compensation was effected, i. e., in which fatigability, *et cetera*, remained and progressed, the sella showed no enlargement (notably that of T. R., fig. 12). In these cases, we had headaches, periodical in type, adiposity, mental and moral deficiencies, *petit mal* and other manifestations. Curiously enough in *all* our cases, the feeding of the pituitary gland in fairly large quantity, disposed of many and at times of *all* of these symptoms. But if the feeding were diminished or stopped, the symptoms reappeared. It seemed analogous to thyroid feeding in myxoedema. One case, which gave a typical early history and seems uncompensated today at the age of 44, still shows the very small sella turcica with a clinical picture of abnormal bony structure much resembling Paget's Disease. On pituitary feeding, this case is improving markedly in its features of fatigability, headaches and heaviness of extremities. It is too early to state whether in her case the cancellous condition of the bones will be restored. Finally, the fourth stage is ushered in by a gradual cessation of the fatigue, amelioration of the headaches, restoration of a normal blood pressure and normal sugar content of the blood. But the adventitious signs of the disturb-

ance of the pituitary gland remain. Thus the fully compensated cases may show acromegaly more or less marked; *and this acromegaly is not to be taken as a diseased condition needing treatment, but simply as the hallmark of a process that has come to a stop—a self-curative process.* It is analogous to the hypertrophied heart become so through the deficiency of the cardiac valves and making up for such deficiency by its enlargement. And that condition likewise, *per se*, needs no treatment. A case that presents acromegalic features, therefore, need not necessarily be a case that calls for therapeutic intervention. It may well be a “finished” case. (W. W. fig. 10) is a good representation of this type. These “finished” cases, must always, however, live within certain limits of exertion and stress. The cases that in the fourth stage do not spontaneously go to full compensation, are those in which we either find a sella turcica which did not enlarge (perhaps because there was no spontaneous effort of the pituitary to become hyperactive) or in which an enlargement of the sella did take place and the pituitary even in its hyperactive condition was not sufficient to compensate. These uncompensated cases go right on with progressive symptoms of fatigability, asthenia, headaches and so forth, making of them easy prey to intercurrent affections.

TREATMENT

The treatment of these cases in any stage is extremely satisfactory. The great point to remember is the probable nature of the process of compensation which the organism is endeavoring to carry out. That would make one believe that suprarenal gland therapy is indicated throughout on account of the patent deficiency of this organ in these cases. And

yet in our hands its administration is disappointing. The whole gland perhaps has given better results than adrenalin, although the latter, either hypodermically or (even against the dictum of the physiologist that it is inert when administered per os) by mouth in larger doses is good to tide over exceptionally bad days of fatigue and exhaustion. But the prime agent—almost a specific one—is pituitary gland in some one of its varied forms. Whole gland feeding in fairly large doses, gr. ii to gr. iii t. i. d. may be given in appropriate cases. Occasionally, pituitrin hypodermically 0.50 to 1.00 c.c. per day or alternate days for one or at most two weeks at a time is excellent as supplementing the feeding of pituitary gland. Occasionally in cases with pronounced genital delay, anterior lobe pituitary gland gives fair results. In those cases with vagotonic symptoms, hyperacidity and conditions resembling gastric ulcer, atropine in doses to physiologic tolerance is indicated, and gives results. But the pituitary feeding in itself, alone, produces highly satisfactory improvement in almost every case. Under its use, the headaches disappear, the fatigability diminishes, the blood pressure and blood sugar content increase, and the case goes on to cure. Gradually the pituitary feeding can be diminished and finally discontinued. In the older cases, in which the sella persists in remaining small (T. R. fig. 12) and (J. S. fig. 11) constant feeding would seem to be necessary; at all events, the patients relapse as soon as treatment is stopped. Indeed, the patients themselves reach that point of accuracy of judgment in feeding the gland to themselves that they can determine the size and frequency of the dosage necessary to maintain them comfortably.

The following case histories are cited as a few among many which show characteristics of the different stages of the syndrome. Only facts having direct bearing are introduced into the case histories.



FIG. 1

Fig. 1. J. M. Case 1. Shows abnormal length of thorax compared with legs. Thighs especially short compared with lower leg. Small genitals. Has large thymus and enclosed sella turcica.

Case 1. J. M. (fig. 1). Ten years; mentally backward; no hair on body anywhere; genitals undeveloped; elongated thorax; spasms in muscles; great

fatigability; is a bed wetter; joints are hyperextensible; has nose bleeds. X-ray of chest shows thymus (fig. 3); skull shows small sella turcica, entirely bridged over (fig. 2). Blood pressure 85; white adrenal line.



FIG. 2

Fig. 2. J. M. Case 1. Sella turcica small and entirely enclosed and "roofed in."

Discussion. This case is presented simply to show the type from which arise the cases presenting the later features of the syndrome and hence may be classed under stage 1.

Case 2. Master F. J. Age, 13½ years; height, 61½ inches. He was brought to the Neurological Institute on account of his predilection for lying and further for his rapid fatigability. He had been discharged from several schools on account of his incorrigibility. The climax was reached when he

appeared as a material witness in a murder trial, his evidence being of the greatest importance in the conviction of the accused. Apart from these facts, he also complained of spasms in the muscles, especially



FIG. 3

Fig. 3. J. M. Case 1. Shows thymic enlargement.

of the calves, which occasionally awakened him by the pain caused thereby. He had frequently also had nocturnal enuresis. Upon stripping him (fig. 4) the examination revealed the following: the body was perfectly hairless, no trace of pubic or axillary hair

being evident. The genitals were small—infantile in fact—but both testicles were descended and the scrotum surrounded the penis like a labial fold. Upon eliciting the cremasteric reflex, however, the testicles



FIG. 4

Fig. 4. F. J. Case 2. Age $13\frac{1}{2}$ years. Shows hypoplasia of genitals and a scrotal fold surrounding base of penis. Absence of hair. Bruise on raised arm from slight pressure.

were drawn up out of the scrotal sac into the inguinal canal where they could not be palpated. He bruises very easily, the dark patch on the left raised arm

being produced by the simple pressure of the examiner's thumb in raising the arm. Hands and feet are somewhat larger than they should be. Stroking the skin of the abdomen produced a marked white line of reaction, which persisted for a rather long time.



FIG. 5

Fig. 5. F. J. Case 2. Pituitary fossa shut in extremely by large clinoids.

His blood pressure was low, 80 mm. Mentally he was well up to his chronological age according to the Binet-Simon scale. Upon close questioning he admitted that he had frequent headaches referable to a point midway between the temples and deep-seated.

The neurological examination was negative. Laboratory examination showed the sugar content of the blood to be .070%. Otherwise blood and urine were negative and the Wassermann was negative. X-ray examination: The sella turcica (fig. 5) was small and encroached upon by large clinoids; the upper thorax showed a thymus shadow.

Discussion. This case is presumably a type of the beginning of the second stage of the syndrome. It presents many of the well marked features of a status hypoplasticus:—small sella, enlarged thymus, low blood pressure, low blood sugar, marked fatigability, spasmophilic and hemophilic attributes in addition to the obvious externals. The mental attributes are those which we frequently see in small and enclosed sellae turcicae. This case is presented simply as a living present example of the early beginnings of the second stage of the syndrome.

Case 3. Private B. (fig. 6). Age 20 years; height 6 feet 1 inch. This case was sent to the Institute by Capt. Reed, stationed at Fort Wood, to determine whether or not the man was a malingerer. His one complaint was that of excessive fatigability after moderate exertion. As a result he could not perform the military duties required of him. His musculature and his whole bearing and appearance when stripped were that of a powerfully and symmetrically built young giant, and seemed to belie his statement of rapid fatigue. His early history could not be obtained with any degree of reliability for, coming from a mountainous district of the South, he was extremely uncommunicative. In early adolescence he was a rover, traveling over many states in divers

occupations, but never steadily at any one. He did say that for the past three years he had been rapidly and steadily growing in height, that this growth was still continuing and with it his fatigability was



FIG. 6

Fig. 6. Private B. Case 3. Feminine distribution of pubic hair; large genitalia; height 6 feet, 1 inch; no hair on face. Seems well-proportioned.

increasing. Stripped, he showed a splendid make-up muscularly. Of note was the fact that he had practically no hair on his lip or chin, no hair in the axillae, pubic hair of the feminine type and rather largely

developed genitals. Stroking the skin produced a white persisting reaction. His blood pressure was between 95 and 100 mm. systolic, 80 diastolic. Blood sugar was 0.062%. X-ray examination showed a



FIG. 7

Fig. 7. Private B. Case 3. Complete closing in of pituitary fossa.

sella turcica (fig. 7) which was extremely small, with thickened anterior and posterior clinoid processes completely roofing in the cavity. A shadow in the pineal region also was evident. The thorax showed a thymic shadow. Neurological examination was negative. Viscera appeared normal.

Discussion. This young man is going through the transition period from the second stage to the third. His low blood pressure, low blood sugar percentage (extreme normal low limit should be at least .075%), white skin reaction line, all go to prove his statement of fatigability. In addition he shows a crowded pituitary fossa and a pineal shadow. We

have found in the past two years in a large percentage of muscular dystrophies, pineal shadows; and in extreme cases of muscle fatigue in the adolescent, short of dystrophy, there were shadows in the pineal region. This parallelism between the myasthenic types and early involution of the pineal gland will be the subject of a future paper. This feature of the case is an example of many similar ones. But presumably early pineal involution also produced his enlarged genitals. He is undergoing the rapid growth incident to the second stage of the syndrome in spite of the fact of the enlarged genitals. Some authors (especially Tandler and Gross) have maintained that the hypoplasia of the genitals accounts for the continuance of the skeletal growth. That is certainly disproved here as a universality. Upon feeding of pituitary gland, this youth improved sufficiently to go back to army life. After the lapse of a few months, he discontinued this feeding and shortly thereafter returned with his old complaint of fatigability. He is again improving on treatment. No white line can now be elicited, and his blood pressure is usually at 120 mm.

Case 4. G. E. R. (fig. 8). Age 22 years; height 6 feet 3½ inches; single; stenographer. Came to the Neurological Institute complaining of loss of memory and lack of sleep; feeling stuporous and extremely fatigued. Has headaches intratemporal in location. Not able to do much manual work on this account and hence took a position as stenographer. Is exempt from military duty, being the sole support of his mother.

Past History. While a child, he was never strong; he took a long time to develop and on account of his

ways—feminine—was always known as “sissy” to his playmates. He realized this appellation to be more or less just. Would easily cry if deprived of his



FIG. 8

FIG. 8. G. E. R. Case 4. Height 6 feet, 3½ inches; feminine pubic hair; no hair on face; musculature seems flabby; feminine attributes.

way and still does so. Always was a bed-wetter, and this weakness persisted to his 19th year. Realizing his feminine attributes, he endeavored to compensate for them by indulging in the most manly of sports—boxing and football. But he was too slow

to amount to anything here. He gave up this conflict and sank to his own recognized level—became a stenographer. He began to get headaches at 17 years of age, at which time his excessive growth started.

Examination. A man powerfully set-up, 6 feet 3½ inches high and proportionately built. (fig. 8.) No hair on face or body except in the pubic region, where it is of feminine distribution. The scrotum also is divided above the penis into typical labial folds. He shaves once in two weeks. His appearance is really



FIG. 9

Fig. 9. G. E. R. Case 4. Sella turcica with anterior cavity eroded and a deepening of posterior fossa.

pugnacious, but is not borne out by his mental attitude. He cries when questioned about the simplest difficulties. His blood pressure is 100 mm., systolic. He has the white line reaction of the skin, and his blood sugar was low. The X-ray of the skull shows

a sella in which erosion of the anterior clinoid is evident and an excavation of the posterior portion of the floor. (fig. 9.) The X-ray of the thorax shows a possible enlargement and persistence of the thymus. Neurological examination is negative.

Discussion. The early history is that of a thymus state. The further progress, especially the headache concomitant with the growth is suggestive of pituitary enlargement. This is partly borne out by the picture of the sella. His headaches are now much less prominent than they were, but his fatigability is marked. His growth seems to have ceased. This case belongs in the third stage—with the gigantism gradually reaching its acme, with the stuporous and drowsy mental condition of a dyspituitarie still present, great fatigability, low blood pressure and low blood sugar content. The enlargement of the sella turcica however gives promise of a gradual efficient compensation taking place. Feeding of whole gland pituitary extract within two weeks measurably improved all his symptoms. It is still being continued.

Case 5. W. W., 32 years; machinist; married; several children; height 6 feet 4½ inches; acromegaly in slight degree. This case has been under our observation since 1912. At first the complaint was one of utter exhaustion to the exclusion of all minor ills. He could not stand at his work, he could hardly walk without becoming exhausted. At 19 he had severe headaches referred to the intratemporal region which persisted in spite of all measures. These headaches he described as "crushing." At the same time his hands enlarged while under our observa-

tion. The fatigability was so great that he would have to take to his bed and remain there. His past history was typical of the thymic. Nose bleeds, general weakness, enuresis, over-extensibility of the



FIG. 10

Fig. 10. W. W. Case 5. Six feet, $4\frac{1}{2}$ inches. Fully compensated case. Great length of leg compared with length of thorax. Feminine waist; feminine pubic hair; acromegalic hands; no hair on face.

joints. His family history was a typically endocrine one. On his mother's side four members of direct and collateral branches had goitre, two with exoph-

thalmos. His father never shaved until the age of 28. Puberty in this patient was reached at 19. Hairy growth in the axilla and on the face remained absent. To this day he has never shaved. During the period of intense headaches and growth, he had various vagotonic symptoms: hyperacidity; excessive perspiration; precordial distress; nausea and vomiting; marked pallor; lack of libido. His gastric distress became so acute that operation was advised at another hospital for gastric ulcer. At this time an X-ray of the skull was taken and showed a large sella turcica, with practically no clinoids present at all and erosion at the edges. His photograph (fig. 10) has some interesting points. The extreme length of leg compared with thorax is noteworthy. The feminine distribution of pubic hair and feminine waist are present. His extremely large hands and generally deficient musculature attract notice. This photograph was taken about a year ago when he was just completing his cure. Today he has gained 30 pounds in weight and is feeling practically well, working constantly as machinist and supporting his family of wife and two children. During the last three years, his blood pressure had gradually risen to 130 mm. systolic from an initial 90 to 100 systolic; his gastric symptoms have abated, the white line of adrenal deficiency is disappearing; his fatigability has passed; libido has returned, and he is to all purposes cured of his malady. His fatigability and headaches in the past three years could always be improved with the administration of whole gland pituitary extract and gradually it became possible to diminish the dose and to allow the compensation to proceed unaided. He has now been with-

out treatment for practically six months. He seems to be a fully compensated case.

Discussion. The history and progress of this case is typical of all cases passing through the complete syndrome and is presented as a type of which I have now seen at least ten examples. It must not be forgotten that he now shows giantism plus acromegaly. That does not mean that his clinical picture indicates treatment. Far from it. He is a finished case. The giantism and acromegaly are incidents merely of the compensatory process—they themselves do not necessarily indicate present disease. This is a point well worth remembering. Many cases showing endocrinopathic features come under our notice and it should be our first aim to determine whether or not they represent processes that have come to a stop through compensatory efforts of which they are the indices. Under such conditions of course no treatment is called for. An interesting case of this nature was seen at Mt. Sinai Hospital, New York, in the service of Dr. Goldenberg, through the kindness of Dr. I. Strauss. A woman, 53 years of age, with typical acromegaly—hands, feet and skull abnormalities, was admitted for some minor ailment. Her history showed that she began to menstruate at 19 years, had intense headaches at 25 years which for three years resisted all attempts to alleviate, and during whose persistence she began to grow acromegalic. When the headaches spontaneously ceased, the abnormal growth ceased, and she passed an uneventful life to the time of the present slight ailment. Her childhood and adolescence were like those described in the first two stages of this syndrome—fatigability, being the prominent symptom. Her

acromegaly then, was completed at about the twenty-ninth year, did not further increase, and she remained well for twenty-three years longer. This was also a "finished" case as far as the syndrome of thymus, adrenal and pituitary was concerned. This case might be many times duplicated.

UNCOMPENSATED CASES

I desire to give rapidly the salient features only of several uncompensated cases belonging to the syndrome.



FIG. 11

Fig. 11. J. S. Uncompensated case 6. Shows pituitary fossa completely enclosed. Stereoscopic plates confirm this. Age 22 years; height 6 feet.

Case 6. Miss J. S. Referred by Dr. Robert T. Morris. Height 6 feet, large hands and feet, extreme fatigability, headaches, vagotonia, rapid growth in past two years with a past history of status thymico-lymphaticus; comes for relief of her headaches and fatigability. Blood pressure 95 systolic; blood sugar .065%; fatigue so great that she must remain prone the greater part of the day. In-

tense white line. Her sella turcica (fig. 11) shows a roofing in by the clinoids. Pituitary feeding gave gratifying results, but must be continuously carried out.

Case 7. T. R. Age 35 years; height 6 feet, 1 inch. Obese (220 lbs.). Early fatigability. Late puberty. Feminine pubic hair. Unmoral. Intense intratemporal headaches. Although wealthy, and of excellent family, commits sexual and other excesses. Frequently in jail. Fatigability and headaches per-



FIG. 12

Fig. 12. T. R. Uncompensated case 7. Age 35 years; height 6 feet, 1 inch. Sella turcica completely shut in and extremely small. Confirmed by stereoscopic plates.

sist. With beginning of headaches growth began. Blood pressure 95 mm. Sella turcica small and closed in by the clinoids (fig. 12); polyuria. Pituitary feeding helped not only his headaches and fatigability, but strangely and unexpectedly his moral sense is elevated and his excesses are no longer indulged in. But the pituitary feeding must be constantly kept up. A few weeks of discontinuance

leads rapidly to the old condition. He has been now practically free of his troubles for two years.

CONCLUSION

The syndrome of thymus—adrenal—pituitary combination is one frequently met with and its various stages are easy of recognition. The main characteristics of fatigability, low pressure, headache and growth are invariable components of the syndrome and depend upon mal-adjustments of endocrine interactivity. Stabilization of the balance may be spontaneously produced providing the sella turcica may be made to accommodate a hyperactive hyperplastic pituitary gland. This is done presumably by erosion of the bony capsule of the gland. In cases of inability of such enlargement of the sella, the syndrome persists, but the symptoms may be alleviated by the feeding of pituitary extract continuously. In the course of the syndrome other glands may be brought into the complex and alter the picture somewhat, but these are vagaries and seemingly have no great determining effect upon the course of events. Once recognized in any of the early stages, the further general progress of these cases can be prognosticated with a great degree of accuracy; and intervention, if necessary, can be undertaken with a large degree of success in the amelioration of the distressing symptoms.

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IS THERE A THYMIC HORMONE?

E. R. Hoskins

Department of Anatomy, University and Bellevue Hospital Medical College, N. Y.

From the frequency with which reference is made to the internal secretion of the thymus, and the various influences which this organ is commonly declared to exert over other parts of the body, it would seem superfluous to question the existence of a thymic hormone. But as a matter of fact, it has never been definitely proven that this organ produces any internal secretion at all.

For some time it has been the practice of workers in biology and medicine to declare that this or that organ or tissue of unknown function has an internal secretion, with little or no valid evidence to support their theories. Recent literature contains several "new ductless glands."

Morphologists having pointed out the fact that in the human species the thymus "usually" begins to undergo involution at "about" the time of puberty, experimentalists seized the fact and built upon this slender foundation various theories of control of sexual development by the thymus. Later it was pointed out that this correlation between the time of thymus involution and sexual differentiation does not exist generally among animals, but varies within wide limits, and also it was pointed out that in the human the thymus in many cases reaches its greatest size before puberty and in many other cases much later than puberty, but the theory had already been firmly established in the minds of many people, and it still persists. Below we shall point out

that the thymus is relatively larger at birth than ever after that time.

Another theory of thymic function arose from the fact that during the greater part of the involution of the thymus, the skeleton is growing rapidly. This theory stated that the thymus controls skeleton growth.

In regard to the theory of the thymus-skeleton relationship it may be pointed out that another lymphoid organ, the pharyngeal tonsil, "usually" begins its involution during infancy. If it so happened that some other striking phenomenon occurred at the same time, there would doubtless have arisen one or more theories on the inter-relationship of the two.

The fact that the thymus and thyroid both have their anlagen in the pharynx gave rise to various theories of the relationship between these two organs.

Whenever in the life of an animal two phenomena occur together, and especially if they are not well understood, there has been a tendency to evolve theories associating the two functionally. Danchkoff ('18) in discussing another subject has well said, "The infinite complexity of developmental processes requires special caution in the attempt to establish a direct causality in the relations between two invariably concomitant phenomena." In no field of biology has such caution been disregarded more frequently than in endocrinology.

Most of the experiments with thymus can be placed under the headings, extirpation and administration of thymic tissue or extracts. 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 because of the relative simplicity of the problem. Removal of the thymus from frogs apparently is not fatal (Vincent, '04), but the animals seem less resistant to infections (Verenke, '99). Allen ('18) has recently shown that frogs will develop without the presence of the thymus. He removed the anlagen of this organ from young frog-larvae before it could possibly have functioned, and yet the larvae grew normally and metamorphosed at the normal time. Allen has not as yet, however, published any observations on the effect the experiment may have had upon the spleen, but he showed conclusively that the thymus is quite unnecessary for the proper development of frogs. The same is probably true for other amphibia.

In feeding experiments with these forms, Guder-natsch ('14) found that thymus fed to larvae delayed their metamorphosis although the animals grew on this diet. Romeis ('15) and Abderhalden ('15) were able to verify these results in part, but Swingle recently ('16) states that such larvae kept by him on a diet of thymus were able to grow and metamorphose normally. Uhlenhuth ('17) feeding thymus to another amphibian (*Amblystoma*), obtained in general, negative results. This author believed that the delay in metamorphosis obtained by thymus feeding is due simply to the fact that thymus is not a sufficient food. He obtained delay in metamorphosis also by a diet of worms. The very numerous recent papers of Osborn and Mendel and others, show that many diets, although fed in abundance, lack certain constituents necessary for growth.

Metamorphosis in amphibia is probably initiated by skeletal changes which in turn depend upon the calcium metabolism. This metabolism is probably dependent upon the thyroid or hypophysis, or both, since removal of either of these two glands will delay if not entirely prevent metamorphosis. In this interference with metamorphosis which is caused by thyreoid removal (see Hoskins ('18)), the thymus appears to be in no way affected, either in size or structure. Gudernatsch's results were obtained by feeding thymus-tissue from mammals, which of course have no need for a "metamorphosis-preventing" hormone, and hence are unlikely to have developed one.

In extirpation experiments with higher animals, the results are conflicting. Klose and Vogt ('10), Lucien and Parisot ('10), Paton ('11), Friedleben ('58), Matti ('12), Soli ('10), and other authors report that following thymus removal in birds and mammals various effects are produced, such as interference with skeletal growth, including rachitic changes, adiposity, emaciation, injury to the thyreoid, no effect on thyreoid, degeneration of testes, no effect on testes, etc. Pappenheimer ('14), Park ('17), and others, state that if the experiments are carefully performed and carefully controlled, the thymus can be removed without producing any harmful effects whatever. Paton and Goodall ('14) noted a decrease in the number of circulating leucocytes after thymus extirpation, and this seems to indicate that the thymus produces leucocytes as indeed is obvious from its microscopical appearance.

Hewer ('16) reports that injury to the thymus by X-ray irradiation results in injury to the function

of the testes. Since complete destruction (removal) of the thymus has no such effect and since unhealthy animals never breed well, Hewer must prove that her treatment did more than injure the health of her animals.

In feeding thymus to animals, Hewer ('14) claimed that the treatment injures the testes, a result not consistent with her report just mentioned. Hoskins ('16) feeding thymus to mammals obtained negative results on the growth of the body and all organs.

R. G. Hoskins ('10) states that feeding thyreoid causes hypertrophy of the thymus, but E. R. Hoskins ('16) obtained negative results with similar experiments.

Calzolari ('98), Henderson ('04), Hatai ('15), and others found that gonadectomy delays involution of the thymus and may even cause hypertrophy. There are also other changes produced by this operation, such as deposition of fat throughout the body, hypertrophy of the suprarenals and hypophysis in the male and decrease in the size of these two glands in the female. The changes that occur in the thymus may be secondary and not show a direct relationship between the thymus and gonads, especially since changes other than that of mere size may occur in organs other than those mentioned. The subject needs further investigation, particularly on the microscopical side. A possible cause of the delay in thymus involution after gonadectomy will be discussed below.

Clinically many functions and diseases are attributed to the thymus. Many of these theories are

based upon the concomitant phenomena already mentioned.

“Hyperactivity” of the thymus is frequently described where percussing indicates a dullness in the region of the sternum or a shadow is shown there by X-ray. This condition is described in cases of “*mors thymica*” and exophthalmic goitre. As a matter of fact it is questionable without an autopsy whether such enlargement of the thymus is not due simply to an unusually large deposit of fat. Often the size of the thymus is maintained in this manner, although relatively little thymic tissue is present. Moreover, the variability of the thymus is so great that the gland often persists normally until late in life, as is disclosed by autopsies of accident cases. Anatomists make an allowance of from one hundred to seven hundred per cent in the normal weight of the thymus at different ages.

Whenever in clinical cases there is an actual overgrowth of thymic tissue (or an early atrophy) this change may be brought about by the factors causing the disease in question, or still other and independent factors may be the cause, rather than that the thymus itself produces the clinical condition under consideration. We may be dealing with concomitant phenomena not directly related. In many cases where the disease is attributed to thymic changes, no autopsy is or can be performed, and the diagnostician does not really know whether or not the thymus is even pathological.

Hammar ('16), who has investigated scientifically the subject of “*mors thymica*,” in a large number of cases, has found that the thymus is often

perfectly normal as compared with that seen in children killed by accident.

Melchior ('17) has pointed out the fact often disregarded, that although an "enlarged" thymus is frequently found in exophthalmic goitre, the symptoms are not different when the thymus is not enlarged.

In inanition and in wasting diseases, the thymus tends to atrophy. This fact is used in the theory of the relation of the thymus to general metabolism. Jackson ('15, '16), Stewart ('18), and others have recently investigated experimentally the subject of inanition. They find that in young starving animals there is a decrease in the size of the thymus, but the same is true of other organs and tissues. Certain tissues, especially the connective tissues, have a very strong growth tendency and where nourishment is insufficient in amount for all bodily needs these tissues grow or maintain themselves at the expense of other tissues and organs with a weaker growth tendency. Among these latter are included the thymus, thyroid, heart, liver, spleen, alimentary canal (including the pancreas), lungs, and other soft parts. In older animals suffering from acute or chronic inanition, there is a marked loss in weight of the spleen, liver, and alimentary canal (including the pancreas), and a less extensive loss in weight of the kidneys, heart, lungs, hypophysis and testes. The thymus in these animals had already undergone "age involution," and hence was not affected. From these experiments it would appear that the loss suffered by the thymus in inanition does not indicate that this organ is affected differently from many other organs and does not

add any definite proof that the thymus has any control over metabolism.

Difficulty in breathing is often attributed to pressure by an "enlarged" thymus against the trachea and bronchi, but an anatomical study would show that these organs are the most unyielding structure within the thorax, and are separated from the thymus by a mass of yielding soft tissues in the mediastinum. It would also be very difficult for the thymus to exert sufficient pressure on the lungs to interfere with breathing on account of the fact that one ordinarily uses much less than the entire expansion of the lungs during respiration. Even with a considerable portion of the thoracic cavity filled with abnormal tissue there would still be left sufficient room for breathing.

The theory that rachitic changes in children are caused by the thymus cannot be proven by any known facts. The theory is based upon the fact already referred to that the skeleton and thymus grow at the same time; upon the changes in the skeleton thought to result from extirpation of the thymus; and upon changes thought to be noted in the thymus of rachitic children. The concomitant growth of the thymus and of the skeleton may not be causally related, the extirpation experiments have been lately discredited, and unless the children are suffering from inanition the thymus is as often normal as not. The faulty metabolism which causes the rachitic condition is sufficient in itself to explain the atrophy of the thymus.

There are theories of thymus function other than those noted above, which rest upon still weaker foundations. For example, Kaplan ('17) associ-

ates a certain dental condition with the thymus by the term "thymodontia." His theory is dependent upon the facts that children have thin teeth and a thymus. They also possess other organs such as tonsils, the pharyngeal, one of which normally begins to disappear in infancy. The dental condition Kaplan describes might as well be called "tonsildontia."

Pighini ('16) states that following vagotomy in chickens there results an atrophy of the thymus. There are also other changes including respiratory and circulatory difficulties which affect the metabolism and may in that way injure the thymus and other tissues easily affected by inanition. Furthermore, the question of thymic involution in chickens has never been adequately worked out.

Haneborg ('16) blames the thymus for chorea minor because this disease occurs between the ages of two and sixteen years, during which time the thymus is normally growing to its maximum size and because thymus administration seemed to be beneficial to his patients. He weakens his argument by the statement that there is much to sustain the assumption that an infection is the primary factor, perhaps an encephalitis. The latter condition alone might well account for the increased irritability of the nervous system in his cases.

"Hyperactivity" of the thymus is described even without determining whether the "enlargement" of the thymus is due to fat, to pathological tissue or to normal tissue. A disease of the thymus itself might cause enlargement of the organ and result in "hypoactivity" rather than "hyperactivity."

The evidence for the belief that the thymus does not produce an internal secretion is both anatomical

and experimental. Danchakoff ('16) has recently shown that the small thymic cells are truly lymphoid in character and that they arise from a polyvalent stem cell of mesenchymal origin, and also arise directly from the large thymic cells. This stem cell produces both lymphocytes and other leucocytes. Experimentally the small thymic cells can be changed into plasma cells and granular leucocytes.

Bell ('05) has shown that the Hassl's corpuscles arise from connective tissue. They are not present in all mammals nor in animals in general. They are not corpuscular as they appear in microscopical sections, but are strands which branch and ramify through the thymus as does other connective tissue. Hewer ('16) has produced them experimentally by injury to the thymus by X-ray irradiation. Similar structures are found in other lymphoid tissue in certain pathological conditions, especially around the parotid gland.

It may be pointed out that with our newer technical methods, it is possible to demonstrate microscopically secretory activity in all organs known definitely to produce a secretion, and in the thymus such activity cannot be demonstrated. The cells which make up thymic tissue belong to the vascular system and their function is no more likely to be the formation of an internal secretion than cells of similar appearance in other lymphoid tissues. If the thymus is a ductless gland then this must probably be true of the tonsils, lymph nodes, spleen, Peyer's patches, and very numerous small aggregations of lymphoid tissue scattered throughout the body. No one would probably be willing to include

all these organs in endocrinology. The involution of the thymus no more indicates a secretory function than does that of the pharyngeal tonsil already referred to, "hyperactivity" of which, as indicated by its hyperplasia, is ordinarily called simply adenoids as is doubtless proper.

The following graph and table prepared from data furnished by Rabinowitsch ('13), Donaldson ('95), and Hammar ('06), shows clearly the temporal relation between the involution of the thymus



The upper line shows the decrease in the percentage of lymphocytes in the blood, from 61 per cent at one year to 23 per cent at puberty (14.8) years. The lower line shows the concomitant decrease in the size of the thymus (amount of thymic parenchyma) from 0.0385 per cent of body weight at birth to 0.0020 per cent at 18.2 years of age.

and the decrease in the percentage of lymphocytes in the blood; and the relation of the size of the thymus to that of the body. During the period of infancy and childhood there is also a loss of lymphoid tissue other than the thymus, including the pharyngeal tonsil and other masses all over the body. In very old people lymphoid tissue is very scant.

The graph shows a marked parallelism between the decrease in the percentage of lymphocytes in the blood and the decrease in the relative amount of thymic parenchyma between birth and puberty.

Age years aver.	Body weight Kg. aver.	Thymus weight gms. aver.	Thymic paren- chyma wt. gms. aver.	Thymus per cent paren- chyma aver.	Thymus per cent body wt. aver.	Thymic paren- chyma per cent body wt. aver.	Lympho- cytes in blood per cent aver.
Birth	3.2	13.3	12.33	93.	.0401	.0385	61.0*
2.6	14.2	23.	19.26	84.2	.0162	.0136	55.5
9.	27.4	26.1	22.08	84.6	.0090	.0080	36.0
14.8	45.5	37.5	25.18	67.1	.0082	.0055	25.0
18.2	62.2	25.6	12.71	49.7	.0041	.0020	23.0
23.3	67.	24.7	4.95	20.0	.0037	.0007	23.0

*Percentage at 1 year, higher at birth. Leucocytes at birth equal 18,000 to 36,000 per cu. mm.

The accompanying table shows that although the thymus reaches its greatest absolute size at about the time of puberty, nevertheless, in relation to the size of the body for all of which it functions, it is seven times as large at birth as at puberty, changing thus from 0.0385 per cent of the body weight at birth to 0.0055 per cent at 14.8 years of age. The table also shows that in the growth of the thymus after birth the connective tissues make up an increasing amount of the entire organ. The amount of connective tissue and fat in the thymus changes from 7 per cent of the organ at birth to 32.9 per cent at puberty and 80 per cent at twenty-three years of age. In old age the non-lymphoid part becomes nearly 100 per cent of the thymus. Again in the absolute amount of parenchyma of this organ it nearly reaches its maximum size at nine years of age when there is present 22.08 grams of lymphoid tissue as opposed to 25.18 grams at puberty. This increase in the amount of lymphoid tissue is relatively much less than the relative in-

crease of the entire body. These figures are of course averages.

In consideration of the theory of the influence of skeletal growth by the thymus, it should be noted in the table that during the period between 14.8 and 18.2 years of age when the skeleton is growing very rapidly the actual amount of thymic tissue decreases nearly one-half, from 25.18 grams to 12.71 grams, and the relative amount nearly two-thirds, or from 0.0055 per cent of the body weight to 0.0020 per cent. The skeleton also grows rapidly before puberty and while the thymus is still large. The inference here is inevitable that the thymus does not control the growth of the skeleton, as is so often claimed.

In its evolution the thymus resembles the tonsils of higher forms. In primitive life (as illustrated by fishes and by young mammalian embryos) the thymus was intimately associated with the gill pouches of the pharynx in much the same relation as that between the pharynx and tonsils of the highest animals today. In the change from aquatic to terrestrial existence the gill pouches, as such, disappeared and the pharyngeal wall was thus pulled medially and separated from the thymus which then lay in the neck as it does now in intermediate forms. With the skeletal changes that occurred in mammals and the shifting caudally of the cervical and thoracic viscera, especially the heart and its great vessels, the thymus was pulled into the thorax, where it now lies in the higher animals. This change of the position of the thymus can be followed in comparative anatomy and in mammalian embryology. One might even theorize that

the thymus is a misplaced tonsil in the higher forms and atrophies finally because it cannot function as a tonsil on account of its separation from the pharynx. Its persistence in the lower forms where it remains in relation with the pharynx would support such a theory. This view would also find support in the fact that in frog larvae where metamorphosis is prevented by removal of the thyroid, the thymus remains in close relation with the pharynx and persists, becoming enlarged with the excessive growth which these thyroidless animals undergo.

A more logical theory of the significance of the thymus is that it functions as a lymphoid organ in infancy and childhood when large numbers of lymphoid cells and leucocytes are needed to combat infections. The large number of leucocytes and especially lymphocytes in the blood during this period of life indicates that these cells are relatively very important to the organism. The question of the relative loss of thymic tissue and other lymphoid tissue all over the body that begins at birth and progresses throughout life, especially in infancy and childhood, must be bound up with the question of the development of immunity from, or resistance to, infections that occurs in every animal. It is a fundamental law of biology that bodily structures the need for which decreases, tend themselves to atrophy.

The loss of vitality that occurs after castration suggests the need of the retention of the thymus and other leucocyte producing tissues as actually occurs.

It is idle to discuss the enlargement of the thymus and other lymphoid tissues in status lymphat-

icus until something more has been learned about this condition which is as yet not understood.

The belief in the lymphoid nature of the thymus is by no means new. Adami and McCrae ('14), in their excellent work on pathology, state on page 563, "To all intents and purposes it (the thymus) is a lymphoid organ." Many others have held the same view.

Whatever be the real function of the thymus, certain it is that its production of an internal secretion has not been proven. The evidence in favor of such a theory is but circumstantial at best and very meagre. It is equally difficult to prove that the thymus does not produce a secretion, but the burden of proof is upon those who support the former theory. A statement is not true because it cannot be proven untrue.

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ACTIVE COOPERATION BETWEEN THE
PHYSIOLOGIST AND THE CLINICIAN AND
COMPARATIVE ANALYSIS OF COORDI-
NATED DATA IN THE STUDY OF THE
INTERNAL SECRETIONS*

Charles E. de M. Sajous, M. D., LL. D., Sc. D.,
Philadelphia.

The purpose of our Association being the study of the internal secretions, you will surely realize that it would give me great pleasure to initiate this, our first scientific meeting, with at least an outline of the great progress accomplished in recent years. Unfortunately, my remarks will rather tend in the opposite direction, although my purpose, I hasten to state, is to suggest ways and means that may enable us to hope at least, for a better outlook.

It happens to have been my lot, in addition to active practice, to edit works which aimed to collate, either in logical sequence, or in encyclopedic form, the progress recorded in the medical literature. This class of work, which has taken up much of my time and labor during the last thirty years, involved a review of all the branches of medicine, including the specialties, fifteen times. From its very start, in 1887, I became impressed with the thought that closer cooperation between the clinician and the physiologist would tend greatly to elucidate our knowledge of disease. Each of the nine series of my *Annual of the Universal Medical Sciences* will, in fact, be found to contain admirable reviews of the contributions to physiology during the corresponding years, by Prof.

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H. Newell Martin, of Johns Hopkins, up to 1890, and by Prof. W. H. Howell, his successor, up to 1896. Unfortunately, the panic of the early nineties, by undermining the resources of the work, imposed the elimination of the department of physiology, with others devoted to auxiliary subjects, from its successor, the Analytical Cyclopedia of Practical Medicine. This is mentioned only to illustrate the importance I have always attached to the active cooperation I urge. Indeed, to us, clinicians, who are responsible for the multitude of lives entrusted to our care, physiological data are as many precious additions to those garnered at the bedside, in the pathological laboratory and through our therapeutic results, for the elucidation of the complicated problems that are constantly surging up before us. For, after all, what is the condition we term "disease," however caused, but "pathological physiology," as Bouchard has well termed it?

Indeed, so close is his connection with physiological problems in his daily contact with disease that the physician sometimes discovers a solution. Thus, a great physiologist, Professor Pawlow, of Petrograd, wrote sixteen years ago (1), after referring to the discovery of gastric secretory nerves: "Physiologists, on the other hand, had fruitlessly endeavored for decades to arrive at definite results upon this question. This is a striking, but by no means isolated, instance where the physician gives a more certain verdict concerning physiological processes than the physiologist himself; nor is it indeed strange. The world of pathological phenomena is nothing but an endless series of the most different and unusual combinations of physiological occurrences which never

make their appearance in the normal course of life. It is a series of physiological experiments which Nature and life institute, often with such an interlinking of events as could never enter into the mind of the present-day physiologist, and which could scarcely be called into existence by means of the technical resources at our command. Clinical observation will consequently always remain a rich mine of physiological facts."

The broad field of endocrinology is in a great measure based on clinical findings, and time may show that the very obscurity which surrounds the whole subject at the present time, is due to the fact that we have too freely ignored the inspirations, in conjunction with physiological discoveries, of the morbid processes that Addison, Graves, Marie, Lannois, Frölich and others have described. I shall illustrate later in the course of my remarks, by a few examples among the many available, the elucidative value of clinical data in physiological questions. It will serve to emphasize anew the material advantage that would accrue from closer cooperation between the physiologist and clinician than now prevails—an opportunity greatly facilitated by our Association and particularly through its organ, *Endocrinology*.

The ways and means favoring such a cooperation being thus available, how should we use physiological and clinical data in our search for truth? Again, time being an important element, in view of the growing recognition by many clinicians of the first order of an unmistakable influence by certain of these organs on various fatal diseases, including some encountered during the present war, how could we hasten progress?

As an example submitted below will show, comparative analysis of coordinated data, i.e., garnering of all available data on a given subject, then arranging these data in logical order and sequence, will not only meet the first requirement, but point to the labors required to complete the work necessary to attain a satisfactory conclusion concerning the identity of a function. Various theories may be suggested by the coordinated data when carefully tabulated; a sound working hypothesis will soon assert itself by the wealth of facts from various directions for which it will afford a ready nidus, while wrong theories will soon meet their doom through lack of corroborative testimony, direct and indirect, and through its inability to find a logical place anywhere.

Purely to illustrate the workings of such a plan—which I have now followed myself, as far as private means could permit, for many years—I will submit a brief review of the present status of the prevailing views concerning the functions of the adrenals, and compare it with the totally different aspect of the question which the plan advocated offers.

In the April, 1917, number of "Endocrinology," you doubtless read the original article written by our fellow member, Prof. Swale Vincent, of Winnipeg, on recent views as to the functions of the adrenal bodies. Among the features reviewed is the discovery of Oliver and Schaefer in the early nineties, to the effect that "the function of the adrenal (or, at least, of its medullary portion) is to help to maintain the normal blood-pressure and to sustain the tone of the tissues innervated by the sympathetic system." You will also recall the experimental data which he adduces to show that Schaefer's view is no longer ten-

able. Those of Young and Lehmann are quoted to show that ligation of the adrenal veins during thirty minutes, to dam back the adrenal secretion into the organs, and then allowing, on release of the ligature, the accumulated secretion to flow into the circulation, failed to evoke the expected result. Very little if any fall of blood-pressure followed ligation of the adrenal veins. "In fact," writes Vincent, "the experiments merely show that adrenin is poured out into the adrenal veins." Similar experiments carried out by Young, but with the adrenal veins tied several hours to exclude the adrenals totally from the circulation, gave similar results, there being no appreciable fall of pressure. Even removal of the adrenals by Austmann and Halliday, with concomitant observation of the blood-pressure, until the animal died, failed to affect the pressure curve more than would have ether administered as long as possible. The older experiments of Moore and Purinton, and the more recent observations of Hoskins and McClure—to which many others might be added—are quoted to show that inasmuch as very small doses of adrenin will lower the blood-pressure, the amount of adrenal secretion poured out into the adrenal veins would tend to keep the blood-pressure down rather than up. Briefly, the one great function upon which the practitioner has depended twenty-six years, the blood-pressure theory, should now be abandoned.

Virtually the same conclusion is reached concerning the second theory which has attracted some attention, the so-called antitoxic theory of Abelous and Langlois, in virtue of which the toxic effects of certain substances are neutralized by a substance elaborated by the adrenals. While referring to a few

isolated records which seem to favor it, Vincent states that "it must be confessed that the antitoxic theory has not been substantiated." On the whole, a few minor suggestions concerning possible functions, including the emotional stress theory of Cannon and de la Paz, and a summary of what he deems to be the state of our knowledge concerning the adrenal bodies, seem fully to substantiate Vincent's remarks early in the article that "we know nothing of the functions of the adrenal body regarded as an organ on its own account."

And the adrenals are not alone in this plight. The functions of the thyroid, parathyroids, thymus, pituitary, pineal and other organs of the series, are likewise well known to be obscure. One and all, viewed from the standpoint of prevailing teachings, stand in the light of another of Vincent's remarks concerning the adrenals: "There is no good evidence of an experimental or clinical nature which warrants us in believing that the adrenal body as a whole has any definite function."

Need we wonder under these circumstances that so erudite and conscientious a surgeon as Prof. W. S. Halsted, of Johns Hopkins, should be driven to write three years ago, after an attempt to elucidate the frequently fatal form of Graves's disease in which the thymus complicates the morbid process: "It must be evident to everyone that there reigns the greatest confusion on the subject of the functions of the glands of internal secretions"?

Gentlemen, it is difficult to conceive how all the work done since Oliver and Schaefer published their first paper on the influence of adrenal extracts on the blood-pressure, twenty-four years ago—or indeed,

since Brown-Séguard published his initial dissertation on the adrenals over sixty years ago—can thus have proven futile. My own belief is that such is not the case. Comparative analysis of coordinated physiological and clinical data tend not only to sustain this opinion, but also to suggest that the adrenals *may* carry on a function of major importance—a function, moreover, capable of accounting for and including, as fragmental expressions of that function, what roles both physiologists and clinicians have attributed to the organ and sustained by considerable evidence.

The main features which led me to submit what might be termed the “respiration theory” fifteen years ago, and which much of the evidence recorded herein, has sustained since then, may be said to have rested upon five main conditions: (1) Addison’s disease; (2) adrenal lesions in acute diseases; (3) certain adrenal tumors, such as hypernephroma; (4) large adrenal grafts; (5) the unsettled state of physiological knowledge concerning respiration and metabolism.

As to Addison’s disease, the older contention that the adrenals were not always diseased, and that we were therefore dealing with a neurosis, is no longer tenable. Inasmuch as the disease has been shown to affect any part of the chromaffine system, including its ganglia, it is to disorders of that system that we must attribute the Addisonian syndrome, the leading or salient symptoms of which are progressive asthenia, weak heart action, vascular hypotension, emaciation, hypothermia, dyspnoea, vomiting, diarrhea, and, only in cases of sufficient duration, bronzing.

In the course of certain infections, diphtheria, scarlatina, malignant endocarditis, typhoid fever, pneumonia, etc., and particularly towards the close of these diseases, symptoms are observed which correspond with those of Addison's disease, viz., extreme asthenia, low blood-pressure, hypothermia, rapid breathing, cyanosis, weak pulse, tendency to syncope and heart failure. The post-mortem adrenal lesions in such cases vary from marked reduction of the residual adrenin and disappearance of chromaffin reaction, with cellular atrophy, to more or less marked interstitial hemorrhages, attaining in some cases the degree of adrenal apoplexy with sudden death. Among the recently described cases of this class may be mentioned those of Josué (2), Goormaghtigh (3), and Moltchanow (4). Excessive exertion in soldiers suffering from malaria, as often noted during the present war by Paiseau and Lemaire (5), or dysentery, as observed by Remlinger and Dumas (6) and Steiger (7), may also bring about adrenal lesions and in some instances adrenal apoplexy. Burns, according to Kolisko (8), may likewise produce this form of hypoadrenia. As I have been able personally to verify, 8 to 12 minim doses of adrenalin given hypodermically, in small quantities of saline solution, are positively life-saving in uncomplicated toxemias.

Hypernephroma, a form of tumor shown by Grawitz, in 1883, to develop from adrenal tissue, either in the adrenals themselves or in the kidneys, vascular walls and other tissues, may be composed of either or both cortical and chromaffin substance, though often merged with other neoplasms, cysts, papilloma, etc. When it occurs between the first and eighth year, as is often the case in the true adrenal

type, it may give rise to abnormally rapid body growth. In a case reported by Owen Richards (9) in a girl of seven years, the development was that of a woman of twenty. Such cases may show marked muscular development and strength. Parhon and Golstein (10) refer to a boy who, between the ages of 9 and 14, attained the size of a "vigorous man." Jump, Beates, Jr., and Wayne Babcock (11) refer to a case of theirs in a girl of seven years, as "remarkably strong." This overdevelopment, however, shows none of the characteristics of acromegaly. Common to this type also is premature sexual development with profuse hirsuties, swarthy skin, etc. There is, as a rule, excessive appetite and thirst; gastric disorders and stubborn vomiting are sometimes observed.

The fourth feature was suggested by the fatal effects of large adrenal grafts. Bra (12), after grafting the adrenals of a dog into the cellular tissue of a child, witnessed its death in three days. Jaboulay (13) lost two cases, within twenty-four hours, after the same procedure. Courmont (14), in reporting a fourth case which likewise died in twenty-four hours, refers to the presence of "a formidable hyperthermia and cardiac collapse" while specifying that there was no infection of the wound. Nor had any been observed in the previously reported cases.

If any clue could be obtained from these clinical conditions as regards the function of the adrenal bodies—or rather of the whole chromaffine system in the light of modern work—it seemed to be that they at least played some important role in (1) metabolism, as shown by their influence on nutrition and general development and (2) on respiration, as shown

by their influence on oxygenation and the respiratory mechanism.

This brings in the fifth and last feature: the unsettled state in physiological literature of the very questions in point.

Concerning respiration, the many facts recorded by physiologists of the rank of Bohr (15), Haldane and Lorrain Smith (16), Vaughan Harley (17), Henriques and others, have tended to show that the diffusion doctrine of respiration is not valid. Pembrey (18), after an impartial study of the question has expressed the view that "the body of evidence has been steadily increasing in favor of the secretory theory, especially as regards the absorption of oxygen." What is meant here by "secretory theory" is that, as expressed by Bohr and Henriques (19), the respiratory process, to account for experimental facts observed, requires, in the lungs, a substance "having greater avidity for oxygen than the blood itself," or as they define it, "a kind of internal secretion." It is this function which from my own viewpoint the adrenal secretion seemed to fulfill.

We shall see later, that this view, which I submitted in 1903 and 1907 and repeatedly since in numerous articles, urging its importance in the intelligent interpretation of many diseased states, has recently (1917) been sustained by the researches of a physiologist, M. L. Menten (20), of the University of Chicago, who writes in this connection: "The presence of adrenalin in the venous blood of the capillaries of the lungs undoubtedly induces changes which meet the conditions suggested by Bohr (21) as requisite for an alternative to the explanation of oxygen secretion, that is, adrenalin could act as a substance

altering the property of hemoglobin so as to give it a greater attraction for oxygen as it passes through the lung.”

COORDINATED DATA IN SUPPORT OF THE RESPIRATION THEORY*

These, reduced to their simplest expression, may be divided into six fundamental functional links:

1. *The adrenal secretion passes out by the adrenal veins then enters the inferior vena cava.*

As to the formation of the secretion, Stoerk and Haberer (22) found that the chromaffine substance develops in the form of intracellular granules which, when sufficiently dense, diffuse out of the cells into the adjoining small vessels and appear in the adrenal venules as a yellowish brown, refractile, mucoid material which constitutes the secretion that passes to the adrenal veins. According to Elliott (23), the adrenals of a normal man should contain from $\frac{1}{4}$ to $\frac{5}{12}$ mgm. ($\frac{1}{15}$ to $\frac{1}{12}$ grain) of adrenin, but fright, anesthesia, infectious diseases and cardiac failure and post-mortem changes may reduce considerably this amount.

The presence of the adrenal secretion in the blood of the adrenal veins is suggested by the following facts: Gottschau (24) traced hyaline granules (found subsequently to be their secretion) from the interior of the adrenals to their veins. This observation was confirmed and amplified by Manasse (25), Aulde (26), and Stilling (27). Pfaundler (28) traced the same granules from the interior of the organ along the adrenal veins to the vena cava itself.

*The name "respiration theory" has seemed to the writer better to denote the process described—pulmonary and cellular—than the "secretory theory," which has no specific meaning, or "oxidation theory," which implies destruction by oxidation of the adrenal product and renders unnecessary the study of any function, since a "destroyed" substance cannot logically be credited with a function.

It is doubtless the adrenal secretion which is carried by the blood of the vena cava, for when blood originating from the adrenals on its way to this great trunk was injected into animals by Cybulski and Szymonowicz (29), it produced the characteristic effects of adrenal extract. These results were confirmed by Biedl (30), Langlois (31), and Dreyer (32), Szymonowicz, Biedl, Dreyer, Salvioli, and Pizzolini (33) found, moreover, that such effects could not be obtained with venous blood obtained from other parts of the body.

2. *The adrenal secretion inevitably reaches the pulmonary alveoli where a reducing secretion is required to account satisfactorily for the absorption of oxygen from the air.*

That the blood of the inferior vena cava containing the adrenal secretion reaches the pulmonary alveoli by way of the right heart needs but to be recalled.

We have seen that the classic diffusion doctrine of respiration has been challenged by a number of prominent physiologists, beginning with Bohr in 1897, and that this investigator and Henriques had concluded that a kind of "internal secretion" "having greater avidity for oxygen than the blood itself" was necessary to explain the phenomena witnessed. Besides their own observations based mainly on aerotometric studies may be mentioned those of Paul Bert (34), who showed experimentally that the absorption of oxygen by the pulmonary blood persisted even when the pressure of this gas was almost *nil*; of Müller, who found that a strangulated animal exhausted the air in its lungs of all its oxygen; of Setschenow and Holmgren (35), Zuntz (36) and

others, who found but traces of oxygen in the arterial blood of asphyxiated animals.

3. *The adrenal secretion has affinity for oxygen, reaches the pulmonary alveoli and affects the oxygen exchange.*

Vulpian (37) found that adrenal juice reduced iron perchloride and iodine. Cybulski (38) recorded a similar action on potassium permanganate. Langlois (39) noted that adrenal extract lost its reducing properties *in vitro* when oxidizing compounds were added. Battelli (40) found that adrenalin did not lose its properties when contact with air was prevented, while Abel (41), Takamine (42), and others deem this property a source of trouble in laboratories, the latter chemist specifying that adrenalin becomes oxidized by contact with the air. A. L. Menten (43), a physiologist, adduces experiments which enable her to conclude that adrenin "does particularly affect the oxygen exchange in that organ"—the lung.

4. *The adrenal secretion influences actively the respiratory phenomena, including the intake of O and the output of CO₂.*

D. E. Jackson (44) found that adrenalin produced prompt dilatation of the bronchioles when these are contracted, wholly independently of any rise of blood-pressure. The immediate relief afforded by injections of adrenalin in asthmatic paroxysms, a treatment now resorted to in preference to any other, is probably due to this fact. Januschke and Pollak (45) noted that injections of adrenin in doses of 1/10 mg. (1/600 grain) caused an increase of the respiratory excursions of the lungs. Though noticeable in normal individuals it was especially marked in animals suffering from muscarin asthma. Nicc,

Rock and Courtright (46) found that whether adrenin were injected in minute doses, causing a fall of blood-pressure or in large doses causing a rise of blood-pressure, it evoked an increase in the depth of the respiration. Byelaventz (47) found experimentally that adrenin increased the gaseous interchanges. Bernstein and Faltz (48) observed that injections of adrenin in doses of 1 mg. (1/60 grain) subcutaneously, in normal individuals produced an increased consumption of oxygen and, conversely, an increased excretion of carbonic acid. The respiratory quotient was likewise increased.

5. *The adrenal secretion influences tissue oxidation.*

Adrenal extracts, as first shown by Oliver and Schaefer (49), cause a rise of temperature when injected subcutaneously in doses of 8.57 Grams of fresh gland, made into an aqueous extract, per kilogram of dog. Reichert (50) also recorded a rise of 1 C. in dogs, accompanied by increased metabolism from adrenalin in doses of 0.001 Gm. per kilo of body-weight. Morel (51) observed a rise of 0.9 to 1.8 F. (0.5 to 1. C.) in guinea pigs after rather large doses injected subcutaneously. Lépine (52) states that the increase of blood-pressure caused by adrenal extract in therapeutic doses is always followed by a rise of temperature. These observations seem controlled by the familiar facts that removal of the adrenals is followed by a steady decline of the temperature until death ensues.

6. *The adrenal secretion takes part in tissue oxidation and metabolism, by becoming a constituent of the hemoglobin.*

That the adrenal secretion can endow hemoglobin with its oxygen-carrying power, i.e., convert it into oxyhemoglobin, as I have repeatedly urged, has been confirmed by the observations of Menten and Crile (53), who noticed that the blood from the adrenal vein invariably assumed a bright red arterial color in from one to twenty minutes after dilution with salt solution, while blood from other organs treated in the same manner showed no change. This was found spectroscopically to be due to an increased formation of oxyhemoglobin. Menten (54) having added adrenalin to diluted human venous blood, found moreover, that it caused an increase in the intensity of the oxyhemoglobin absorption-bands (of which she gives photographs) and remarks that similarity between the spectra of adrenal vein blood and those obtained from venous blood to which adrenalin was added "is unquestionably very strong evidence that it is adrenalin which is responsible for the increased amount of oxyhemoglobin found in the adrenal vein blood."

RELATION TO OTHER THEORIES

The foregoing data, selected from labors of observers of recognized ability and standing, seem to suggest that the main disorders we, clinicians, attribute directly to the adrenals—the whole chromaffine system—are due, in so far as their symptomatic phenomena are concerned, to disturbances of that phase of metabolism and its corollary, nutrition, influenced by that system. Recalling the five clinical features which led up to this analysis, it would seem that Addison's disease and adrenal insufficiency due to infections may on good ground be attributed to deficient tissue oxidation, while typical adrenal hypernephro-

mata and large adrenal grafts produce their morbid effects through excessive oxidation.

True, various observers have not noted an appreciable alteration of protein metabolism in Addison's disease, but they lose sight of the clinical fact that the anorexia and inadequate assimilation of proteins may account for this. If, as observed by Senator (55) and others, the diet of these cases is increased and properly balanced, there is a notable gain. Particularly is this true if, as I have urged, adrenal gland or adrenalin is administered in *judicious* doses, i.e., doses adjusted to the blood-pressure and hypothermia, simultaneously. This coincides with the observation of Addis, Barnett and Shevky (56) that adrenalin administered subcutaneously in rabbits increases the urea excretion, provided the doses are not too small or too large. In the latter case, (as I have frequently observed in various nutritional disorders treated with adrenalin) cellular metabolism is interfered with by the undue constriction of the arterioles produced by the adrenal principle, and the resulting deficiency of arterial blood supplied to the cellular elements. Emaciation may thus be caused by its prolonged use by cases in which the disease present does not include emaciation in its pathology, bronchial asthma for instance. In one case, observed in consultation, the loss of weight exceeded thirty pounds. On the whole, there can be no doubt that the adrenal secretion influences metabolism.

This apparently applies likewise to the influence of adrenal products on the *blood-pressure*. There is no doubt that therapeutic doses raise the blood-pressure and that, as illustrated farther on in this paper, its continued use may induce a more or less perma-

ment rise of 50 mm. Hg. The clinic, therefore, supports the discovery of Oliver and Schaefer that adrenal extracts raise the blood-pressure. An increase of the rate of metabolism such as that induced by the adrenal principle also affects both smooth and skeletal muscles as also first observed by Oliver and Schaefer.

The *antitoxic function* attributed to the adrenals by Abelous and Langlois and others finds support in the fact that catabolism, that phase of metabolism in which tissue wastes, including the intermediate toxic wastes, are broken down, is partly due to oxidation. The conversion of these toxic wastes into eliminable end-products would then depend in a measure upon the integrity of the adrenals. Many clinical facts tend to sustain this view.

Finally, while the *adrenal cortex*, as much clinical evidence has shown, markedly influences both the sex characters and the premature development of sexual organs, hirsuties, etc., exaggerated oxidation, in which the organ *in toto* may take part, partly accounts for this morbid process, probably as a corollary to the specific role played by the cortex in the latter.

It would thus seem as if the adrenals through their dual action, specific and general, on metabolic activity were able to account for and explain the various "functions" that have been attributed to them. They all become, in the light of the foregoing, however, but fragmental expressions of a general function, thus justifying their authors for their deductions, though restricting them to their proper precincts.

VULNERABLE POINTS OF THE RESPIRATION THEORY

It is purely as a clinician—and one indeed, always ready to accept gratefully any degree of enlightenment—that I submit the following analysis of the weak points of the respiration theory that might be urged against it.

The minute quantity of circulating adrenin fails to meet the needs of the respiration theory. Analysis of this question, if current teachings are taken as standard, suggests that the minimum concentrations given are not based on a sound foundation. Thus, according to Trendelenberg (57), this concentration is one part in one or two billions in the carotid blood of normal rabbits. Yet, we are taught by physiologists that adrenin is destroyed in arterial blood.

Again, we are told that it is by oxidation that adrenin is destroyed, while as we have seen, Abel, Takamine and others, found this property a source of trouble in laboratories. And yet no precaution seems discernible in the various procedures recited by the different authors who assayed blood to determine adrenin concentrations. Under these conditions it is very likely that at least a part of the adrenin is oxidized in the course of these procedures. Even the figures given for the adrenal veins are open to suspicion since, as shown by Menten (58), dilution of their blood caused an increase of oxyhemoglobin, which would entail a decrease of adrenin.

When the destructive effect of oxygen on adrenin is taken into account it seems also that there should be but one vascular area capable of affording a reliable assay, viz., the venous field comprising the adrenal veins, the vena cava, the right heart and pulmonary veins up to the air cells, where the blood be-

comes arterial. Once at the air cells, the adrenal product should be destroyed and remain so throughout all arterial channels and the whole venous tree (unless resupplied, so to say, in the subsidiary adrenal tissues) until the adrenals *per se* are again reached. The concentration in the adrenal veins is 1 part in one million, according to several investigators quoted by Barger (59). The venous channels between these veins and the air-cells being, of course, much larger, it is probable that Battelli's concentration 1 part to 10 or 20 millions (60) is the correct one for caval blood i.e., one thousand times greater than Trendelenberg's.

On the whole, the actual minuteness of circulating adrenin in arterial blood cannot justly be cited to controvert the many concordant data submitted in favor of the respiration theory.

The great quantity of adrenin needed to produce the effects recorded would kill by paralyzing the alimentary canal. The invalidity of this objection is emphasized by the teaching of physiologists that "adrenin circulating in the blood is rapidly destroyed" by oxidation. Such being the case the adrenal secretion would meet its doom on reaching the alveoli, thus preventing any action either on the stomach or intestines.

Abundant clinical experience also shows that such an action is not produced either when adrenalin or the adrenal gland are given by the mouth or adrenalin is injected hypodermically, endomuscularly or rectally during short or prolonged periods in therapeutic doses. This applies also to children. I could produce a large number of cases in which 3 to 7 minims given orally several weeks served only to act as tonic, and

to increase the appetite. In keeping with the observations of Loeper and Verpy (61), it often promoted the secretion of HCl where hypochlorhydria existed. A medical patient suffering from asthma wrote recently, requesting my opinion concerning the continued use of adrenalin: "I have employed it for *several months* once a day, sometimes twice a day, hypodermically in doses of 10 minims of the 1-1000 solution." His blood pressure rose from 130 to 180, he lost flesh and feared a permanent rise. Not a gastric symptom occurs, however, in the history of this case.

If inhibition of the rhythmic contractions of the intestine occurs in the lower animals, as shown by Ott, Magnus and others, even when injected in very low concentrations (1 to 20 millions, Magnus) (62), no appreciable effect of this sort is observable when adrenin is given in the therapeutic doses used in man. Possibly it occurs as an ephemeral effect of the constriction of the arterioles of the intestines similar to that caused by adrenalin throughout the body.

INVESTIGATIONS NEEDED TO DETERMINE THE VALIDITY OF THE OXIDATION THEORY

Some physiologists hold that the adrenals "in some way influence the metabolism of contractile tissues." If the word "metabolism" is actually meant here, it would seem as if the word "destruction" (of the adrenal secretion in the blood) should be replaced by its *conversion* into something else that is not subject to destruction by oxidation. I have long held that it entered the hemoglobin, and endowed it with its power to become oxyhemoglobin; we have seen that Menten found that the adrenal product actually becomes converted into that body.

If then it does become converted into oxyhemoglobin, the adrenal secretion or principle must be taken up by the red corpuscles. Mulon (63) has found that the latter gave some of the reactions of adrenalin. Again, Traube, in 1853, concluded that hemoglobin could not fulfill the functions attributed to it without the aid of a catalyst, a substance capable of hoarding oxygen and crowding it, as it were, on the tissues as an "accelerator." Poehl (64) found that the adrenal principle was a catalyst, while Jolles (65) pointed out that the activity of a given volume of blood as a catalyst corresponded with the number of red corpuscles it contained. This suggests that the adrenal secretion (not necessarily adrenin, which does not represent the secretion *in toto*) is the corpuscular catalyst which supplies the tissues with oxygen.

In this connection, and possibly accounting for the small proportion of secretion produced excepting under stress, such as fright, excitement (Cannon), hard labor, disease, etc., its active principle may be an oxidizing enzyme—"adrenoxidase," as I once termed it. As Bayliss (66) states, "enzymes are merely a particular class of catalysts, considered for convenience apart, owing to the fact that they are produced by living organisms and are for the most part of *unknown chemical composition*." As an enzyme, adrenoxidase could act as an oxidizing catalyst without itself being destroyed. Now the oxidizing ferment of Bunge and Schmiedeberg (67), Jaquet (68), Abelous and Biarnés (69) and adrenin give heat reactions very similar to those of adrenin; while Menten (70) also refers to the influence of temperature on the activities of adrenin within fixed limits, a peculiarity of enzymes.

The adrenals or other chromaffine tissues would thus only be required to replace actual losses of the enzyme, the residual body asset of which would be conserved as the oxygen carrier and accelerator of the hemoglobin and constantly be re-used, while having lost its identity as adrenin. This would afford a legitimate nidus for the "function" suggested by MacMunn (71), who, having found haemochromogen in the adrenals, concluded that these organs served to break down worn out hemoglobin and histohaematis. From my viewpoint, this process would serve to extract from them what constituents might serve for the elaboration of the adrenal secretory product.

Finally, much might be learned by trying to explain all the respiratory phenomena that have been attributed by as many physiologists and clinicians to adrenin in the foregoing pages to a function other than that of pulmonary and tissue respiration.

Need I urge in the presence of all these facts that a systematic cooperation between the physiologist and the clinician, *each seeking to aid the other through the special knowledge he possesses*, would greatly hasten our knowledge of the endocrine glands? Need I urge that all recorded data, physiological and clinical—of which the foregoing are but a few on the question treated—carefully tabulated and checked, then coordinated logically, *irrespective of any preconceived theory*, might open new fields which we would all, working in harmony, cultivate?

The respiration theory is only submitted here as one of the many fields of this kind. It may die a normal death; if it does, we shall at least have learned that the soil in that one area is sterile, and that another coordination of data of the many available

may prove more fruitful. Many lines of thought may thus have to be dropped by the wayside, but the day must finally come when success will reward honest effort.

Of course, the coordination of all available data is no small task; but it is one to which I hope to devote my remaining days, with financial help the nucleus of which is available. All our members will be asked to criticize to their hearts' content and to contribute from their store of observation or special knowledge, and if the true scientific spirit is shown in suggesting possible criticisms, our Association and its journal "Endocrinology," will, I feel confident, prove a blessing to mankind in its far-reaching influence upon our knowledge of disease.

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IODIN AS THE ACTIVE PRINCIPLE OF THE THYROID GLAND

W. W. Swingle

Department of Biology, Princeton University

The relation of iodine to the thyroid gland has been for many years a matter of great interest to clinicians and experimentalists, and it has long been recognized that this substance holds an important place among the constituents of the gland.

For several years the writer has been engaged in research on problems involving the thyroid, and this last spring obtained some results in the course of a series of iodine-feeding experiments which should prove of interest to clinicians and other readers of this magazine. The complete account of these experiments has appeared elsewhere (*Jour. of Exp. Zoology, Abstracts, Endocrin.*, 1918, **2**, 200), hence only a summary will be given here.

The problem briefly stated was to test the relation of iodine to the physiological activity of the thyroid and the general problem of amphibian metamorphosis, by feeding this substance and various of its compounds to normal and thyroidless frog larvae. Most of the investigators who have dealt with the problem of the relation of iodine and its compounds to the thyroid, have used mammals as experimental material, forms, which in the author's opinion, offer no such sure and certain criteria for judging the effects of iodine administration and thyroid activity upon the organism as do frog larvae. The investigations of Gudernatsch (since followed by those of Morse, of Lenhart and of Swingle) showed that any

increased stimulation of thyroid activity, as for instance feeding extract of the gland, is at once indicated by metamorphic changes in the tadpoles. The idea was to utilize such somatic changes as an index of the effect of iodine feeding upon the physiological activity of the thyroid in the normal animals, and to see if animals whose thyroids had been removed very early in embryonic life would react to iodine.

For the experimental work, the larvae of the common leopard frog, *Rana pipiens*, and the toad, *Bufo lentiginosus* were used. The animals of all cultures came originally from the same batch of eggs, hence were of the same age. Iodine and two of its compounds were used in the original work: iodine crystals, iodoform, and potassium iodide. Since the publication of the original work, an experiment was tried in which potassium iodate was fed. The iodine crystals were ground exceedingly fine and mixed with wheat flour in the proportion of one to one-hundred, enough water was added to make a thin paste; this was allowed to dry at room temperature, and when dry finely crumbled and fed to the larvae.

The normal animals with thyroid glands intact, were started upon the iodine, KI, and iodoform diet when they were ten mm. in length; none showed indications of limb-buds. Within a few days of the first administration, the larvae fed iodine crystals showed all of the characteristic symptoms of hyperthyroidism. They had developed limb-buds, growth had ceased, bodies were emaciated, eyes bulged out, and the tails of the larvae showed signs of resorption. The control animals for this culture showed none of these body changes.

Shortly afterwards the larvae to which iodoform was fed showed marked metamorphic changes. Still later, the animals of the KI-fed culture revealed these metamorphic changes, though to a less degree than the animals of the other cultures. The reaction was much slower in regard to the time of appearance. Within two weeks of the first feeding of iodine crystals the larvae of the iodine-fed culture had completely metamorphosed. This was true of both toad and frog larvae. The animals used as controls for all of these cultures revealed no indications whatever of metamorphic changes. This same experiment with slight modifications in the method of administering iodine and its compounds was carried out with four sets of larvae. The results obtained were the same in all cases.

In the meantime, cultures of larvae, the thyroid glands of which had been removed at the four mm. stage, were started on the iodine crystal diet. These animals when first fed were ten mm. in length, and were controlled by other thyroidless and normal larvae of the same age. In a remarkably short time—five to six days,—all of the thyroidless animals showed marked signs of “hyperthyroidism.” The hind legs of the animals had appeared, growth had ceased, bodies were emaciated and eyes bulgy. Within two weeks’ time these thyroidless animals had come to complete metamorphosis. The controls, on the other hand, showed no indications whatever of metamorphic change. Microscopic examination of the thyroidectomized animals failed to show any vestiges of the thyroids, nor were there any signs of accessory glands.

The writer was under the impression at first that perhaps the mixture of flour, iodine and water had produced a substance which simulated the physiological action of thyroid secretion. This erroneous idea was due to the fact that in some previous experiments it had been observed that frog larvae are very soon killed when iodine crystals are placed in the container.

In order to test the point, whether it was iodine itself or the mixture of flour, iodine and water that accelerated metamorphosis, cultures of normal and thyroidless larvae were placed in weak aqueous solutions of iodine. The solutions were made by placing quantities of iodine in a few cubic centimeters of water and mixing thoroughly. Two c.c. of such a solution added to 500 c.c. of water was sufficient to bring about metamorphosis in the experimental animals. Normal and thyroidless animals living in such solutions of iodine undergo transformation from the larval to the adult form as rapidly as those fed upon the flour-iodine mixture.

Tests were also made regarding the rapidity of action of the various iodine compounds in accelerating metamorphosis. The results show that iodine crystals bring about the reaction quicker than any of the compounds used; iodoform is slightly less potent than the iodine crystals; potassium iodide is much slower than iodoform, and potassium iodate has practically no effect.

Microscopic examination of the thyroid glands of larvae reared in iodine solutions or fed on the iodine-flour mixture from the earliest feeding stage to the time of metamorphosis, shows that the thy-

roids of such animals are very much smaller than those of control larvae of the same age and held at the same size by under-feeding.

Discussion. The results of the experiments just cited appear to indicate very strongly that iodine is the active principle of the thyroid gland, and that this substance functions within the organism as a hormone itself without the intermediation of the gland. It has been shown by investigators that frog larvae whose thyroid glands have been removed early never develop into frogs, but permanently retain their larval characters. Yet iodine feeding brings about metamorphosis in these thyroidectomized animals in an abnormally short time. The fact, too, that the thyroid glands of animals fed iodine from the free feeding stage until metamorphosis, are much smaller and less developed than those of normal animals of the same age and size, is further evidence that iodine is the active principle.

The function of the thyroid, then, appears to be chiefly that of extracting and storing the physiologically active iodine, rather than elaborating an active hormone itself. That the tissues of animals are capable of utilizing iodine directly without the mediation of the gland, is shown by the results of feeding iodine to thyroidless larvae. In this connection the results of a series of experiments as yet unpublished, may be of interest. The writer has been able to demonstrate that normal blood serum acts as a solvent for iodine crystals to the extent of .00075 gms. per c.c.

All of the active substances so far extracted from thyroid tissue contain iodine, the more active they are

the more iodine they contain. This is clearly shown by Kendall's Alpha substance reported in a previous issue of this journal. The same principle holds true of goiters. The higher the iodine content of such glands, the greater their physiological activity when fed to lower animals. The work of Hunt and Seidell and of Lenhart is of interest in this connection.

The fact that iodine is capable of functioning within the organism without the gland tissue, should prove of interest to clinicians because of its bearing upon iodine therapy in the treatment of toxic goiter. If all of the symptoms of "hyperthyroidism" can be produced in thyroidless frog larvae by over-feeding with iodine, it is logical to suppose that the symptoms of "hyperthyroidism" in man are due to the same cause.

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THE EFFECT OF THE X-RAY UPON THE RESPONSE OF TADPOLES TO THYROID STIMULATION*

Carey P. McCord and Carlton J. Marinus
Detroit, Michigan

INTRODUCTION

The experiments carried out by Gudernatsch (1), in 1912 upon the growth of tadpoles after thyroid gland feeding, have been repeated in this laboratory during four summer seasons. In short, Gudernatsch observed that tadpoles whose normal metamorphosis into frogs occupied from three to six months, completed this metamorphosis in five to ten days when small quantities of thyroid gland substance was added one or more times to the living water of the tadpoles. This induced early differentiation into frogs, including all the gross changes normally distributed over several months. The miniature frogs so produced, although apparently anatomically perfect, were unstable and regularly died after a few days.

In all essential respects our findings have been in accord with Gudernatsch's reports. The experiments of this laboratory were extended to include low life forms other than tadpoles and also tadpoles of certain frog species whose metamorphosis normally extends over two or more years. An effort was made to determine the influence of thyroid feedings upon the growth and differentiation of tadpoles whose natural development had been deviated by diverse procedures.

*From the Research Laboratories, Parke, Davis & Co., Detroit, Mich.

The present report concerns itself with observations made as to the development of thyroid fed tadpoles which had been exposed to the action of the X-ray.

Three distinct theories have been advanced to explain the action of the Roentgen ray upon normal tissue cells. One of these adhered to by O. Hertwig (2), and his coworkers (1912), is that the rays exert a specific destructive action upon the chromatin of the cells. Opposed to Hertwig's hypothesis is the older theory proposed by Schwartz (3), (1903), who concludes from the observation of the destructive action of the Roentgen ray upon the lecithin of egg yolk, that the injury to the cells is due to the destruction of the lecithin which they contain.

Richards (4), (1914-15), has shown that the activity of various enzymes or ferments, of both animal and vegetable origin, is susceptible to change through the influence of Roentgen rays. He concludes from his experiments that, "a short radiation has the effect of accelerating the activity of these enzymes (diastase and pepsin), while longer radiation is inhibitive. Between these strengths lies a point at which the radiation is non-effective." His observations on pepsin and diastase have since been extended to include other enzymes, the results all tending to confirm his original conclusions. He advances the theory, therefore, that, "life processes are subject to marked change under the influence of radiation, a slight exposure being accelerative in most cases, while a more intense treatment is inhibitive or destructive. As a causal factor in these effects, the demonstrable injury to the chromatin of the cell is undoubtedly important; but there are also good evi-

dences that the modifiability of enzymes under the action of the rays likewise plays a considerable part either directly or indirectly in the resulting injury.”

MATERIALS AND METHODS

The tadpoles collected to participate in these experiments conformed within the acceptable limits in weight, length and in stage of development. These were maintained in large shallow trays under good condition as to light, air and aeration of living water. The food, apart from thyroid gland materials, consisted of green algae supplemented at intervals with small quantities of desiccated beef liver.

Tadpoles of the species *Rana catesbiana* (bullfrog) exclusively were used. The individuals of this species normally live for at least two years in the larval state. This fact permitted the use of larvae representing two widely different stages of development. The younger group (Experiment A) was composed of tadpoles approximately one year old. At this stage the individuals exhibited no signs of differentiation into the adult form. The second group (Experiment P) was composed of tadpoles not quite two years old. These tadpoles would under the natural conditions have completed their metamorphosis before the end of the summer. The controls in this experiment actually did complete their metamorphosis, but long after the conclusion of the experiment.

In both experiments (1st and 2nd year groups) the tadpoles were divided into four equal and similar lots. Two lots in each experiment were then subjected to the rays from a Coolidge tube according to the following standardized formula:*

*The tadpoles were irradiated by Dr. George C. Chene, Detroit. Our thanks are due him for his courtesy.

	Experiment A.	Experiment D.
Current	6 milliamperes	12 milliamperes
Spark Gap.....	8 inches	7 inches
Distance from Anode.....	12 inches	12 inches
Time	2½ minutes	4 minutes

Tadpoles of Experiment A were irradiated a second time one week later, under identical conditions except that the current was doubled.

In each experiment one irradiated group and one untreated group were placed on thyroid feedings while the second irradiated group and the second control group were kept on the desiccated liver and algae diet. The thyroid was administered by scattering 100 mgms. of the commercial desiccated product in the living water.

After the death or complete metamorphosis of all the thyroid-fed tadpoles of Experiment A, and tabulation of the accrued data, the two remaining control groups were again divided. Half of each group was placed on thyroid treatment identical with that described above. This second feeding was started one month after the irradiation of the tadpoles.

The alterations in size and shape of the tadpoles incident to their development were recorded by means of a method of "shadow photography." This procedure afforded a permanent and relatively accurate record of the growth. For the purposes of carrying out this photographic mensuration a temporary dark room was constructed near the tables containing trays of tadpoles. In this dark room was placed a small shallow rectangular glass container (2"x4") with a smooth flat bottom. Photographic printing paper was cut in such size as to fit exactly into the rectangular container. One piece of this paper was placed in this container sensitive side up. Superimposed upon the sensitive paper was a mask of

transparent celluloid upon which had been printed lines at millimeter intervals. Representative tadpoles to be measured were taken from their trays, placed in small beakers in a constant quantity of clear water. To this was added a few drops of chloroform (two to ten, depending upon the size of the tadpoles) to prevent their moving while being photographed. As soon as the tadpoles were motionless they, together with the water, were poured into the rectangular chamber previously prepared. Directly above the chamber, at about the height of 18 inches, a high power nitrogen electric lamp was placed to whose light exposure was made for two or three seconds. The motionless tadpoles resting on the millimetered mask served as a negative and the linear dimensions were directly printed out on the sensitive paper. The chloroform was found to be harmless for all except very young tadpoles. It is necessary however that immediately after being photographed the tadpoles be removed from the chloroform water. This method of recording dimensions is much less tedious than actual photography and is more rapid and less irksome than the actual measurement with dividers at frequent intervals of many hundreds of tadpoles.

TECHNICAL DATA AND COMMENTS

The effects of thyroid feeding on normal tadpoles varies with the age of the individuals. This is to be expected in view of the nature of the changes induced. In our experiments with two-year-old tadpoles (*Rana catesbiana*) which had reached the stage in development immediately preceding the initiation of metamorphosis, thyroid feeding served simply to induce a premature and accelerated differentiation. Thyroid-treated tadpoles differentiated into normal frogs,

wholly indistinguishable from the controls.

In the case of one-year-old tadpoles, thyroid feeding was invariably followed by the death of the individuals. Certain somatic changes occurred before death, which were obviously similar to those changes which take place in the metamorphosis of older individuals. The alterations which were macroscopically observable occurred in approximately the following order:

1. Marked diminution in general size.
2. Alteration in the shape of the body, the rounded, well-fed larval shape giving way to the slender, trim adult form.
3. Elevation of the eye-balls above the dorsal surface.
4. Increase in width and size of the mouth.
5. Acceleration of growth of hind legs.
6. Thinning and eventual breaking through of the ventral body wall at points corresponding to the future site of the fore legs.
7. Noticeable growth of the fore leg buds.
8. Disappearance of the "fin" from the tail.
9. Shortening of the tail.

It was observed that the tadpoles all reached a certain stage in this abnormal metamorphosis, at which point death occurred. The examination of a large number of specimens preserved shortly after death demonstrated that all were very similar in the extent to which the changes outlined above had occurred, and that the date of death affords a valuable criterion as to the reaction of the tadpole to thyroid treatment. This fact has been noted before and other workers have taken the time of death of the treated tadpoles as the end-point in the quantitative estima-

tion of thyroid activity. (Marine and Rogoff, 1916, C. H. Lenhart, 1915.)

The following table indicates that in experiment A (one-year old tadpoles) the irradiated tadpoles reacted earlier than did those that were unexposed. At the outset of the experiment equal numbers (17) of tadpoles composed each of the four lots to be compared. Under thyroid stimulation both the normal tadpoles (A) and X-rayed tadpoles (A₂X) which were thyroid fed responded to thyroid stimulation and died upon attaining to a certain phase of metamorphosis, however, the X-rayed tadpoles earlier attained to this point.

TABLE I.

DATE	A Thyroid	A ₂ X Thyroid plus X-Ray	A ₂ Control	A ₂ X Control plus X-Ray
5-20	17	17	17	17
5-21	17	11	17	17
5-24	(17) 14*	8	17	17
5-25	11	4	17	17
5-26	4	1	17	17
5-29	4	0	17	17
5-31	3	0	17	17
6-1	2	0	17	17
6-3	0	0	17	17

*Three killed for photographing.

The first death in the non-rayed (A) group occurred four days after the first death in the irradiated group, or when the irradiated tadpoles had been reduced to a fourth of their original number. So also the last survivor in the non-rayed group lived five days longer than did the last of the irradiated group. The exposure of tadpoles to the action of X-rays in some unknown manner determined an increase in the rapidity of their reaction to thyroid stimulation.

This conclusion is supported by photographic evidence. In figure I are shown views of average individuals from groups A₁ and A₂X. (Thyroid-fed

and thyroid fed, X-rayed, respectively.) These photographs were made on the same day and under identical conditions of focus, and of distance of the object from the lens.

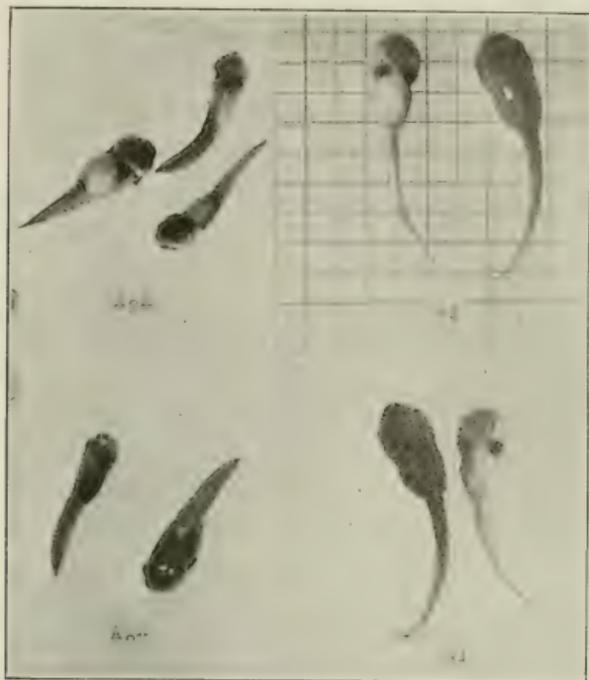


FIG. 1

Figure 1. Photographs (made at the same time) of average tadpoles from group A_2X : (thyroid-fed and X-rayed) and from group A_1 , (thyroid-fed but not exposed to X-rays). The relative size of the tadpoles may be estimated from the millimeter lines included in the one photograph.

The metamorphosis of the individuals in A_2X is obviously further advanced than those in A_1 . This is indicated by the following points:

1. Smaller size.
2. More triangular shape.
3. More prominent eye balls.
4. Larger mouth.
5. Shorter tail.
6. Presence of fore-leg buds (discernible as

small white spots in the center of the dark area of skin rarefaction). Under the binocular microscope fore leg buds were also discernible on the tadpoles of A_1 . They were much smaller, however, than on the other tadpoles.

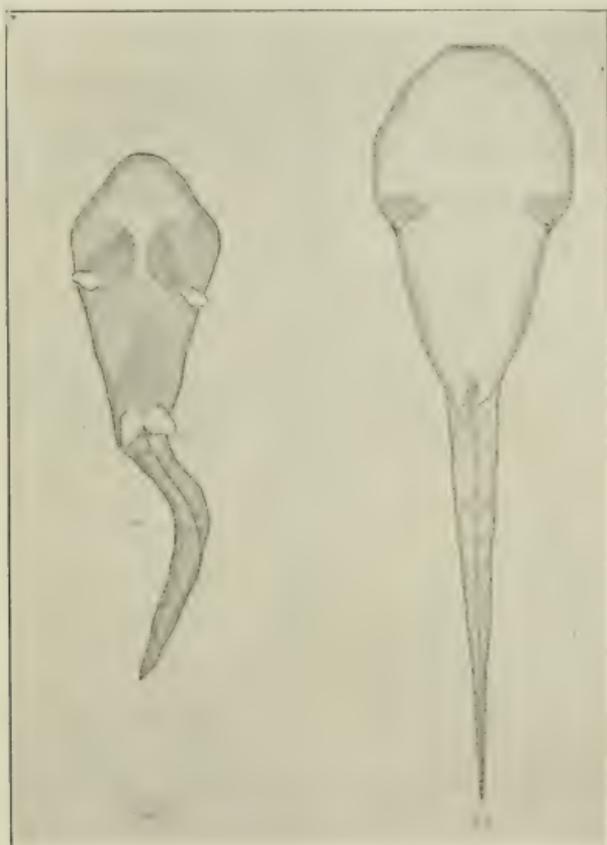


FIG. 2

Figure II. Drawings three times natural size of average tadpoles, illustrating the differences in the degree of metamorphosis attained at a certain time by members of groups A_1 and A_2X , respectively.

Groups A_3 and A_1X , which had not been thyroid-fed and which had exhibited none of the phenomena of metamorphosis were now divided and half of each group placed on thyroid feedings. As before, the

X-rayed tadpoles began to differentiate before the unexposed individuals showed any signs of change. The difference was not so marked in this case, undoubtedly because of the time (30 days) which had elapsed since exposure to the X-rays. It is significant that the irradiation was, in some measure, effective after such an interval of time.

It might be maintained that the changes induced in young tadpoles by thyroid feedings are so abnormal as to furnish no dependable index to their reactivity. For this reason tadpoles which would normally metamorphose within the space of a few months, were subjected to the same treatment.

Table II gives the relative condition of the tadpoles July 2nd, at which time the thyroid-fed tadpoles were in the midst of the metamorphosis process. The results are in accord with those already outlined.

TABLE II.

State of Metamorphosis	P ₁	P ₂	P ₃	P ₄
	Thyroid	X-Ray Thyroid	X-Ray	
Number of tadpoles (7/2).....	12	5	11	19
Number of tadpoles with 4 legs.....	3	3	0	0
Number of tadpoles with 3 legs.....	2	1	0	0
Number of tadpoles with 2 legs.....	7	1	11	19
Per cent of tadpoles with 4 legs.....	25%	60%	0%	0%
Per cent of tadpoles with 3 legs.....	16.7%	20%	0%	0%
Per cent of tadpoles with hind legs only.....	58.3%	20%	100%	100%

In the tadpoles entering into this experiment, no developmental differences were detectable in group P₂, which had been X-rayed, and in group P₁, which were normal. That is, the X-raying of the tadpoles brought about no demonstrable alteration in growth-differentiation processes. Both the X-rayed and normal tadpoles completed their metamorphosis at the anticipated time. Also, no differences were observable in the rate of response to thyroid feeding in the X-rayed tadpoles, group P₂, and the non-rayed

thyroid-fed tadpoles, group P₁. The metamorphosis of both groups was hastened, but, equally so, individuals composing both groups completed their metamorphosis and survived. In so far as the results of observation on this small number of test animals permits, it is inferred that the exposure to the X-ray exerts no gross effect upon the process of metamorphosis, either in normal tadpoles or in thyroid-fed tadpoles.

The observation that the irradiation is without demonstrable effect upon normal tadpoles is important in considering the mechanism of the reaction produced upon thyroid-fed tadpoles. Several observers have shown that following intensive exposure to X-rays there may be found a slight increase in nitrogen metabolism of normal animals. (Baermann and Linser (5), 1904, Benjamin and Van Reuss (6), 1906.) If the results recorded in this paper are due to the direct action of the rays upon metabolism, the same phenomenon also occurs in those tadpoles which received no thyroid material. The occurrence of changes in the metamorphosis of the thyroid-fed groups only, is an indication that these changes are due to an altered susceptibility on the part of the tadpoles to the thyroid hormone.

This interpretation is apparently in keeping with Richard's theory of the mode of action of the Roentgen rays. He states that a small dose of the rays serves to increase the activity of certain, and presumably of all, enzymes, while large doses produce the opposite effect. In our experiments, weak irradiation of the tadpole increased the activity of a normal hormone (thyroid), administered subsequent to the irradiation. According to Richard's theory, strong

irradiation should decrease the activity of the hormone when given under identical conditions.

In the event that further experiments prove that large doses of X-rays produce an effect opposite to the results here recorded, it may be inferred that the thyroid hormone normally acts in conjunction with the intracellular enzymes to produce the phenomena commonly associated with thyroid activity. Such an interaction has often been postulated by writers on the thyroid gland, but experimental evidence has hitherto been lacking.

SUMMARY

Selected tadpoles were subjected to the action of Roentgen rays in small amounts. Certain individuals were then treated with preparations of thyroid gland and the rate of their metamorphosis compared with the metamorphosis rate of (1) normal tadpoles, of (2) thyroid-fed tadpoles which had not been irradiated, and of (3) irradiated but not thyroid-fed tadpoles. The results of our experiments indicate that irradiation is without apparent effect upon normal tadpoles, but determines a slight but distinct increase in the susceptibility of young tadpoles to thyroid stimulation.

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THE USE OF ADRENAL PRODUCTS IN ADDISON'S DISEASE*

Judson Daland, Philadelphia
Lieut. Commander M. C., U. S. Navy

Male, aged 40, American, married, was admitted to the Medico Chirurgical Hospital in October, 1911, complaining of extreme weakness, almost like that of approaching death, attacks of dangerous collapse, dyspnoea, loss of weight and marked constipation. The family history was negative.

He had a mild attack of smallpox at the age of 26; diphtheria at the age of 10 and pneumonia at the age of 27 years. Prior to 1911 brownish spots were noted on the skin of the face, neck and hands, which gradually increased in size and depth of color. In July, 1911, weakness was first observed which gradually increased, and during the preceding five years there had been a gradual loss of flesh. During 1911 he lost weight rapidly and weighed slightly less than 100 pounds when admitted to the hospital; whereas in 1906 he weighed 135 pounds.

In August, 1911, while at work in his office he suffered a collapse, which recurred in five minutes. From time to time chills followed by fever were complained of, the temperature occasionally rising to 103° F.

From the age of 11 to 14 he worked in the coal mines as a breaker boy and later in the switch yard. From the age of 34 to 43 he was a street car conductor, and is now an official in the Street Carmen's Union. For many years he chewed daily from two to three ounces of tobacco and smoked two or three cigars;

*Read before the Association for the Study of Internal Secretions, Chicago, June 10, 1918.

drank coffee to excess but avoided alcohol. Habits of eating and sleeping were markedly irregular.

Physical examination revealed emaciation; visible carotid and epigastric pulsations; diffuse apex beat and prolongation of the first sound of the heart; pulse slow, very weak and easily extinguished by slight pressure; radial and temporal arteries sclerosed; marked spinal curvature to the left from the first to the fifth dorsal, and to the right from the fifth dorsal to the second lumbar vertebra, and a roentgenogram showed the signs of ostitis, rather than tuberculosis. There was increased fremitus and impaired resonance over the apices of the lungs corroborated by an X-ray examination and interpreted as indicating healed tuberculosis. The von Pirquet test was positive. The right kidney was movable and slightly tender on pressure. The renal efficiency test showed the first hour 52%, the second hour 28%, total 80%. There were pigmented areas of the skin varying in color from light to dark brown, more marked on exposed surfaces, particularly the neck and face, also on the thighs, about the nipples and umbilicus and the scapula where the suspenders exerted pressure. The pigmented areas of skin distributed over the forearms and hands were of mahogany or bronze color, but pigmentation was absent over the spinal region which was subject to the pressure of the weight of the body while lying in bed. There were areas of leucoderma over various parts of the body, especially over the right temple, where the hair had turned white, and these areas seemed dryer than the surrounding skin. There were marked pruritis and numerous scratch lesions. The muscles were markedly flabby, relaxed and atrophied. There

was a negative history of venereal disease and a negative Wasserman reaction. The temperature was continuously subnormal, at times 96° F.

The pulse varied between 56 and 98 per minute; the heart was overacting. Examination of the blood revealed 59% erythrocytes, 74% hemaglobin and 11,200 leucocytes, of which there were 65.5% polymorphonuclears, 21.3% large lymphocytes and 8% small lymphocytes. Later a mild eosinophilia occurred which was non-parasitic and toxic in origin.

October 21st in the recumbent posture the pulse was 60 per minute, systolic pressure 80 mm. and diastolic 60 mm. Numerous urinalyses gave negative results.

The following day 1 drop of a 1 to 1000 adrenalin chlorid solution was given thrice daily.* After the third dose no change was noted in the blood pressure. After four doses of two drops each had been given, the systolic pressure was 90 mm., the diastolic 60 mm. and the patient volunteered the information that he felt somewhat stronger. On October 25th three drops of adrenalin chlorid solution were given four times daily, and the systolic pressure rose to 110 mm. and the diastolic remained 60 mm. From October 25th to November 1st, 1911, five drops of adrenalin chlorid solution were administered three times daily, after which the systolic pressure was but 100 mm. and the diastolic 70 mm. Then followed an interval of five days during which no medication was given, at the end of which time the systolic pressure was 90 mm. On November 13th, 1911, 8c.c. of an infusion of digitalis was given four times a day. After ten doses had been administered the systolic pressure was 110 mm.

*The adrenalin in all cases was administered hypodermatically.

and the diastolic 80 mm.; the first sound of the heart was somewhat blurred and the second sound at the apex was reduplicated. The digitalis was withdrawn and four days later the systolic pressure was 98 mm. and the diastolic 70 mm. On November 24th, 1911, adrenalin chlorid was given in gradually increasing doses and on December 2nd, 11 drops thrice daily were administered, causing the heart to beat violently, shaking the entire chest, and a faint, soft, mitral systolic murmur became audible. The systolic pressure was 112 mm. and the diastolic 88 mm. Adrenalin chlorid was discontinued, and four days later the murmur had disappeared, but there was marked reduplication of the second sound at the base of the heart; the systolic pressure was 110 mm. and the diastolic 90 mm.

The administration of adrenalin chlorid slightly raised the blood pressure, when therapeutic doses were given, but toxic doses were dangerous, causing cardiac dilatation. Digitalis only slightly increased the blood pressure.

In January, 1912, 15 grains of adrenal gland (B. W. & Co.) were administered three times daily. January 15th, the systolic pressure was 110 mm., the diastolic 88 mm. and the blood examination revealed a marked increase in red cells, and a *disappearance* of the leucocytosis and eosinophilia, possibly due to adrenal extract. Until discharged from the hospital in January, 1912, the systolic blood pressure varied from 102 to 110 mm., while the diastolic remained constant at 80 mm. Upon leaving the hospital he had gained 10 pounds in weight, strength was greatly increased, and the profound malaise, dyspnoea, and syncopal attacks had disappeared. Soon after re-

turning home he endured a serious mental strain in conducting a carmen's strike, apparently with no ill effect, and believing himself cured and contrary to advice discontinued the adrenal gland extract. Soon thereafter profound weakness, dyspnoea, and one attack of collapse occurred. He consulted Dr. Martin T. O'Malley of Scranton, Penna., who as a student happened to attend the clinic when this patient was presented to the class, and remembering the patient advised the prompt use of adrenal gland extract in 15 grain doses thrice daily.

Marked improvement was soon observed. Later the patient returned to his physician complaining of tachycardia, painful cramps in the muscles of the extremities, pain in the chest, dyspnoea, pulse from 110 to 140 per minute, occasional slight rises in temperature, insomnia, ocular fullness and staring eyes. At this time the patient was supposed to be taking one dram of adrenal extract thrice daily, but investigation revealed that the druggist had dispensed thyroid extract instead of suprarenal extract. Improvement promptly followed the omission of the thyroid extract and the substitution of adrenal extract. Experimentally, toxic doses of adrenal extract grs. 90 t. i. d. were administered, which caused mental and physical weakness, irritability and insomnia, which disappeared when the dose was diminished. Maximum benefit was secured from 35 grains of adrenal extract thrice daily.

During 1914 he was able to perform work with no discomfort except when the use of adrenal extract was discontinued. In January, 1914, an attack of pneumonia supervened, and for a long time the patient complained of general weakness, exhaustion

after light exertion and coldness of the hands and feet even on the hottest days. During 1915 an attack of pleurisy occurred; otherwise he felt well while taking the adrenal extract; but if it was omitted he began to lose energy, was unable to work, complained of subjective and objective coldness of the extremities, profound weakness and recurring collapse. Physical examination in January, 1915 and 1917, gave the same results as when first examined, except that strength had greatly increased. On January 15th, 1917, the systolic blood pressure was 95 mm. and the diastolic 60 mm. Blood examination showed the erythrocytes 64%, hemaglobin 60%, leucocytes 6,800; polymorphonuclears 61.6%, large lymphocytes 7.3%, small lymphocytes 25.6%, eosinophiles 3.6% basophiles 1.6%.

In October, 1917, the patient died of asthenia, following neglect, and unfortunately an autopsy could not be secured.

BLOOD PRESSURE OBSERVATION

Date	Pulse	Sys.	Dias.	Remarks:
10-21-11	60	80	60	
10-22	56	80	50	3 doses adrenalin each gtts. i. Blood pressure recorded one hour after
10-23	64	90	60	third dose.
10-24	64	110	60	4 doses gtts. ii.
10-25	60	90	60	At bedside; 4 doses gtts. iii.
10-27	60	110	60	Adrenalin gtts. iv.
10-30	72	100	70	
11-1-11	68	100	70	
11-16	76	110	80	Adrenalin gtts. v. Left hospital for a few days.
11-17	76	110	80	10 doses of infusion of digitalis dr. iv.
11-19	78	98	65	Reduplication.
11-20	76	98	70	No digitalis for 24 hours.
11-24	72	105	90	
11-25	84	110	90	
11-26	72	100	80	Adrenalin gtts. ii. and iii.
11-27	72	106	82	Adrenalin 2 doses, gtts. iv.
11-28	72	98	78	Adrenalin 2 doses, gtts. v.
11-29	72	104	80	Adrenalin 2 doses, gtts. vi.
11-30	72	104	84	
12-1-11	76	108	90	Adrenalin gtts. viii.
12-2	68	112	88	
12-3				Adrenalin gtts. ix.

Date	Pulse	Sys.	Dias.	Remarks:
12-4	84	110	86	Adrenalin gts. xi. Faint mitral systolic murmur. Pulse irregular; distinct mitral systolic murmur; reduplication; adrenalin omitted.
12-5	88	96	76	
12-6	80	108	84	
12-7	96	110	82	
12-8	88	110	90	Heart regular; murmur less marked.
12-10	84	106	82	
12-11	54	110	84	No murmur; reduplication.
12-12	54	122	90	
12-13	76	108	86	Reduplication.
12-14	92	106	86	Faint mitral systolic murmur; marked reduplication.
1-15-12	60	95	60	
1-16	72	95	70	Returned home for one month.
1-17		90	80	No murmur or reduplication.
1-18		90	70	
1-19		85	70	
1-20		85	70	
1-21	78	85	72	
1-23		87	75	
1-24		95	79	
1-25		95	75	
1-29		95	80	
1-30		95	80	
1915.				
1-5-15	74	110	85	
1-11	64	100	70	
1-15	70	110	80	
1-16	74	105	80	
1-17	70	105	80	
1-18-15	70	105	80	
1-20	72	100	80	
1917.				
1-5-17		92	70	
1-15	76	95	60	

EXAMINATIONS OF THE BLOOD

1911.	Erythrocytes	Hemoglobin	Leucocytes	
Oct. 26.	69%	74%	11,200	
Nov. 13.	76%	64%	10,600	Polymorphonuclear 66.5% Large Lymphocytes 21.3% Small Lymphocytes 8.0% Eosinophiles 4.0% Basophiles 0.5%
Nov. 20, 1912.	77%	75%	11,000	
Jan. 16 1915.	85%	98%	6,800	
Jan. 5 1917.	82%	86%	8,000	
Jan. 15.	64%	60%	6,800	Polymorphonuclear 61.6% Large Lymphocytes 7.3% Small Lymphocytes 25.6% Eosinophiles 3.6% Basophiles 1.6%

In view of the existence of the classic symptoms of terminal Addison's disease it is probable that the suprarenal gland had almost entirely disappeared probably due to the advancing tuberculosis as this is the most common of all causes; and furthermore the apices of the lungs showed evidence of healed tuberculosis and the von Pirquet test was positive. The tender right kidney and the ankylosis of the vertebral joints may have been due to tuberculosis.

When first seen in October, 1911, it was believed that he was in danger of death from collapse at any time; and under the best circumstances he was expected to die within a year, whereas he did not die until six years after treatment was begun. It is fair to assume that the prolongation of life was secured by the administration of appropriate doses of the suprarenal gland extract. It is interesting to note that the adrenalin was only slightly beneficial and in toxic doses produced cardiac dilatation; that digitalis in therapeutic doses produced only slight benefit and in full therapeutic doses was detrimental. It would appear that toxic substances manufactured in the course of Addison's disease may produce leucocytosis or eosinophilia, which disappeared apparently due to the influence of adrenal extract. The influence of toxic doses of thyroid extract in one suffering from Addison's disease was an interesting involuntary experiment.

This case illustrates that marked increase in vitality and strength may be secured by suprarenal extract without as great an increase in the blood pressure as would be expected.

ABSTRACTS

220. (ADRENAL) Two cases of suprarenal disease. Osborne (O. T.), *Am. J. Med. Sc. (Phila.)*, 1918, **156**, 202-5.

Two cases are described. In the first pigmentation and circulatory weakness were unusually pronounced. Under treatment with adrenal and pituitary tablets the circulation temporarily improved and the pigmentation greatly decreased. The patient died shortly after. Autopsy showed complete destruction of the adrenals. In the second case pigmentation also was very marked. Under treatment with adrenal tablets and iron the pigmentation largely disappeared and the circulation and weight improved. The prognosis was regarded, however, as bad. The author considers that the poor circulation did not alone account for the marked asthenia present in both cases, but that the weakness was partly intrinsic in the muscles.

—R. G. H.

221. (ADRENALS) Antibody production after partial adrenalectomy in guinea pigs. Gates (F. L.), *Jour. Exp. Med. (Balt.)* 1918, **27**, 725.

Experimentally it is possible to remove from three-fourths to seven-eighths of the adrenal tissue of guinea pigs without causing symptoms of adrenal insufficiency. In order to determine antibody production after partial adrenalectomy guinea pigs were immunized to bacillus typhosus or to hen corpuscles at varying intervals before or after operation, and the curves of antibody formation traced for two to three months after immunization. Comparisons with antibody curves of control animals similarly immunized failed to show that adrenalectomy had any influence upon the rise or persistence of antibodies in the blood. Acute adrenal deficiency was not deemed necessary. If the adrenal glands were the site of antibody formation or played an essential part in immunity processes, it does not seem probable that the small remainder of adrenal tissue would effect quantitatively the antibody response to a given antigen infection as do the entire normal glands. Therefore, not only are the adrenal glands not one of the important sources of typhoid agglutinins, or of hemoagglutinins or hemolysins, but they play no essential part in the mechanism by which these antibodies are produced and maintained in the body.—H. W.

222. (ADRENALS) "Le role des surrénales dans l'action du pneumogastrique sur le coeur." (The role of the suprarenals on the action of the vagus nerve on the heart). Roger (H.) Jour. de physiol. et de path. gen. (Paris), 1917, 17, 187.

Roger removed both suprarenal glands of the rabbit by laparotomy, then after an interval of about one-half hour stimulated the peripheral stump of one divided vagus nerve. Electrical stimulation produced a more pronounced vagal inhibition of the heart and lowering of the blood pressure than is produced in controls from which the suprarenals have not been excised. The cardiac escape from vagal inhibition was later than normal and without the usual secondary rise of blood pressure above the normal level. On the slow and continuous intravenous injection of epinephrin, in a concentration and rate so adjusted as to produce no change in blood pressure or heart rate, vagal stimulation in the desupulated rabbit produced typically normal responses. The author believes that the intervention of the suprarenal glands in the normal animal is responsible for the progressively diminishing effects of repeated vagal stimulations on the heart rate and blood pressure and for the secondary rise in blood pressure following vagal inhibition.—

A. L. T.

223. (ADRENALS) Sulla funzione delle capsule surrenali. (On the function of the adrenals.) Pisani, from an article of Roger. Presse méd. Nov. 22, 1917, Rivista crit. di clin. med. (Firenze) 1918, 19, 19.

Under the influence of a violent nervous impression a sudden hyperfunction of the adrenal medulla is found with consequent increased blood pressure. If the adrenals were previously removed there is marked and steady hypotension. The excitation of the vagus, which determines a sudden, but temporary bradycardia in normal rabbits, causes a severe and durable bradycardia if the adrenals are previously removed. This would signify a reaction against the action of the vagus determined by the adrenals, which would bring forth a predominating action of the sympathetic. The problem though is not always so simple, since the same author found out that the black pigment of the adrenals is antagonistic to the action of the adrenalin.—G. V.

224. (ADRENALS) The influence of certain conditions on the rate at which epinephrin is liberated from the adrenals into the blood. Stewart (G. N.) and Rogoff (J. M.). Am. Jour. Physiol. (Balt.), 1917, 42, 585-86.

Data elsewhere reported. See abstracts in this journal, 1917, 1, 348; 1917, 1, 508; 1918, 2, 54; and 1918, 2, 157.—L. G. K.

225. (ADRENALS) The physiology of the melanophores of the horned toad, *Phrynosoma*. Redfield (A. C.) Jour. Exp. Zool. (Phila.), 1918, 26, 275.

Stimuli from the thoracic cord are carried to the adrenals and cause the secretion of adrenin which is carried by the circulation to the melanophores in the skin. This adrenin helps control the movement of pigment granules of the melanophores in the changes of color which the animal undergoes at various times.—E. R. H.

226. (ADRENALS) Über die nach zentraler Reizung zur Störung des Kohlehydratstoffwechsels führenden Vorgänge. Eine kritische Studie zur Frage: Zuckerstich und Nebenieren. (Disturbances of carbohydrate metabolism produced by central lesions.) Kahn (R. H.) Pflüger's Archiv (Bonn), 1917, 196, 326-394.

Experiments dealing with the disturbances of carbohydrate metabolism produced by central lesions—diabetic puncture, etc.—may be grouped in 4 classes, with the following main results: (1) **Extirpation of both adrenals.** Rabbits survived many months, and subsequent diabetic puncture was not followed by glycosuria, although the glycogen content of the liver was normal. Hyperglycaemia is not produced in such animals by CO poisoning or by diuretin, nor do they exhibit emotional or salt glycosuria. Salt glycosuria is diminished in dogs and unaffected in cats. (2) **Chromaffin and adrenaline content of the suprarenals.** The adrenal gland extirpated after diabetic puncture exhibits distinct loss of chromaffin substance and adrenaline compared with the control adrenal removed before the puncture. Previous section of the corresponding splanchnic nerve in the above experiment protects the adrenal from the effect of diabetic puncture. The same phenomena after diabetic puncture are seen in the cat, ape, and dog. Cats and dogs exhibit loss of chromaffin tissue and adrenaline in the suprarenals after asphyxia and CO poisoning. The above changes persist for a considerable time after diabetic puncture and CO poisoning in rabbits and birds. The chrome affinity of the paraganglia of the abdominal aorta is diminished for a considerable time after diabetic puncture. (3) **Nervous isolation of the liver.** Section of the nerves and vessels to the liver, with the exception of the portal vein, is still followed by hyper-

glycaemia in half the cases, although the conditions are extremely unfavorable for its occurrence. Isolation of the liver and the right adrenal from the central nervous system, leaving the connections of the left adrenal intact, was almost always followed by pronounced hyperglycaemia. (4) **Adrenaline content of the blood.** Adrenaline cannot be detected by the biological method in blood vessels remote from the suprarenal veins after diabetic puncture and other central nervous excitants or after active (i.e., which produce glycosuria) subcutaneous injections of adrenaline. Blood from the vena cava opposite the suprarenal veins has an increased adrenaline content after diabetic puncture, asphyxia, etc. There is no definite increase of blood-pressure after active subcutaneous injection of adrenaline or diabetic puncture.

A critical survey of all the facts suggests that certain elements in the brain maintain a continual tonus in the liver cells via the splanchnics and the peripheral ganglia in the abdomen. This neurogenic tonus is increased by central stimulation (diabetic puncture, etc.). Other elements in the brain near to the above are to be regarded as secretory nerve centres for the chromaffin tissue and particularly for the adrenals. Their stimulation leads to an increased output of adrenaline, which reaches the liver cells by the portal vein and hepatic artery. Excitation travels via the splanchnic and peripheral sympathetic ganglia or direct. Stimulation of the central nervous elements causes simultaneous increase in the neurogenic tone of the liver cells on the one hand, and an increased inner secretion of the chromaffin tissue on the other. Both together cause glycogen mobilisation with hyperglycaemia and glycosuria. Increased tonus of the liver cells is not a sine qua non for the disturbances of carbohydrate metabolism, however, and similarly under favorable conditions increased tonus alone is sufficient to produce abnormal glycogen cleavage in the liver and slight hyperglycaemia.—Physiol. Abst., 1918, **3**, 130-31.

227. (ADRENIN) Adrenalin content of suprarenals after death from beriberi. Ono (S.) Tokyo Igakukai Zasshi, 1917, **31**, 1-10. Jap. Med. Lit. (Seoul), 1918, **3**, 26.

On the basis of the post-mortem examination of ten acute beriberi cases, and of two which occurred during pregnancy, the author finds a medullary hypertrophy of the suprarenal and an increased adrenalin content. The chemical examination was made by the Comessatti method and the average for the left gland was 14.96 mg. It is as yet unknown what relation exists between the clinical manifestations of beriberi, especially

of the acute type, and this adrenalin-hyperfunction.—Quoted. See No. 97, p. 162, Vol. II Endocrinol.

- 228. (ADRENIN) Adrenalin injections, and their effect upon the viscosity of the blood.** Yamada (S.), Chugai Iji Shimpo. 1917, No. 893, pp. 669-75. Jap. Med. Lit. (Seoul), 1918, 3, 23.

A rise in the viscosity of the blood was noted about 10 to 30 minutes after the injection of adrenin, which gradually decreased again in a few minutes. After a second injection the reaction occurred more slowly, in 50 to 80 minutes. The reaction was not constant in all the persons examined.—Quoted.

- 229. (ADRENIN) A method for maintaining an artificial circulation through the tibia of the dog, with a demonstration of the vasomotor control of the marrow vessels.** Drinker (C. K.) and Drinker (K. R.). Am. Jour. Physiol. (Balt.), 1916, 40, 514-521.

A method of perfusing bone marrow is described, and the existence of vasomotor nerves to the marrow is demonstrated. Electrical stimulation of these nerves or the injection of epinephrin into the perfusion fluid causes vaso-constriction. In one case after the administration of ergotoxin phosphate "a slight but rather doubtful degree of active dilatation was secured." The authors do not consider this reliable evidence for the existence of an active dilator mechanism.—L. G. K.

- 230. (ADRENIN) Constriction from adrenalin acting upon sympathetic and dorsal root ganglia.** Hartman (F. A.), Kilborn (L. G.) and Fraser (L.); Am. Jour. Physiol. (Balt.), 1918, 46, 521-525.

It was shown by the methods used in previous researches (see abstracts in Endocrinol., 1917, 1, 510, and 1918, 2, 160, abstr. 91) that adrenalin not only causes dilatation, but occasionally can produce constriction also in the hind limb by acting upon the sympathetic and dorsal root ganglia, and in the small intestine by acting upon the superior mesenteric and dorsal root ganglia.—L. G. K.

- 231. (ADRENIN) Die Hemmung der Kochsalzausscheidung im Harn durch Adrenalin. (Inhibition of sodium chlorid excretion through the kidney by adrenin).** Buleke (W.), and Weis (P.). Deutsches Arch. f. klin. Med. (Leipzig), 1917, 123, 163-203.

Adrenin given subcutaneously in man and rabbits inhibits the NaCl output in the urine. The same occurs on intravenously injecting Ringer's solution to which adrenaline has been added. This leads to retention of salt. The urinary nitrogen runs parallel to the NaCl in rabbits, and in man depends on the amount of urine formed. The kidney itself is the point of attack. It does not appear to be a purely vascular effect, but the kidney cells are affected, and in disease they are more sensitive to the action of adrenaline than they are normally.—*Physiol. Abst.*, 1918, 3, 130.

- 232. (ADRENIN) Disappearance of the pigment in the melanophore of Philippine house lizards.** Ruth (E. S.) and Gibson (R. B.) *Philippine Jour. Sci. (Manila)*, 1917, **12B**, 181-188.

These pigment cells neither contract nor expand. The color is discharged by adrenaline, both in vivo and in vitro. Bleaching occurs when the lizard is in white surroundings, and it is assumed that the pigment varies during life owing to the action of a hormone (probably adrenaline).—*Chem. Abstr.*

- 233. (ADRENIN) L'azione dell'iodio e dell'adrenalina studiata su cellule viventi fuori dell'organismo. (Effect of iodine and of adrenin in tissue cultures.)** Cervello (V.) and Levi (G.), *Arch. di fisiol. (Firenze)*, 1917, **15**, 219-228.

Tissues from embryo chicks grow well in iodised plasma. Adrenaline is not favorable to such growth.—*Physiol. Abst.*, 1918, 3, 55.

- 234. (ADRENIN) On the adrenalin in the blood of one who is suffering from a primary glaucoma.** Kusama (K.) *Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo* 1917, **17**, 137-157.

The author employed Trendelenburg's test for comparing the amount of adrenin present in the blood of healthy persons (ten cases) with that in the blood of thirteen patients suffering from glaucoma. The adrenin content was found to be decreased in the blood of the latter, and therefore, contrary to the belief of some investigators, the rise in blood pressure in glaucoma is not due to an increased output of adrenin. A more marked reduction was found to occur in cases of chronic inflammatory than in acute inflammatory or absolute glaucoma.—L. G. K.

- 235. (ADRENIN) The action of the autonomic drugs on the surviving stomach.** Smith (M. J.) *Am. Jour. Physiol. (Balt.)*, 1918, **46**, 232-43.

These experiments were carried out on strips of the surviving stomach suspended in Tyrode's solution. The drugs were added in definite amounts to the solution containing the strip. Strips were taken from the following regions of the stomach— antrum, perantrum, body and fundus. Longitudinal, circular and oblique strips were used.

Pilocarpine was found to cause a contraction of all regions of the surviving stomach of the guinea-pig, rabbit, cat, dog and human subject. Atropine antagonizes the action of pilocarpine and produces a relaxation. Nicotine produces a similar effect to pilocarpine, except that the fundus and cardiac sphincter of the cat's stomach may relax, and the antrum and body of the rabbit's stomach may slightly relax before contracting.

The reaction of the different parts of the stomach to epinephrin may be relaxation (cat and human), or relaxation of some parts and contraction of others (guinea-pig, rabbit, dog). The reaction of the sphincters to epinephrin is always that of contraction. After ergotoxine those regions of the dog's stomach that contract from epinephrin may relax from administration of adrenin.

The author concludes that the sympathetic innervation of the stomach is inhibitory in the cat and in man, but inhibitory in certain regions only while predominantly augmentory in other regions of the stomach of the guinea-pig, rabbit and dog.

—L. G. K.

236. (ADRENIN) The effect of adrenalin on the irritability and contractility of mammalian nerve muscle preparations after death. Gruber (C. M.) and Fellows (A. P.) *Am. Jour. Physiol. (Balt.)*, 1918, **46**, 472-477.

The tibialis anticus muscles of the cat were perfused with warm Ringer's solution containing only the oxygen absorbed from the air. The animal was killed with ether at the commencement of the perfusion. The nerve was stimulated by means of a Sherrington shielded electrode. The author found that the addition of adrenin to the perfusion fluid at varying intervals after the death of the animal increased both the muscular activity (height of contraction) and the irritability (decreased threshold of stimulus) of the nerve muscle preparation to electrical excitation. Adrenin therefore affects dying muscles in a similar manner to fatigued muscles.

Three possible points of action of the adrenin are mentioned: (a) It may assist or hasten the conversion of glycogen into sugar. (b) It may help to transform fatigue products by hastening the reconversion of lactic acid into sugar. (c) It

may assist in the destruction of fatigue products by increasing the rapidity of the oxidation of lactic acid into carbon dioxide and water.—L. G. K.

237. (**ADRENIN**) The effects of adrenin on the distribution of the blood. VII. Venous discharge from the adrenal glands. Gunning (R. E. L.) *Am. Jour. Physiol. (Balt.)*, 1918, **46**, 362-365.

The author found that the intravenous injection of adrenin produced no active changes in the venous outflow of the adrenal glands, and therefore concludes that the splanchnic nerves carry no vasomotor fibres to the adrenals.—L. G. K.

238. (**ADRENIN**) The inhibitory effect of adrenalin upon the spinchter muscle of the iris. Joseph (D. R.). *Am. Jour. Physiol. (Balt.)*, 1917, **42**, 608.

Adrenalin solutions of various concentrations when applied to the spinchter pupillae after either partial or complete excision of the muscle cause a prompt and unmistakable relaxation. The relaxation is maximal with stronger solutions (1:1000 to 1:100,000), but only partial with very dilute solutions (1:10,000,000). The duration of the effect varies directly with the concentration. The spinchter muscles of the bovine, swine, sheep, goat and human irises were tested. In its response to adrenalin the spinechter of the iris resembles the intestinal strip.—L. G. K.

239. (**ADRENIN**) über der Adrenalingehalt der Nebenniere des Menschen bei verschiedenen Todeursachen. (Adrenin content of human adrenals after death by various causes.) Luckseh (F.), *Virchow's Archiv (Berlin)*, 1917, **223**, 290-300.

The normal amount of adrenaline is 4 mg. per gr. of dry adrenal weight. This figure falls in infectious and other diseases, and may reach 0.35 mg. or in infants 0.13. In Addison's disease the figure is lowest, in nephritis the highest.—*Physiol. Abst.*, 1918, **3**, 130.

240. (**ADRENIN, PITUITRIN**) The regulation of renal activity. VII. The balance between the regulation by adrenalin and by pituitrin. Addis (T.), Shevky (A. E.) and Bevier (G.) *Am. Jour. Physiol. (Balt.)*, 1918, **46**, 129-146.

See previous abstracts in *Endocrinology*, 1918, **2**, 161, 162, 189.

The subcutaneous injection of amounts of adrenalin which increase the urea excreting activity of the kidney, and of amounts of pituitrin which depress that activity, have no effect when they are injected together in a certain balanced proportion. All grades of stimulation or depression may be induced by the injection of mixtures of adrenalin and pituitrin in which this balance is deflected by a preponderance of one or the other. In the rabbit the removal of both suprarenal glands is followed by a depression of the urea excreting activity of the kidney, which is greater than that which follows control operations in which the suprarenals are not removed.

The authors conclude that under physiological conditions the urea excreting activity of the kidney is determined by two main factors. There is a fixed and mechanical regulation through the urea concentration of the blood, but there is also another and overruling type of regulation which acts through the medium of the central nervous system. It is suggested that variations in the balance between the rates of secretion of the active principles of the adrenal and pituitary glands may play a part in regulating this nervous mechanism.—L. G. K.

241. (ADRENIN PITUITRIN) Azione di varie sostanze, e specialmente della pilocarpina e della atropina sopra alcuni organi muscolari lisci. (Action of various substances on smooth muscle) Bottazzi (F.), *Atti d. r. acc. medico-chir.* (Napoli), 1917, reprint, pp. 33.

Pilocarpine increases the tone of various intestinal preparations, most of all the dog's small intestine, but the effect is always completely annulled by atropine. The effects of these alkaloids on the retractor penis muscle are very uncertain and inconstant (in contrast to de Zilva's experiments, which could not be reproduced). Their effect on the uterus is likewise irregular. On the other hand, the uterus is affected in a constant manner by adrenaline, p-hydroxyphenylethylamine, B-iminazolyethylamine, and hypophysine. The first two caused relaxation of the non-pregnant, and contraction of the pregnant uterus of the bitch. In the cat they always caused contraction, which is not in agreement with the results of Cushny and others. Speculating on the adrenaline-ergotoxine vasomotor reversal, and the fact that adrenaline always causes contraction of the pregnant uterus, the author suggests that the inhibitory innervation of the organ may in pregnancy be paralysed by substances as yet unknown.—*Physiol. Abst.*, 1918, 3, 103.

242. (AUTONOMIC NERV. SYST.) Asthma considered in its relation to the vegetative nervous system. Pottenger (F. M.) *Am. J. Med. Sc.* (Phila.), 1918, 155, 417-24.

A general discussion of the etiology of asthma relating the malady particularly to reflexes mediated through the vagus nerves.—R. G. H.

- 243. (AUTONOMIC N. S.)** Le azioni antagonistiche autonomi. (The action of antagonistic autonomies.) Spadolini (I.), Arch. di fisiol. (Firenze), 1917, 15, 1-167.

Rather more than one-half of the paper is devoted to a critical review of earlier work, the remainder to observations on the autonomic innervation of the urinary bladder and of the small intestine. Excitation of the hypogastric nerves in dog and cat may lead either to inhibition or to augmentation of the vesical contractions according as the stimulus is weak or is strong respectively. Similarly, adrenaline in small doses may inhibit, whilst in larger doses its effect may be the converse. The nervi erigentes are motor in function. Analogous effects were observed on the small intestine, when the vagi or the splanchnics were stimulated. Excitation of either of these nerves may produce either inhibition or the converse, according to the intensity of the stimulus. The writer regards the parasympathetic fibres (of vagi and nervi erigentes) as being responsible for relatively rapid contractions, and the sympathetic fibres as being pre-eminently tonic in function. The response to a given stimulus is in any case a function of the condition of the muscle.—Physiol. Abst., 1918, 3, 18.

- 244. (AUTONOMIC NERV. SYST.)** Pharmacodynamic examination of the vegetative nervous system in typhoid fever. Matsuo (I.) and Murakami (J.). Arch. Int. Med. (Chgo.) 1918, 21, 399-410.

A study was made of the reactions of typhoid patients to pilocarpine, atropine and adrenin. In 38 cases 14 showed abnormal irritability of the parasympathetic system and 11 cases showed hyperirritability of the sympathetics. Three cases were sensitive to all drugs, 7 cases were sensitive to pilocarpine and adrenin and 3 only to pilocarpine.

- 245. BONE MARROW, Internal secretion of.** Ord. (G. W.). Lancet (Lond.), 1918 1, 385.

The suggestion is made that marrow does something more than minister to bone nutrition. Some bones have little or no marrow, and the way it is so safely housed, and the serious results (shock, death, etc.) that follow extensive bone removal, are considered to support this view.—Physiol. Abst., 1918, 3, 132.

246. (CORPUS LUTEUM) The non-effect of corpus luteum preparations on the ovulation cycle of the rat. Corner (G. W.) and Hurri (F. H.) Am. Jour. Physiol. (Balt.), 1918, 46, 483-486.

On each of the four days following littering a benzidine compound, staining the corpora lutea blue, was injected intra-abdominally into rats. This was followed by the intra-abdominal administration of desiccated corpus luteum substance in normal saline, given every other day for twenty days. The rats were then killed and the ovaries examined in serial sections, the number of stained and unstained corpora lutea being compared. It was found that in all cases ovulation had continued unchecked, showing that the intra-peritoneal injection of mammalian corpus luteum substance does not inhibit ovulation in the rat.—L. G. K.

247. (DERCUM'S DISEASE-ADRENIN) Istografia, Istochimica e Patogenesi dei lipomi di Dercum. (Histology, histo-chemistry and pathogenesis of Dercum's lipomata.) Martelli (C.) Tumori (Rome) 1918, 6, 1.

The author begins with an accurate description of the severe symptoms determined by the formation of such lipomata, and insists on the good effects brought about by adrenalin therapy during the following asthenic period.

Upon examination of one of these tumors the author found it histologically like the common lipoma, made of adult fatty cells. There are, besides, hyperaemic zones with perivascular micro-cellular infiltrations, due to inflammatory processes. He finds also mononeuritis of the few nervous fibres, and an elastic, pre-colloid hypertrophy of the tumor, which makes its consistency more dense than that of the surrounding fatty tissue.

The chemical composition of the lipomatous cells is chiefly that of neutral fat mixed (in 2 to 3 per cent of said cells) with fatty acids, which show also a granular appearance in the interstitial tissue. Common lipoids are found in greater amount either as cuticle and lipid grains, or spread in the subcuticular stratum at the periphery of the adipose vesicle. Very scanty, if present, are the special lipoids as lecithine, lipochromes and cholesterine. There is no calcium.

Compared with the common lipomata, Dercum's lipoma does not show either embryonal elements or lecithinic cells, or phenomena of atrophy. It appears like an accumulation of adult fatty vesicles (at rest), quite like those of the normal subcutaneous adipose tissue, only a little smaller, pressed to-

gether and rich in lipoids with hyperemic foci and micro-cellular infiltrations inserted.

As for the pathogenesis the author claims that such lipomata are the expression of disturbed equilibrium of lipogenesis (connected with multiple endocrine-sympathetic disfunctions—mostly suprarenal) which forms in the subcutaneous connective tissue in parts rich in elastic tissue. This formation may be either slow, as in the indolent lipomata, or (very seldom) sudden and painful—in form of an anaphylactic discharge (Dereum's)—almost as if the organism were to free itself of a toxic product (probably lipoid and very likely in connection with suprarenal insufficiency) and were to localize such product under form of lipomata in the subcutaneous tissue.—G. V.

- 248. (DIABETES) Diabetic polyneuritis.** Pitres (A.) and Marchand (L.) *Prog. méd.* (Paris), 1917, **32**, 295.

A case is described at length. The prognosis is usually favorable.

- 249. (DIABETES) The application of the Auer-Kleiner morphine test in human diabetes.** Epstein (A. A.) *Proc. Soc. Exp. Biol. and Med.* (N. Y.), 1918, **15**, 89-90.

An attempt was made to utilize as a clinical test for latent diabetes the fact that morphine in dogs causes a rise in the blood-sugar. Within the practicable limits of dosage no unequivocal effect was produced in man.—R. G. H.

- 250. (DIABETES) The rate of dialysis of diabetic blood-sugar.** Kleiner (I. S.), *Proc. Soc. Exp. Biol. and Med.* (N. Y.), 1918, **15**, 81-2.

The fact that the sugar of diabetic blood was found to diffuse less readily than a similar concentration of sugar in normal blood is thought to indicate that the diabetic blood-sugar is held in some sort of loose combination.—R. G. H.

- 251. DIABETES, Salt metabolism in.** Beard (A. H.) *Arch. Int. Med.* (Chgo.) 1918, **21**, 716-39.

This paper is a report of an elaborate study of the problem. Two points of general interest were brought out: 1. Increase of weight on unrestricted chlorides is invariably associated with their retention. The edema usually disappears following the disappearance of the glycosuria. 2. Sodium bicarbonate ad-

ministration has no constant influence on carbohydrate tolerance in diabetes.—R. G. H.

252. (DIABETES) Über die Kohlenhydratverwertung des normalen und diabetischen Muskel. (Carbohydrate content of normal and diabetic muscle)—I. Forschbach (J.) and Schaffer (H.), *Arch. exp. Path. Pharm. (Leipzig)*, 1918, **82**, 344-367.

It is generally supposed that the tissues in diabetes are sugar-laden, and this is regarded as an explanation of their lessened resistance towards infective agents. This view is disputed. In the muscles the sugar content is not increased in diabetes.—*Physiol. Abst.*, 1918, **3**, 119.

253. DIABETES INSIPIDUS, A case of, as sequel to gunshot wound of the head. Graham (E. A.) *Ann. Surg. (Phila.)*, 1917, **66**, 529.

Additional support that diabetes insipidus is an expression of a disturbed function of the hypophysis, or neighboring tissue.

254. DIABETES INSIPIDUS, Control of symptoms of by subcutaneous injections of extracts of hypophysis cerebri. Barker (L. F.) and Mosenthal (H. O.), *Jour. Urol. (Balt.)*, 1917, **1**, 449.

A most favorable effect was obtained by this method. Tethelin and adrenaline were of no value.

255. DIABETES INSIPIDUS from hemorrhage in the neurohypophysis and peduncle. Luzzatto. *Lo Sperimentale*, Nos. V-VI, 1917. *Rivista crit. di clin. med. (Firenze)* 1918, **19**, 91.

A case of polydipsia and polyuria with progressive cachexia is reported by Luzzatto, who at the post-mortem examination found an old hemorrhage destroying the posterior lobe of the hypophysis and cutting the peduncle at its entrance into the posterior lobe. The surrounding parts of the brain do not show any abnormality, so that the author brings out such a finding as a severe objection against Camus and Roussy's theory (Lesions of the optopeduncular basilar region as a cause of Diabetes insipidus).—G. V.

256. DIABETES MELLITUS, Influence of the war on. v. Noorden (C.) *Med. Klinik (Berlin)*, 1916, **12**, 991.

Nervous stress alone does not elicit diabetes, but it aggravates the condition, probably by whipping up the adrenals.—
Chem. Abstr.

257. DUCTLESS GLANDS and War.

The Medical Research Committee call attention to over-activity of the endocrine organs in times of intense stimulation. In the siege of Paris (1871) Graves' disease was common. So far in the present war its frequent sequela, myxœdema, has not had time to occur. Alexander (*Med. Klinik*, 1917, **13**, 994-996), notes a case of Graves' disease following a bomb explosion. Reference is also drawn to the following paper in relation to the adrenal glands: Ramond and Francois (*Bull. et mém. soc. méd. des hop. de Paris*, 1917 [3], **41**, 1001-1003), who have noted the frequency of Addison's disease; here adrenal exhaustion increases liability to tubercular infection. Among other points noted is that in war cases the blood-pressure is well sustained until near the end.—*Physiol. Abst.*, 1918, **3**, 50.

258. (ENDOCRINE GLANDS) Animal diastases. II. Blood diastase of rabbits. Watanabe (C. K.), *Am. Jour. Physiol.* (Balt.), 1917, **45**, 30-43.

This is increased by the intravenous injection of human saliva, parenteral administration of starch (slightly, amylase also appearing in the urine), intravenous or intraperitoneal injection of NaHCO_3 in large doses. The latter also causes hyperglycæmia. Ether anaesthesia and adrenaline cause hyperglycæmia, but no change in the diastase of the blood. Pituitrin, ingestion of HCl, small doses of Na_2CO_3 , and thyroid feeding have no appreciable effect on blood-sugar or diastase.

259. (ENDOCRINE GLANDS) Azione degli estratti di ghiandole endocrine sui processi di regenerazione. (Effect of endocrine gland extracts on regeneration). Piccoli (G.), *Arch. di fisiol.* (Firenze), 1917, **15**, 199-208.

The tails of newts were amputated a week before injecting gland extracts. Taking the number of dividing nuclei as the criterion, an increase was noted with pituitary and adrenal (small dose) extracts; a diminution occurred with thyroid and a large dose of adrenal extract, and no change with extract of testis. Taking the rate of growth of the stump as the criterion, adrenal, thyroid, and testicular extracts all caused a diminution; a small dose of pituitary produced no change, but a large dose caused an increase.—*Physiol. Abst.*, 1918, **3**, 52.

260. **GLYCOSURIA, renal.** Beard (A. H.) and Grave (F.)
Arch. Int. Med. (Chgo.) 1918, **21**, 705-15.

The continued presence of any considerable amount of sugar in the urine is nearly always indicative of insufficiency of the endocrine function of the pancreas. Beard and Grave present a detailed study of a case of glycosuria, however, of renal origin. In order to differentiate a renal from a pancreatic glycosuria it is necessary to demonstrate: 1. A urine containing dextrose in amount unchanged to any great extent by fluctuations of carbohydrate intake. 2. A blood sugar of normal percentage. Cases of true renal diabetes are very rare.
—R. G. H.

261. **(HORMONES).** The destruction of hormones, pro-enzymes, and enzymes, by ultra-violet radiation. Burge (W. E.). Am. Jour. Physiol. (Balt.), 1916, **40**, 137-138.

Data elsewhere reported. See abstract in this Journal, 1917, **1**, 66.—L. G. K.

262. **HYPERNEPHROMA, Vaginal metastases of.** Gellhorn (G.) Am. J. M. Sc. (Phila.), 1918, **156**, 94-104.

Metastases of hypernephromata in the vaginal wall are rare, the author having found only nine cases in the literature. A tenth case is reported.—R. G. H.

263. **(HYPOPHYSIS) Abuso de la pituitrina (Abuse of pituitrin)** Artega (J. F.), Rev. Med. y Ciruj. (Havana), 1916, **21**, 71-2.

Two cases are described in which reckless use of pituitary injections led to unhappy results—in one case a barely averted rupture of the uterus and in one to a tear of an old scar in the cervix, causing profuse hemorrhage. The author thinks that none but competent specialists should be allowed to use medications of such potency.—R. G. H.

264. **(HYPOPHYSIS) An improved apparatus for testing the activity of drugs on the isolated uterus.** Pittenger (P. S.). Jour. Am. Pharm. Assoc. (Easton, Pa.), 1918, **7**, 512.

A detailed description of the author's apparatus and method for testing pituitary preparations on the isolated uterus.
—F. F.

265. **HYPOPHYSIS cerebri: its structure and development.** Parker (K. M.), Sci. Progress (Lond.), 1918, No. 47, 450-464.

A review of recent work. The physiological side of the subject is only cursorily mentioned.—*Physiol. Abst.*, 1918, **3**, 52.

266. (**HYPOPHYSIS**) Hypophyseal tumors through the intradural approach. Adson (A. W.), *Jour. A. M. A.*, 1918, **71**, 721-26.

The technique of this operation is described and illustrated. The results of six cases are reported and the advantages of this method of operation pointed out.—R. G. H.

267. (**HYPOPHYSIS**) Physiological assay method of the U. S. P. IX. Pittenger (P. S.), *Jour. Am. Pharm. Assoc. (Easton, Pa.)*, 1917, **6**, 871.

Pittenger states that more concordant results are obtained, in the standardization of liquor hypophysis, by employing the whole one horn of the uterus of a 350 to 425 gram guinea pig, instead of only a segment of the one horn from a 250 gram guinea pig. The author suggests improvements in the lever arrangement by means of which the uterine contractions are recorded on the kymograph.—F. F.

268. (**HYPOPHYSIS**) Pituitary disturbance in its relation to the psychoses of adolescence. Tucker (B. R.), *Jour. A. M. A.*, 1918, **71**, 330-32.

Author's abstract previously published as No. 127, *Endocrinology*, 1918, **2**, 171.

269. (**HYPOPHYSIS**) Preliminary note on the value of beta-aminazolethylamin hydrochloride as a standard for testing pituitary extracts. Pittenger (P. S.) and Vanderkleed (C. E.) *Jour. Am. Pharm. Assoc. (Easton, Pa.)*, 1917, **6**, 131.

A criticism of the standard adopted by the U. S. Pharmacopeia, ninth revision, for liquor hypophysis.—F. F.

270. (**HYPOPHYSIS**) Production of transplantable growth. Erdmann (Rhoda), *Proc. Soc. Exp. Biol. and Med. (N. Y.)* 1918, **15**, 96.

The stimulating effect of tethelin upon new growths was shown by the author in the following manner: Embryonic heart tissue of the chicken is cultivated after twelve days' incubation, for three days in a plasma medium. Then pieces 1 mm. square are implanted subcutaneously in a fowl. After ten days small protuberances develop which upon section appear as

cystic formations. If one of these protuberances is treated with injections of tethelin it becomes three times as large as its untreated neighbor.—R. G. H.

271. (HYPOPHYSIS) *Recherches experimentales sur l'hypophyse de la grenouille. (Experimental researches on the hypophysis of the frog).* Houssay (B. A.) *Jour. de physiol. et de path. gen. (Paris)*, 1917, 17, 406.

The hypophysis of the frog (*Leptodactylus ocellatus*) is made up of the three parts: glandular, intermediary and nervous portions. The glandular part contains both acidophil and chromophil cells. Hypophysectomy was performed by an incision through the palate, leaving a flap of bone and membranes with which to close the wound after the operation is completed. Total hypophysectomy frequently, but not invariably is fatal within a few days. Occasionally animals survive for many weeks. The same operative manipulations without removal of the gland is not fatal. A previous grafting of the hypophysis appeared to lessen the mortality. Reflex excitability is not diminished. Hypophyseal extract from the frog exerts a pressor effect, increases cardiac systole, acts as a galactagogue, dilates renal vessels and produces diuresis, being thus analogous to the action of hypophyseal extract of higher vertebrates.—A. L. T.

272. (HYPOPHYSIS) *The pituitary in relation to loss of memory and inability to concentrate the attention.* Basile (G.) *Polielinico (Rome)*, 1917, 24, 458.

Certain cases showed more or less loss of memory, insomnia and an inability to concentrate the attention in association with diseased sphenoidal sinus or tumors in the nasopharynx. It is regarded as probable that such lesions involved the pituitary body, giving rise to the mental symptoms.—*Physiol. Abst.*, 1918, 3, 132.

273. (HYPOPHYSIS) *Über das Vorkommen von Reiszellen in der Hypophyse. (Giant cells in the hypophysis.)* Simmonds (H.) *Virchow's Archiv. (Berlin)*, 1917, 223, 281-90.

True giant cells were noted in certain conditions, mainly in elderly women.—*Physiol. Abst.*, 1913, 3, 132.

274. **HYPOPHYSIS, THYROID AND PARATHYROIDS,** *Studies of.* Kamo (K.) *Kyoto Igaku Zasshi*, 1917, 14, 1-39. *Jap. Med. Lit. (Seoul)*, 1918, 3, 33-34.

The hypophyses of puppies thyroidectomized $1\frac{1}{2}$ to 5 months previously were always found to be hypertrophied even to $2\frac{1}{2}$ times the usual size, the anterior lobe being chiefly affected. Marked histological changes also occurred, among which may be mentioned the appearance of enlarged eosin-staining granular cells. These were not present in adult animals similarly treated, although the hypophyses were enlarged. No special alteration took place in the middle lobe.

The hypophyses of parathyroidectomized dogs and puppies were not particularly changed in the anterior lobe, but the middle lobe showed an increase in volume in puppies and an increase in colloid substance in full-grown dogs.

The parathyroids remaining after thyroidectomy were always hypertrophied, but exhibited no cellular changes. A thyroid rest, overlooked in total thyroid-parathyroidectomy, underwent great hypertrophy; the follicles were very unequal in size and contained a thin fluid.

Adrenalin glycosuria was greatly decreased by total thyroidectomy in dogs, and adrenalin had no toxic action on these animals when given in reasonable doses. It was, however, quite toxic for parathyroidectomized dogs, and the violent symptoms of tetany were suppressed by the administration of thyroid extract.

The histological and physiological independence of the thyroid and parathyroids was considered proven, even though at times there may seem to be antagonism and at other times a complimentary action between them.—L. G. K.

275. INTERNAL SECRETIONS, General physiological relation of. Sewall (H.) Col. Med. (Denver), 1918, 15, 45-47.

A general discussion of well-known data.—R. G. H.

276. (INTERNAL SECRETIONS) Internal Secretion in learning. Dunlap (K.), Psychobiology (Balt.), 1917, 1, 61-64.

The author suggests as a hypothesis that the direct influence of emotion on action and particularly the influence of pleasure (or satisfaction) and pain (or dissatisfaction) on the formation of habits are due to the "fixing effects" of a hormone. The nervous discharge is supposed to leave an arc or certain important points in the arc in such a condition chemically that this unknown hormone, which is discharged into the blood during pleasure, may a few moments later "fix" it. The effects of pain in preventing the fixing of the reaction may likewise be due to a negating agent (perhaps adrenalin).

The theory is entirely speculative and as yet unsupported by experimental evidence.—L. G. K.

- 277. INTERNAL SECRETIONS, Progress of the year in the study of, with report of five cases.** Ruggles (A. H.) Rhode Island Med. Jour. (Providence), 1917, **1**, 170-75.

A brief review of some of the recent literature. Five cases are reported with a few superficial details. They are: (1) Thyroid intoxication with mental symptoms; (2) Hyperthyroidism following extirpation of ovaries, treated with ovarian substance; (3) Adrenal insufficiency (?); (4) Adrenal insufficiency treated with suprarenal tablets; (5) Anemia with adrenal insufficiency. The diagnosis of adrenal insufficiency was apparently made largely on the presence of Sergent's "White line."—R. G. H.

- 278. INTERNAL SECRETIONS, Some relations between the emotions and glands of.** Cannon (W. B.) Jour. Lancet (Minneapolis) 1916, **36**, 685-88.

An address detailing the well-known work of Cannon and his collaborators on the relation of the emotions to adrenal and thyroid discharge.—R. G. H.

- 279. INTERNAL SECRETIONS, The.** Guenther (A. C.) Nebr. State M. J. (Norfolk, Nebr.) 1918, **3**, 15-19.

A general review of the more important literature. Nothing new.—R. G. H.

- 280. (INTERNAL SECRETIONS) The defective child from the standpoint of the internal secretions.** Harrower (H. R.) So. Cal. Pract. (Los Angeles) 1917, **32**, 101-106.

An enthusiastic general discussion of the topic.—R. G. H.

- 281. (INTERNAL SECRETIONS) The diagnosis of the internal secretory disorders.** Harrower (H. R.) Med. Herald (St. Joseph, Mo.), 1916, **35**, 186-88, 217-19, 257-60, 295-98, 333-37, 361-65. Also published in Western Med. Times (Denver) 1916, **35**, 502-4, 558-61, **36**, 9.

Preliminary serial publication of material which afterward appeared in book form.—R. G. H.

- 282. INTERNAL SECRETIONS, The relations of, to neurology and psychiatry.** Hammes (E. M.) Jour. Lancet (Minneapolis), 1916, **36**, 449-52.

An interesting general discussion of the topic with description of three cases illustrating respectively: hypothyroidism; hyperthyroidism, associated with insanity (melancholia), and partial gonadectomy with hypogenital symptoms benefited by testicular extract.—R. G. H.

- 283. (INTERNAL SECRETIONS)** The activation of muscle catalase by liver. Burnett (T. C.) *Am. Jour. Physiol.* (Balt.), 1918, **46**, 63-66.

In these experiments the liver and leg muscles of the rat were used as being at the two ends of the scale of catalytic activity, the liver being the most active and muscle the least (excepting the brain). Both were perfused till free from blood by saline solution introduced through the aorta. The tissues were then passed through a meat grinder and the pulpy mass obtained was used in weighed quantities.

It was found that when a small amount of liver was added to a much larger quantity of muscle in either neutral or acid hydrogen peroxide the catalytic activity of the combined mass was much greater than the total activity of the two taken separately, as measured by the volume of oxygen produced in a given time. Blood was also found to have a similar marked accelerating effect on muscle catalase, while thyroid, spleen and kidney produced only a small amount of acceleration. Pancreas and testes appeared to cause a slight retardation.

The suggestion is made that this accelerating action may be due to an internal secretion of the liver. Its presence in the blood would also account for its effect in producing acceleration.—L. G. K.

- 284. (MONGOLISM)** Ricambio azotato nell' idiozia mongoloide e nella mixo-idiozia ed influnza su di esso della Tiroidina. (On the mongoloid idiocy and on the mixo-idioy and of the influence on them of the thyroid treatment.) Caronia (G.) *La Pediatria* (Naples) 1918, **26**, 336.

The author emphasizes the difference of effect of the thyroid treatment on these two forms of idiocy, as found from personal research. The children to be examined were first kept ten days on a diet chiefly of milk, eggs, bread and cereals, so that the nitrogenous dosage was rendered very easy. Then, keeping on with the same diet, for six days the food was examined as well as the urine and the faeces. After an interval of ten more days, while the thyroid treatment was begun, there was a period of six other days, during which analysis of food, urine and faeces was made, without dropping the treatment.

For the determination of the total nitrogen Kjeldahl's method has been used for food, urine and faeces. For the urea, Mörner-Syovvist's; for uric acid, Folin-Shaffer's; for ammonia, Folin-Spiro's; for the amino-acids, Henriquez-Sorensen's. The residual nitrogen (creatinine and purinic bases) was not determined.

Conclusions: (a) The nitrogenous metabolism (in the microcephalic mongoloid idiocy) is normal as regards the total retention of nitrogen, but irregular in regard to the various nitrogenous elements of the urine. There is a conspicuous retention of nitrogen and increased elimination of amino-acids. Under the influence of the thyroid the metabolism comes soon to a negative balance at the expense of the tissues, about as we find it in hyperthyroidism.

(b) In mixo-idiocy the metabolism is also irregular as regards the relations between the various elements of the urine (increased elimination of amino-acids). Under the thyroid treatment, though, the metabolism improves, showing better oxidation by diminished elimination of amino-acids and giving normal amount of the residual nitrogen and of uric acid.—G. V.

285. (ORGAN EXTRACTS.) The effects upon the gastric secretion of organic extracts. Rogers (J.), Rahe (J. M.), Fawcett (G. C.), and Hackett (G. S.). *Am. Jour. Physiol. (Balt.)*, 1916, **39**, 345-353.

The authors were of the opinion that the equivalent of a specific gastric hormone is to be found in some substance common to many extracts which favorably affects the nutrition and consequently the activity of the gastric epithelial cells, and has some relation to their nerve supply. They accordingly tested the effects of the subcutaneous injection of organ extracts on the gastric juice of dogs in which the Pavloff isolated stomach pouch and fistula had been established.

The thyroid, or only the non-coagulable portion of an aqueous extract of the thyroid, was found to contain a substance which is an active stimulant of both gastric secretion and gastric motility. Only the "residue," or non-coagulable portions, of aqueous extracts of the parathyroid, thymus, spleen and liver were found to have a similar effect. Both the coagulable and non-coagulable portions of an aqueous extract of the pancreas are vigorous stimulants of gastric secretion. The pituitary and adrenal residues inhibit the flow of gastric secretion. All the stimulating residues seem to act upon a peripheral gastric mechanism of which the nervous system is an essential part. Injection of other organ extracts gave entirely negative results.—L. G. K.

286. (PANCREAS) Role of the pancreas in glycolysis. Lepine (R.) Rev. de méd. (Paris), 1917, 35, 289.

A protest against incriminating the pancreas alone. Certain other glands with an internal secretion are unmistakably involved in glycolysis.

287. (PANCREAS) The effects of painting the pancreas with adrenalin upon hyperglycemia and glycosuria. Kleiner (I. S.) and Meltzer (S. J.) Jour. Exp. Med. (Balt.) 1918, 27, 647.

The authors in repeating experiments of earlier workers find that in the majority of cases painting the pancreas with adrenalin is followed by glycosuria which varies in different animals. The results of earlier experiments lead to the inference, first, that painting the pancreas with adrenalin caused a marked glycosuria and hyperglycemia, and second, that the glycosuria and hyperglycemia produced by intraperitoneal injections were of pancreatic origin. To decide this point the authors performed experiments in which the pancreas was isolated from the rest of the peritoneal cavity and found that the glycosuria produced was about one-third, and the rise in blood sugar about two-thirds that obtained by painting the unisolated pancreas. They therefore conclude, first, that the painting of the isolated pancreas produces only mild glycosuria and hyperglycemia; second, that the greater production of sugar observed after painting the unisolated pancreas cannot be of pancreatic origin, but due to the escape of adrenalin to the peritoneum. As evidence of this conclusion experiments were performed in which the adrenals were painted. The effects on sugar production was apparently as intense as that obtained by painting the unisolated pancreas. Whether the production of sugar after painting the unisolated pancreas is due to the escape of adrenalin to some definite organ covered by the peritoneum or whether the peritoneum as a whole is responsible for sugar production, it appears that, when sugar production follows intraperitoneal injections of adrenalin, it is not of pancreatic origin.—H. W.

288. (PANCREAS) Über die Bedeutung der Langerhansschen Inseln für den Kohlehydratstoffwechsel. I. Mitteilung. Das Verhalten des Blutzuckers nach Unterbindung des Ductus Pancreaticus bei Kaninchen. (The significance of the islands of Langerhans in carbohydrate metabolism. I. The retention of the blood sugar after ligation of the pancreatic duct in rabbits.) Kamimura (N.) Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo 1917, 17, 95-126.

The author found that ligation of the pancreatic duct in rabbits resulted in complete atrophy of the parenchyma of the pancreas with the exception of the islands of Langerhans, which did not appear to show any change. No digestive disturbances resulted, and no lasting hyperglycemia or glycosuria occurred. Artificial hyperglycemias were produced in various ways (injection of adrenin and diuretine, hemorrhage and the intravenous introduction of sugar), but the animals showed no difference in their behavior towards these factors than did other normal rabbits.

These facts support the accepted belief that as long as the islands of Langerhans remain normal the carbohydrate metabolism is not interfered with in disturbances of the pancreas.—L. G. K.

289. (PANCREAS) Über die Bedeutung der Langerhansschen Inseln für den Kohlehydratstoffwechsel. II. Mitteilung. Zytolytisches Immuneserum der Pancreas inseln. (The significance of the islands of Langerhans in carbohydrate metabolism. II. Cytolytic immune serum of the islands of Langerhans.) Kamimura (N.) Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo 1917, 17, 127-136.

A serum, supposedly cytolytic to the islands of Langerhans, was prepared as follows: Saline extracts of rabbits' pancreas, the ducts of which had been previously ligatured so that only the islands of Langerhans remained in an unatrophied condition, were injected into the peritoneal cavity of a young dog. After several injections, at intervals of five to ten days, the dog was bled and the serum so obtained was injected into rabbits, some of which had previously had the pancreatic duct ligatured. Glycosuria was not produced in these animals, thus confirming the earlier work of Ssobolew and Klimenko. In some cases there was a slight increase in the blood sugar content, but the author did not attribute this to the action of a specific serum. The serum produced no noticeable pathological changes in the islands of Langerhans.

—L. G. K.

290. (PARATHYROIDS) Guanidine hydrochloride and blood-sugar. Watanabe (C. K.), J. Biol. Chem. (N. Y.), 1918, 33, 253-265.

Paton's views on the relationship of guanidine to tetany are confirmed. It is further shown that hypoglycaemia is produced both by guanidine and removal of the parathyroids (rabbits).

291. (PARATHYROIDS) Über tödlich verlaufende Tetanie. (Fatal tetany). Stankovic (R.), Wien. klin. Woch. (Wien.), 1917, 30, 1107-1108.

Five fatal cases in soldiers on active service are recorded. They had been exposed to privations mental and bodily. The condition is attributed to parathyroid insufficiency, and there was no evidence of compensatory action in other endocrine organs. (Med. Research Committee.)—Physiol. Abst., 1918, 3, 130.

292. (PITUITARY) Dystrophia adiposogenitalis (Fröhlich's syndrome). Madigan (J. J.) and Moore (T. V.) Jour. A. M. A. (Chgo.), 1918, 70, 669.

Clinical report of a case of dystrophia adiposogenitalis in a boy 10 years of age. The author believes the condition had a prenatal origin because of a hereditary taint upon the maternal side, blindness from birth, nystagmus at three or four months of age, very small optic disks and a genital aplasia of such a nature that it must have dated well back into the prenatal history of the child.—H. W.

293. (PITUITARY) The pituitary gland in epileptics. The conformation of the sella turcica (2nd paper). Munson (J. F.) Arch. Int. Med. (Chgo.), 1918, 21, 531.

The sellas from a series of unselected epileptic subjects present a wide variation in type. The average size seems a trifle smaller than figures given for normals and the contained gland seems to weigh less. Roofing of the fossa can be seen in Roentgenograms, but contrary to impressions given by the statements of other writers, the author believes that the gland in reality is well exposed and pressure seems a remote possibility. Bony changes are present but seem to be the anomalies which might well be present in a similar series of nonepileptic cases. The author concludes that there is no characteristic change to be seen in epileptic sellas.—H. W.

294. (PITUITRIN) Uterine inertia. Titus (P.) Jour. A. M. A. (Chgo.) 1918, 71, 890-93.

The author regards pituitrin as of relatively little use in the practice of obstetrics. Its use in the first stage of labor is regarded as indefensible. Having had three cases of hour-glass contraction of the uterus with retained placenta as a result of its use in the second stage, he has come to the conclusion that its safest use is in the third stage to control uterine

relaxation and hemorrhage. He comments ironically on the free use of pituitrin by mid-wives.—R. G. H.

295. **RICKETS, The modern views on the nature of.** *Rivista crit. de clin. med.* (Firenze) by "Y" 1918, 19, 189:

Rickets is considered as a disease of development, determined usually by dysfunction, first of one and then of all the glands of the thyro-parathyro-thymic group. The thymus lesions would alter the metabolism of calcium and cause a diminished specific activity of the cartilage cells; the parathyroids would be the cause of the spasmophilic symptoms; the exophthalmus and the lymphocytosis would be charged to a dysfunction of the thyroid.—G. V.

296. **SECRETIN, Its mode of action in producing an increase in the number of corpuscles in the circulating blood.** Downs (A. W.) and Eddy (N. B.). *Am. Jour. Physiol.* (Balt.), 1918, 46, 209-221.

The authors have previously shown that the injection of secretin is capable of producing a marked increase in the number of erythrocytes and leucocytes in the circulating blood. Believing this increase to be due to direct stimulation of the bone marrow and lymph glands, the authors investigated the changes in the blood picture and the histological appearances of these organs after prolonged administration (8 weeks) of secretin to two rabbits. The results were compared with those obtained from two controls.

A marked increase in the leucocyte count was obtained (146.7 per cent in the third week), and a less pronounced increase in the erythrocyte count (18.5 per cent in the eighth week). At autopsy the thyroids and spleen of each of the secretin rabbits were much heavier, and the liver was slightly heavier than the same organs in the control animals. Smears and sections of the bone marrow showed that cells of all types were much more numerous in the treated rabbits. The lymph glands of the secretin animals also showed evidence of increased activity. The enlargement of the liver and spleen was attributed to the rapid accumulation in them of the debris of broken down immature erythrocytes produced by the over-active bone marrow. Alterations in the relative proportions of the different varieties of leucocytes was also found to take place and nucleated red corpuscles appeared in the blood of the secretin rabbits.—L. G. K.

297. (SEX) A demonstrtaion of the origin of two pairs of female identical twins from two ova of high storage metabolism. Riddle (O.), Jour. Exp. Zool. (Phila.), 1918, 26, 227.

The author advances further data for a theory of sex differentiation to which he still adheres despite all cytological opposition. He states that he obtained two pairs of identical female twin doves, each pair of which was produced from a single ovum. The two yolks were of very large size, and were produced under conditions known to favor the production of females. The author claims that the fact that these two cases of identical twins were from ova of high storage metabolism and were of the female sex lends support to his theory that germinal differentiation of sex is a differential metabolism. Practically all other biologists believe that sex is determined by the chromosomes of the germinal cells.—E. R. H.

298. (SEX) A microscopical study of the reproductive system of foetal free-martins. Chapin (C. L.) Jour. Exp. Zool. (Phila.), 1917, 23, 453. A microscopical study of the material described by Lillie in the same Journal.

In early stages the free-martin resembles the normal female embryo but it gradually comes to resemble the male in many ways. Such changes occur in the gonad in which the sex cords may resemble either the primary cords of the ovary or the seminiferous tubules of the testis. Other organs which in the sterile free-martin tend to resemble those of the male are the rete, Wolffian body and duct and the Mullerian ducts which normally form the uterus. The changes in these organs vary greatly and are believed to depend upon the amount of male internal secretions which get into the female, and upon the stage of development at which this introduction occurs.—
E. R. H.

299. (SEX) Another case of gynandromorphism. Harman (M. T.) Anat. Rec. (Phila.), 1917, 13, 425.

The author describes very briefly a cat in which the sex organs on right side consisted of an ovo-testis, uterine tube and uterus, while on the left side they were of the normal male type. The subject of gynandromorphism is discussed.—E. R. H.

300. (SEX) Studies on sex in the hermaphrodite Mollusk *crepidula plana*. II. Influence of environment on sex. Gould (H. N.) Jour. Exp. Zool. (Phila.), 1917, 23, 225.

The author has shown that in a certain mollusk the colony both in natural and under experimental conditions develops all female animals until one of these reaches a point where fertilization is needed and then males develop. The males never develop under any other conditions. If the large females are removed, development of males ceases, and on the other hand males will develop from animals which have already begun to differentiate into females if the conditions are proper.—E. R. H.

301. (SEX) The free-martin; a study of the action of sex hormones in the foetal life of cattle. Lillie (F. R.) Jour. Exp. Zool. (Phila.) 1917, 23, 371.

In cattle twins the sterile free-martin and its mate are rarely if ever monozygotie. The female zygote contains factors for both sexes. The quantitative difference between the male and female factors of the female zygote necessary for the differentiation of female characters are reduced in the free-martin by internal secretions from the male twin, and the free-martin therefore becomes a sex intergrade. In these cases the author found that the two animals receive blood from the same chorion. This permits the internal secretions from the male to be carried into the female and interfere with her normal sexual differentiation, thus producing the sterile free-martin. Different degrees of intersexuality may be produced in these free-martins. Absence of normal ovarian tissue may influence their later development by the absence of certain inhibitions normally brought about by the ovary. Sex differentiation is controllable within variable limits in certain groups of animals including mammals. The paper is well illustrated.—E. R. H.

302. (SPLEEN) Histological examination of the spleen in various infectious diseases. Kozumi (K.), Tokyo Igakkwai Zasshi, 1916, 30, 1-30. Jap. Med. Lit. (Seoul) 1917, 2, 2.

Contains nothing new.—L. G. K.

303. (SPLEEN) The spleen during hibernation. Mann (E. C.) and Drips (D.) Jour. Exp. Zool. (Phila.), 1917, 23, 277.

The spleen of the gopher is congested early in hibernation. Splenectomy does not interfere with hibernation, hence the spleen is not primarily directly concerned with hibernation.—
E. R. H.

304. (TESTIS) The effects of testicular transplants upon vasomotor irritability. Wheelon (H.) and Shipley (J. L.) Am. Jour. Physiol. (Balt.); 1916, 40, 394-400.

Previously published 1917, 1, 482, but not included in index.

305. **(THYMUS) Enlarged, in infancy.** Herrick (J. F.), Surg. Gyn. and Obst. (Chgo.), 1916, **22**, 332; abstr. Arch. Ped. 1916, **33**, 792.

Enlargement of the thymus gland often causes death directly or indirectly. It is a question whether the pressure is exerted solely on the trachea or on other organs as well. The chief symptom of a thymic enlargement is a respiratory disturbance which simulates a foreign body in the trachea. This is in the form of a mild stridor both at inspiration and expiration, or it may be a very severe dyspnea with fatal termination. After fits of vomiting, coughing or crying there seems to be a few minutes of relief. Pressure on the trachea, on the vagi, and on the heart are assigned as causes of death. The diagnosis of the stridor caused by a foreign body and that caused by an enlarged thymus may be made from the gradual onset, slowly increasing difficulty, absence of foreign body in the skiagram, dullness to the side of the sternum and an enlarged gland in the X-ray shadow. It is nearly impossible to differentiate an enlargement of the mediastinal glands from one of the thymus. In an enlarged thymus, dullness is usually higher up. The thymus patient is usually well nourished, although pale and pasty looking, and without a history of tuberculosis. Slight cachexia and elevation of temperature often suggest tuberculosis in a thymus case. The author reports 6 cases, ranging in age from 4 weeks to 3 years. The X-ray treatment seems to be the most satisfactory and safest method. Extirpation is both dangerous and uncertain.—M. B. G.

306. **(THYMUS) Persistence of thymus gland in relation to sudden death of adults.** Taguehi (K.), Kyoto Igaku Zasshi, 1917, **14**, 1-14. Jap. Med. Lit. (Seoul) 1917, **2**, 2.

The author in a review of three cases of sudden death discusses the findings of the post-mortem examinations in their relation to forensic medicine.

The first, a woman of 23, died during anaesthesia for a curettage during which less than 15 cc. of chloroform was given. The autopsy revealed a large thymus, a mild grade of hypertrophy and fatty degeneration of the heart, and nephritis.

A 14-year-old boy was drowned and the verdict, based upon the post-mortem examination, was that the accident had occurred as a result of heart failure incident to an enlarged thymus.

A strong and well nourished man, aged 57 years, died within an hour after the administration of 1 cc. of typhoid vaccine, with symptoms of chilliness, exhaustion, headache,

dyspnoea, vomiting etc. The status thymicus was evident with characteristic findings, such as definite persistent thymus, lymphoid hypertrophy, hypogenesis of the papillary muscles of the heart, narrowing of the aorta, imperfect calcification of the xyphoid process, and costal cartilages, and a general deficiency as compared with what would be expected of a man of that age.—L. G. K.

307. (THYMUS) Status lymphaticus. Symmers (D.) Am. J. M. Sc. (Phila.), 1918, 156, 40-58.

The paper comprises a discussion of the definition, clinical aspects and clinical signs of status lymphaticus, followed by an analysis of 249 cases seen at autopsy at Bellevue Hospital. There were 212 males and 37 females in the series. There were 118 cases which were well marked, 89 recessive and 42, border line, tending, however, toward recessive. In the 118 cases the thymus was hyperplastic in every instance. In 70 cases designated recessive the gland was "practically invisible." The only noteworthy histological change in the thymus was hypertrophy of the lymphoid follicles, but the lymph nodes often had peculiar necrotic germinal areas, especially in the subjects that had met sudden death from trivial causes. In later stages the necrotic areas were replaced by characteristic whorls of connective tissue cells. The author believes that the sudden death that is frequent in status lymphaticus is due to anaphylaxis, the sensitizing substance being derived from the necrotic lymphoid tissue. The blood vessels in a considerable number of the cases showed gelatinous alterations or hypoplasia,—a condition predisposing to cerebral hemorrhage. A high incidence of status lymphaticus was noted in cases showing emotional instability and chlorosis. For many interesting details the original should be consulted.—R. G. H.

308. (THYMUS) Über Beziehungen zwischen Thymus und Carcinom (Relationship between the thymus and carcinoma)
II. Kammer (G) and Morgenstern (O.), Biochem, Zeitsch. (Berlin), 1917, 84, 281-331.

The authors claim to have proved that there is a close relationship between the destructive action of serum upon cancer cells and the condition of the thymus.—Physiol. Abst., 1918, 3, 140.

309. (THYROID) A case of complete cretinism with normal mentality as the result of thyroid therapy. Hoag (W. B.), Arch. Ped. 1916, 33, 303.

Hoag presented a girl $5\frac{1}{2}$ years old, who first came under his care at the age of $3\frac{1}{2}$ months. At that time, she presented the appearance of a typical cretin. At the time of reporting, she was 40 inches in height and weighed 43 pounds; she talks and plays like any other child and the mother stated that she did not then show any abnormality. Thyroid treatment had been begun at the time he first saw the child, with one quarter of a grain of thyroid extract twice daily, this being gradually increased, until for a time, when she was 4 years old, she showed signs of excessive dose, when getting 5 grains a day. She has now been getting 3 grains a day for the past few months. The case showed the results possible with thyroid medication if the case is seen early enough.—M. B. G.

310. (THYROID) Cerebral manifestations in a case of exophthalmic goitre. Heuer (G. J.) *Am. J. Med. Sc. (Phila.)* 1916, 151, 339.

Heuer reports the cerebral manifestations in a case of exophthalmic goitre. This is of special interest and statistical value in that it is the first of the grave cases to be operated upon. His case is that of a man, 23 years of age. Family history unimportant. The illness was at intervals of six years' duration. The symptoms of nausea, asthenia, dyspnea, dysphagia and diplopia gradually became worse. Examination revealed the presence of a bilateral thyroid enlargement, bilateral ptosis, fixation of the globes, exophthalmos, tachycardia and extreme nervousness.

Summary of Cranial Nerve Examination: Olfactory undisturbed; diplopia: complete ophthalmoplegia externa. The pupils reacted to light. The sensory fifth nerve was unaffected. the motor markedly involved. Involvement of the seventh was shown by the mask-like face. Involvement of the remaining cranials was shown by the symptoms of dyspnea, dysphagia and dysphonia. Marked hyperesthesia was also noted.

Symptoms suggesting involvement of other glands like adrenal, hypophysis and thymus are discussed. After operation temporary improvement was noticed. Patient died from acute respiratory failure. No postmortem. A discussion of the previously reported cases indicates necessity for consideration of surgical interference, even though nerve palsies are present.—C. McP.

311. (THYROID) Development of certain types of malignant tumors of the thyroid. Wilson (L. B.) *Am. Jour. Physiol., (Balt.)*, 1918, 45, 573.

Malignant tumors of the thyroid are often overlooked in their early stages since many of the malignant types closely resemble benign adenomas of "fetal" type. Both benign and malignant adenomas apparently have their origin in embryonic tissue which at first consists of relatively small cells with indistinct outlines and relatively large, round or slightly oval, densely staining nuclei. These cells are irregularly arranged and are separated by scarcely discernible septa which consist essentially of thin-walled, flattened blood vessels. In the second stage the cells are arranged in cordon-like masses or long band-like platelets between which are the same sinusoid vessels. In the third stage the cordons or platelets are broken into roundish masses with the formation of acini, some of which may contain colloid. This is the most critical stage. If the acini become well developed the tumor is apt to remain benign. If the acini are irregularly or imperfectly developed the tumor is apparently more apt to become malignant, if it is not already such.

A study of the histology of supposedly benign encapsulated thyroid tumors removed at operation, in relation to these stages of development, is important for the early diagnosis of malignant conditions.—L. G. K.

312. (THYROID) Eczema due to deficient thyroid secretion in which the administration of thyroid acted as a specific.
Edelman (M. H.), Arch. Ped. 1916, **33**, 932.

Edelman presented a patient, a boy, 3½ years old, who had had an eczema since the age of 4 months. He was breast fed up to the age of ten months. The eruption was of the scaly weeping type, involving the cheeks, forehead, chin, scalp, neck, shoulders, chest and upper and lower extremities. In spite of three years constant treatment by pediatricists and dermatologists, the eruption became more pronounced.

The interesting points in this case were (1) the premature grayness of the mother and her sister and their rather pasty complexions, suggestive of deficient thyroid secretion, which made it seem probable that the mother was responsible for the child's condition; (2) the persistency and extent of the eczematous condition in spite of careful dietetics and local treatment, which suggested a rather complex etiology; (3) the eczema seemed to bear no relation to the food. The improvement under thyroid extract and the regression when this medication was withdrawn, pointed to a condition of hypothyroidism. Fairly large doses of thyroid extract should be administered at first, in order to remove the results that might have been produced by privation of thyroid secretion; later smaller doses were given to maintain a normal equilibrium and pre-

vent a recurrence. The reviewer has found that in his experience, it is safer to start with small doses and gradually work up to the point of tolerance, as we do not know the degree of susceptibility of the patient toward thyroid. Edelman gives less food to these patients because of the lessened metabolic powers, as proven by Talbot in his work on the metabolism of a cretin. He gradually increases the food as they improve. Some clinicians feel that the opposite course should be pursued, that, as the thyroid may produce a loss in weight, plenty of food should be given.—M. B. G.

313. (THYROID) Effects of external temperature, morphine, quinine and strychnine on thyroid activity. Mills (C. A.) *Am. Jour. Physiol.* (Balt.), 1918, **46**, 329-339.

Rabbits, guinea-pigs and cats were used in this research. The animals were kept on a constant diet, and in a room maintained at a temperature of 12° to 18°C. A portion of the thyroid gland was then removed and examined microscopically, after which the animals were subjected to cold (-5° to 10° C.), heat (27° to 37° C.) or injections of quinine, morphine or strychnine. At the close of the period of treatment the remainder of the thyroid was compared with the portion previously removed. The author found that high external temperatures cause a diminished activity of the thyroids as judged by their morphological appearance, together with a slowing of the rate of growth. Low external temperatures, on the contrary, increase the thyroid activity and also seem to cause a faster rate of growth. Morphine and quinine appear to decrease the activity of the gland, probably as a result of the lessened metabolism and diminished heat production; while strychnine causes greater thyroid activity, very likely by increasing metabolism through its action on the spinal cord.—L. G. K.

314. (THYROID) Further experiments with thyroidectomy in Amphibia. Hoskins (E. R.) and Hoskins (Margaret M.) *Proc. Soc. Exp. Biol. and Med.* (N. Y.) 1918, **15**, 102-4.

Thyroidectomy was performed upon a large number of frog larvae, at a 6 to 8 mm. stage. After the tadpoles reached a length of about 18 mm. the growth of the operated animals was accelerated and they ultimately reached a length of 72 mm. as against 50 mm. in normal controls.

In the absence of the thyroid secretion the anterior lobe of the hypophysis underwent hypertrophy—a fact which probably accounts for the experimental gigantism that developed. The sex glands were further advanced in development in the

operated than in the control animals. This precocity is also accounted for by the hypophyseal hypertrophy. The other endocrine glands were larger in the experimental than in the control animals, but whether this was absolute or relative had not yet been determined.—R. G. H.

315. **(THYROID) Goitre in children.** Buford (C. G.), *Surg. Gyn. and Obst. (Chgo.)*, 1915, 20, 35; abst. *Arch. Ped.*, 1916, 33, 953.

The subject is divided by the author into (1) goiter of infancy under one year of age, and (2) goitre of childhood, one year to adolescence, (3) goitre of adolescence. Almost 90 per cent of the older cretins show goiter. Certain results can be brought out of cretinism by early thyroid feeding. It is possible that in some the gland is delayed in development and in the performance of its duties, and if not fed thyroid these children may be permanently damaged. Goiter among newly-born children seems rare to the author, who has seen one case in a baby six days old. Brooks reports several cases which have appeared about the second day after birth and says that they invariably disappear.

In the goiter of children there is almost uniformly an area well defined in the gland. About 9 in 10 show the lesion in the right lower pole of the right lobe. As the mass enlarges, it encroaches upon the median line. In early cases the tumor is hard and well defined. In the more advanced cases the induration is more distinct and the anterior border more rounded. In the still more advanced cases, the tumor is rotund, outlines definite, consistency firm or fluctuating, neck enlarged and capsulation quite complete. When these encapsulated masses are removed they are found to be benign adenomas. These types of goiters are often associated with diseased tonsils.

The symptoms associated are largely proportionate to the apparent changes of the gland. The patients are usually below standard in health and stature. Muscles are soft and posture drooping; fatigue comes easily. They are languid, do not enjoy play and are irritable. The hair usually has a gritty feeling. Moist cold hands with a coarse or fibrillary tremor limited to the hands is sometimes characteristic. The pulse ranges from 80 to 120.

The treatment is thyroid feeding. The goiter may disappear in six weeks under treatment. Adolescent goiter usually appears as a bilateral affection. When unilateral the enlargement is usually in the right lobe. When there is no suggestion of hyper-thyroidism, iodine or thyro-iodine should be given.—

M. B. G.

316. (THYROID) Goitre in pregnancy. Watson (L. F.) Jour. A. M. A. (Chgo.) 1918, 71, 875-77.

As a result of a consideration of the literature and of his own cases, a few of which are cited, the author concludes that "pre-existing goitre, either simple or toxic in type, is usually aggravated by pregnancy. The symptoms and growth of hyperplastic goitre in pregnancy can usually be controlled by quinine and urea injections into a portion of the thyroid gland. Should symptoms progress in spite of conservative measures, a rapid delivery is indicated. Operation on the thyroid is indicated to relieve pressure symptoms of solid goitres. Cystic goitre may be promptly relieved by quinine and urea injections. Pregnant women with subthyroid conditions should receive iodids or thyroid throughout gestation." In the author's experience untoward results have not followed the quinine and urea treatment. He uses only small doses (5 to 10 minims) at one to three-day intervals.—R. G. H.

317. (THYROID) Goitre in the southeast. Jones (E. J.), Jour. A. M. A. (Chgo.), 1918, 71, 712-15.

The incidence in the Southeast of the several types of goiter departs in no significant way from the incidence in other areas where thyroid troubles are not definitely endemic. Sixty per cent of all goiters are listed as nontoxic; excluding from consideration the symptomless goiters of puberty, 64 per cent of the nontoxic goiters are adenomas. Goiter in this territory is relatively rare; the colored race exhibits less tendency to a pathologic condition of the thyroid than does the white race; men are less frequently affected than published figures indicate; the occurrence of nontoxic goiters in families is suggestive, but not significant; no particular water supply is under suspicion. There appears in this series no significant relation between pelvic disease and a pathologic condition of the thyroid. Maximum double resection in diffuse enlargements is wise.—Author's summary.

318. (THYROID) Heteroplastic grafts with thyroid from cases of Graves' disease. D'Agata (G.) Lo Spirem. (Firenze) 1918, 71, 392-404.

Transitory functional alterations were observed. These were ascribed to the absorption and entrance into the circulation of substances arising in the transplanted thyroid tissue.—Chem. Abst. 12, 1317.

319. (THYROID) La crosse de l'aorte dans le goitre exophtalmique. Folley (C.), Soc. d. Biol. (Paris), 1918, 166, 311-312.

Dilatation of the aorta is an early and constant symptom of exophthalmic goitre.—Physiol. Abst., 1918, 3, 137.

- 320. (THYROID) Nervous and mental symptoms in exophthalmic goitre.** Barker (L. F.), Jour. A. M. A. (Chgo.), 1918, 71, 327-29.

A general discussion of the topic not lending itself to abstracting.—R. G. H.

- 321. (THYROID) Sounds in exophthalmic goitre.** Reisman (D.) Jour. A. M. A. (Chgo.) 1916, 66, 1381.

Of clinical interest. Reisman reports having heard a bruit, synchronous with the heart beat, over the eyeball in a case of exophthalmic goitre. The sound is heard when the bowl of the stethoscope is placed over the eye, the lid being closed. The sound is not constant and occurs also in aortic insufficiency. It has been reported previously by Snellen, Donders, Hunter, Carrington and Drummond.—C. McP.

- 322. (THYROID) Sulla diagnosi e cura degli stati ipertiroidi. (The diagnosis and treatment of hyperthyroidism.)** Pisani, from Maranon. Revista Ibero-Am. de cien. med. (Madrid) June, 1917. Rivista crit. di clin. med. (Firenze) 1918, 19, 58.

According to Maranon several types of hyperthyroidism are found classed in regard to their different functional manifestations:

(a) Cardio-vascular; (b) nervous type (the neuroses from fear are almost always forms of hyperthyroidism); (c) diabetic type where, besides some thyroid symptoms, the glycosuria depends more on the nervous influence, than on the diet; (d) tubercular type (where, though, a nice separation from actual tuberculosis is not always feasible); (e) digestive type (hyperchloridria, diarrhea, etc.); (f) Kraus's cardiac goiter.

The different aspects are caused by peculiarities of the thyroid secretion and still more by the patient's constitution and, finally by the conditions of the other endocrine glands. This last statement is found true in about 95 per cent of cases.

The therapy of any of such forms must be mostly medical; surgical only when the medical fails. After quoting the various medical treatment as carbohydrates, climate, cold applications, electricity (the author would recommend the galvanofaradic) and radiotherapy (rather doubtful), he seems to recommend calcium, phosphorous and atropin. He disclaims any benefit from iodine treatment, which he would allow only

very seldom and with the utmost caution. Coming to the opotherapeutic preparations, he declares the thyroid treatment uncertain and often dangerous; if chosen, very small doses are to be given. He does not find justified the use of thymus, as exciting the thyroid. The hypophysis is good as cardiogenic. Parathyroid preparations are only symptomatic remedies for the tachycardia. Pancreas preparations give negative results.

In conclusion he advises ovarian therapy in some cases determined by ovarian insufficiency; suprarenal in cases of decided hypotension; the pluriglandular combined according to the needs, and finally, in acute cases, he insists on anti-thyroid sera.—G. V.

323. (THYROID) Temporary loss of voice following thyroidectomy. Guthrie (D.) *Jour. A. M. A. (Chgo.)*, 1918, **71**, 715-18.

The causes of temporary loss of voice are given by the author as follows: (1) Trauma to the inferior recurrent laryngeal nerves; (2) trauma to the larynx and trachea; (3) syphilis; (4) hysteria. An operative technique for the avoidance of the first two is described and illustrated. The suggestion is offered that all patients who have insignificant goitres but complain of interference with speech be submitted to a Wasserman test. The significance of hysteria in these cases and methods of treatment of the condition are discussed. The need of the assistance of skilled anesthetist is especially emphasized.

—R. G. H.

324. (THYROID) The active constituent of the thyroid. Kendall (E. C.) *Jour. A. M. A. (Chgo.)* 1918, **71**, 871-72.

A somewhat fuller treatment of the topic has been published by the author in *Endocrin.*, 1918, **2**, 81.—R. G. H.

325. (THYROID) I. The blood sugar in thyroid and other endocrine diseases. Janney (N. W.) and Isaacs (V. I.) *Arch. Int. Med. (Chgo.)* 1918, **22**, 160.

Experiments upon dogs demonstrate that hypoglycemia results from hypoendocrine function in the case of the thyroid gland, where hyperglycemia regularly develops after thyroidectomy. This finding, therefore, offers an explanation for the low blood sugar value observed in myxedema, cretinism, Addison's disease, pituitary diseases and other less clearly defined endocrine disturbances such as muscular dystrophy. The increased glucose tolerance, as determined by testing the urine in diseases of the ductless glands, is probably best explained as

due to the hypoglycemia present in these conditions. Experimentally it was found that the assimilation of glucose from the blood was delayed following thyroidectomy. The same changes were demonstrated in cretinism, exophthalmic goiter, and hypophyseal disease. Determinations of the fasting blood sugar value and the glucose tolerance are considered by the authors as useful procedures in the diagnosis of endocrine diseases.—H. W.

326. (THYROID) II. The influence of thyroidectomy and thyroid diseases on protein metabolism. Janney (N. W.) and Isaacson (V. L.) *Arch. Int. Med. (Chgo.)*, 1918, **22**, 174.

This paper presents the results of experimental work upon dogs and clinical patients relative to urinary nitrogenous substances following thyroidectomy. No selective action of the thyroid was observed on urea and ammonia, but the urinary purines decreased following thyroidectomy and were greatly increased in experimental hyperglycemia. There was also noted a tendency to a low purine excretion in the cretin and a high excretion in a case of exophthalmic goiter. Creatinin was not found to be increased in the urine even when large amounts of body tissue were being broken down in experimental hyperthyroidism. Therefore it appears that creatinin is not a direct product of protein catabolism and also, that creatinin metabolism is independent of thyroid influence. The experimental work does not support the view that any marked diminution of nitrogen excretion follows thyroidectomy in animals. Also, cretins fail to show a particularly low output of nitrogen. Such findings lead to the belief that the decrease in the protein breakdown, observed by others in cretin metabolism, is due rather to an inability for growth and repair of tissues to take place.—H. W.

327. (THYROID) III. Studies in thyroid therapy: the effects of the thyroid hormone as determined by clinical, metabolic and dietetic investigations. New points of view on thyroid function in health and disease. Janney (N. W.) *Arch. Int. Med. (Chgo.)* 1918, **22**, 187.

The author describes therapeutic experiments with Dr. Kendall's thyroid preparation, the effects of thyroid administration on metabolism, and of diet in thyroid diseases. The effects of thyroid preparations on the protein metabolism were followed over continued periods, with estimations of the nitrogen intake, output and balance. The results of a series of experiments on control individuals indicate that the normal

organism is more sensitive to minute doses of thyroid than had generally been supposed. The earliest observable effect was a tendency for a positive nitrogen balance to diminish, this condition being at times associated with a loss of weight. Hence, the smallest amount of hormone added from without, in the case of normally functioning thyroids, tends to cause nitrogen loss. In the cretin identical amounts of thyroid which caused nitrogen loss with or without toxicity in normal individuals led to a large gain in nitrogen accompanied with improvement in the clinical symptoms. "This effect was so delicate that the nitrogen balance could be used as a gauge of the correctness of the dosage. Therefore, the therapeutic action of the thyroid is anabolic and constructive." In exophthalmic goiter the hormone was less satisfactory. However, the author believes that the symptoms of toxicity exhibited on the doses employed do not indicate that the hormone acts differently from other thyroid preparations in these toxic cases. In spite of the known tendency to nitrogen loss in exophthalmic goiter, the nitrogen balance became increased when 0.02 mg. of the hormone iodin was administered.

Diets supplying increased calories do not improve the clinical condition of cretins, since only a reduced amount of food can be assimilated by the untreated subject. Cretins should therefore be maintained on a liberal diet, and not subjected to forced feeding. In the dietetic treatment of exophthalmic goiter neither a high protein nor a high carbohydrate diet is followed by as good results as is a mixed diet of adequate caloric value.

From the results of his own work and a critical review of the literature the author is led to doubt the adequacy of the "hyperthyroid theory" of exophthalmic goiter. A tentative theory is put forward which assumes that the result of the premature discharge of a "hypothetical toxic intermediary product" would result in an impoverishment of the gland of the thyroid hormone. Such a theory would explain the fact that in Graves' disease goiters are poor in iodine, and especially in the Alpha-iodine proteins. The decreased production of the normal hormone due to this cause would tend to be accompanied or followed by signs of thyroid insufficiency. Thus the deficiency symptoms can be accounted for; also the concomitant occurrence of hypothyroid and hyperthyroid symptoms, and the tendency of exophthalmic goiter patients to develop myxedema.

Such considerations indicate first, that the depressed nitrogen excretion in cretinism is not due to absence of stimulatory effect, but rather to the failure of normal repair and growth

processes which are controlled by the thyroid; second, that a gain, not a loss, of nitrogen is a result of the therapeutic action of the thyroid, and that a loss of nitrogen is due to a toxic action of the gland.—H. W.

- 328. (THYROID) The energy of metabolism in a cretin.** Talbot (F. B.) *Am. Jour. of Obst. (N. Y.)* 1916, **74**, 549.

This subject was a typical cretin, three years and eight months of age, and was studied in the respiratory chamber devised by Benedict. They found his basal metabolism per kilo body weight was $40\frac{1}{2}$ calories, and per square meter of body surface, 898 calories per twenty-four hours. In the absence of normal data in children of the same age this metabolism was compared with that of a normal eight months' baby and a normal ten months' baby. The metabolism of the cretin was decidedly lower than that of the two normal babies. Unfortunately, results after treatment with thyroid have not been sufficiently accurate to use. These results were consistent with those of Magnus Levy and the more recent work of Dubois. The practical application of these findings is that the cretin requires less food than children with sufficient thyroid activity and that after treatment with thyroid extract would require more food than before treatment.—W. H.

- 329. (THYROID) The influence of thyroid preparations given parenterally on nitrogenous metabolism and on the blood in myxedema.** Peillon (G.) *Mitt. Grenzg. Med. Chir. (Jena)*, 1916, **29**, 245-69; *Physiol. Abst.* **1**, 489.

Thyroid preparations increase the N metabolism, especially when given parenterally. The effect is proportional to the I content of the preparations. Another effect is an increase of leucocytes and a decrease of lymphocytes.—*Chem. Abst.*, 1918, **12**, 1487.

- 330. (THYROID) The influence of iodothyroglobulin and thyronucleoprotein on nitrogenous metabolism in myxedema and Graves' disease.** Courvoisier (H.), *Mitt. Grenzg. Med. Chir. (Jena)*, 1916, **29**, 70-84; *Physiol. Abst.* **1**, 489.

In myxedema, thyronucleoprotein causes N retention, and the blood picture characteristic of the disease is exaggerated; iodothyroglobulin increases the output of N, and the blood picture returns to normal. If both preparations are given together, the effect of the thyronucleoprotein comes first, followed by that of the thyroglobulin. In Graves' disease, iodothyro-

bulin increases the excretion of N, and renders the blood picture worse; thyronucleoprotein causes retention of N and does not affect the blood.—Chem. Abst., 1918, **14**, 1487.

- 331. (THYROID) The effect of thyroid preparations on metabolism and the blood picture in myxedema and cretinism.** Lanz (W.), Mitt. Grenzg. Med. Chir. (Jena), 1917, **29**, 285-308; Physiol. Abstracts **1**, 489.

In hypothyroidism, iodothyroglobulin causes a negative N balance. The P-containing constituent (nucleoprotein) has no action. Activity is proportional to the I content.—Chem. Abst. 1918, **14**, 1487.

- 332. (THYROID) The action of thyroid preparations in thyroid disease.** Kocher (A.), Mitt. Grenzg. Med. Chir. (Jena), 1918, **29**, 309-19; Physiol. Abstracts, **1**, 489.

A commentary on the work described in the preceding abstracts, which was carried out under K.'s supervision.—Chem. Abst. 1918, **14**, 1487.

- 333. (THYROID) The principles of thyroid surgery.** Mayo (W. J.), Jour. A. M. A. (Chgo.), 1918, **71**, 710-12.

A general paper not suitable for abstracting.—R. G. II.

- 334. (THYROID) The prognosis of exophthalmic goitre.** Stanton (E. MacD.) Am. Jour. Med. Sc. (Phila.), 1918, **156**, 369-75.

This is a study based on the analysis of some 1600 cases in the literature. The results are tabulated in a novel way, showing the number of years of life after operation, years traced, years cured or improved, etc. In other words the time factor is introduced systematically. The author's conclusions are quoted:

“Removal of a portion of the thyroid gland of patients suffering with exophthalmic goitre produces a profound immediate effect noticeable within a few days of the operation and characterized chiefly by an improvement in the subjective symptoms of discomfort felt by the patient, but also accompanied by a marked fall in the pulse rate, a diminution of the tremor and an increase in weight.

“This initial improvement, however, seldom amounts to a cure. The exophthalmos usually persists for months or years. The heart remains irritable, the pulse becoming rapid with

exertion or excitement and at irregular periods we may expect acute exacerbations of toxic symptoms, which may alarm both the patient and the surgeon.

"The general tendency is, however, toward improvement rather than recurrence, and after a variable length of time a few patients may have failed to improve or even have grown worse; but the great majority, I believe about 80 per cent, will have continued to improve, so that finally practically all traces of their former trouble disappears.

"It is useless for the surgeon to claim that there is no medical side to the treatment of exophthalmic goitre. After five or six years there is probably little to choose between the medical and surgical end-results as regards either the mortality or the condition of the surviving patients.

"Patients surviving operation have been promptly relieved of the more distressing subjective symptoms, and the majority of them will have been able to return to their normal work in about half the time that it would have taken them to reach the same state of improvement under medical treatment. Against this is the primary mortality which must always accompany operations for exophthalmic goitre unless we are to deny the chance of operative relief to many cases most in need of the relief.

"In the future the man best able to treat exophthalmic goitre will be the one who has developed the judgment necessary to enable him to select the treatment, medical or surgical, best adapted to the individual case. The decision will depend upon many factors, not the least of which will have to do with the social condition of the patient, and whether she or he can afford the time and expense necessary for the prolonged rest required to effect a medical cure."—R. G. H.

335. (THYROID) The relationship of the so-called idiopathic cardiopathy to exophthalmic goiter. Symmers (D.) Arch. Int. Med. (Chgo.), 1918, **21**, 337.

This paper should be of special interest to the clinician and pathologic anatomist. The author describes six cases of so-called idiopathic cardiopathy, all of which showed naked eye changes in the thyroid gland. In five cases the thyroid was considerably enlarged, in one case diminished in size. From a thorough study of these cases the author concludes that the symptomatology of the condition described by clinicians as thyrotoxic cardiopathy is identical with the symptomatology of the lesions familiarly known among pathologic anatomists as idiopathic dilation and hypertrophy of the heart. Such cases.

are therefore believed to constitute a clinical and pathological entity and not an atypical form of exophthalmic goiter.—H. W.

- 336. (THYROID) Vincent's syndrome (clinostatic bradycardia, hypotension and acrocyanosis).** Marchetti (G.) *Rivista crit. di clin. med.* (Firenze) 1918, **19**, 296.

By clinostatic bradycardia the author means the difference in number of the pulsations from standing to reclining position, which, instead of being 8-9, may be 15-20-25-30. Lying down the patient's pulse count goes down to 58-53-40 a minute. The hypotension is more accentuated in a standing position. The acrocyanosis shown by damp, cold, cyanotic hands and feet as well in winter as in summer. The syndrome is found in young people who show insufficiency of the thyroid. The thyroid treatment with KI or Na I brings forth rapid, constant and lasting benefit. The ovarian treatment may be a valuable coadjutant in some cases.—G. V.

- 337. (THYROID EXTRACT) Spasmus nutans.** Gordon (M. B.) *N. Y. Med. J.* 1916, **104**, 453.

The writer gives a clinical report of three cases of this type of functional hyperirritability of childhood. In all three instances, he found rickets to be associated and probably an etiological factor. He administered thyroid extract in two of the cases with good results.—M. B. G.

- 338. (THYROID EXTRACT) The treatment of rickets.** Gordon (M. B.) *N. Y. Med. J.* 1916, **103**, 696.

In addition to general, hygienic and corrective dietetic measures, the writer states that in the line of remedial agents, the use of thyroid extract has proven efficacious in his experience. This may be started with one-eighth grain doses twice daily and gradually increased to as much as one grain three times a day. The child should be watched for untoward symptoms, but to avoid these, the extract is given ten days on and ten days off. In the interim, the elixir of the glycerophosphates of lime and soda in half dram doses two or three times a day is given. This may be changed at times to the compound syrup of hypophosphites. In other cases, especially in those associated with convulsions, thyroid extract, one-eighth grain, with calcium lactate, two grains, two or three times a day has proved beneficial, the thyroid being increased gradually to one grain three times a day.—M. B. G.

339. **(THYROID HYPOPHYSIS)** The influence of thyroid and hypophysis removal upon general body growth and upon the development of the limbs of *Rana* and *Bufo*. Allen (B. M.) *Anat. Rec. (Phila.)* 1918, Vol. 14.

From a large number of tadpoles of these two types, the thyroid gland was removed, while from others the anterior lobe of the hypophysis was removed. In both species the removal of either of these glands caused the development of the limbs to be very greatly retarded from the time of their first appearance. In *Rana pipiens* removal of the hypophysis caused a marked retardation of general body growth, to which a corresponding retardation of limb growth was closely correlated. These tadpoles finally attained a total length of 48.9 mm. and a hind leg length of 1.48 mm. This was in marked contrast to the continued growth of the general body dimensions and of corresponding hind-limb length in thyroidless tadpoles of this species. In *Bufo lentiginosus* the results were not so divergent. The removal of the anterior lobe of the hypophysis early caused a color change from black to golden yellow. The absence of either gland caused retardation in limb development. Tadpoles deprived of the anterior lobe of the hypophysis reached a length far in excess of that reached in normal tadpoles. The limbs grew to about three-fifths the length attained in normal toads at metamorphosis. Thyroidless specimens grew somewhat larger than the foregoing, reaching a length of trunk almost twice that of normal toads at metamorphosis, while the hind legs and forelegs grew to a length greater than found in normal toads at metamorphosis. In none of the operated tadpoles did the fore limbs break through the skin.—E. R. H.

340. **(THYROID, PARATHYROID)**. The effect of thyro-parathyroidectomy on the blood coagulation time in the dog. Simpson (S.) and Rasmussen (A. T.). *Am. Jour. Physiol. (Balt.)*, 1916, 40, 148.

Data elsewhere reported. See abstract in this journal, 1917, 1, 350.—L. G. K.

341. **(THYROID, PARATHYROID)** The effect of thyro-parathyroidectomy on heart and circulation. Part 1. Action on nervous control of heart. Burns (D.) and Watson (A. McL.). *Journ. Physiol. (London)*, 1918, 52, 88-94.

The authors conclude from previous work that the symptoms of tetania-parathyreopriva (especially the increase in pulse-rate) are due to the presence of excessive amounts of guanidin and in this research have investigated the action of

the salts of guanidin on the vago-cardiac inhibitory mechanism.

The carbonate hydrochloride, and lactate salts of guanidin were injected in doses ranging from 50 mgms. to 1200 mgms. per kilo. The minimal current necessary to inhibit the heart through the vagus was determined in a normal animal before and after injection. The current was raised in the latter case. A solution of calcium lactate restored the inhibitory mechanism to normal.

The minimal current was then determined in an animal before and after parathyroidectomy with the same result as above, the difference being only in degree.

The guanidin effect is first a nicotine action, i. e., on the synapse; after more extensive application, an atropine action, i. e., on the terminal ganglia.—W. E. B.

342. (THYROID THYMUS) The effects of the ductless glands on the development of the flesh flies. Kunkeld (B. W.) Jour. Exp. Zool. (Phila.), 1918, **26**, 255.

The author found that thyroid fed to fly larvae, apparently hastened maturity slightly in most cases, that the larvae were shorter than normal. His results with thymus feeding were essentially negative. His results with thyroid are in line with the well established theory that thyroid feeding stimulates metabolism.—E. R. H.

The abstracts in this number have been prepared by the staff, assisted by:

- W. E. Blatz, University of Toronto.
- Frederic Fenger, Armour Laboratories, Chicago.
- W. Harrison, Detroit.
- L. G. Kilborn, University of Toronto.
- C. McPeck, University of Ohio, Columbus.
- A. L. Tatum, University of Chicago.
- H. Wheelon, Washington University, St. Louis.

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ENDOCRINOLOGY:

*The BULLETIN of the ASSOCIATION for the
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CYCLIC CHANGES IN THE INTERSTITIAL CELLS OF THE OVARY AND TESTIS IN THE WOODCHUCK (*MARMOTA MONAX*)

Andrew T. Rasmussen

(From the Departments of Histology and Embryology, and of Physiology,
Cornell University, Ithaca, New York; and The Institute of
Anatomy, University of Minnesota, Minneapolis, Minnesota)

Four plates (36 figures)

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INTRODUCTION

The significance of the so-called interstitial cells found in the ovary and testis of many mammals and of some lower orders is still a much-debated subject. Since the introduction of the term "interstitial gland" by M. Bouin in 1900 with reference to the ovary and later applied to the testis by P. Bouin and P. Ancel ('03), these cells have received much attention in connection with the supposed internal secretory activity of the gonads, for which there is much evidence not only from experimental but also from strictly clinical sources and especially in the rapidly increasing field of organotherapy. One is particularly struck with the number of reports in current clinical literature on the more or less successful use of ovarian extracts and transplants in female disorders.

The question of cyclic changes in the interstitial cells of the testis and the relation of such periodicity to the various sexual phenomena, has been recently considered (Rasmussen '17) in a paper on the occurrence of a definite and well-marked seasonal hypertrophy of these elements in the male woodchuck. While similar changes have been reported in other animals, the various phases of atrophy and hypertrophy do not correlate well with any particular one of the other sexual phenomena. The interstitial cells of the testis are taken up again in this paper because a number of cytological details have been reinvestigated and because a comparison of the cyclic changes in these elements and the homologous cells of the ovary seemed desirable.

Essentially the same problems that are met with in the testis are encountered in the ovary, where similarly there are several tissues to which the endocrine function may be attributed and where there is much uncertainty as to the exact role played by each of the morphological components.

Of the many lines of inquiry followed in working with the interstitial cells of the ovary, a number stand out rather prominently; namely, comparative investigation as to their presence and relative abundance in the adult of different species, their morphological alteration during various periods of life as correlated with the sexual cycle, the effects of ovarian extirpation and transplantation, and their origin. The effects of X-rays

and of ovarian extracts together with histological findings in the ovary in various functional and developmental disorders, have also yielded many suggestive facts. It is not the purpose here to analyze the mass of literature that has necessarily accumulated since this has been done at various intervals and from various points of view in many papers of which the more recent ones are those by Anna Schaeffer ('11), Van der Stricht ('12), Pardi ('14a, '14b), Aschner ('14), Kingsbury ('14), Firket ('14) (best review of literature on non-mammalian forms), O'Donoghue ('16) (on marsupials), and Boring and Pearl ('17) (on birds). The publications by Tandler and Grosz ('13), Biedl ('13), Blair Bell ('16) and Falta ('16) may also be mentioned.

In regard to the presence or absence of interstitial cells in the ovary of adult mammals, it may be well to call attention to the fact that of more than one hundred species so far examined—of which Fraenkel ('05) and Anna Schaeffer ('11) alone investigated eighty-one—fully fifty per cent. are said to have none. In many of the species reported as not possessing interstitial cells during adult life, it is known that these elements may be plentiful in earlier stages of development. In some orders, e. g. Ungulata, they are rarely found; while in others, e. g. Rodentia, they are nearly always present. There may be considerable variation in closely related forms. In several cases there is disagreement among workers as to the presence of these cells in the ovary. This variation in opinion is primarily due to a difference as to what constitute interstitial cells and hence an interstitial gland. Falta ('16, p. 370) states explicitly that in women we understand by "interstitial gland" a cell complex that develops from the theca interna of atretic follicles. Many do not, however, agree that these hypertrophied cells are comparable to typical interstitial cells found in the stroma in many other mammalian ovaries.

A second source of error in conclusions drawn from the examination of a few specimens of a given species is the more or less periodic change which the interstitial cells may undergo in animals, so that at certain times they are very inconspicuous and may be largely or even entirely overlooked in preparations stained by ordinary means; while at other times, usually related

to active stages in the sexual cycle, they are easily detected. A failure to recognize the possibility of such fluctuations is undoubtedly responsible for some of the disagreement.

The primary object of this paper is to describe such variations in the interstitial cell content of the ovary of an animal, the woodchuck (*Marmota monax*), which has a single sexual cycle per year, the successive cycles being interrupted by about four months of profound dormancy so that there is no overlapping of any of the phases. The latter point is of much advantage since it is obviously very difficult to make reliable deductions where structures developed in one phase are carried over to the same or some other phase of the following cycle or cycles. The fact that this animal becomes reduced in weight and exists for months without food and with a rectal temperature of 6° C. to 15° C., when normally in the active state the body temperature is in the neighborhood of 37° C., and with all the physiological processes enormously reduced, should also present a situation that might throw some light on the behavior of the interstitial cells under modified functional conditions.

The bearing of these observations upon the problem of the significance of the interstitial cells naturally rests upon the assumption, generally accepted, that functional activity is correlated with structural changes, although it has not been proved that hypertrophy of these cells corresponds to increased secretory activity upon their part. One must agree with Gley ('17, p. 212) that there is a pressing need for physiological studies testing this assumption.

CYCLIC CHANGES IN THE INTERSTITIAL CELLS OF THE OVARY HISTORICAL

Because of the availability of material and the size, great abundance and uniform distribution of the interstitial cells of the ovary in the rabbit, this animal has been used more than any other species in investigations of morphological variations in these elements. However the earliest record of such changes is generally attributed to MacLeod ('80) who found that in the mole the lateral and greater portion of the ovary, which represents the medullary portion of the typical mammalian ovary and is separated from the cortical tissue by a distinct groove at certain seasons of the year, is minimal in June. By the last of October the entire ovary has increased to five times its former

size and the lateral portion which now constituted nine-tenths of the entire organ was much darker in color and consisted of medullary cords separated by great masses of interstitial cells which were responsible for the enlarging of the ovary. During this increase in the interstitial cells, follicles had been developing and were beginning to undergo atresia. No information is given as to when atrophy takes place. This must occur some time before the following June. While he examined the ermine and bat, no changes in the interstitial cells of these animals are mentioned.

Leydig ('57) noted that the division of the mole ovary into two superimposed parts did not exist at all seasons of the year since he did not find it so in June, but gives no further details; while Wagner ('79), in a description of the modifications going on in the ovary periodically with the recurrence of rut and gestation, considered the medullary portion of the ovary of the mole to be a corpus luteum.

According to Tandler and Grosz ('11), the mole litters during the last of April and first of May—fertilization having taken place in March when spermatozoa are abundant in the male. An increase in the interstitial cells of the ovary thus takes place months after the rutting season. In the testis of the mole of this species, Tandler and Grosz ('11), found a similar hypertrophy of the interstitial cells. This reaches a maximum in August, or about two months ahead of the corresponding changes in the female. In the testis also these elements are minimal during the rutting season.

A suggestion of periodicity in the interstitial cells was made by Paladino ('87), who describes a continual degeneration and regeneration of the ovarian parenchyma (including the interstitial cells) and noted that these processes are not going on at a uniform rate at all ages or even in the adult, being, in the latter case, especially marked at the time of heat and pregnancy, during which times he also noted, especially near the hilus, marked down-growths of the germinal epithelium into the medulla and other evidences of regeneration apparently compensatory for the marked degeneration that had gone on. He worked on the pig, horse, cow, sheep, goat, rabbit, guinea-pig, cat, dog and man and apparently found the above to be true in general.

Child ('97) found the stroma cells of the ovary of pregnant rabbits and of a pregnant dog to be much hypertrophied and to possess a centrosome and sphere—structures not demonstrable by this author in these cells in adult rabbits at other times except shortly after parturition. He could not find a centrosome and sphere in these elements in the cat or in the white rat at any time, although he noted that at the time of preg-

nancy the stroma cells undergo hypertrophy somewhat the same as in the rabbit and dog. Child is evidently describing changes in what are now generally termed interstitial cells for he found intermediate stages between spindle-shaped stroma cells and polyhedral cells with a spherical nucleus. He states that in non-pregnant rabbits the stroma consists largely of the long spindle-shaped cells with deep staining nuclei and boundaries that are difficult to make out; while the ovaries of pregnant rabbits (and dog) contain relatively few of these spindle-shaped stroma cells, but instead a great many of the larger cells with abundant cytoplasm, one or two distinct centrosome and a vesicular nucleus eccentric in position.

Child raises the question as to what is the relationship of these ovarian changes to pregnancy. A number of subsequent investigators have attempted to throw light on this particular question, using mostly the rabbit as material; yet not only does the question remain unanswered, but there is great diversity of opinion as to what changes if any, in these (interstitial) cells, actually do occur during pregnancy, as the following review of the literature will show.

Lane-Clayton ('06) found in the rabbit an increase in the size of the interstitial cells of the ovary with the progress of pregnancy, reaching a maximum at about the twenty-second day. They increase in diameter from 17 to 32 micra or about five times in volume. The whole ovary increases, which is fully accounted for by the hypertrophy of the interstitial cells. Commencing a few days before parturition, they diminish again, reaching a minimum about six weeks later, which is maintained till the next pregnancy supervenes.

Pardi ('14b) similarly found in the rabbit an increase in size and in lipid content of the interstitial cells during the major portion of pregnancy, those in the virgin being 22 to 23 micra in diameter while in the pregnant animal they increase to 27 or 28 micra. This increase is solely in the cytoplasm, according to this author. The nucleus remains unchanged. There may also be an increase in number by a transformation of stroma-cells. The whole ovary increases in size directly with these changes.

An increase in the lipoids during pregnancy has been recorded by Ciulla ('09) and Ciaccio ('10). The latter author from a study of the cat, dog, rat and guinea pig, in addition to the rabbit, also thinks that there may be an increase in number of interstitial cells by a hypertrophy of stroma elements.

Others have failed to find any striking change during pregnancy or other phases of the sexual cycle in the rabbit. Limon ('02) maintains that when once formed they remain un-

changed. Allen ('04) says that a description of the interstitial cells in a six months old virgin rabbit applies equally to early pregnancy and he is inclined to think from an examination of a number of adult rabbits that pregnancy makes no difference in the number of atretic follicles (from which interstitial cells may be derived). Zalla ('07), who worked on the rabbit as well as on ten other species, could not establish any appreciable or constant change in the interstitial cells during pregnancy. Regaud and Dubreuil ('08), while not denying the possibility of a slight increase during gestation in the rabbit, did not find a regular correlation between degrees of hypertrophy of the interstitial cells and duration of pregnancy, all stages of variation in these elements being encountered at any particular stage of pregnancy. They found later ('09) that there is a tendency for this tissue to develop during the spring months.

And finally the third possibility, namely, that the interstitial cells decrease during pregnancy, has been strongly defended for the rabbit, as well as for other animals, by Aschner ('14), who maintains that the interstitial cells of the ovary increase till rut, being maximal at the beginning of pregnancy, and that there is a distinct retrogression as corpora lutea develop. The next period of follicular growth and increased atresia is accompanied by an increase in the interstitial cells.

Montuoro ('03) found a decrease in the amount of lipoids in the interstitial cells during pregnancy in the rabbit; but Pardi ('14b) argues that this must be due to faulty technique, Montuoro having used osmic acid and paraffin imbedding, resulting in a loss of some of the more soluble lipoids.

The rabbit has been used for many other lines of research upon this subject, but the above is believed to be a fairly complete résumé of the particular phase with which we are here concerned. It is evident that in spite of the amount of work done on this supposedly very favorable animal, there is still great need for a careful checking up of this entire line of investigation on this as well as on other species. A number of other animals have received some attention and to the results obtained we may briefly refer.

From an examination of the ovaries of 250 dogs, Aschner ('14) found during pregnancy a similar decrease in the interstitial cell to that described by him in connection with the rabbit. He disagrees radically with Fraenkel ('05, '11), Aimé ('07), Schaeffer ('11) and others who claim that there are no interstitial cells in the ovary of the adult dog. It was noted above, however, that Child ('97) described the ovarian stroma of a pregnant dog as containing polyhedral cells essentially similar to those in the rabbit. While Ciaccio ('10) cites the dog as an example of an animal in which the interstitial gland,

represented only by scattered elements, shows marked hypertrophy during pregnancy and moderate infection and intoxication. Asehmer explains that the discrepancy in the observations between himself and Fraenkel, etc., may be accounted for on the grounds that these cells are readily changed by disease, inanition, poisons and by defects in the glands of internal secretion. These conditions, he claims, may so decrease the fatty content of the ovary that Sudan III gives no stain in frozen sections. In reviewing the phylogenetic and ontogenetic conditions, he concludes that the higher one goes in the animal scale the more the corpus luteum dominates and the more the interstitial cells are depressed. Such an inverse proportional development of the interstitial gland and corpus luteum was also noted in a number of animals by Cesa-Bianchi ('07a) and Anzilotti ('09), and calls to mind the classification of mammals proposed by Bouin and Ancel ('09), who place in one group animals in which ovulation is spontaneous so that at definite periods there develop one or more corpora lutea regardless of fertilization. Such animals do not have an interstitial gland. In the other group they place animals in which corpora lutea develop only at coitus and hence possess only corpora lutea of pregnancy; but they have an interstitial gland which takes the place of the periodic corpora lutea. Exceptions to this rule have, however, been recorded. This point is discussed by Kingsbury ('14), Loeb ('17) and others and need not be further considered here.

In marsupials O'Donoghue ('16) finds that subsequent to ovulation the interstitial cells and their nuclei undergo hypertrophy, although they never become as large as the cells of corpora lutea. At this time they appear very epithelioid and glandular, and in consequence he regards them as masses of secretory tissue. The maximal enlargement is reached about the time the corpora lutea become fully formed and appear to remain active longer than the luteal cells, being in an active condition long after birth of the young and after the corpora lutea have commenced to decline.

Athias ('16) says that in the guinea pig the interstitial cells increase at puberty and gestation at the expense of atretic follicle. Although Loeb ('17, p. 300) states that just prior to ovulation a sudden simultaneous degeneration of all but the smallest follicles sets in and that the theca interna of atretic follicles is strongly developed five to seven days after ovulation, he regards the ovary of the normal adult guinea pig as not possessing true interstitial cells. In earlier publications ('11, p. 341 and '14, p. 39) he speaks of their being represented only by small shrinking connective tissue cells of the theca interna filling the place of lost parts of the follicles which are in process

of atresia. In the most recent paper ('18, p. 48) we find the unqualified statement that typical interstitial cells are not present in the ovary of the normal guinea pig. This divergence of opinion is extreme when we consider that Limon ('02, p. 185) claims that interstitial tissue (composed of interstitial cells) is abundant in the ovary of the adult guinea pig and describes them (p. 165) as being 12 to 15 micra in diameter with a nucleus of 4 to 5 micra in diameter and as forming dense cords and compact masses of cells. Fraenkel ('05, p. 500) says in connection with the four types of ovaries as regards the nature and arrangement of the interstitial cells:

“Den Haupttypus habe ich in Uebereinstimmung mit Limon oben beschrieben. Der grösste Theil des Ovariums ist von diesem Gewebe eingenommen, welches durch Bindegewebsstränge, die mit Rinde und Hilus communiciren, in Läppchen und Fächer eingetheilt ist. Die Zellen liegen sehr dicht, sind dunkel gekörnt oder enthalten feinste Tröpfchen. Ihn repräsentiren am schönsten die Nager, wie Kaninchen, Meerschwein, die Meerkatze, ferner unter den Beutlern die Petro- und Onychogale.”

Bouin and Ancel ('09, p. 465) from their own investigations include the guinea pig with the rabbit, mouse and cat as examples of animals with an interstitial gland in the ovary in contrast with women, primates, dog, mare, sow and cow, which possess no interstitial gland but instead periodic corpora lutea. A number of others have described interstitial cells in the guinea pig ovary specially in connection with cytological studies; but it is not always clear that they have reference to adult animals—the only ones admissible in this discussion.

The technique to be employed in the investigation reported here was tried out on guinea pig ovaries and certainly there are many comparatively large cells (10 micra and more in diameter) with spherical or nearly spherical nucleus (5 micra in diameter) and with lipoid-laden cytoplasm—the three principal criteria of interstitial cells—not only in the theca interna of atretic follicles but also in groups in the stroma between follicles and about blood vessels in the medullary portion of ovaries of an adult animal. It is difficult to see how these can be ruled out from the so-called interstitial cell category. At least—and this is the reason for dwelling upon this point—these are what is now in general meant by interstitial cells and this paper deals with such elements. As for differentiating them from the ordinary stroma elements of the guinea pig ovary, better differentiation was obtained with acetic-osmic-chromic fixer and sodium alizarinsulphonate and crystal violet stain on guinea

pig than on wood chuck material. It may still be objected that these groups of cells in the stroma proper are the remains of atretic follicles. O'Donoghue ('16), for example, thinks that during degeneration of follicles some of the theca cells merely pass through a stage in which they resemble interstitial cells, and that the interstitial cells constitute a tissue *sui generis*. To this one can only reply in the words of Kingsbury ('14, p. 73): "So consistently has this mode of thecal origin of the interstitial cells of the adult ovary been supported by the observations of nearly all who have devoted careful study to this phase of the subject that it may be accepted as clearly proven." As to whether these cells collectively constitute a gland is a separate question. One must agree with Loeb ('17) and many others that there is a lack of clearness in the definition of interstitial gland of the ovary, to say nothing of its specific function.

Since a large number of investigators considers that the hypertrophied cells of the theca interna of atretic follicles in women are homologous to the interstitial cells of the stroma in animals, a consideration of the human ovary must be included in this review if it is to be reasonably complete; for an increase in atresia and the accompanying hypertrophy of the theca interna cells of involved follicles, has been described in the human ovary during pregnancy by De Sinety ('77), Cohn ('03, '09), Böshagen ('04), Pinto ('05), Seitz ('06), Basso ('06), Walwart ('07, '08), Fellner ('09), Greggio ('10), Potter ('10), Wolz ('12), Meyer ('13), Keller ('13), Pardi ('14b) and Schottländer ('14). While all these authors do not agree as to the significance of this hypertrophy, most of them consider it an expression of secretory activity. Wallart and Schottländer maintain that here is a similar increase during menstruation in human subjects. Fraenkel ('05, '11), Aimé ('07), Bayer ('08), Bouin and Ancel ('09), Schaeffer ('11), Foster ('17) and others can, however, see nothing in the adult human ovary that could be considered an interstitial gland, although Fraenkel ('05) describes an enlargement of the theca cells during pregnancy. Aschner ('14) from an examination of seventy-eight cases concluded that the interstitial cells are not only much less in evidence in the adult and even at puberty than at birth, but decrease still farther with the appearance of corpora lutea—a general principle that this author finds applicable to a number of different animals as already noted. He considers, however, that the interstitial tissue constitutes a distinct morphological structure.

The whole subject is fraught with uncertainty and conflicting opinion. This is probably illustrated nowhere else so well as in the case of the human subject. To illustrate this point, although not strictly pertaining to cyclic changes a number of

recent opinions may not be out of place. Thus Kingsbury ('14), while finding no difficulty in demonstrating interstitial cells in the human ovary (presumably adult), regards them as transitory elements coming from and returning to ordinary stroma cells, and finds it difficult to escape from the conclusions of Fraenkel ('05, '11) that a tissue so inconstant in its presence, even in mammals, does not deserve the dignity of being termed a gland. This is the opinion also of O'Donoghue ('16). Blair Bell ('16) greatly minimizes the importance of the interstitial cells, claiming that the gonads as a whole play only a subsidiary part in connection with a determination of secondary sexual characters and other internal secretory functions ascribed by many to this organ and in particular to the interstitial tissue. Falta ('16), on the other hand, says that the function of the interstitial gland in man is today already so sharply delimited and is concerned with functions so important and extensive in influencing the conformations of the body, that it is hard to believe that so important an organ is absent in women.

In contrast to the uncertainty in regard to cyclic changes in the interstitial cells of the ovary of many of the forms so far discussed, is the marked annual periodicity described in a number of hibernating animals.

Cesa-Bianchi ('07b), from an examination of serial sections of more than one hundred ovaries of the bat, found that in late March and early April, immediately after the hibernating period, the ovary increases to several times its former size, due to a great increase in interstitial cells, which become completely filled with lipid and pigment.

In May and June when nearly all females contain foetuses, the ovary is still large and yellow but follicles are so reduced in number that one would hardly recognize the organ as an ovary. The interstitial cell masses have become lobulated rather than columnar. This condition prevails during the remainder of the summer.

Just before bad weather sets in in the autumn and before dormancy intervenes, the interstitial cells rapidly decrease and finally well into the winter season have nearly disappeared. The ovary loses its yellow color and diminishes in volume.

It is to be remembered that in the bat copulation takes place in the autumn; but fertilization and segmentation of the ovum does not occur until after waking up in the spring, when hypertrophy of the interstitial cells again occurs.

Similar changes, except to a less degree, were observed by this author in the badger, squirrel, marmot and hedgehog.

Van der Stricht ('12) noted an increase in the number and size of interstitial cells of the ovary in the bat during winter and particularly in the spring after waking up. The nucleus

of these cells becomes slightly larger and stains less densely. The cells become arranged in acini-like groups which are especially numerous and conspicuous during second maturation and ovulation and persists during the summer to a lesser and lesser degree as autumn is approached. In September and October such groups are no longer in evidence, the interstitial cells having materially decreased.

Asehner ('14) states that a decrease in the fatty content and the interstitial cells of the ovary of the hedgehog and tenrec (*Centetes ecaudatus*) takes place during hibernation, while an increase occurs in the spring. This investigator suggests that the large amount of interstitial tissue in the ovaries of rodents, insectivores, bats, etc., may be related to the fertility of these animals, since a great many follicles are produced and hence much atresia follows. Paladino ('87) similarly noted that degeneration and regeneration in the ovary is more extensive in the more prolific animals.

Only two references were found which dealt with the interstitial cells of the ovary of a hibernating animal of this country. In connection with the subject of hibernation and the pituitary body, Cushing and Goetsch ('15) incidentally report that in the ovaries of two hibernating woodchucks killed in February, there was a small amount of interstitial tissue, but no interstitial cells were definitely recognized. There were no mature follicles. In an animal sacrificed late in March, one ovary contained several corpora lutea and but little interstitial substance containing a few immature follicles. In a fourth animal, which was sacrificed early in May and which had been in captivity all winter and awake several weeks, there were fully formed follicles and one corpus luteum and an increase in the interstitial cells.

Drips ('17), while studying primarily the corpus luteum of the spermophile (striped gopher, thirteen-lined ground-squirrel or technically *Citellus tridecemlineatus*), noted that the interstitial cells were most conspicuous during early pregnancy and least noticeable just before hibernation took place.

On the whole it appears that an observable increase in the size and possibly in the number of interstitial cells of the ovary of some animals occurs more or less synchronously with rutting and may persist to some extent during pregnancy. There is, however, so much disagreement in connection with several of the species studied that it is impossible to draw conclusions as to the extent of such changes. It is evident that a serious obstacle in the way of accuracy in judging of the degree of hypertrophy or atrophy in the interstitial tissue in most animals, is the irregular and scattered arrangement of the cells. Even in the rabbit, where they are most regularly arranged, there are

great differences in the recorded observations. There is, in consequence, a necessity for much detailed cytological work along this line before it is clear just how extensive cyclic changes occur and with which phases of the general sexual cycle such alterations are related.

PRESENT INVESTIGATION

Material and Methods

This report is the result of an investigation of 144 (72 pairs) of ovaries taken from woodchucks killed at various seasons of the year, the technique employed being the same as that used on the interstitial cells of the testis (Rasmussen '17).

All the animals except two were captured in the vicinity of Ithaca, New York. The ovaries of the two exceptions were obtained from Dr. T. G. Lee of the University of Minnesota. They had been collected somewhere south of Minneapolis several years ago and were well fixed in Zenker's fluid and preserved in alcohol. I take this opportunity to thank him for this material which was especially valuable because both the animals from which it was obtained were pregnant, one containing six very young fetuses (uterine enlargements being 8 mm. to 9 mm. in diameter) and the other one seven older fetuses 40 mm. to 45 mm. in length.

The 72 animals involved were killed at intervals so that a larger number were sacrificed at the more critical periods. The number killed in the respective months of the year are as follows: 1 in January, 7 in February, 6 in March, 12 in April, 9 in May, 1 in June, 13 in July, 10 in August, 1 in September, 4 in October, 2 in November and 6 in December. While most of those used between the months of October and the following March had necessarily been kept in captivity from the preceding September, a few controls were obtained directly from the normal habitat in February and March. This is obviously important because these animals do not breed in captivity, as far as our experience goes, and unless material is available from animals that have not been kept for any length of time in captivity, one would not be justified in concluding that the findings represent the conditions as they exist normally. All the illustrations on the ovary accompanying this paper except figures 8 and 17 are from animals killed either in the field, im-

mediately upon being brought to the laboratory or at most two days after being captured. After March and until October material was available again directly from the normal habitat.

The artificial burrows in which nearly all the animals were allowed to hibernate in captivity have been previously described (Rasmussen '15). These burrows are such that the conditions are essentially the same as in the natural ones and in them woodchucks have successfully become dormant for a number of years. Five animals involved were shipped to the Institute of Anatomy, University of Minnesota, where they were kept in a small room in which the temperature was kept between -5° C. and $+13^{\circ}$ C. Only occasionally and then for only a few hours did the temperature go below 0° C. and above $+10^{\circ}$ C. during the hibernating period.

In addition to the technique used on the testis as referred to above, fifteen animals were injected with neutral formalin and potassium dichromate as advised by Cowdry ('16b) and quoted by Scott ('16). Perfusing the animal with Loeke's solution sufficiently to produce a degree of edema in the ovaries before the fixer is allowed to enter the vascular system was found especially useful in opening out the dense stroma and separating the individual cells, making them stand out more prominently. This material as well as that fixed with the aceto-osmic-chromic fixer used on the testis, when stained with acid fuchsin and methylgreen according to the directions given by Cowdry, gave the most instructive cytological picture by bringing out in sharp contrast mitochondria and other granules in the cytoplasm. If sections from material fixed in solutions containing osmic acid are passed rapidly through the higher alcohols and clearers, covered with a thin layer of xylol-balsam and using no cover glass, but allowing the balsam to dry quickly, the lipid granules darkened with the osmic acid may be retained. If very much lipid is present, other cytoplasmic granules are masked too much and it is then better to allow the large lipid granules to be dissolved out. In this case a cover is used. The lipid then appears as vacuoles. It will be interesting to see how the acid fuchsin and methylgreen stain will last in uncovered preparations since it is known to fade in a year or two ordinarily when covered.

While in most cases it was necessary to cut both ovaries into pieces to provide material for the various fixers, a sufficient number of whole ovaries were fixed to provide for complete serial sections representative of the different seasons of the years. Sections were cut 3, 5 and 10 micra in thickness. For cytological details the thinnest sections were necessary.

Results

Conditions during autumn.—From September to November the ovaries are small, each varying from .0005 to .0015 per cent. of the net body weight. During this period there is a slight increase in size as winter is approached, due largely to growth of follicles. There are no corpora lutea present. Only occasionally is there any evidence of such structures having been present, the evidence being the presence of large pigmented cells in an area composed mostly of connective tissue still more or less radially arranged. Follicles in nearly all stages of development are present (Fig. 1). Since both ovaries are alike in practically every case during this and other periods of the year when no corpora lutea are present, the percentage weights given refer in all cases to a single ovary.

In the stroma both of the cortex and medulla are many cells varying in size from 4 to 13 micra in average diameter (most of them being from 5 to 9 micra), containing a round vesicular nucleus from 3.8 to 7 micra (mostly 5 micra) in diameter, with a variable amount of cytoplasm as shown in figure 24. The cytoplasm is rarely free from one or more comparatively large lipid granules that darken with osmic acid. These are the so-called interstitial cells as distinguished from the ordinary stroma cells which have an elongated more or less spindle-shaped granular nucleus and only a small tip of cytoplasm (containing a few mitochondria) at each end.

The variation in size and shape of the interstitial cells and the lipid (shown in black or as vacuoles) and mitochondrial content (red) are shown in figure 24. The size of the cells varies directly with the lipid content. There are only a few cells with as much lipid as is shown in cell e of this figure. As a result it is difficult to give an adequate idea of the amount of interstitial tissue in a general view. In figure 1, which is a photograph of a longitudinal section through an ovary of this

period, the darker areas are due to the osmic acid of the fixer having blackened the lipoid of the interstitial cells. The amount of lipoid in this particular case is, however, greater than is usually the case at this time of the year. In many instances a photograph of this kind would show practically no dark areas in the stroma, but appear essentially as figure 7, not because there are no interstitial cells but because each cell contains only a few lipoid granules and many sections through cells show none, as in cell b of figure 24, and hence there is not enough contrast to show anything at so low a magnification. (X $7\frac{1}{2}$).

In the cortical portion of the ovary there are usually masses of interstitial cells closely associated with the follicles, occupying a triangular area on the hilus side of the follicle. Irregular rows and columns of cells are also found in regions between follicles. These have their long axis directed towards the hilum. The septa of ordinary stroma and the blood vessels undoubtedly are responsible for this arrangement. In the more central part of the ovary, the interstitial cells are in close proximity to the blood vessels and medullary cords, often forming a wall about these structures. This relationship to the vascular system and medullary cords is shown in figure 10, which, however, is a photograph of a later stage when the interstitial cells have much enlarged. The interstitial cells constitute the dark areas. In the center of many of the interstitial cell masses is a medullary cord, not seen very plainly in the photograph. The close association of interstitial cells with the blood and lymph vessels has been described by many authors. Some have taken this as evidence of the secretory activity of these cells.

Mitochondria are packed closely in the scanty protoplasm about the nucleus and between the large lipoid granules. Nearly all mitochondria are spherical as may be seen in figure 24. In a preliminary report of this work (Rasmussen '18) it was stated that there were also short rods. It appears from a closer study of the best fixed material that these rods can usually be resolved into two granules. Still there are a few very short ones, from $1\frac{1}{2}$ to 2 times as long as they are wide, each of which appears to be a single body.

Mitochondria have been described in the interstitial cells of a number of animals by Mulon ('10), Athias ('11, '12), Levi ('13), Cattaneo, and Pardi ('14b), usually as rods and granules. Pardi in the rabbit indicates only 6 to 8 rods to 100 or 200 round mitochondria.

In the woodchuck the mitochondrial content appears to vary directly with the size of the cells during this stage.

The nucleus is usually somewhat eccentric, nearly spherical, with a very attenuated chromatin network and one or two distinct nucleoli. There are some elongated cells, as figure 24a, in which the nucleus is also elongated. These are evidently transitional stages in the formation of typical interstitial cells from the ordinary stroma cells or cells that appear to have migrated from the germinal epithelium as will be discussed later. In these elongated cells the chromatin is more granular (not indicated in the figure because in the over fixation necessary to bring out mitochondria, the nucleus appears nearly homogenous with the acid fuchsin-methylgreen stain. The nucleus tends to vary in size directly with the size of the cell. In general this is also true of the nucleolus.

In winter during hibernation.—Hibernation commences in November and continues till some time in March. During this period, just as in the autumn, the ovary shows great individual variations in weight, varying from .0008 to .0023 per cent. of the net body weight. The average weight is about .0014 per cent. This range of variation is met with during all parts of the period, although the ovaries appear to constitute on the average a slightly greater proportion of the body weight toward the end of hibernation. But since during dormancy the body weight falls $\frac{1}{4}$ to $\frac{1}{3}$ of its original weight, this increase does not indicate an actual enlargement of the ovaries. Both ovaries of the same individual are strikingly alike. A section of a typical ovary representative of late hibernation is shown in figure 2. As is clearly evident by comparing this figure with figure 1, there is no follicular development during winter sleep. On the contrary, there is much atresia. Most of the large follicles and many of the smaller ones have become atretic and as usual the cells of the theca interna acquire lipid

and in other respects come to be indistinguishable from interstitial cells in other parts of the stroma. The conditions are the same in animals taken directly from their normal habitat and in those kept in captivity.

Some of the interstitial cells during dormancy are slowly enlarging so that a number are 16 micra in average diameter. A few cells may be even larger, especially late in this period, but most are between 8 and 10 micra. The enlarging is due principally to an increase in the lipoid. As spring is approached there are a greater and greater number of cells containing as much lipoid as is shown in figure 24 e. By the last of February, as shown in figure 2, the interstitial cell masses are noticeably more prominent than before hibernation commenced.

With an increase in the size and lipoid content of the interstitial cells during this period there is an increase in the number of mitochondria, and in the largest cells some of the mitochondria appear somewhat larger while no rods are evident. These large mitochondria may, therefore, only be the elongated ones that have assumed a spherical form. Levi ('13) in the guinea pig and other forms records an increase in the mitochondrial content with hypertrophy of these cells to a certain point and that they persist during fatty infiltration to an extreme degree. Athias ('11, '12), however, in both guinea pig and bats describes the mitochondria as being inversely in proportion to the lipoid, while Pardi ('12b) in the rabbit could see no difference with hypertrophy of the interstitial cells during gestation.

The nucleus has enlarged, being from 4 to 8 micra in diameter (most of them being about 6 micra). The nucleoli tend to enlarge in about the same proportion.

There is therefore no sudden change in the interstitial cells with the onset of hibernation nor any decrease in the activity of these elements during dormancy as far as the criteria of amount of lipoid, number of mitochondria and size and prominence of the cells are concerned. The statements made in the literature that the interstitial cells of the ovary decrease during winter-sleep are in most cases based on the few observations made on hibernating animals in which the period

just preceding and the early part of hibernation have not been carefully investigated and where the assumption has been made that since the interstitial cells are more prominent in the summer than in winter, that the decrease has taken place at the onset of hibernation. As we shall show later, in the woodchuck the decrease takes place during full activity in the summer, and as already indicated there is a slow but unmistakable increase in the interstitial tissue during lethargy although no food or water is available for several months. A general idea of the appearance of the stroma at the close of hibernation as compared with that preceding dormancy after a sharp nuclear stain is obtainable by comparing figure 16, which is from an animal killed in autumn, with figure 17, which is from an animal sacrificed March 18 within 48 hours after waking up. In the left hand portion of each figure are many interstitial cell nuclei which appear more or less round in contrast to the long, spindle-shaped nuclei of stroma cells (although there are intermediate forms). The round nuclei are much more prominent and in general somewhat larger in figure 17. These differences are reflections of the differences existing between the entire cells. The irregular distribution of the interstitial cells in the woodchuck makes quantitative statements only of a very general character possible. In the bat it also appears (Van der Stricht '12) that the interstitial cells are minimal during September and October and that they tend to increase during winter.

Asehner ('14), it may be recalled, claims that in dogs the interstitial cells of the ovary are diminished by inanition. The type of inanition involved during hibernation appears not to produce such an effect in the woodchuck, at least.

In the spring after hibernation and during rutting and beginning pregnancy.—Immediately after waking up from winter sleep (which in the vicinity of Ithaca, New York, usually occurs about the middle of March) the rutting season commences and the ovaries enlarge rapidly due to a ripening of numerous follicles and to a rapid increase in size of all of the many interstitial cells that have remained comparatively small. Before the end of March the ovary may represent .0050 per cent. of the net body weight. The lipoids of many of the interstitial

cells increase so that the mitochondria, which appear to have reached their limit in number, are crowded in between the large fatty granules as illustrated in figure 25 b, where the lipoid is seen as vacuoles. Others have less lipoid and more cytoplasm rich in mitochondria as illustrated in figure 25 a, where the lipoid granules are represented in black. There are also intermediate forms.

During the early spring increase there appear in many of the larger cells additional granules somewhat larger in size than the mitochondria but having, as far as the technique here employed would indicate, very similar staining reaction. In figure 25, cell a contains three and cell b two such granules. They are best demonstrated in the material fixed in Meves' fluid. They may be of the nature of secretion granules or they may be other lipoids sufficiently chromated to take the stain. That they are produced from mitochondria, as Mulon ('10) believes to be the case in regard to secretion-like granules in the interstitial cells of the rabbit ovary, is also possible. These granules will be further discussed later.

While females captured in April usually contain foetuses, some may be found not to have become pregnant as late as early in May. In these late cases extreme hypertrophy of the interstitial cells is found. This may be due to a prolonged rutting period, as would be suggested by the results obtained by Regaud and Dubreuil ('09) who found that prolonged cohabitation with the male produced a noticeable hypertrophy of the interstitial cells of the ovary in the rabbit.

The maximal development of the interstitial tissue encountered is shown in figure 3. This is from an animal shot in the field while chasing about with a male (which was also shot and found to possess testes with ripe spermatozoa and interstitial cells maximal) about six weeks after woodchucks were observed in general to become active that particular season. The great size of the ovary is apparent since it is reproduced at the same magnification as figures 1 and 2 and represents .0085% of reduced body weight. Both ovaries were alike. Six ovaries representing this stage were obtained.

The abundance of interstitial cells may be judged from figure 4 which is an enlarged view of the area outlined in white in

figure 3. The blackened lipid granules, which serve to identify the interstitial cells, are here shown with greater contrast. A still higher view of a thinner section with a nuclear stain is shown in figure 18, which is directly comparable with figures 16 and 17. Many of the interstitial cells are over 20 micra in average diameter, containing a nucleus as large as 12 micra and nucleoli as large as 3 micra in diameter. The chromatin becomes more attenuated as the nucleus enlarges. Most of the cells are in the neighborhood of 16 micra and the nuclei about 8 micra in diameter. The size to which these cells may develop is shown in figure 26 b. They are often arranged in irregular groups, the individual cells being poorly separated from each other, as illustrated in figure 26 a. The quantity of lipid in the individual cell varies from an amount that fills completely the cell as in figure 25 b to relatively a few granules such as is shown in some of the cells in figure 26. The cells not completely filled with lipid are by far the most numerous in these extreme cases. Such cells contain a correspondingly large number of fuchsinophile granules of various sizes as shown in figure 26. The smallest granules—evidently mitochondria—are greatly masked by the larger ones and are seen only in the best fixed material 3 micra, or less in thickness. The larger granules are more easily fixed and stained, being fairly clear in ovaries fixed in Zenker's fluid and preserved for several years in alcohol before being imbedded and stained with iron hematoxylin. In such preparations they appear essentially the same as the so-called secretion granules of neighboring lutein cells.

Various forms of granules have been observed in the interstitial cells of the ovary of several mammals by a number of investigators by employing copper hematoxylin, iron hematoxylin, and other stains. The fuchsinophile granules figured by Montuoro ('03) in the interstitial cells of the rabbit appear to be very similar to those here described. This author shows cells, containing very little fat, which are practically filled with such granules. He found the interstitial cells of older adults to be relatively richer in metaplasia, possibly due to a replacement of the fuchsinophil granules by fatty droplets such as evidently occurs in the woodchuck a little later when atrophy commences, as will be shortly explained.

In figure 3 it will be noted that there is considerable atresia. In one very large atretic follicle and two adjacent smaller ones the intensely black color is due to the abundance of lipoid in the hypertrophied theca cells. The other smaller atretic follicles scattered throughout the ovary contain less lipoid. There is no essential difference between these hypertrophied theca cells and interstitial cells not related to follicles. The theca cells acquire lipoid more rapidly and tend to become somewhat larger in size. A medium-sized atretic follicle of this period is shown in the center of figure 22. The cytological details of the theca cells may be represented by figure 26. The theca interna (T) can be distinguished from the surrounding stroma (IC) by its heavier lipoid content, indicated in black. There can be no mistaking of derivatives of the granulosa for hypertrophied theca cells in this case because the basement membrane (M) is still intact and within are a few remains of the atrophied granules as well as a fairly well preserved ovum and a little of the discus proligerous indenting the lower side of the egg membrane.

The similarity in appearance of interstitial and lutein cells has been commented on by many writers and especially by Van der Stricht ('12), who found in the bat a marked encroachment of the corpora lutea upon the stroma so that the outlines of the former are not clearly defined, but cords of interstitial cells become continuous with the corpus luteum. Such interstitial cells have the same aspect as lutein cells. There is some similarity between these two elements when the interstitial cells are maximal in the woodchuck. A typical lutein cell is shown in figure 29 and is seen, however, to be much larger than the largest interstitial cells; to be free from lipoids, which blacken with osmic acid; but to be literally filled with granules that resemble in almost every respect the larger fuchsinophile granules of the interstitial cells. In very early corpora lutea there are apparently lutein cells containing a few such fatty droplets but they soon disappear in the case of corpora lutea of pregnancy. Later towards the end of gestation and after parturition, such lipoid appears again, evidently as an expression of degeneration. In corpora lutea resulting from rupture of follicles not followed by pregnancy, the lipoid appears much earlier.

Two such corpora lutea are shown in figure 3 (CL') where the fatty content appears black.

Usually there is no difficulty in distinguishing corpora lutea from atretic follicles; but in one animal, containing very young fetuses, was found what was taken to be a corpus luteum much younger than the others and with considerable blood in the large central cavity. On following the series along it was found that it contained an ovum (indicated by O in figure 20). The theca interna had already been largely incorporated, as normally occurs in corpora lutea, so that it is not possible to exclude the cells of the theca interna from being the source of the large luteal-appearing cell, especially since what appears to be a few degenerating granulosa cells are found about the egg and in the adjacent lutein tissue. The rest of the tissue cannot be distinguished from neighboring corpora lutea of pregnancy. However, only material fixed in Zenker's fluid and stained with iron hematoxylin, was available. In all probability this is another example of an abnormality where the granulosa cells have changed to lutein cells before the ovum has been discharged such as has been described in some other animals (c. f. Corner '15).

Captivity, and isolation during the spring.—Seven females which had hibernated in captivity and after waking had been with active males (which had also hibernated in captivity) for two to four weeks, were sacrificed between April 10 and April 24. None of these animals were pregnant. While the interstitial cells were more prominent than in animals killed just at the close of hibernation, the degree of hypertrophy just described was not found in a single case. Nearly all the interstitial cells, especially in animals that had been awake the longest, were very rich in lipoid and contained many mitochondria, essentially as represented in figure 25b. They contained, however, very few of the large fuchsinophil granules.

The ovary in no case had enlarged much, if at all. Many atretic and some medium-sized normal follicles were present about as indicated in figure 8. This figure shows the maximum interstitial cell development observed in animals kept in captivity. It is taken from another female which was kept till May 18 (three weeks longer than the seven animals above men-

tioned) and which had been isolated from males since February 6 preceding. In this animal there had evidently been ovulation, judging from the young corpus luteum present. The other ovary showed two corpora lutea slightly older in appearance. Only two large ripe follicles were encountered in all these eight females kept in captivity during the spring.

Since in the woodchuck captivity does not interrupt the male sexual cycle (as far as the appearance of the testis is concerned, Rasmussen '17), it seems probable that the failure of these animals to breed in confinement is due to its effect on the female. This is suggested by the scarcity of large mature follicles in the ovary. However, M. Regaud, in discussing a paper by Branca ('03) on the testes of certain animals in captivity, reports (p. 198) that in the European marmot (belonging to the same genus as the woodchuck) no spermatogenesis occurs in males kept over winter—the testes in the spring remaining essentially as they are in winter during hibernation at which time the tubules hardly contain any cells of spermatogenic origin.

During pregnancy and lactation.—At the beginning of pregnancy the stroma is thus largely occupied by great masses of enlarged interstitial cells rich in lipoid and other granules. The growth of the corpora lutea together with the fact that frequently there is an unequal number of corpora lutea in the two ovaries, now become prominent factors in the weight of this organ, and are responsible for the unequal size frequently met with from now on till July or August. The ovary with the largest number of corpora lutea is always the heavier, one frequently being several times the weight of the other. The largest ovary obtained was one containing 5 corpora lutea and weighed .285 g. (.01163 per cent of net body weight) and was three times as heavy as the other ovary which contained only one corpus luteum. This was in the last of May, at least several weeks after parturition.

In the initial development of corpora lutea there is an inrush of the theca and neighboring stroma, carrying along with them many interstitial cells. In figure 9 the arrow indicates a group of interstitial cells (identifiable by their lipoid content, shown in black) thus being carried into a young corpus luteum in the direction indicated by the arrow. The fate of these cells

cannot be stated. They soon lose the lipoid that blackens with osmic acid and either revert to connective tissue elements associated with the vascular framework of the corpus luteum, disappear entirely or become lutein cells. The source of the lutein cells and the fate of the intruding theca cells, etc., is still a disputed question and one that cannot be entered into here. Corner ('15), who discusses at length the literature on the subject, believes it probable that in the sow some of the theca cells may remain in the fully formed corpus luteum as special cells distinguishable from the other lutein elements.

With the progress of pregnancy the interstitial cells in all parts of the ovary decrease in size but become relatively richer in lipoid at the expense of the larger fuchsinophile granules as seen in figure 27a, which is a group of two cells undergoing atrophy and in which there are only five of these larger granules left in the particular section drawn. Practically all these coarse granules had disappeared in an animal containing foetuses 45 mm. in length.

Mitochondria, as was also shown by Levi ('13) in a number of other animals, largely persist during this extreme fatty infiltration. The fatty globules of the regressive stages are slightly smaller and more closely packed than those present during the progressive stages and apparently produce a deformity of the nucleus. Occasionally, however, a number of individual droplets may fuse forming spherules even larger than the largest ones represented in figure 26. This lipoid is then gradually absorbed and as a consequence the cells diminish in size, as shown in figure 27, till, in many cases at least, only fragmented and shriveled nuclei are left as in e of this figure. These picnotic nuclei apparently disappear quite rapidly. The interstitial cells left in the stroma between adjacent corpora lutea, are the first to disappear—probably on account of the pressure produced by these growing structures.

By the time of parturition many of the interstitial cells have disappeared entirely and the others are in various stages of decline. A general view of this condition is shown in figure 5. The interstitial cells remaining are in groups which appear intensely black because of the large amount of lipoid. In each dark area will be found side by side all the forms shown in figure 27. This process goes on during lactation. Figure 5 is

from a lactating animal in which the uterus still was greatly congested giving evidence of recent parturition.

The figure indicates the large amount of atresia that has taken place. All the follicles large enough to show in the photograph, except one, are in advanced stages of degeneration, each appearing as an intensely black ring indicative of the heavy lipoid infiltration in the theca cells. Normal fully developed follicles may, however, persist for a considerable time after pregnancy has taken place. There were several such follicles in an animal with foetuses 40 mm. to 45 mm. in length.

The particular ovary from which figure 5 was taken contained only two corpora lutea and these were to one side of the median plane so that a section showing a good general view of the stroma nearly missed one corpus luteum and is not through the greatest diameter of the other. However, sufficient is included to show the lipoid which appears in the lutein cells at the expense of the secretion-like granules, as illustrated in detail in figure 31 a.

In passing it may be noted that Van der Stricht ('12) in the bat and Corner ('15) in the pig regard the lipoid that appears in young lutein cells as secretion products. In the spermophile Drips ('17, '18) considers that the fatty droplets which appear in abundance comparatively late in pregnancy, during the decrease in the fuchsinophil granules, and which persist for about six weeks afterwards, as an internal secretion having to do with the normal involution of the uterus. In the woodchuck there seems to be no valid reason for considering the lipoid which appears in the corpus luteum during late pregnancy and immediately thereafter as being different from that which two months later completely fills these cells (fig. 6) and which evidently is an expression of degeneration. The uterus in the woodchuck appears to return to normal rapidly and long before there is very much lipoid in the lutein elements.

The gestation and lactation periods are apparently not known in the case of the woodchuck. The facts could not be determined because the animals would not breed in captivity. General observations show, however, that they become permanently awake during the second half of March (in the locality concerned) and most of them soon become pregnant for the

majority of those caught in April contain foetuses. Lactating animals are obtainable in May and many young are seen in June.

In midsummer.—By July the interstitial cells have greatly diminished. In the last half of the month the medullary portion of the ovary is very poor in lipoid (fig. 6). There are, however, many cells nearly round in form and from 4 to 8 micra in diameter (nucleus from 3.8 to 6 micra), which rarely contain more than two or three lipoid granules and many that contain none. Such cells are fairly rich in mitochondria, considering the scanty cytoplasm. They may be represented by b and d of figure 24, d of figure 27 and figure 28. In the cortical zone there are in addition a considerable number of cells with somewhat more lipoid and occasionally as large as 12 micra. There are also many cells entirely free from lipoid with more or less elongated nuclei as well as spherical which appear to have been newly derived from cells that have migrated down from the germinal epithelium as shown in figure 21 and as will be discussed under another heading. It is therefore difficult to say how many of the interstitial cells of this stage are survivals of the retrogression of the hypertrophied cells of earlier months and how many are new derivatives from either ordinary stroma cells or other cells which apparently have migrated into the stroma from the germinal epithelium and which migrate into the masses of atrophic interstitial cells and degenerating corpora lutea. The appearance of the center of the larger groups of retrograding cells into which no migratory cells appear to have penetrated, would indicate that many interstitial cells persist as lipoid free cells essentially like figure 24 b. The nuclei of other stromal elements that transform into interstitial cells do not become round before more or less lipoid has made its appearance in the cytoplasm.

Now and then a cell, such as is shown in figure 28, is encountered which almost certainly is derived from the larger lipoid-laden cells, as is evident from the presence of a large spherule which appears to be the remains (now probably pigmentary in character and more resistant to absorption) of the granular content once so abundant. This is altogether probable for pigmentary degeneration of the hypertrophied interstitial

cells, while not common such as it is in the testis of this species, does occasionally occur, and a few large pigment-laden cells are seen at this time of the year and later. Such cells have all the characteristics of the pigment cells of the testis which will be mentioned again a little later. They are easily picked out by copper hematoxylin, iron hematoxylin, acid fuchsin, crystal violet and Sudan III after chromation because of the lipochrome content.

The lutein cells have by this time become densely infiltrated with lipoid so that the corpora lutea, which may still be maximal in size, make exceedingly conspicuous structures in material fixed in osmic acid, as is illustrated in figure 6. Most of the lutein cells in such corpora lutea are like figure 31 b, although all the cells are not in the same stage of retrogression. After this stage has been reached, the lutein cells rapidly lose their lipoid and finally disappear completely. Figure 31 shows several stages of this fatty infiltration and the subsequent atrophy.

In August, corpora lutea in various stages of atrophy are regularly seen. With the disappearance of the corpora lutea, the ovary diminishes greatly in size, falling down to about .0008 per cent of the body weight. A typical ovary just before the last traces of corpora lutea have been absorbed is shown in figure 7. The black area consists of atrophied lutein cells that have not yet disappeared. In such degenerating corpora lutea are found a few cells, such as are shown in figure 31 d, resembling interstitial cells. Their source is not clear. They may have been derived from lutein elements as Van der Stricht ('12) suggests. This investigator asks the question if it might not be that such cells as appear not to degenerate completely in the bat are the original theca cells. It has also been mentioned that there is a migration of cells into such degenerating corpora lutea from the outside and this may be the source of the cells in question. Certainly the lutein cells practically all undergo complete atrophy and leave very little evidence, aside from an occasional pigment cell, of their former presence.

There is during this period and also earlier, during late gestation, renewed development of follicles. Primary follicles become very numerous and some of these are enlarging and

sinking deeper into the ovary. Mann ('16) and Drips ('17) describe a similar development of follicles before the period of hibernation in the spermophile.

Conclusions

The observations seem to warrant the conclusion that there is an annual cycle going on in the ovary of the woodchuck in connection with interstitial cells. This consists of a very slow hypertrophy of some of the cells during late autumn and during hibernation, which is followed by a more rapid development, in which all the interstitial cells are involved, during the spring after waking up from winter-sleep. The maximum is reached at the time of ovulation and beginning pregnancy and especially in those individuals that do not become pregnant till a month or so after the majority of the females conceive. Retrogression consisting of a decrease in size and number of cells, follows with the progress of pregnancy and by July, which is several weeks after lactation has ceased, they have reached a minimum. During retrogression there is renewed activity in the downgrowth of cells from the germinal epithelium which appears, as will now be discussed in further detail, to give rise to new elements that transform into interstitial cells which, in connection with those that have resulted from atrophy of the enlarged cells of the existing cycle, are ready to commence the next cycle.

ORIGIN OF THE INTERSTITIAL CELLS OF THE OVARY

The origin of the interstitial cells of the ovary has been much debated. His ('65), Tourneux ('79), Janosik ('85, '88), Child ('97), Plato ('97), Coert ('98), Rabl ('98), Regaud et Policard ('01), Limon ('02), Allen ('04), Saimont ('05), Aime ('07), Von Winiwarter ('08), Ciaccio ('10), Popoff ('11) (in the dog), Athias ('11), Van der Stricht ('12), Kingsbury ('14) and Firket ('14) all have derived them directly from the stroma-cells, which are considered a type of connective tissue. O'Donoghue ('16) admits that in marsupials they may have arisen from the stroma cells at a very early stage. Janosik ('88), Schottländer ('91, '93), von Kölliker ('98), Rabl ('98), Clark ('98), Regaud et Policard ('01), Van der Stricht ('01, '12), Limon ('02), Cohn ('03, '09), Allen ('04), Saimont ('05), Seitz ('06), Aimé ('07), Wallart ('07), Regaud et Dubreuil ('07, '09), Benthin ('11), Popoff ('11) (in weasel and mole), Aschner ('14) and Kingsbury ('14), that is, many of the authors already named and some others, consider that they also come from the cells of the theca interna of atretic follicles. This

would appear, after all, to be only an indirect derivation from the stroma cells and one that is prominent in later stages of development and in the adult. v.d.Broek ('10) insists that in marsupials they originate independent of either atretic follicles or corpora lutea. Against the connective tissue origin are the views of Nussbaum ('80), Schulin ('81), Horz ('83), Paladino ('87), Lane-Claypon ('06), Ganfani ('07, '08) and Milroy ('17), who believe they are epithelial in origin, being derived from the mesothelial covering of the ovary. Popoff ('11) believes there is a double origin in the mole where they appear to originate also directly from the epithelium as well as from the theca interna. Firket ('14) describes also a double origin in the chick where the interstitial cells appear to come both from the stroma and from the medullary cords. But since in the fowl ovary some of the elements that have been considered interstitial cells by many are now regarded by Pearl and Boring ('18) as lutein cells which appear in groups mostly in the theca interna, it is not clear how this will affect the conclusions of Firket.

A number of other sources that have been suggested, especially by older workers, are of historical interest only and need not be mentioned here.

It appears, therefore, that of the two sources of interstitial cells, the stromal origin, either direct or indirect through the theca interna of atretic follicles, is held by the vast majority—the epithelial as the exclusive source or in addition to the stromal origin being supported by only a small minority.

A thorough-going investigation into the embryology has been carried out on so few animals that it is not surprising some disagreement should prevail and possibly there is some difference in animals of different species. Then too, the ordinary stroma cells of the ovary are not all typical connective tissue and if traced far enough back it is difficult to exclude them from having arisen from the coelomic mesothelium. There is some typical connective tissue, especially along the larger blood vessels and in the tunica albuginea. This in general has migrated into the ovary through the hilum. It appears altogether probable that many of the stroma cells may retain, even in the adult, many embryological characteristics so that they are capable of further differentiation such as occurs during ripening of follicles and atresia when the theca cells become quite different from the ordinary stroma cells, from which they are almost universally recognized as having been derived. If such hypertrophy can take place, there should be no serious difficulty in understanding the derivation of interstitial cells from ordi-

nary stroma cells not related to follicles. In mammals the hypertrophied cells of the theca interna, especially of atretic follicles, are regarded by the great majority of investigators as differing in no essential from other interstitial cells—a view also fully supported here upon the evidence presented by the woodchuck (fig. 22). Such a connective tissue (stromal) origin has, however, been urged as an argument against the theory that they are secretory in function.

This subject of the origin of the interstitial cells of the ovary, while in a sense quite separate from that of cyclic changes, was forced into the discussion because of the activity noted in the germinal epithelium in adult woodchucks especially during the rapid decline of the interstitial cells. Even during the latter part of dormancy the epithelium shows some degree of activity judging from a thickening seen here and there due to a proliferation of cells so that a second layer forms beneath the superficial one, as is illustrated at point a in figure 21. Such activity increases with awakening when cells soon appear to be leaving the germinal epithelium, penetrating the tunica albuginea usually in a very oblique manner, as illustrated in figure 11. During pregnancy this migration is conspicuous. A general view from a pregnant animal (foetuses 40 to 45 mm. in length, killed April 17) is shown in figure 11. A more detailed view of the superficial part of the same section is shown in figure 12. The cells of the germinal epithelium are seen to form a very irregular outline in places. The degree of differentiation of the stain (iron hematoxylin) has left the nucleus of the cells black while the outlines of the cytoplasm are indistinguishable. The ordinary connective tissue cells of the tunica albuginea are not visible. This contrast is possible because of the larger size and hyperchromatic character of the nuclei of the cells of the germinal epithelium and of those cells that appear to migrate from it.

These migratory cells are apparently somewhat amoeboid and in penetrating the tunica albuginea assume very irregular shapes as is recognizable in figure 13 and shown in more detail in figure 23 (d, e, f, g, h, i). In most places the tunica albuginea remains intact, making it necessary for the cells to take a very oblique and devious course in order to get through as shown in figures 12 and 13. In a few limited areas, as shown in

figure 14, the tunica albuginea becomes interrupted due, apparently, to the large number of cells passing through it. In such places the cells stretch in a continuous mass from the germinal epithelium to the cortical layer of follicles.

In penetrating into the ovary some of these cells surround and come in close association with both primary and secondary follicles as shown in figure 15, where they may be recognized by the dark oblong nucleus. They are seen frequently to be in contact with the basement membrane of the granulosa and in all probability may become constituent parts of the theca interna. Deeper in the ovary they enter groups of interstitial cells and since there exist all the intermediate forms that one could wish, as illustrated in figure 19, between them and typical lipoid-laden interstitial cells with vesicular nucleus, it appears that they are a source of interstitial cells.

Wherever these cells are encountered, some of them give the appearance at first sight of being in process of division. The rare occurrence of any form of multiplication in the interstitial cells of adult animals, stimulated a more careful study of such apparently dividing cells. A variety of representative cells are shown in figure 23 (d, e, f, g, h, i). It seems that what appeared to be a typical chromosome arrangement in dividing cells as suggested in f and g of figure 23, is really due to folding of the cells, possibly because of the resistance offered by the stroma. Although there are many suggestions of amitotic cell division, such as is shown in figure 23 e, no unmistakable evidence that such actually occurs was seen. Direct cell division has however been described in the interstitial cells of the ovary. Some of the figures published by Regaud and Dubreuil ('06) as evidence of amitosis in young interstitial cells of the rabbit ovary simulate closely what has just been described here in the woodchuck.

One disappointing feature is the scarcity of valid proof of cell division in the germinal epithelium such as would be expected if the cells are rapidly increasing in number. Only occasionally is a mitotic figure seen (fig. 14 M). Such forms as are shown in a and b of figures 23 are numerous, but these are only sharply bent cells evidently due to lateral pressure in the epithelium. A possible factor entering here is the fact

that nearly all ovaries after removal from the body were weighed on an ordinary chemical balance and unprotected from the drying influence of the air. As a consequence the small organ rapidly cooled and the germinal epithelium, except in protected places, was affected by drying. However, a few ovaries were dropped immediately into the fixer and still in these evidence of much cell division is wanting.

Later in the season, in July and August, when the corpora lutea are rapidly degenerating and the interstitial cells are greatly reduced, groups and columns of cells from the germinal epithelium penetrate the tunica albuginea in regions between corpora lutea and near the hilum, as is shown in figure 21. Some of these groups, consisting of one cell surrounded by a few slightly smaller ones, are suggestive of oögenesis. The formation of definitive ova in nearly mature animals by a differentiation of cells from the germinal epithelium, has been described by von Winiwarter and Sainmont ('08) in the cat and by Kingery ('17) in the white mouse, showing that the tunica albuginea is no barrier to a migration of groups of cells from the epithelium to the interior of the ovary, at least in some animals, and that oögenesis may take place long after it is generally supposed that such occurs, as far as participation of the germinal epithelium is concerned. In the woodchuck, however, there are not the necessary intermediate stages between such groups of cells as shown in figure 21 b and primary follicles to warrant the conclusion that any of these cells leaving the germinal epithelium in groups in adult woodchucks ever become oöcytes. It appears rather that they form cords that extend into the medulla or remain in the more superficial part of the ovary as irregular masses and cords of cells as illustrated in figure 21 in the region about the point marked C.

The nucleus of these cells when first formed tends to double on itself. Not rarely is a picture such as is represented in figure 23 c observed where every cell in a cross section of one of these cords has a curved or s-shaped nucleus.

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garded as mitochondria. Van Winiwarter ('12) has demonstrated their presence in the form of granules and filaments in all the interstitial cells of the human testis, but in less quantity where other cytoplasmic inclusions are more numerous. In the opossum they were observed by Jordan ('11) and have recently been described by Duesberg ('18) as being exceedingly numerous, mostly rods, short and curved, and crowded into several heaps. Since these structures are so generally present in other living cells, it seemed improbable that they should be absent in the interstitial cells of the woodchuck testis.

Having had no difficulty in demonstrating mitochondria in the homologous cells of the ovary and in other tissues of the woodchuck especially with acid fuchsin and methyl green after either neutral formalin-bichromate or acetic-osmic-chromic fixation, 14 additional animals were injected with neutral formalin and potassium bichromate as advocated by Cowdry ('16b). This new material and that part of the tissue from the former study which was well fixed in the acetic-osmic-chromic mixture were investigated principally by staining with acid fuchsin and methyl green. The results are shown in figures 32, 33, 34, 35, and 36, in which the mitochondria appear as small red granules. Nearly all these granules are round. A few are slightly elongated, but they are never filamentous.

The pigment, normally yellow in color, may remain unstained or stained only on the surface, as shown in the four large composite granules of figure 32, p. When stained they may take the acid fuchsin or this stain may be replaced by methyl green, depending upon the amount of dichromatization and the length of time the respective stains are allowed to act. In well fixed material it is possible to gauge these factors so that all fuchsin will be driven from the pigment by the methyl green and leave only the mitochondria red as shown in figure 32, e. Intermediate colorizations are, however, frequently obtained in which the pigment has been stained only on the surface of the granule so that the yellow becomes modified either towards the red or the green. These different effects may be obtained on the pigment within a single cell as is shown in figure 32, p and b. But where some of the pigment has taken the red stain, it is usually possible readily to distinguish it from mitochondria.

which are much smaller than even the smallest pigment granule. Then too there are a few very small interstitial cells, frequently irregular or slightly elongated in form, which contain no pigment to complicate the picture. In these the mitochondria are exactly the same as those found in the cells that do contain pigment. The mitochondria of the interstitial cells show best in preparations that also exhibit most clearly the mitochondrial content of the neighboring spermatogenic tissue. So it is believed that there is no question about the presence of mitochondria in the interstitial cells both of the ordinary and of the heavily pigmented type.

The suggestions given by Cowdry ('16b) on the causes of failure and the remedy were of great value in discovering the proper time intervals for each block of tissue. An evident source of trouble in earlier attempts to utilize acid fuchsin and methyl green was the excess of fixer left in the tissue by the very rapid washing and dehydration employed. It was necessary to leave some of the acetic-osmic-chromic fixed material for ten minutes in the potassium permanganate. The necessity of apparently excessive fixation was not fully realized, as is apt to be the case with the uninitiated.

As the ordinary interstitial cells enlarge in spring, the mitochondria increase in number simultaneously with the appearance of the large lipoid granules, as shown in figure 33, a, where the lipoid which blackens with osmic acid appears as vacuoles. Many of the mitochondria also appear to become larger. They are most numerous in the perinuclear cytoplasm, but appear through the cytoplasm between the fatty globules and dispersed pigment, the latter being shown in blue in figure 33. As the cells continue to enlarge there appear in the central cytoplasm granules, which are distinctly larger than the mitochondria and many intermediate in size, all of which stain like mitochondria and hence make it difficult to say which are mitochondria and which are not (fig. 34, a). It appears to be a less perfect preservation and staining of these large granules which were described in the first report, where granules of a lipoidal character were shown to be associated with the dense central cytoplasm.

From the presence of intermediate granules and in view of the many accounts of the transformation of mitochondria into secretion granules and various metaplastic products (cf. Cowdry '16 a), it could easily be believed that the larger fuchsinophil granules have developed from mitochondria; but such a transformation has not been proved in this case. These large fuchsinophil granules are more easily preserved and show in preparations not sufficiently well fixed to demonstrate mitochondria. In well fixed tissue, however, all attempts failed to distinguish by color reaction the two types of granules, although the technique permits of considerable selective staining by varying the amount of dechromatization and stain differentiation. In the pancreatic cells, for example, the long filamentous mitochondria situated in the basal part of the cells may be left red while the round zymogen granules nearer the lumen are bluish green.

As shown in figure 34 a, a few of the large fuchsinophil granules may be found at the very periphery of the cell, but nearly all are confined to the central cytoplasm.

In midsummer, usually in July when the enlarged cells are undergoing atrophy (fig. 35), there is an absorption of all of the large fatty globules which occupy mostly the peripheral cytoplasm. In most of the cells many of the large fuchsinophil granules also disappear (fig. 35, a). When atrophy is complete, as is shown in figure 36, none of the typical large fuchsinophil granules are left, though a considerable number of mitochondria persist.

The mitochondria, which are scattered throughout the cytoplasm of the pigment cells, decrease with the gradual disappearance of these cells; but as long as pigment cells are recognizable, mitochondria are demonstrable within them (p of figures 36, 32, 33 and 34).

THE SOURCE OF THE PIGMENT GRANULES

During the midsummer involution of the interstitial tissue, when most of the fuchsinophile granules disappear from many of the cells, there occurs a marked increase in pigmentation of the testis. This is evidently due to a transformation of the fuchsinophil granules that are not absorbed, into a pigment,

which is easily differentiated from mitochondria. In figure 35, a, all of these large fuchsinophile granules except three have been so changed that they can be made to take the methyl green while the mitochondria remain red. The three large red granules have not yet become sufficiently changed to be thus distinguished. When the final stage of atrophy is reached some pigment remains in all but a very few of the smallest cells (fig. 36, a, b and c.) This pigment largely persists till hypertrophy commences again in the following spring when it decreases markedly, becomes dispersed in the abundant newly acquired cytoplasm (fig. 33, a), and in most cases disappears entirely.

In the formation of the large pigment cells it appears that the fatty globules which blacken with osmic acid (shown as vacuoles in fig. 34, a) are absorbed as usual and are not transformed bodily into lipochrome as was rather suggested in the earlier report. Simultaneously with this absorption there is a marked increase in the large fuchsinophile granules. In figure 35, b, where is illustrated a transformation stage, the large amount of these fuchsinophil granules is shown just before the last trace of lipid is gone. To the right of the nucleus are three bluish-green granules. These are pigment. All the fuchsinophil granules finally appear to undergo pigmentation and the result is a cell like p in figure 36, where the pigmentation is shown either in yellow or bluish-green. This particular cell is somewhat larger than usual, showing the size they may attain.

It further appears that the large pigment granules are aggregations of the smaller ones. This is seen in figure 32, p, but is especially evident just after these cells are formed (fig. 36, p). This coalescence becomes more intimate with time so that the individual droplets involved are not seen as is indicated in figures 33, p and 34, p.

COMPARISON OF THE INTERSTITIAL CELLS OF THE TESTIS AND THE OVARY

The foregoing account in connection with the former report on seasonal changes in the testis shows that the interstitial cell cycle, not only in time but also in many cytological details, is somewhat similar in the male and the female woodchuck.

This is easily seen by comparing the right hand row of figures in plate 4 with the parallel arranged left hand row of figures in the same plate. In both cases there is a rapid hypertrophy in the spring after hibernation; but in the ovary this has been preceded by a gradual increase which has been going on during hibernation and sometimes longer; while in the testis there is practically no change till after dormancy. Involution of this tissue is also more gradual in the ovary, where in the case of pregnancy it is going on during April, while in the testis the interstitial cells continue maximal till June or July. The minimal stage is, however reached at about the same time, that is by August. In both cases there is no sudden change with the onset of hibernation, an observation also made by Mann ('16) on the spermophile.

It is, of course, impossible to say with certainty exactly how long the interstitial cells remain hypertrophied in a given individual because tissue cannot be removed from the same animal at various intervals through the year and still leave the animal normal and because the animals involved were captured promiscuously in the field and hence have not a known history. The above comparisons are deduced from the conditions generally prevailing among animals sacrificed at certain periods of the year and showing collateral evidences of being at a given stage in the sexual cycle.

One would be tempted to suggest that the longer hypertrophic stage of the interstitial cells of the testis is related to a longer period of sexual activity in the male. This, however, is not warranted by the presence of ripe spermatozoa for a sufficiently long time nor by the general habits of this species, since they are said to live together in pairs.

During hypertrophy of the interstitial cells of both ovary and testis, the number of mitochondria increase and there appear larger fuchsinophil granules and still larger fatty globules in the cytoplasm. There is considerable individual variation in the relative number of fuchsinophil granules and the larger lipid bodies—the two constituents being inversely proportional to each other in both the ovary and the testis.

During atrophy of the interstitial cells of the ovary, the large fuchsinophil granules disappear first leaving large cells

that contain only mitochondria and the large fatty globules which are next absorbed. In the testis the fatty matter and large fuchsinophil granules either disappear more or less together or the former is lost first.

In nearly all the interstitial cells of the testis some of the large fuchsinophil granules, and in a smaller number of them apparently all of these granules, become pigment which remains for months to nearly a year. Such pigmentation rarely occurs in the interstitial cells of the ovary.

While most of the interstitial cells of the adult ovary are rarely or only for a short time entirely free from lipoids that blacken with osmic acid, those of the adult testis practically contain such fatty matter only after spring awakening and until July or August.

In the mole a somewhat similar correspondence exists between the duration of hypertrophy of the interstitial cells of the testis and of the ovary, but in both cases the time of hypertrophy does not coincide with the breeding period of early spring and the maximum enlargement of the interstitial cells of the ovary comes somewhat later in the year than in the case of the interstitial cells of the testis. Sufficiently complete descriptions are not given of other animals to make any further comparisons.

As to whether the interstitial cell hypertrophy in either the testis or the ovary is a cause or an effect is debatable. While the presence of the fatty globules and other granules has been taken as evidence of secretory activity, such a conclusion does not necessarily follow. One would expect that if such were the case, the changes in such content would more closely correspond to some particular phase of the sexual cycle than they do, especially in the testis. The interstitial cell activity of the ovary is fairly closely related to ovulation and beginning pregnancy, except in the mole. It would seem, however, very desirable to have the mole as well as many additional species further investigated before drawing conclusions.

An important alternative to the secretory theory of the interstitial cells, is the view that the periodic increase is merely an expression of hyperemia and the general changed metabolism accompanying ovulation and pregnancy. It seems diffi-

cult to prove that such is not the case. And, as emphasized by Kingsbury ('14), it is equally hard to exclude the probability that the interstitial cell hypertrophy is related to degenerative changes in the gonads. This is especially true of the theca cells of atretic follicles. Why the interstitial cells not related to follicles are involved is not so well harmonized. Many pathological findings, especially in hermaphrodites, are further difficulties in the way of a satisfactory explanation. In short, the secretory function of the interstitial cells of both the testis and the ovary, while in general assumed, is full of uncertainties. A good statement of the present status of the internal secretory activity of the testis has recently been made by Wheelon ('17).

Neither spermatogenesis nor follicular development are interrupted or modified during atrophy of the interstitial cells, indicating that at least some phases of the primary function of the gonads are independent of interstitial cell activity.

SUMMARY

1. The literature on cyclic changes in the interstitial cells of the ovary is reviewed and indicates in general a hypertrophy of these elements during rut and pregnancy.

2. A marked annual periodicity in the interstitial cells of the ovary of the woodchuck (*Marmota monax*) is described as consisting of a gradual enlargement during winter followed by a more rapid hypertrophy after hibernation. The cells become three to four times their original diameter. Maximal increase is seen in females that have not become pregnant until late in the breeding season.

3. The increase in the size of the cells is due to an accumulation of lipoid and secretion-like granules in the cytoplasm, though the nucleus also increases. Mitochondria similarly increase in number and some, possibly, in size.

4. Retrogression sets in with the onset of pregnancy and the growth of corpora lutea and continues until July.

5. In the decline the lipoid and large fuchsinophil granules and finally the entire cell disappear in many cases. The cells that survive atrophy retain a number of mitochondria, but the other granules are absorbed.

6. Pigmentary degeneration is rarely observed.

7. The interstitial cells of the ovary are minimal in size during late summer and early autumn, but tend soon to acquire lipid and slowly to enlarge.

8. During late involution of the interstitial cells the follicles show a tendency to grow. By autumn a number of fairly large Graafian follicles and many smaller ones are evident.

9. The origin of the interstitial cells of the ovary is briefly discussed and shown to be regarded by the vast majority as having come from connective tissue, or stroma of the ovary, either directly or indirectly through the theca interna of atretic follicles. A few investigators insist on an epithelial origin.

10. Proliferation of the germinal epithelium in adult ovaries indicates strongly a formation of new interstitial cells from elements that migrate into the ovary from its covering epithelium. This is most noticeable from late in pregnancy till late summer.

11. Transformation of stroma cells into interstitial cells in adult animals is also evident. There appears to be no difference between the hypertrophied cells of the theca interna of atretic follicles and interstitial cells that are not related to follicles.

12. The persistence of full-sized corpora lutea of pregnancy until many weeks after parturition and the appearance of an abundance of fatty globules in the lutein cells before they decrease in size was observed. All corpora lutea have disappeared by September.

13. A restudy of the interstitial cells of the testis of the woodchuck is included. The presence of mitochondria in the form of round granules in all types of interstitial cells is reported. These mitochondria increase in number and some also in size during hypertrophy.

14. A better demonstration of the small lipid granules of the central cytoplasm shows that they have many of the staining reactions of mitochondria but are distinctly larger in size.

15. These small granules and not the larger and more peripherally placed fatty globules are believed to be the source

of the lipochrome, or pigment, which is formed during atrophy of the interstitial cells of the testis.

16. The large pigment granules are formed by the coalescence of smaller ones.

17. The general similarity in the interstitial cells of the testis and of the ovary is shown. The main differences between them are the more sudden hypertrophy and subsequent atrophy that occur in those of the testis and the almost entire absence of pigmentary degeneration in those of the ovary.

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Plate 1

EXPLANATION OF FIGURES

1. Photograph of longitudinal section of ovary of active adult woodchuck; just before hibernation (Oct. 26). Meves' acetic-osmic-chromic fixer, 10 micra, no stain, no cover. X 7. Shows distribution of interstitial cells, which are co-extensive with the blackened lipid, which is unusually abundant for this time of the year.
2. Photograph of adult ovary, comparable to figure 1 in thickness, plane of section and technique. X 7. Animal taken from normal habitat while dormant. Typical ovary of late hibernation (Feb. 25). Shows an increase in interstitial tissue as judged from the amount of lipid.
3. Photograph, comparable to figures 1 and 2, showing extreme hypertrophy of interstitial cells as met with late in the rutting season (last of April and first of May). X 7. Somewhat greater development than normally occurs at the beginning of pregnancy earlier in the season. CL are young corpora lutea. CL' are corpora lutea of earlier ovulation not followed by pregnancy.
4. Photograph of area outlined in white in figure 3 under higher magnification. X 30. Shows the extent of lipid-laden interstitial cells in the stroma.
5. Photograph comparable in every way to figures 1, 2 and 3, showing in black the characteristic interstitial cell content of late pregnancy and early lactation (May 8). X 7.
6. Photograph of typical ovary of midsummer (July 28) after interstitial cells have nearly reached a minimum. Shows characteristic fatty content of corpora lutea just before they commence rapidly to disappear. Same technique as in figures 1, 2, 3 and 5. X 7.
7. Photograph of typical ovary of late summer when interstitial cells are minimal in size and number and almost free from lipid. The single dark area is the remains of a corpus luteum which has not yet entirely disappeared. Same technique as other general views in this plate. Aug. 30. X 7.
8. Photograph of ovary of adult animal isolated in captivity till May 18, showing the small size of the ovary and the relative amount of interstitial tissue in females kept in captivity during the spring. Comparable to other general views in this plate. X 7.
9. Photograph showing migration of interstitial cells (identifiable by their black lipid content and indicated by the arrow, which also shows the direction of movement) with neighboring stroma into a portion of a young corpus luteum. A portion of the corpus hemorrhagicum (CH) is present. Same technique as in preceding figures. X 60.
10. Photograph showing relation of interstitial cells (dark areas) to vascular channels, which appear as prominent light areas because the blood has been washed out. In the center of each interstitial cell mass is usually a medullary cord. Zenker's with only 4 drops of acetic acid per 100 c.c., 5 micra, copper hematoxylin. X 45.

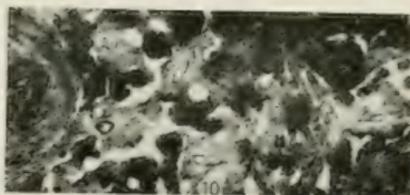
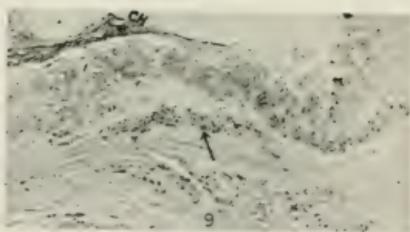
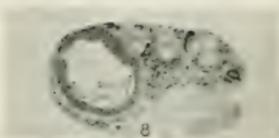
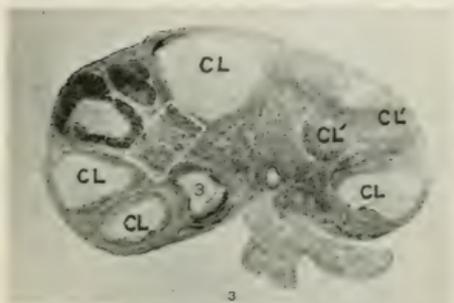
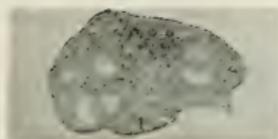


Plate 2

EXPLANATION OF FIGURES

11. Photograph of ovary of pregnant woodchuck (foetuses 40 mm. to 45 mm. in length). Shot in the field April 17. Zenker's, 10 micra, iron hematoxylin. X 67. Shows general view of cortex where cells appear to enter the ovary from the germinal epithelium.

12. Photograph of portion of figure 11 under higher magnification. X 333.

13. Photograph of peripheral portion of section of ovary of old adult showing cells leaving germinal epithelium. Early autumn (Sept. 5). The uninterrupted portion of the tunica albuginea is marked T. Carnoy's, 4 micra, iron hematoxylin. X 333.

14. Photograph of another portion of same section as figure 13 showing tunica albuginea apparently interrupted by cells from the germinal epithelium passing through it. A mitotic figure is seen at M. X 333.

15. Photograph of portion of adult ovary, in which the corpora lutea are rapidly being absorbed and many follicles are developing (Aug. 16), showing close relation of cells with oval and hyperchromatic nucleus to young follicles. Carnoy's, 3 micra, iron hematoxylin. X 333.

16. Photograph of medullary stroma of adult ovary as it appears in early autumn, showing relatively few cells with round vesicular nuclei. Carnoy's 4 micra, iron hematoxylin. X 200.

17. Photograph of medullary stroma of adult ovary as it appears at the close of hibernation (Mar. 18). Animal sacrificed within 48 hours after waking up. To be compared with figure 16. Shows a noticeable increase in size and number of round nuclei (nuclei of interstitial cells). Carnoy's, 4 micra, iron hematoxylin. X 200.

18. Photograph of medullary stroma of adult ovary when interstitial cells are maximal. Note large size of cells and vesicular nuclei. Carnoy's, 4 micra, iron hematoxylin. X 200.

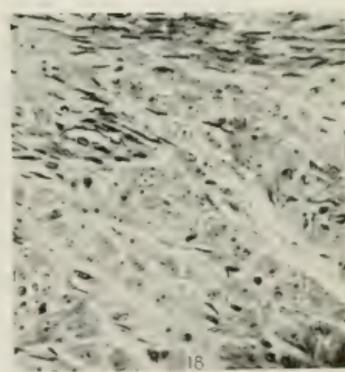
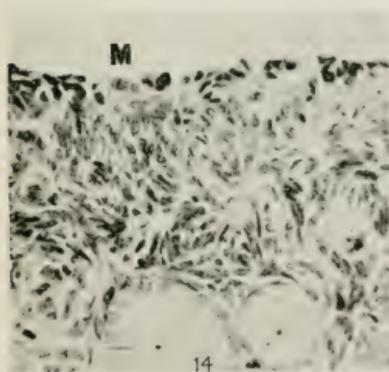
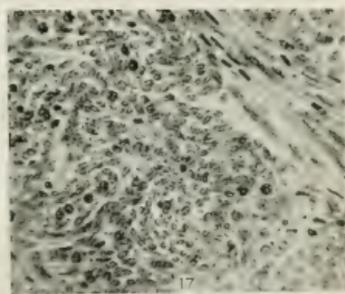
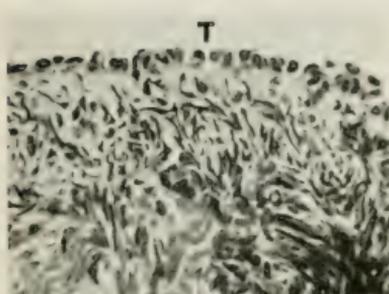
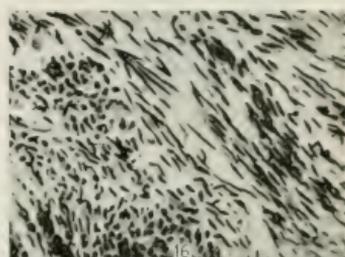
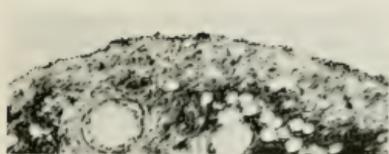


Plate 3

EXPLANATION OF FIGURES

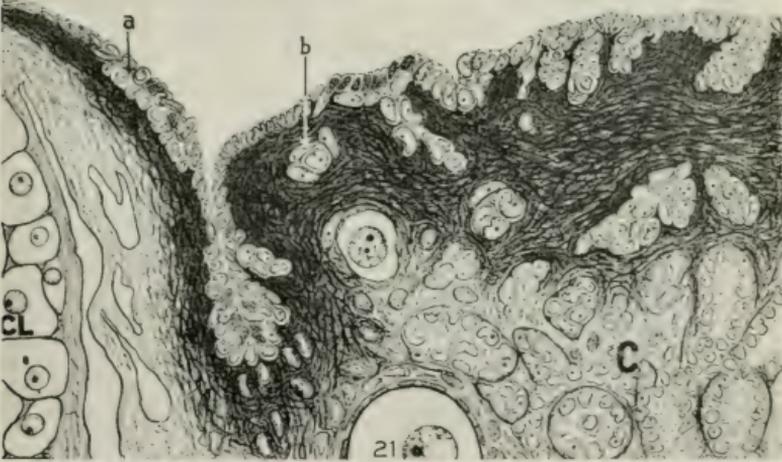
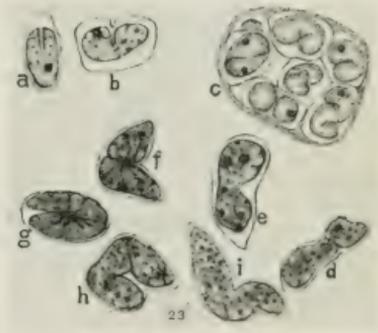
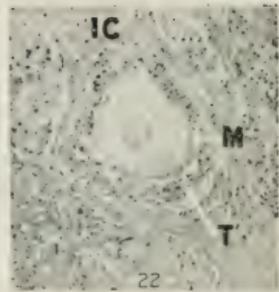
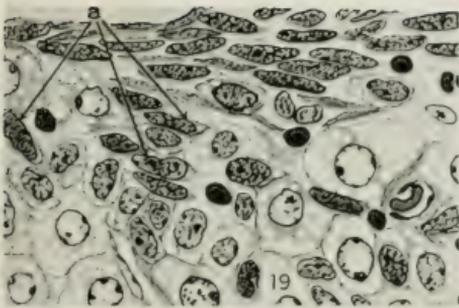
19. Camera lucida drawing of stroma of adult ovary showing transitional stages between elongated cells (free from fatty globules, with hyperchromatic nucleus and with but little cytoplasm which is difficult to demonstrate) and typical interstitial cells with lipoid-laden cytoplasm (indicated as vacuoles) and round vesicular nucleus. Zenker's with only 4 drops of acetic acid per 100 cc., 4 micra, iron hematoxylin. X 800. a, early indications of cytoplasmic increase. Solid stained nuclei are lymphocytes.

20. Photograph of a corpus luteum-like structure still containing an ovum (O). Early pregnancy (uterine enlargements 8 mm. to 9 mm. in diameter, April 27). Zenker's, 10 micra, iron hematoxylin. X 30.

21. Camera lucida drawing of portion of adult ovary during mid-summer when corpora lutea (CL) are degenerating, showing characteristic down growths of germinal epithelium, giving rise to the irregular masses and cords of cells shown in the region marked C. Tunica albuginea is dark. X 500.

22. Photograph of atretic follicle and adjacent stroma when interstitial cells (IC) are maximal. M indicates the basement membrane of the granulosa and T the theca interna. Lipoid is black. Acetic-osmic-chromic fixer, 5 micra, acid fuchsin, no cover. X 44.

23. Camera lucida drawings, showing certain nuclear characteristics. Carnoy's, 5 micra, iron hematoxylin. a and b are from the germinal epithelium of pregnant female and show what might be regarded as indications of direct cell division, but which is believed to be merely a folding. X 1000. c is a section through cell cord newly derived from the germinal epithelium, showing the tendency for the nuclei to fold and twist. X 1000. d, e, f, g, h and i are cells encountered in the stroma especially in mid-summer, showing a variety of forms they may assume. Nucleus is granular and hyperchromatic. Appear to have been derived from the germinal epithelium and may transform into typical interstitial cells. X 1500.



EXPLANATION OF FIGURES

All figures in this plate X 1000. Acetic-osmic-chromic or neutral formalin-dichromate fixation, 3 micra, acid fuchsin and methyl green stain. Large fatty globules appear black or as vacuoles. Mitochondria and larger (secretion?) granules are red. Nucleolus either blue or red.

24. Types of interstitial cells of ovary in autumn before hibernation. a and c are transitional stages between elongated cells in the stroma and typical interstitial cells. Red granules are mitochondria.

25. Largest interstitial cells of ovary found immediately after waking up from hibernation. a is an intermediate stage between cells of figure 24 and of figure 26. Note appearance of a few red granules distinctly larger than mitochondria.

26. Interstitial cells of ovary at maximum hypertrophy during spring. a is a group of four cells with indistinct boundaries. Note numerous large and intermediate fuchsinophil granules.

27. Successive stages in atrophy of interstitial cells of ovary (late spring and early summer).

28. Interstitial cell (of ovary) that has survived atrophy (midsummer).

29. Lutein cell for comparison with interstitial cells. Shows typical granular cytoplasm.

30. Intermediate stages between ordinary stroma cells and interstitial cells of ovary.

31. Stages in degeneration of lutein cells for comparison with interstitial cells.

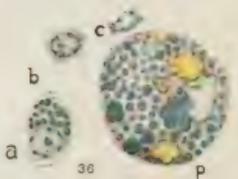
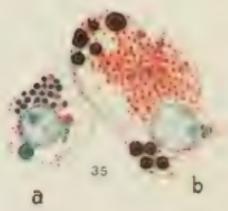
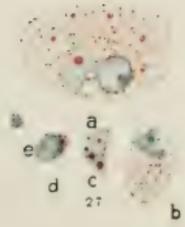
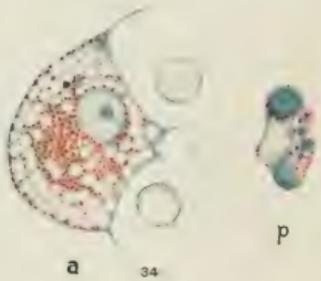
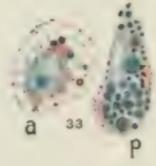
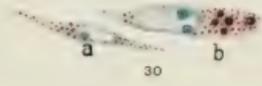
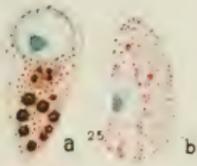
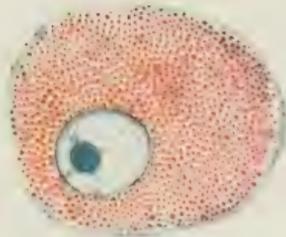
32. Interstitial cells of testis as they are in autumn. b contains three pigment granules, one yellow (natural color), one red and one blue. Pigment in c is blue. p is a "pigment cell," showing nucleus crowded to lower border of cell and cytoplasm filled with pigment granules, which are mostly blue, four red, one orange and four yellow (natural color) stained red only on the surface. Shows coalescence of smaller granules to form larger ones. Mitochondria appear as small red granules.

33. a is an interstitial cell of testis in early stage of spring hypertrophy. p is a pigment cell of this stage. Fatty globules appear as vacuoles, pigment blue, mitochondria red.

34. a is an interstitial cell of testis during maximum hypertrophy in spring and early summer. Pigment (blue) nearly absent. There are many fuchsinophil granules (red) and large fatty globules (vacuoles). The group arrangement often seen is indicated. p is a pigment cell of this time of the year just before complete atrophy. Mitochondria red. Pigment blue.

35. Interstitial cells of testis during midsummer atrophy. b is destined to become a pigment cell as p of next figure. Newly formed pigment is blue. Small red granules are mitochondria.

36. Interstitial cells of testis just after atrophy (Aug. 5). a represents the majority and contains some pigment (blue) and mitochondria (red). p is a newly formed pigment cell. Mitochondria are red and pigment is blue or yellow (natural color) stained only on the surface. Formation of larger granules from coalescence of smaller ones is evident.



THE ROLE OF THE THYMUS IN PEDIATRICS

Murray B. Gordon, M. D.

Assistant Clinical Professor of Pediatrics,
Long Island College Hospital, Brooklyn, N. Y.

(From the Department of Pediatrics, Long Island College Hospital)

This paper is offered as a review of the literature of the past few years on the subject of the thymus. The study of this gland, both from an experimental and clinical viewpoint, has given the various investigators contradictory results and has therefore given rise to opposing opinions as to its role in the general body metabolism. An attempt is made here to give an unprejudiced review.

The thymus is susceptible to all infections and conditions affecting the general nutrition of the body. Pathological involution often results. In acute diseases like starvation, pneumonia, acute nephritis and acute infectious diseases, this change is usually followed by a return of the organ to the normal. In chronic disorders, however, a return to the normal does not take place, the gland instead undergoing a permanent sclerosis with resulting permanent involution. Hereditary syphilis, tuberculosis and diphtheria produce atrophy and degeneration. Respiratory diseases (according to Charkowski) if not tubercular, do not interfere with the development of the thymus. In the course of an acute disease the thymus may be decreased to one-fifth or one-sixth of its normal weight.

Function—The function of the thymus is still an open question. There is a tendency among investi-

gators lately to question the former findings of Klose, Vogt and Matti that it is an organ of internal secretion and to give it now the same or similar function as that possessed by other hematopoietic organs like the spleen and lymph glands.

Sajous thinks that it is not the source of an internal secretion. He considers that the "function of the thymus is to supply, through the agency of the lymphocytes, the excess of nucleins which the body, particularly the osseous, nervous and genital systems, requires during infancy, childhood or even later, if need be, to construct the nuclei of its cells." He thinks that the thymus, due to its richness in nucleins, takes part in the oxidation and auto-protective processes of the body, and that it has some important relation with metabolism as regards the role of phosphorus in the body. Conclusive evidence on these points, however, is lacking.

The experiments of Klose and Vogt seemed to indicate that the thymus is essential to life, has a profound influence on growth and development of the body and presides especially over calcium metabolism of bone. They found that the removal of the thymus in animals was followed by marked disturbances in growth, that the animals developed a condition resembling rickets and showed well-marked changes in the adrenals and thyroid. The thymus was removed in ten days' old puppies. This was followed by a latent period of two to three weeks, then by a condition of adiposity lasting about two to three months, this in turn giving way to a cachexia and an impaired mentality resembling idiocy and finally culminating in death in about four months. It was claimed that extirpation of the thymus in children is

followed by the same results. Klose and Vogt considered that the bone and other changes were due to an acid intoxication and that one of the functions of the thymus is either to inhibit the formation of nucleic acid or else to neutralize its excessive formation. They also claimed that the total removal of the thymus in the young resulted in rickets, but that in adults extirpation was followed by osteoporosis and osteomalacia. Basch, Matti, Gudernatch, Rochford and others have reported substantiating observations.

Considerable experimental study in the laboratories of other careful investigators has failed to confirm these results. Park assails the work of Matti, Klose and their followers on the ground that the changes found in the animals were due to poor hygienic surroundings in the kennels. Some of the results were obtained by extirpation of the thymus in guinea pigs. Park made a careful study of serial sections through the neck region of this animal and showed that a guinea pig has so much accessory thymus tissue as to render complete thymectomy impossible. Earlier reports of results following thymectomy in this animal must therefore be interpreted as partial only.

Pappenheimer claims that removal of the thymus does not produce disturbances in growth or development and that no pathological changes are found after thymectomy anywhere in the body. He arrived at the following conclusions:

“1. In some species of animals, complete removal of the thymus arrests growth, especially the proper development of the skeletal system.

“2. We have no data as to results of removal in human beings.

“3. We have no experimental work which gives us a clue as to the effects of an excessive or perverted secretion.

“4. We are not yet justified in assigning to the thymus a definite role in the causation of any known disease.”

E. R. Hoskins, using albino rats, found that thymus feeding resulted in no constant effects on body weight or on that of individual organs.

Park extirpated the thymus in animals and found that no difference could be detected between the experimental animals and the controls, either as to procreative activities, growth or conditions in endocrine glands. He did not obtain rickets in any of his thymectomized animals.

Swingle fed fresh thymus and powdered commercial thymus to 150 frog larvae and found that it had no effect on growth or on the gonads.

Inter-relationship between thymus and organs of internal secretion.

Investigators are divided as to the relationship between the thymus and the organs of internal secretion, depending upon their belief as to whether or not the thymus itself has an internal secretion. Basch, Matti, Gudernatch, Paton, Henderson, Rachford and others claim that they have demonstrated this relationship and believe that the thymus has an inhibitory action on the thyroid, adrenals, gonads, spleen and pancreas. Halnan and Marshall, however, observed no pathological changes following thymectomy; their experimental animals did not show any abnormalities of growth or development after the removal of the thymus, nor did removal of both testes

and thymus in young guinea pigs alter the growth of the animals up to the time of sexual maturity. Park, Swingle and others also found that the thymus persists after castration.

Heidinger found seven cases of enlarged thyroid in twelve cases of thymic death in the new born. Garre and Capelle found 95 per cent of fatal cases of exophthalmic goitre to have enlarged thymuses. There have been many other reports of a combination of exophthalmic goitre and thymus hyperplasia. (Virchow, Crotti, Hart, Weber, Gluck and others). Mackenzie noted that in 36 post mortem examinations of cases of exophthalmic goitre, the most constant feature next to thyroid enlargement was the presence of an enlarged or persistent thymus. Hart believes that there is a pure thymogenic form of exophthalmic goitre.

Behlow makes the statement that he has looked for thymic enlargement in all cases of glandular dyscrasia and that he has found it in several instances. He also thinks that X-Ray examination of the chest in cases of Addison's disease will show an enlarged thymus.

Myesthenia gravis, while not properly a disease met with in children, will be considered here, as it may be the result of a condition which has its inception during childhood or even in utero. Bell quotes Starr, who had reviewed 250 cases of this condition and had noted a pathological state of the thymus in 28 of the cases that came to autopsy. Of 56 autopsies published since then, the thymus was found to be enlarged in 17 and contained a tumor in 10. Hart thinks that in this disease the affected individual has a "lymphatic constitution": in other words, is

constitutionally inferior and therefore predisposed from birth to the development of such a condition. He also believes that the thymus in myesthesia gravis exerts a pathological function and is frequently, if not always, the cause of the disease. He states that the removal of the thymus produces a cure, but admits that there are cases without thymus hyperplasia. His theory has not been substantiated.

Absence or deficient activity of the thymus, according to several observers, produces mental disorders in children. Bourneville found that in 28 mentally defective children, the thymus was absent. He has shown, based upon the findings of a large number of autopsies, that in over 70 per cent of mentally defective and epileptic children, the thymus was absent. Katz found that there was a normal thymus in every case of 61 normally mental children from 1 month to 13 years old, as shown by autopsy. Sajous believes that, while no type of idiocy can be referred to deficiency of any one gland, still, "deficient activity of the thymus results in deficiency of nucleins supplied to the brain through lymphocytes, causing idiocy." Harrower makes the statement that thymus hyperplasia is accompanied by defectiveness and by the hypoplastic type of individual.

Status Thymo-Lymphaticus

Post mortem examinations of cases of sudden death have in several instances revealed an enlarged thymus as the only pathological finding, with or without an accompanying hyperplasia of the lymphoid tissue of the body. This has led many to accept the thymus as the causative factor of the death, explain-

ing it on the basis of physical compression of the trachea or of the great vessels in keeping with the anatomical arrangement of the thymus.

Antero-posterior diameter of the superior opening of the thorax is 2 to 3 centimeters. A finger placed behind the episternal notch can feel the impact of the rising thymus. The thymus follows the up and down movements of the trachea and larynx during acts of coughing, swallowing and hyper-extension of the head. Grawitz believed that it was possible for the thymus to become wedged in between the upper part of the sternum and the vertebral column in such a way as to compress the trachea at that point, causing death from asphyxiation; this space is now known as the "critical space of Grawitz." Another place taken as a critical space where the trachea may be compressed is at the crossing of the innominate (Klose, Matti). Death may also be caused by direct pressure on the base of the heart. Herrick suggests that the respiratory symptoms are probably caused by pressure on other organs, for how can one explain the fact that the trachea, which is cartilaginous, should suffer compression and the neighboring veins and arteries should not?

Classification of thymus cases by various observers can be summed up in the following grouping:

A. Status Thymus (No changes in lymphatics).

1. Simple hyperplasia with clinical and anatomical evidences of compression.

2. Simple hyperplasia without any symptoms.

3. With an accompanying increased activity of the thyroid which may cause clinical symptoms of exophthalmic goitre.

B. Status Thymo-Lymphaticus.

1. Enlarged thymus associated with general enlargement of lymph tissue like adenoids, tonsils, spleen and mesenteric glands.

To both groups may be added congenital enlargement of the thymus and lymph glands. Cases of congenital thymus enlargement have been reported by Heidinger, Kayser, Somma and others, but the question has been raised by some as to their being true cases of this condition. Crotti suggests that asphyxia neonatorum may possibly be due to congenital thymus hyperplasia.

Hanmar has done pioneer work in disproving the old ideas as to thymic death. His has been the most reliable work performed, as all his experiments, observations and deductions were carried out with mathematical accuracy and precision. He claims that thymic death is not of thymus origin and he seems to have proved his case. The thymus in cases of sudden death from internal causes differ in no respects from thymus in healthy children. He compared the microscopic findings in 16 children from 3 weeks to 15 months old and analyzed and compared them with an equal number from apparently well children killed by accident or dying from external causes. He arrived at the following conclusions: (1) The two so-called critical spaces are so near together that they can be considered as one, particularly in the new born. (2) The statement that the trachea is greatly compressed immediately before the bifurcation where the innominate artery crosses is erroneous, for the innominate artery lies above the bifurcation. If the trachea was actually compressed at that point by the thymus, that part of the thymus

lying immediately opposite, just above the base of the heart, must have been responsible. (3) Since the thickest portion of the thymus lies at the level of the base of the heart, just below the critical point, drawing the thymus upward would intensify dyspnea, since it would bring the thicker mass of the thymus between the top of the sternum and the spine. It would not relieve dyspnea produced by pressure of the thymus on the trachea. (4) If ascent of the thymus relieved inspiratory dyspnea, it was proof that the point of compression of the trachea did not lie above the thickest part of the thymus, but at, or below the thickest portion in the neighborhood of the bifurcation. The thymus is not forced upward into the neck with each inspiration but recedes into the thorax; it is forced up into the base of the neck during expiration, so that if it produced dyspnea by compression of the trachea, it would produce it during expiration and not during inspiration.

Hammar proved that the notions of mechanical compression of the trachea by the enlarged thymus are largely false. His anatomical preparations show that an enlarged thymus may exert pressure close to the bifurcation or on the bronchi, particularly in the new born, but he does not say that it actually does.

He also disproved that enlargement of the thymus is constant in thymic death. He showed that it was not possible to distinguish any fixed type; in fact, in the majority of glands, variations were within the normal limits. He studied 14 cases, 13 of which were in children (ranging in age from 9 days to 16 years). He estimated the exact amount of parenchyma, minus the fat and connective tissue, by serial

sections and reconstruction and in the same manner determined the exact relation of the medullary to the cortical substance. He counted the number of Hassal's corpuscles. He found that of the 13 children, the thymuses of only two were enlarged, while the others showed amounts of parenchyma that were within the normal limits. The cortical medullary index was high (normal). He arrived at the conclusion that no morphological ground exists on which to rest a theory of hypofunction or dysfunction.

Other theories of thymus death.

Tracy advances the view that there is a superabundance of "Hormone X" in the blood stream and insufficiency of adrenin. The existence of Hormone X has not been substantiated.

N. Paton believes that thymus death is a pluriglandular syndrome and that in the absence of secretions of these glands and because of general imperfect development, death is more easily produced by trauma which would otherwise be ineffectual.

McNeil says that "status lymphaticus is an abnormal condition in the body in which if anaphylactic phenomena occur, they do so in an exaggerated way." He advances the theory that it is an intensified anaphylactic condition but produces no proof.

Wooley, with others, thinks that the clinical phenomena are due to over-functioning of the thymus. There has not been any supporting evidence to warrant this conclusion.

Another theory that has not been substantiated is one that tries to explain the symptoms as end results of an intoxication from the products of a faulty metabolism.

Symptoms of enlarged thymus

Enlargement of the thymus may cause no symptoms at all and the first warning of the presence of the condition may be a sudden paroxysm of severe dyspnea which may or may not terminate fatally, or else there is a sudden death from some slight cause or following a trivial operation. The chief complaint is nearly always a cough or attacks of choking which come and go, frequently in paroxysms. Friedlander calls attention to three definite symptoms, i.e., dyspnea, stridor and suffocative attacks with cyanosis. The dyspnea is the most striking sign and may be constant or intermittent with or without paroxysms. The stridor is inspiratory in character, and may be aggravated by fits of anger, exertion or sudden retraction of the head; it is more marked in sleep because of the position of dorsal decubitus assumed.

Diagnosis of enlarged thymus

Diagnosis of this condition depends upon physical examination and X-ray examination. While some clinicians question the possibility of making a positive diagnosis of a normal thymus by means of percussion, there have been many who have been able to demonstrate an enlargement by this method. A favorite with many is the so-called "threshold method." The child is placed on his back in the mother's lap. Percussion is begun well out in the chest, with such light strokes that when the ear is within a few inches of the area under percussion only the faintest possible resonance is heard. When sound disappears, dullness begins. Some observers outline the borders of dullness by the tactile sense of resistance rather

than sound. The outer limits are determined much more easily than the lower boundary. This latter, which may be obtained by auscultatory percussion, is relatively less important. The percussion outlines, determined in this way, according to Benjamin and Lange, correspond remarkably closely to the Roentgenograms. A clinical diagnosis of thymic enlargement is never absolutely positive without X-ray confirmation.

Friedlander was the first to treat this condition fully by the X-rays. His first case has since had an anesthetic and has been operated without any bad results. He summarizes the treatment as follows: (1) In the X-ray we have an agent which is at the same time safe and efficacious in the treatment of enlarged thymus and status lymphaticus. (2) It is possible to induce not only an involution of the thymus, but also in cases of status lymphaticus, to reduce the size of the spleen, of the lymph nodes and to change the lymphatic picture to a normal one. (3) The dosage of the X-ray can be regulated according to the necessities of the case. Where the symptoms of thymic asthma are urgent, the exposures can be given on successive days. A thymus partially involuted by the X-rays is capable of regeneration. The shadow of the normal thymus occupies a V-shaped area which scarcely extends beyond the limits of the median bony structures. An enlarged thymus gives a wide median shadow above the heart, appearing like a broad cap superimposed on the shadow of the heart and great vessels. This shadow is suggestive of thymic enlargement when it extends for some distance on either side of the bony structure, above the heart shadow and continuous with it.

Cook advises that children with retarded mental development, if suspicion is directed toward the thymus, should have the thymus rayed. In the so-called lymphatic type of children, he suggests thymus raying as a pre-operative procedure.

Operative Procedures

Immediate operation should be performed in children if the mechanical symptoms are alarming. Tracheotomy may be of avail. The operation most frequently done now is that of thymectomy, the earlier ones of exothymopexy and resection of the upper part of the sternum having been to a great measure discarded.

Organotherapy.

Rational organotherapy is at present impossible owing to very unsatisfactory knowledge of the gland and its functions. None of the diseases in which thymus treatment has been tried has been shown to be related to either thymus hypo-function or dysfunction. As Sajous has shown, if any results attend its administration, they are probably due to the high nucleic content of the thymus. It has been used for cretinism and hypothyroidism in conjunction with thyroid for the possible effect on the osseous development. This relationship between the bony system and the thymus must be cleared up before this empiric treatment can be given a scientific basis. It is used also in rickets, Addison's disease, infantilism and osteoarthritis. Sajous advises it in the condition known as progeria, a premature senility in which the child attains senility in a few years; he thinks the condition is due to deficient activity of the thymus.

Hanaborg recently advocated its use in chorea, having obtained good results in 16 cases of this disease. He thinks it plausible to assume that acute articular rheumatism may so affect the thymus that the secreting function is impaired and the unstable nervous system of the child feels the lack of the normal restraining influence of the thymus. Thymus extract seems to have a sedative effect on the nervous system. It controls convulsions, these recurring when the treatment was suspended. Thymus insufficiency, in his opinion, may be an added factor to the infection, but he gives salicylates in addition.

Hanaborg's work awaits confirmation.

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The abstract department of Endocrinology has been freely consulted and utilized in the compilation of this review.

4402 Twelfth Avenue, Brooklyn, N. Y.

THE NEWEST "HORMONE"

Swale Vincent,
Winnipeg

In the "Archives Italiennes de Biologie" for August, 1918, appears a résumé of a paper by Professor Marfori entitled "Sur la fonction hormonique des ganglions lymphatiques" (10). The original paper was published in Italian in 1916 (9). The author of this communication has performed some experiments with extracts made from lymphatic glands, and has arrived at the conclusion that these organs furnish an internal secretion, which he calls "lymphogangline." The methods by which he has reached this conclusion, and the grounds upon which he bases it, will be referred to later on. For the present it will be essential to give some account of the history of investigations upon tissue and organ extracts. The account which I am about to give may possibly save future workers from wasting time and paper upon a careful description of phenomena which are either well known or the presumption of which might follow directly from those already recorded.

The study of the effects of intravenous injections of organ extracts came into prominence after the publication in 1894 by Oliver and Schäfer (11, 12, 13) of their important discovery of the extraordinary pharmacodynamical effects produced by extracts made from the chromophil tissue included in the adrenal body. Since that time observers have worked with extracts from every organ and tissue in the body, with the hope of discovering some remarkable

physiological action which might rank in importance with that of adrenin from the chromaphil tissues. The result of all these labors, as far at any rate as the action upon the blood-pressure is concerned, can be very readily and simply stated. One other tissue besides the chromaphil, namely, the nervous portion of the pituitary body, contains a *pressor* substance. All other organs and tissues furnish a *depressor* substance or depressor substances.

Oliver and Schäfer noted, in addition to the effects of adrenal extracts, that pituitary preparations also produce a rise of blood-pressure. Schäfer and the present writer (19, 20) found that a *depressor* principle is also present in pituitary extracts, and recorded "a certain similarity of physiological action between nervous matter and the infundibular part of the pituitary." Schäfer and Moore (18) had previously noted, in a casual manner, a lowering of blood-pressure on injection of brain extracts.

Professor W. A. Osborne and the present writer (14, 15, 16) found that extracts made from all parts of the nervous system produce a marked fall of the blood-pressure, which occurs after section of both vagi and after the administration of atropine. The question at once arose as to the chemical nature of the active substance, and our experiments led us to the conclusion that this could not be choline (as had been suggested by Mott and Halliburton) because this substance, when administered to an animal under the influence of atropine, produces a rise of blood-pressure, while our extracts of tissues, on the contrary, always produced a fall. Halliburton (6) maintained that the active substance was choline; in other respects his results were the same as ours.

The present writer, working in conjunction with Mr. Sheen (25, 26), confirmed the statements of Osborne and Vincent, and added some new facts. They reported that depressor principles can be extracted, not only from nervous tissues, but also from all kinds of muscular tissue, kidney, liver, spleen, testis, ovary, pancreas, and lung. They note also that others had extracted a depressor substance from thyroid and thymus.

By this time it was clear to most observers that tissues generally impart to extracts a substance or substances the most striking action of which, when tested physiologically, is a lowering of the blood-pressure. There are of course other actions also, as for example, that on the pupil. This was not noticed by the present writer until recently, and with the strength of the extracts employed, was only slight. It was also clear that in most of these cases at any rate there is no reason to regard the presence of such substances as evidence that the tissues in question furnish an internal secretion. It would for example be nothing short of preposterous to assert that the presence of depressor substances in brain extracts has any direct bearing upon the problems of brain physiology. I believe that no one up to the present time has suggested that the depressor action of brain extracts points to an internally secreting function of the higher nerve centers.

Again, the present writer, working in conjunction with Dr. Cramer (23, 24), made a further attempt to isolate the depressor principle or principles in nervous tissue extracts. We found, it is true, a choline-like body in these preparations, but from physiological and chemical considerations, were con-

vinced that this could not be the actual active substance. The tests for choline employed by previous observers were unreliable. This was confirmed by Webster (27), who worked under my direction. Vincent and Cramer pointed out that normal blood contains a depressor substance.

Popielski (17) has ventured to give a name to the unknown depressor substance discovered through its physiological action by my co-workers and myself. He calls it "vaso-dilatine." Schwartz and Lederer (21) arrived at the same conclusions as Vincent and Cramer; so also other observers.

Although the chemical nature of the depressor substance is not certainly known, it is probable that it is B-Iminazolyethylamine [Dale and Laidlaw (3), Barger and Dale (1)]. This probability seems to apply at any rate to the principle found in the intestinal mucous membrane. There may of course be other active substances present in organ extracts.

An account of this literature is given in my book on internal secretion (22) published in 1912. Biedl (2), whom Marfori quotes, warns investigators against assuming that a physiological activity shown by an extract of an organ is in itself any proof of an internally secreting function.

The manner in which these results have been interpreted has not always displayed a proper critical attitude. Thus Livon (7, 8) divides the glands of the body into two groups, "hypertensive" and "hypotensive," according as their extracts cause a rise or a fall of blood-pressure. If we insist upon such a division, we have to place the chromophil tissues and the nervous portion of the pituitary body in the first, and all the other organs and tissues of the body

in the second group. Gautrelet (4, 5) holds views similar to those of Livon, and thinks that the "hypotensive" glands owe their activity to the presence of choline. The point of view of these two observers is fairly typical of those who believe that the normal blood-pressure is maintained by a series of antagonistic chemical messages arriving from the different glands and tissues of the body. This point will be referred to again later on.

It will thus be seen that considerable attention has been paid already to the depressor action of tissue extracts, and the chemical nature of the active substance. I have for some years taught my students that organs and tissues of the body yield to extracts a substance or substances which lower the blood-pressure. But I have warned them not to assume that this fact bears any direct interpretation in the direction of internal secretion. The fact is at this time perhaps largely of historical interest. I have also urged my laboratory workers not to write papers describing in detail the physiological action of extracts of the vermiform appendix, of the vocal cords, or of the fingernails, because nowadays no one would accept the theory that these structures are to be classed with the endocrine glands.

But now Professor Marfori appears on the scene and gives a careful account of the physiological action of extracts of lymphatic glands! It is remarkable that he makes no reference to any of the literature quoted above. Surely he cannot imagine that it is irrelevant to his subject. He describes the action of lymphatic gland extracts on the heart, on the blood-vessels, on the pupil, on adrenalin glycosuria, and lays stress on the antagonism between the active

principle and adrenin, and finally, with a great flourish of trumpets, announces a new hormone — "lymphogangline." His results, although they occupy fourteen pages of the "Archives," can be stated in a very few words. Extracts of lymphatic glands reduce the frequency of the heart beats (after the administration of atropine), lower the blood-pressure by vasodilatation, contract the pupil, and hinder glycosuria of adrenal origin. Now this last action is only mentioned in his "conclusions." It is not referred to in the body of the paper, and no evidence in support of the statement is put forward. It is possible that this evidence is given in the original paper in Italian, but I have not been able to consult this. Most if not all of these actions are the same as those obtained by the use of extracts of brain, spleen, or any other organ or tissue (with the possible exception of the constriction of the coronary vessels, which point I have not tested). The effect on the pupil is certainly seen with other extracts than those of lymph gland, though I have not tried it with a large number. With the preparations of the strength I have usually employed (one in three or four parts of saline) the effect is not very marked, though quite distinct, but Marfori uses very concentrated decoctions (one gram of the gland to one cubic centimeter of normal saline solution) and no doubt obtained a greater contraction. There is no reason to believe that the effect is a specific one. The reduction in frequency of the heart beat, especially after the administration of atropine, is by no means peculiar to extracts from lymphatic glands. Vincent and Sheen did not test this point very carefully, though one of their tracings shows the effect very clearly, even in an animal

without atropine. I have recently found that brain and spleen extracts reduce the heart frequency, especially after atropine.

The state of affairs, then, seems to be this, that extracts of chromophil tissues stimulate sympathetic nerve-endings, extracts of the posterior lobe of the pituitary body have an action which is in some respects of the same character, while extracts of other tissues have an effect directly opposite. But surely this does not justify us in assuming an internally secreting function for all parts of the body. If such were justified, then observers might have already named a whole series of "hormones"—"nervine," "musculine," "jecorine," "testine," "ovarine," and so on. It may possibly save some labor on the part of future workers if I announce in this place that extracts of the haemolymph glands, of the corpora lutea, of the lining membrane of the arteries, of parathyroid, of the pineal body, and of different kinds of bone-marrow all have the same or very similar activities. If it is still possible to find some organ or tissue which has not up to the present time been extracted and tested, we shall not be anxious to hear about it, unless it should happen to contain a pressor and not a depressor substance, or should reveal in other directions the presence of some new and remarkable active principle.

Current views on the whole subject of internal secretion demand a severely critical investigation. There is no branch of physiology littered with so many vague, unproved, and in many cases unprovable hypotheses. The terminology is becoming inordinately complicated, and one meets with a newly coined word every few months. The term "hormone"

is in everybody's mouth, yet how little do we know about these bodies! Only one alleged hormone has been chemically identified, and this has not been proved to be a hormone at all. It is perhaps not altogether a matter for rejoicing that the word was ever introduced. The term "internal secretion" is better in many ways and is at any rate sufficiently definite to describe the little-known substances derived from organs which are admittedly organs of internal secretion. It seems to be established that the thyroid gland, the parathyroid bodies, the adrenal body ("cortex"), the pancreas (possibly the "islets of Langerhans"), the duodenal mucous membrane, the reproductive organs (possibly the "interstitial" cells) and the pituitary body¹ furnish internal secretions which are of great importance in the economy. Yet in none of these cases has the chemical nature of the active secretion been ascertained.² Adrenin, the substance isolated by Takamine from chromophil tissues, has not yet justified its claim to constitute an internal secretion.

There has been for some years a tendency among the members of a certain school of physiologists, especially in France, to attribute an internally secreting function to all the organs and tissues of the body. This is exemplified by the views of Livon and Gautrelet quoted above. I imagine that the tendency has been derived, at any rate in part, from theories of the activity of adrenin in the animal body. It has been assumed that this substance is secreted by the adrenal bodies (or rather, by the chromophil

¹The pineal gland ought probably to be included in this list.

²Kendall's work on the thyroid principles may point to an exception in the case of this gland.

tissues) in order to help to maintain the normal blood-pressure, and to preserve the tone of other sympathetically innervated structures. This matter cannot be discussed here, but it is not going too far to say that there is no satisfactory evidence that the secretion of the chromaphil tissues is of any use whatever in the normal state of the animal. Moreover, it is not clear that the circulating blood contains any adrenin. If we have to admit all this in the case of the chromaphil tissues which undoubtedly contain an extraordinarily powerful drug found in no other tissue,¹ how much more must we recognize that there is no evidence that a lymph gland furnishes an internal secretion. The function of a lymph gland is to manufacture lymphocytes, and, although it *may* perform other functions in addition, we have no right to allocate rashly extra duties to an organ which has already, as we may imagine, sufficient labor to accomplish. We have not here as in the case of the adrenal bodies, a gland of unknown function, for which we seek to find some *raison d'être*. The lymphatic glands are not in the ordinary acceptance of the term, secreting glands. They are not formed of a highly specialized epithelium, and their structure does not suggest any kind of secretory activity. The substance yielded to extracts by a lymphatic gland is not powerful, and is not specific, but common to all organs and tissues. Reviewing the whole matter, it seems abundantly clear that there is not the slightest reason for believing that these bodies carry out any endocrine function. It follows that the term "lymphogangline" as applied to the active principle in the

¹That is to say in the mammal. We must of course bear in mind the occurrence of adrenin in the "parotoid" gland of *Bufo aqua* (Abel).

extracts, is both useless and dangerous, and it is to be hoped that it will not find any place in the literature.

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A CASE OF MYXEDEMA WITH TUMOR OF PITUITARY BODY AND LESIONS OF OTHER ENDOCRINE ORGANS

W. H. Good, M.D., and A. G. Ellis, M.D.,
Philadelphia

(From the Laboratories of the Jefferson Medical College Hospital)

The following case report is thought worthy of recording because of the long clinical history and the autopsy findings.

J. R. B.—, act, 58 years, married, electrician. Mother died of yellow fever, father in accident. Has had three children, one dying of tuberculosis, and another now sick with it. Never drank to excess, denies venereal disease, Wasserman negative, typhoid 36 years ago, severe scarlet fever in childhood. About fifteen years ago for three consecutive winters had severe attacks of grippe, after the last attack noticed the paleness of his skin, teeth dropped out, gums became sore, heavy black mustache dropped out and was replaced by a few white stubby hairs. Three years ago had a severe accident, fracture of humerus and fore arm and possibly a small depressed fracture of the top of the skull. For the last five months has been feeling much worse, had to give up his position as foreman electrician and became a night watchman, fatigues easily, feels cold all the time, always sleepy. Five weeks ago gave up work entirely.

Examination, 11.21.12. General appearances, stout, (180 lbs. ?), pale, white skin, dry and loose, marked swelling not pitting on pressure over the back of the hands and upper and lower eyelids, brow wrinkled, face expressionless, hair scanty and fine, beard and mustache replaced with a few white hairs, axillary and pubic hair almost absent, lips and tongue bluish, eyes congested, some exophthalmos, no edema of the ankles. He sits quietly in a rocking chair all day, hardly moving, not interested in anything, least movement fatigues him, drowsy, very placid, very different from normal some weakness in legs causing staggering movements at times, speech slow and thick as if he was too fatigued to trouble himself, memory poor, responds to a question after quite a latent period, thought seems to linger in his mind, and he keeps repeating and musing over some prominent word for sometime after he answers a question. He has been impotent and without sexual desire for possibly fifteen years back.

The pulse is 84, valve sounds of poor quality, no murmurs, no hypertrophy, systolic pressure 85 mm, diastolic 60 mm. The temperature is 96.4. the patient feels chilly most of the time, appetite poor, constipated, urine scanty, acid, sp.gr. 1020, no albumen, no sugar, no casts. Blood showed hemoglobin 85%, r.b.c. 3,650,000, w.b.c. 3020 with a marked increase in the lymphocytes.

The testicles were greatly atrophied.

He had the typical myxedema picture of subnormal activity of all the functions of the body, thermogenic, circulatory, urinary, digestive, metabolic, muscular and mental, like a frog on a cake of ice.

About seven months later as the symptoms did not clear up as completely as it seemed they should under desiccated thyroid, further examination was made. The X-rays showed that the posterior clinoid processes of the sella turcica had disappeared. The carbohydrate tolerance was found to be over 250 grams of glucose, and there were some changes in the eye grounds.

Ophthalmological report by Dr. E. B. Mongel on 10.15.14.

Vision in both eyes with glasses 6/7.5. About the same without glasses. Anterior ocular segment normal except for conjunctival irritation both palpebral and bulbar. Pupils equal, round 2 mm., respond promptly to light and accommodation. Tension normal. All associated ocular movements normal.

With ophthalmoscope;—Media in both eyes clear except for occasional vitreous opacities. Retina slightly hazy and oedematous, choroid irritated. **Optic nerves well outlined**, oval axis about 90°, temporal halves both nerve heads pallid, grayish, particularly the right eye quite marked, no fine vessels visible. Central physiological excavation, otherwise no gross pathological changes.

Visual fields:—Concentric contraction 15° to 20°, more marked **above** and **outward**. Scotoma localized 15° above, well shaped outline.

Evidently pituitary pressure on the optic chiasm.

Examination on 2.20.15. Vision with glasses the same, 6/7.5. Right optic nerve head almost all grayish white. Reduction in field of vision right eye more than in left, about 20° in right and 15° in left. Also enlargement of the physiological blind spot. No other pathological changes in the fundus.

The X-ray findings, the increased carbohydrate tolerance, the testicular atrophy, and the ophthalmological report seemed to indicate clearly pituitary involvement.

Treatment was begun 11.21.12. One grain of desiccated thyroid (U.S.P.) was given three times a day. The improvement was immediate and marked, the patient losing his drowsiness and becoming more active and talkative.

11.29.12. Brighter, anxious to get the morning paper, bowels moving regularly, urine more free, patient complains of severe boring headache. For two days received but two one-grain tablets of thyroid daily.

12.3.12. Complains of extreme hyperaesthesia of legs and uncomfortable desire to stretch constantly, temp. 98, pulse 85; taking care of his chickens again.

12.13.12. For several days has been taking four grains of thyroid daily. Complains greatly of deep muscle ache; headache better, sweats easily, something he has not done for years.

12.19.12. Pulse 96, temp. 97.8. Pains in knees and legs much better, bowels regular, memory better, drowsiness gone, anxious to be busy.

12.25.12. For the last few days has felt "stretchy" again with painful aching of the legs and some dyspnoea on exertion; feels greatly prostrated; pulse 88, temp. 97.8. Decrease thyroid to three grains daily.

12.30.12. Feeling better again, cold weather does not trouble him. Thyroid increased to four grains.

1.2.13. Had to decrease to three grains again. Hemoglobin now 95%. r.b.c. 5,035,000, w.b.c. 5600.

1.6.13. Today had a typical metabolic explosion; they have been coming on at irregular periods of two to nine months for some years back; possibly the attacks he called grippe of fifteen years ago were of this nature. After breakfast he began to feel ill, finally having a severe chill, lasting an hour and a half; bluing of nails and lips, excruciating pain in the back, severe pressure headache; vomited several times; followed by fever, profuse sweating, great thirst, temp. 103, pulse 120 and small, constant flow of rambling foolish speech and hysteroid mannerisms with delirium.

1.7.13. Slept some during the night; the rambling semi-delirium ceased about 8.00 P. M. He has been sweating all day long and complains bitterly of his back ache. Temp. 96.4, pulse 90, bowels not moved today, the first time since early in his treatment. These metabolic crises are usually more severe with incontinence of urine and feces, and more stupor than delirium.

1.9.13. The crisis is entirely over, except he is very costive. He has lost much weight in the last seven weeks; is four inches smaller in the waist and an inch in the collar. Has not taken any thyroid for four days; starts in again with one-fifth of a grain t.i.d. slowly increasing (B&W one grain tabloid).

2.1.13. Had an erection last night, the first in fifteen years, quite painful. Had another but not severe crisis today. Has been coming to my office for a week. Weighs 146 lbs., the least in years.

2.19.13. Feeling fine; after last crisis was off thyroid for a week, again taking three one-grain B & W tabloids (three-fifth grain U.S.P.) daily.

3.24.13. Improving slowly but steadily, passing 60 to 100 ounces of urine daily; cannot take more than three one-grain tabloids daily.

4.21.13. Feeling fine, back at his work at night watchman, taking one and a half grains of U.S.P. thyroid now. On account of his sexual impotence, lack of return of hair to normal, and incomplete return to normal condition under thyroid treatment alone, three grains daily of desiccated pituitary was added to the treatment.

5.12.13. Cannot take the pituitary as it causes tinnitus and dull disagreeable pains in the legs. Compared with two years ago, he says he is "a new man, feels differently all together," "can use his injured arm much more freely." Taking two and one-fifth grains thyroid daily.

6.9.13. "Feeling perfectly splendid, has not an ache or pain." Works out in his garden a great deal, feels but little fatigue. Hemoglobin 100%. r.b.c. 4,760,000, w.b.c. 4900, polymorphonuclears 32%, small lymphocytes 53%, large 13%, eosinophiles 2%.

7.14.13. Gave him 250 grams of glucose with no appearance of it in the urine. X-rays report by Dr. Zulick showed probable pituitary involvement, as the posterior clinoid processes of the sella turcica have disappeared. One grain of desiccated pituitary t.i.d. was again begun.

7.21.13. Worst week he has had for months, sleepy, nausea, vertigo, headache, very tired, temp. 96.5, pulse 75. Stop pituitary.

8.18.13. Feeling fine again. Temp. 97.6, pulse 76, blood pressure systolic 74, diastolic 52. Taking two or three grains of thyroid U.S.P. daily, occasionally stopping for several days.

9.22.13. Again add two or three grains daily of pituitary to the treatment.

12.22.13. Since taking the pituitary has improved more rapidly; occasionally have to stop it on account of pain over the heart, nausea, or vertigo.

8.27.15. Has been very comfortable with two grains of pituitary and three of thyroid daily, occasionally taking a little more or less according to his condition and symptoms. Pulse 70, temp. 96.2, blood pressure systolic, 98; diastolic, 68; weighs 146, hemoglobin 90%, r.b.c. 3,963,000, w.b.c. 5325, polymorphonuclears 42%, small lymphocytes 46%, large 8%, eosin 3.7%.

One grain of desiccated testicle added to his treatment on two occasions caused him to feel very miserable.

2.8.17. On the 4th going to work was exposed badly, was taken with a chill at work, taken to the Jefferson Hospital with severe pain in his side and temperature of 104. Died this morning following a collapse yesterday with Cheyne-Stokes breathing. Diagnosis pneumonia.

Several observations made in this case seem worthy of especial mention. One was the association of marked involvement of the thyroid, pituitary, and testicles, with persistence of the thymus. The marked leucopenia, especially of the polymorphonuclears, is also of interest.

From the clinical standpoint, the small dose of thyroid used is of interest; this was never more than five grains a day of the U. S. P. desiccated thyroid, and usually but three grains, and often in the earlier months of treatment it had to be discontinued for several days entirely on account of the great prostration it caused.

Another feature in this case worth noting was the peculiar metabolic crises at irregular periods,

closely simulating a malarial paroxysm. These seemed to be an integral part of the disease. The attacks fifteen years ago, which he thought were grippé, and which seem to be the beginning of the disease, were very probably these same crises.

The duration of the disease with the marked involvement of the pituitary, as shown by the X-ray examination, three and a half years ago, and the final pathological finding of hemangio-endothelioma of the pituitary, probably indicates a benign tumor that finally underwent malignant degeneration.

Pathological Findings:

The autopsy notes are here condensed to those that have a direct bearing on the case.

Body is that of a well-nourished white man. Pubic hair is entirely absent. The testes are small and soft. The faeial expression is feminine rather than masculine. There are scattered stubby hairs on the chin and region of the beard and no mustache except a few hairs on the left side. The hair of the head is thin, fine, and soft. The subcutaneous abdominal fat is 4 cm. thick.

Removal of sternum shows yellowish-gray tissue in the region of the thymus. The left lobe is 13 cm., the right 10 cm. in length; laterally the greatest width is 2.8 cm. and the thickness 0.5 cm. Weight, 14 gm.

Heart weighs 270 gm. No noteworthy changes, except slight fibrosis.

Left lung shows lobar pneumonia, with acute pleuritis.

The thyroid gland is very small and pale in color. The left lobe is 3x1.7x1.3 cm.; the right 3x1.5x1.1 cm. Weight, 5 gm. Parathyroids are not seen.

Spleen weighs 200 gm. It is moderately soft.

The adrenals are small and the surrounding fat is rather intimately adherent. Incision shows them to be very thin, medulla showing only at the central point. With small pieces of adherent fat, each weighs 5 gm.

The kidneys have evidence of cloudy swelling.

The prostate is an illy-defined mass of soft gray tissue without lobulation. The left testis is pale and very soft. Weight, 14 gm.

The skull is thinner than the average. Removal of the brain reveals an enormously enlarged pituitary body. It is a roughly globular mass 4.7 cm. laterally, 4 cm. anteroposteriorly, and 3.5 cm. vertically; weight, 35 gm. The superior surface is lobulated, mainly due to furrows caused by nerves. The inferior surface is smooth and the border is fairly regular in contour. A part of the surface is gray but much of the tumor is dark red, apparently due to hemorrhages. It is surrounded by what appears to be

a thin capsule. Incision of a lobule on the superior surface exposes dark red tissue from which blood escapes. The pituitary fossa is much enlarged, being 4 cm. laterally. With the exception of a remnant of the right posterior one, the clinoid processes have disappeared.

The brain is firm and has a deep depression caused by the tumor. The optic commissure is flattened, both it and the nerves anteriorly being ribbon-shaped. They were stretched tensely over the tumor before they were severed. The infundibulum cannot be identified.

Microscopic Findings:

Sections from different parts of the pituitary mass are entirely of new growth. This is composed of fibrous stroma and masses of round or oval cells. The stroma is fairly prominent in some areas, scanty and poorly staining in others. The tumor cells are in small or large masses and are closely placed. Blood vessels are numerous, many of them between or in the cell masses in fibrous tissue so scanty as to be scarcely demonstrable. A conspicuous feature is extensive hemorrhage. This is in large areas and separates the cells. It appears to be recent and the tumor cells are not necrotic. The fibrous band forming a capsule of the tumor is thin and at many points is invaded by tumor cells which are even upon the outer surface, although not in definite groups.

The thyroid gland has undergone most extensive atrophy and fibrosis. In many areas only connective tissue can be seen. Between these are areas in which are acini of various sizes but all smaller than the normal. The larger are lined by cells that are mostly flattened. Collections of small round cells are at points.

The testis is also the site of extensive atrophy and fibrosis, the latter process not so conspicuous as in the thyroid. The tubules are bordered by thick bands of connective tissue that are very prominent. In some of the tubules epithelial cells are still present but either in the form of a layer or two that are shrunken from the wall or not intimately attached to it, or simply an irregular mass of desquamated cells that fills the tubules. Spermatogenesis is entirely lacking. Areas of such tubules are bordered by others in which cells are completely lacking. The walls of these tubules have shrunken and obliterate the lumina. In some places the new tissue between the tubules is almost mucoid in character, this probably partly accounting for the extreme softness of the organ.

The capsules of the adrenals are thick and at many places are fibrous bands or a network of fibrous tissue that extends into the zona glomerulosa; at points this zone is fairly well replaced by the new tissue. The entire cortex is narrow. Some of the cells of the fasciculata stain poorly and the fat content is below the usual. A quite distinct band of fibrous tissue separates the reticularis from the prominent medulla and this is broadened in many places by extensions that partly supplant the reticularis. This new tissue is very vascular. The medulla is broad and has some increase of connective tissue. The cell clusters are not distinct. The cytoplasm is granular and in many cells partially fragmented.

The thymus is largely adipose tissue but in it are many islands of cells containing typical Hassall's bodies.

The skin of the chest has a thin epidermis and a compact, deeply stained corium in which papillae are not prominent. In certain places the thin epidermis and almost smooth corium suggest the condition seen over a healed wound.

Diagnosis: Hemangio-endothelioma of pituitary body; atrophy and sclerosis of thyroid gland, testes, adrenals and skin; persistence of thymus gland; lobar pneumonia; congestion, intralobular cirrhosis and fatty infiltration of liver.

From the history of the patient and the pathological findings, any statements as to the duration of the tumor and the order of involvement of the various organs would appear to be mere speculation. The case is therefore reported without comment or discussion of literature as a contribution to the subject of interrelated lesions of the endocrine glands.

For permission to publish the pathological findings we are indebted to Dr. S. Solis Cohen.

SOME POINTS OF CONTACT BETWEEN ENDOCRINOLOGY AND GYNECOLOGY

Emil Novak, Baltimore, Md.

(From the Gynecological Department of the Johns Hopkins University.)

Many gynecological patients present, as incidental points of interest, endocrine disturbances of one form or another. In some, however, the endocrinopathy dominates the picture, both etiologically and symptomatically. This is particularly true of certain types of menstrual disorder which are mere manifestations of internal secretory disturbances. It is with this group of cases, in which gynecology and endocrinology seem to come into closest contact, that we shall deal in this paper.

The two great functions of the female generative organs, reproduction and menstruation, are both profoundly influenced by disorders of the ductless glands. This is especially true of the menstrual function. It is now definitely known that the cause of menstruation is an internal secretion of the ovary, and that the element of the ovary which is concerned in the process is almost certainly the corpus luteum. The menstrual function is thus brought into the most direct relationship with the ductless gland apparatus. Although the ovary is commonly spoken of as the cause of menstruation, it would seem to be important to emphasize the fact that it is merely the portal—the point of contact—through which the entire endocrine system exerts its influence upon the generative organs.

Amenorrhœa—The majority of menstrual disorders are, of course, due to one form or another of anatom-

ical lesion in the uterus or adnexa. A certain group, however, is undoubtedly the result of internal secretory disturbance. The most clearly defined type of menstrual disorder which is undoubtedly of endocrine origin is that observed in connection with the well known adiposo-genital dystrophy, or Froehlich's syndrome. The principal characteristics of this syndrome are adiposity and sexual hypoplasia, the latter characterized in women by the occurrence of amenorrhea. This association of symptoms is encountered with great frequency by every gynecologist. Even in the early days of gynecology, the fact was well recognized that scanty menstruation or amenorrhea is often noted in patients who have taken on a great deal of weight. Instead of explaining the amenorrhea as being caused by the adiposity, or vice versa, we now know, thanks to the researches of Cushing and others, that both are manifestations of the same underlying cause—hypopituitarism.

The adiposo-genital syndrome furnishes a striking example of the intimate relationship existing between the various links of the endocrine chain. At first thought, one does not associate the pituitary body with the menstrual function, or look upon hypopituitarism as a cause of amenorrhea. Since the immediate cause of menstruation is the ovarian hormone, it is obvious that the effect of hypopituitarism must be exerted through the medium of the ovary. To be more explicit, if perhaps somewhat theoretical, it would seem that hypopituitarism entails a deficient activity of the corpus luteum—in other words, that under normal conditions the two secretions are synergistic. If this conception were correct, one might be justified in assuming that the pituitary is the acti-

vator of the ovarian secretion, and in this indirect way influences menstruation. And yet there is evidence that the mechanism of the amenorrhea observed in this group of cases is quite different.

A recent case of my own, unique in my experience, offers evidence that even during the amenorrhea of Froehlich's syndrome, ovulation still takes place, and that corpora lutea are therefore being formed. A young white woman of nineteen, married, was referred to me by Dr. B. S. Hanna, because of amenorrhea of five months' duration. She had gained thirty-seven pounds in weight during the past year. Examination of the pelvic organs showed the uterus to be small in size and normal in position, there being no evidence of pregnancy. The amenorrhea having persisted in spite of treatment by thyroid and ovarian extracts, the patient returned for examination three months later. At this time, eight months after the last menstrual period, the uterus was found to be enlarged to the size of a two and a half months pregnancy. In other words, the patient had become pregnant during the continuity of the amenorrhea associated with her adisposo-genital dystrophy. The occurrence of the pregnancy is, of course, absolute proof that ovulation had taken place—in other words, that corpora lutea had been formed in the ovary. In spite of the presence of the latter, however, menstruation had not occurred. It would seem that the corpus luteum hormone in this condition was either neutralized or antagonized by some other endocrine element, probably of pituitary origin. This phenomenon is analogous to the occurrence of amenorrhea in the lactating woman. It is a well known fact that pregnancy, and therefore ovulation

and corpus luteum formation, frequently occurs in nursing women. In these cases, the corpus luteum hormone is either inhibited or neutralized by the internal secretion of the lactating breast.

Uterine Bleeding—Excessive uterine bleeding, in the form of either menorrhagia or metrorrhagia, is almost always due to one or another of the numerous pathologic conditions which may occur in the uterus or adnexa—retained products of conception, cancer, myoma, polypi, salpingitis, ovarian neoplasms, etc. In a certain proportion of cases, much more frequently than was formerly believed, such bleeding may be observed in the entire absence of any demonstrable pelvic disease. It is suggestive that such functional uterine hemorrhage, as it is called, is noted most frequently at puberty or at the menopause, when endocrine equilibrium is most unstable. The awakening of ovarian activity at the pubertal epoch, and its cessation at the climacterium, may well be expected to disturb the delicate endocrine balance which spells normality.

Menstrual disorders, including uterine bleeding, are often observed in connection with derangements in the function of the thyroid. There has been some discussion as to whether excessive menstruation is more likely to be associated with hyper- or hypo-thyroidism. My own experience leads me to believe that, while either association is possible, it is with deficient thyroid function that we are more likely to encounter uterine hemorrhage. Hertoghe (1) and Sehr (2) both hold to this view, the latter reporting that in a series of fifty-five cases of functional hemorrhage he found thirty-eight with definite indications of hypothyroidism. As a matter of fact it is probable that

excessive menstrual hemorrhage may be observed with either type of quantitative disorder of thyroid function. There can be little doubt that other elements in the endocrine chain—the pituitary, thymus, suprarenal, etc.—may at times be responsible for uterine bleeding and other menstrual disorders, but our knowledge on these points is so imperfect that it is scarcely profitable to do more than allude to them.

From a theoretical point of view the form of endocrine disorder which one would naturally think of as most likely to cause uterine hemorrhage would be over-function of the ovary, or hyperoöphorism. Although such a condition may undoubtedly exist, its study presents many difficulties. In the first place, it is open to question whether we can produce hyperoöphorism experimentally, although this possibility has been claimed by Adler (3). The latter, by feeding ovarian extract to a girl of twenty-one, whose menstruation had always been normal and very regular, claims to have brought on the menstrual period, for the first time in the girl's life, four days before the expected date, the amount and duration being also much greater than normal. The same observer has studied the problem from an altogether different angle, by means of the reactions of the sympathetic nervous system to various drugs, according to the method first worked out by Eppinger and Hess (4). His conclusions are that over-function of the ovary is the cause of functional uterine bleeding. As I pointed out in a previous paper (5), however, Adler's results are open to serious question, inasmuch as his methods of study seem to take no account of the fact that the

ovary is only one of the endocrine organs contributing to the menstrual impulse.

Although the ovary is no doubt the immediate cause of menstruation, we must not overlook the fact that it is, after all, only one element in the rather complex menstrual machinery. It is commonly conceded that the ovary is responsible for the marked pelvic and uterine hyperemia which is so striking a feature of menstruation. No matter how extreme such a hyperemia might be, it would not in itself explain such a wholesale exodus of blood elements from the endometrial vessels as is observed during this process. Inflammatory hyperemia may be far more marked than the physiological congestion of menstruation, but it is rarely associated with any great degree of hemorrhage. In other words, we must assume that during menstruation there is some local factor in the endometrium which increases the permeability of the blood vessels, upon which it appears to exert a more or less selective action. The work of Schickele (6) and others indicates that this local factor, whether it be a hormone or enzyme, is formed as a result of ovarian activity, being apparently a by-effect of the ovarian hormone. Here, then, is another point of contact between the endocrine apparatus and the reproductive apparatus.

Dysmenorrhea—The occurrence of dysmenorrhea as a result of endocrine disorders is certainly much less frequent and much more difficult of demonstration than that of either amenorrhea or excessive menstruation. As a matter of fact, only one example suggests itself, and in that the relationship is somewhat indirect. Spasmodic dysmenorrhea is extremely common in young multiparous women, and

is the cause of much suffering and invalidism. The underlying condition in these cases is a greater or less degree of uterine hypoplasia, of the foetal, infantile or subpubescent type, according to the classification which I suggested in a recent paper on the subject (7). It is far more frequent to observe dysmenorrhœa in the mild degrees of uterine hypoplasia—the subpubescent group—than in the more extreme forms, such as the uterus foetalis or rudimentarius. In the latter variety, amenorrhœa is the predominating gynecological symptom. When dysmenorrhœa is observed in young unmarried women with underdeveloped uteri, the symptom is brought into relationship with the endocrine apparatus by virtue of the fact that disorders of the latter are unquestionably to blame for the uterine hypoplasia, and indirectly, for the dysmenorrhœa.

Knowledge of this fact should point the way to future efforts to find a satisfactory treatment for this condition. Certainly no one can deny that the results of present-day treatment of this syndrome—whether by drugs, simple dilatation, the use of stem pessaries, or the performance of plastic operations on the cervix—are such as to provoke little enthusiasm among gynecologists. It is true that the same statement applies even more forcefully to organotherapy in such cases; but the fault lies not so much with the general logic of such treatment as with the still nebular nature of our knowledge concerning endocrine relationships, as well as the methods of preparation of gland extracts.

Sterility—Much of what has just been said concerning dysmenorrhœa applies also to the discussion of at least one type of sterility—that associated with

uterine hypoplasia. It is quite possible that our helplessness in this, one of the big problems of gynecology, is due to the fact that we have paid too much attention to the study of mere anatomic defects in the reproductive organs, and too little to the possibilities of a perverted physiology of the generative apparatus. Although I shall not enter into the discussion of this subject, there is much reason to believe that sterility in this group of cases is due to a physiological defect in the endometrium—the absence of some factor, whether hormone or enzyme, which is essential to the implantation of the fecundated ovum. Organotherapy offers nothing as yet in the treatment of such cases, but I firmly believe that the time will soon come when those cases of sterility which are of endocrine origin will be successfully treated by appropriate organotherapeutic measures.

In this brief review I have indicated, in a superficial way, only a few of the more important points at which endocrinology and gynecology come into more or less intimate contact. The field of endocrinology is the whole living body—that of gynecology, as of other specialized branches of medical or surgical science, is often confined to a special region. And that is just the point upon which I would like to put a final emphasis—that the gynecologist whose range of vision is so limited as not to extend beyond the ileo-pectineal line will not only miss much of the fascination he might otherwise find in his work, but that, encircling himself with such a narrow horizon, misinterpret or perhaps overlook clinical manifestations which are at times veritable signboards as to therapeutics.

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HORMONE CONTROL OF RENAL FUNCTION

Since the work of Magnus and Schäfer on diuresis from pituitary extract, numerous investigators have studied the effects of different hormones on secretory activity of the kidney. There is still conflict of opinion not only concerning the method of action of pituitary extract in producing diuresis, but also as to whether it has a diuretic function. The same may be said of the other hormones which affect the kidney.

In considering the effects of glandular extracts we must bear in mind that the extracts used by different investigators are not necessarily of the same composition, due to different methods of preparation and to the presence in some cases of decomposition products. Until the individual hormones are isolated there is apt to be some confusion in the results obtained. For example Schäfer (1) says that pituitary extract is likely to cause two effects which are antagonistic to one another. He supposed that the gland contained two substances, one which stimulates, the other which depresses kidney activity.

The work of Schäfer and his associates (2) made it appear that pituitary diuresis could occur without an increase in volume of the kidney. They were led to believe that this diuresis was due to a direct excitation of the kidney cells because atropine did not antagonize the action. Others have supported the theory of direct excitation of kidney cells (3). Among them Gabriels (4) obtained constriction together with diuresis in the perfused kidney.

Another school of workers holds that the diuresis is entirely dependent upon the vascular changes produced. Among these Houghton and Merrill (5) main-

tain that the increased urinary flow depends upon the increase in blood pressure; and even more to the point King and Stoland (6) always obtained kidney dilatation accompanying diuresis. Recently Knowlton and Silverman (7) have determined the oxygen consumption of the kidney accompanying pituitary diuresis and find that it is not increased. Moreover throughout all of their experiments there was an increased blood flow through the kidney accompanying the pituitary diuresis. Pituitary diuresis they picture, therefore, like that occurring from the injection of Ringer's solution in which the oxygen intake is not increased (8) and is supposed to be due to increased filtration pressure.

As to the production of diuresis by the pituitary, the mass of evidence seems to be in its favor. That already given, together with grafting experiments (1, 9) and pituitary stimulation (10) proves conclusively that pituitary products can produce at least a transient diuresis.

On the other hand, a newer school demands attention. Their work even goes so far as to suggest anti-diuresis as a normal pituitary function. Motzfeldt (11) working with unanesthetized animals, rabbits mostly, found that a water diuresis could be checked by intravenous or subcutaneous injection of pituitary extract. Addis, Barnett and Shevky (12) went farther, proving that there was an actual decrease in the urea excreted, while the blood urea increased in rabbits. There are the negative experiments of Rees (13), who was unable to obtain a change in the amount or specific gravity of the 24 hour output of urine by subcutaneous injection of pituitary preparations. He used both cats and rabbits.

Certain clinical evidence also supports the idea of an anti-diuretic function for the pituitary. This is the successful use of pituitary extract in reducing the polyuria of diabetes insipidus (14). Motzfeldt and others suppose that there is hypofunctioning of the pituitary in this disease.

How can these contradictory findings be explained? In the researches where diuresis has been obtained, the experiments were mostly of short duration and upon anesthetized animals. Longer experiments upon unanesthetized animals have shown either a negative or anti-diuretic action in rabbits at least (12, 13). Whether rabbits or other animals are used may have something to do with it as Houssay (15) has found that although oliguria is produced in their case, in dogs and human beings the effects are variable and sometimes contradictory. Looking at the situation impartially, a normal diuretic function of the pituitary is seriously questioned; indeed it appears that the normal function may be anti-diuretic.

The possibility of adrenalin control of the kidney has not been investigated so extensively as in the case of pituitary extract. It has been demonstrated that adrenalin produces diuresis (5) and recently Addis, Barnett and Shevky (16) have shown that this is accompanied by an increase in the urea excreted. These authors think that adrenalin stimulates (secretory) sympathetic terminations. Cow (20) on the other hand has not only demonstrated a direct vascular connection between the medulla of the suprarenal and the kidney, but has shown that under certain conditions adrenalin is poured by this path into the kidney, producing a diminution in the flow of urine.

Gunning (17) has also found that intravenous injections of adrenalin cause an inhibition in urine flow in both anesthetized and unanesthetized dogs. The inhibition, however, is very brief, as he says that it persists until shortly after the blood pressure reaction is complete. Although he did not observe diuresis following, it would be well to base conclusions upon urine flow over longer periods of time as Addis and his collaborators did. Moreover the determination of some constituent in the urine, such as urea, per unit of time, is highly important. It may also well be that very small amounts of adrenalin such as that absorbed from subcutaneous injection cause diuresis which can be detected over periods several hours in length, while larger doses which are effective immediately produce the opposite result. However the hypothesis that the adrenal produces some substance which is necessary for the maintenance of normal kidney function needs further confirmation. The work of Marshall and Davis (18) is very suggestive. They found decreased excretory power in the kidneys of adrenalectomized cats. Of course this might be explained by the lowered activity of the tissues in general.

It is possible that other hormones may influence kidney activity. Cow (21) extracted a diuretic substance from the mucous membrane of the alimentary canal, especially the duodenum. He suggests that this substance is carried by water on its way into the blood stream from the gastro-intestinal tract. Pituitary (19) has shown that secretin is also diuretic in action.

The question of hormone control of the kidney is

extremely important, and although it appears that we are well along toward its solution, there are many points still unsettled. It is only through carefully controlled experiments of long duration by both laboratory and clinical workers that it can finally be answered.

F. A. H.

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THE ENDOCRINE GLANDS IN THE INSANE

In spite of its importance relatively little attention has been devoted to the possibilities of fruitful investigation in the field of endocrinology as related to the insanities. Holmes in Chicago and Mott in England have especially emphasized the importance of such study. In 1916 Farrant (1) published a resumé on "The causation and cure of certain forms of lunacy" that is deserving of more attention than the disturbed condition of the times has allowed it to receive. The problem had been then under investigation for seven years.

The work was based upon an assumption that toxemias play an important role in the insanities and that the endocrine glands suffer particularly as a result of the toxemias. Faulty action of these glands in turn might be expected to add further to the abnormal chemical environment of the brain cells and thus aggravate the mental disorders. The research consisted of (1) the microscopic examination of sections from the pineal, pituitary, thyroid and sex glands at different ages and periods of life as puberty, menopause or at childbirth; (2) a determination of the effects induced in these glands by acute and chronic toxemias; (3) a determination of the changes in cases of lunacy.

From 3000 sections it was found that the glands mentioned vary at different ages and periods of life; a tendency to atrophy toward the close of life was observed. The pineal reacts to certain toxemias by an ultimate fibrosis. A similar fibrosis was observed in case of the hypophysis; intermediate stages of the reaction were seen as cysts and adenomata which

Farrant interprets as evidence of hyperactivity. The thyroid also reacts by hypertrophy, cyst formation and adenomata.

In primary and secondary amentia atrophy of the pineal gland, hypophysis and thyroid were found in three classes of cases. In dementia precox an alteration was found in the glands which varied with the duration of the disease. Alterations and degenerations were found also in other dementia cases. In the manias, melancholias, maniac depressions and other insanities changes, hypertrophic or atrophic, were found in the thyroid, pituitary and sexual glands.

Clinical examinations were made in 1000 cases to determine from physical signs and symptoms the condition of the endocrine glands. The thyroid was frequently found to be abnormal in youthful, adolescent and adult lunatics; in size it showed variations from a considerable hypertrophy to marked atrophy with corresponding variations in symptoms from exophthalmic goitre to myxedema and cretinism. The hypophysis had given rise to symptoms of augmented or of depressed activity in idiocy, dementia precox and other forms of insanity. Skiagrams of the sella turcica showed corresponding evidence of hypertrophy or atrophy. Symptoms of pineal malfunction were noted in case of children and adolescents. Alteration in the size of the testes was found associated with other endocrine gland changes. Testicular atrophy was well shown in cases of pituitary deficiency.

Certain therapeutic deductions follow from these findings: Toxemias if present should be removed by

medicinal or surgical means and the glands, if hypertrophic, allowed to involute. If the glands are atrophic their deficient secretion should be compensated for by the administration of corresponding endocrine gland products. Good results may be expected if cortical brain lesions have not occurred.

It is to be hoped that when interrupted scientific investigations can be resumed a considerable degree of attention may be given to such investigations as those summarized. Careful post-mortem examinations should be made of the various endocrine glands with adequate attention to evidence of secretory activity. The glands should be weighed and the ratio of the weight to that of the body as a whole and to that of other glands should be noted, making due allowance, or better, possibly, discarding cases in which emaciation or obesity are disturbing factors. The tissues should be secured as soon after death as possible and fixed in small pieces, preferably in one of the formalin-dichromate mixtures. The microscopic sections should be cut in paraffin at a thickness of about 4 micra and the special staining methods used that permit careful cytological study. Full descriptions of improved technique adapted to such studies have been published by Cowdry (2) and Bensley (3). Goetsch (4) has used Bensley's technique in his recent study of the functional activity of thyroid adenomas.

It must be emphasized, in conclusion, that the ordinary conventional autopsy is but poorly adapted to solving endocrine problems such as the one herein suggested. An ordinary thick celloidin section of a gland stained with hematoxylin and eosin reveals relatively little regarding secretory details.

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ETIOLOGY OF GRAVES' DISEASE

The trend of the literature of recent years is toward a conclusion that Graves' disease is essentially a hyperthyroidism. Various lines of evidence point to this conclusion and many well informed writers use the terms interchangeably. Perhaps the most significant fact justifying this practice is that the nitrogen metabolism runs high both in the disease and in true experimental hyperthyroidism. On the other hand, hypothyroidism, whether experimental or clinical, is characterized by a reduced nitrogen metabolism. The reduced metabolic level of a cretin can be raised by the feeding of thyroid substance or by such a purified derivative as thyroxin.

The simplest explanation of these facts would be that the thyroid furnishes a hormone which serves as a general cell stimulant. In the lack of this stimulant the cells function at a reduced rate. On teleologic grounds, however, such a belief is difficult to justify. Why should an organism or a cell be intrinsically adjusted to a low level and be dependent upon a more or less gratuitous stimulant to keep it up to "normal"? It would seem simpler that the cells would spontaneously function at the proper level. The real explanation is probably not so simple.

The crucial experiment to determine whether or not Graves' disease is actually the result of, or equivalent to, pure hyperthyroidism would obviously be to reproduce the symptomatology of the disease by the administration of thyroid material. Crotti, in his recent monograph, concludes that this has been satisfactorily done. Carlson, on the other hand, was unable in a series of careful experiments to produce the

picture of Graves' disease experimentally either in man or animals.

One observation which is apparently well attested renders untenable the conception that Graves' disease is a simple hyperthyroidism. This observation is that the disease may exist simultaneously with hypothyroidism. Thyroid secretion cannot be both augmented and depressed at the same time any more than can a physical object be simultaneously up and down. Various labored explanations of the paradox have been offered but they have the defect of leaving the contradictory fact still standing. Moreover, cases in which thyroid medication has proved beneficial in Graves' disease have been repeatedly described. The blood picture—a reduction of neutrophils, lymphocytosis and mononucleosis—is the same in both Graves' disease and myxedema. It would seem, then, that there is some element in common in the etiology of the two conditions.

The literature bearing upon this problem has recently been reviewed by Janney (1) in an extensive article in which an alternative theory is proposed. If, as he says, the hyperthyroid theory is discarded we have remaining as the only possible explanation dysfunction of the thyroid as the cause of Graves' disease.

The central idea in Janney's theory is that there is a toxic element in Graves' disease, the toxin being derived possibly from the thyroid hormone. This, according to Kendall, (2) contains the indol nucleus and might readily be split into intermediate decomposition products, one or more of which may be toxic. Under ordinary circumstances the hypothetical toxic

body would be further acted upon in the thyroid gland itself and be discharged only in some harmless or even beneficial form. On the other hand, the toxic body might be produced as a substance antecedent to the hormone proper. "It is possible that various factors might disturb the normal synthesis of the hormone, the result being the premature discharge of the toxic intermediary product into the circulation. The factors producing this condition might be disturbances in the nervous control of the thyroid metabolism, such as could be produced by fright, emotion, shock or direct organic injury such as trauma, thyroiditis, or again, histologic and gross changes in the parenchyma of the gland; that is, the well-known causes of exophthalmic goiter.

"The result of the premature discharge of the hypothetical toxic intermediary product would be an impoverishment of the gland of the thyroid hormone, which would explain the fact that Graves' disease goiters are poor in iodine, and especially in the active alpha-iodine proteins. The decreased production of the normal hormone due to the cause mentioned would tend to be accompanied or followed by signs of thyroid insufficiency."

It is on these grounds that Janney accounts for the occurrence in Graves' disease of such conditions as goiter, cutaneous symptoms (atrophy, pigmentation, scleroma, brittleness and loss of hair, trophic nail changes), abnormal depositions of subcutaneous fat (rare), osseous changes (imperfect ossification and epiphyseal union) fatty degeneration, especially of the heart and somatic musculature, mononucleosis, metabolic disturbances similar to or identical with

those in hypothyroidism—delayed glucose assimilation, creatinuria and growth disturbances in youthful cases. Certain symptoms such as weakness, loss of weight and creatinuria may properly be ascribed to either the presence in the blood of the hypothetical toxin or to a deficiency of the normal hormone. In exophthalmic goiter showing deficiency symptoms judicious thyroid medication would, according to these views, be indicated. As to whether there actually is a toxic substance present in the blood of Graves' disease the evidence is relatively meager and not very convincing, but the matter is at least worthy of further careful research.

In any case, Janney's work will serve as an effective challenge to that numerous class of writers who use the terms Graves' disease or exophthalmic goiter and hyperthyroidism interchangeably. The trouble in Graves' disease may be that the chemical inlet to the thyroid is blocked rather than that the outlet or the gland capacity is enlarged.

R. G. H.

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THE ADRENIN TEST FOR THYROID DISORDERS

For more than a decade investigators have been seeking a reliable test for the presence of thyroid hormone in the blood. Two motives chiefly have prompted the quest. Physiologists and pathologists have been impeded in their investigations of thyroid functions by lack of reliable means of recognizing true hyperthyroidism except in its grosser aspects. Clinicians, recognizing the importance of the thyroid gland in various obscure disorders, have felt an acute need of a test which in borderline cases would serve to determine whether or not the thyroid was involved.

The acetonitrile test of Reid Hunt (1) of which much was heard a decade ago, was one of the first that offered promise of wide usefulness. Hunt reported that thyroid substance fed to mice protected them from poisoning upon subsequent administration of properly graduated doses of acetonitrile. Later work has shown that the test is not sufficiently delicate nor reliable to be of much practical use.

In the physiological laboratory of the University of Chicago much effort has been devoted to a search for a thyroid test. The use of cretin rabbits has, in the light of experience in that laboratory, seemed most promising (2).

Of recent years attention has been centering more especially upon the neurocirculatory apparatus as furnishing the most sensitive test object. In Asher's laboratory at Berne the problem has been under study for some ten years. Asher and Flack (3) published the results of some interesting observations in 1910. They set out to show that during and following stimu-

lation of the laryngeal nerves, which they regard as secretory to the thyroid, a given dose of adrenin would produce a greater circulatory response than before such stimulation. They felt justified in concluding that (a) stimulation of the laryngeal nerves causes secretion of the thyroid gland; (b) thyroid secretion sensitizes sympathetic endings to the action of adrenalin. Their results were not entirely convincing and certain details of their experiments made some of these results questionable. Asher and Flack had, however, the correct conception, but did not succeed in working it out in a convincing fashion, as subsequent work has shown.

In 1915 Oswald (4) reported on the effect of iodothyreoglobulin on the circulation. It produces no alteration in blood pressure or pulse rate. But after intravenous injection of this substance, which Oswald calls the true secretory production of the thyroid, adrenin causes a rise in pressure—which may be twice as high and twice as long as before. This effect is manifest, however, only after a short latent period and persists for a considerable time, having been demonstrated after the lapse of $1\frac{1}{2}$ hours. It is Oswald's belief, therefore, that iodothyreoglobulin renders sympathetic endings over-sensitive to the action of adrenin. These studies are suggestive.

Cannon and his associates showed further that thyroid secretion sensitizes the sympathetic nervous system to the action of adrenin. In a series of experiments, published in October, 1916, Levy (5) shows that in cats, after stimulation of the cervical sympathetic in the neck, a procedure which we now know causes secretory activity of the thyroid, there can be demonstrated an increase of the effectiveness

of adrenin in raising arterial pressure. This increase may be as much as 200 to 300 per cent. He has further shown that the injection of adrenin, even in minute amounts, produces a similar effect.

When the thyroid glands have been previously removed, cervical sympathetic stimulation or adrenin injection does not produce an increase in the pressor response to adrenin. He therefore concludes that stimulation of the cervical sympathetic or adrenin injection causes the thyroid to discharge and that thyroid hormone thus thrown into the circulation sensitizes the vasomotor system. Kendall's Thyroxin produced a similar sensitizing effect. This effect is not due simply to cumulative adrenin discharge since the same result is obtained when the adrenal glands are removed.

In 1912 Barker and Sladen (6) tested the reactions to adrenin in 21 cases, including three of exophthalmic goitre and four of "hyperthyroidism" associated with other conditions. A considerable degree of hypersensitiveness to adrenin was manifested in the vasomotor response. The dose used (0.001 gm.) was so large, however, that the results were somewhat equivocal. Certain individuals supposedly normal will react to this dosage.

In view of these facts Goetsch (7) attempted to determine whether there would not be an increased sensitiveness to adrenin in all cases manifesting symptoms of "hyperthyroidism." He began by using a hypodermic dose of 0.00075 gm., or 10 minims (1-1000 sol.) observing the effect upon the pulse, blood pressure and the constitutional reaction, over a period of 1½ hours. In all cases of "hyperthyroidism," whether mild or marked, a positive reaction

was obtained. Later he found that this dose would occasionally produce a slight reaction in what one would regard as possibly a normal individual. Consequently 0.0005 gm. doses (0.5 cc. of 1:1000 sol.) was later used, an amount which is insufficient to cause any but the very slightest increase, less than 10 in fact, in blood pressure or pulse and practically no subjective symptoms whatever. This dose was then used as the standard. If thyroid secretion sensitizes the sympathetic endings to the action of adrenin, then it is reasonable to suppose that a sudden increase of adrenin in the circulating blood should call forth active responses throughout the domain of distribution of the sympathetic system.

This result was found to be remarkably constant. Not only does a "hyperthyroid" patient react constitutionally to a subcutaneous dose, but also locally to an intradermic dose of one minim of 1:4000 solution of adrenin. This latter reaction depends upon the excessive contraction of the smooth muscle in the small vessels of the skin, supplied by the sympathetic and is characterized by a central large area of blanching surrounded by a peripheral zone of reddening due to neighboring secondary vasodilation. In the blanched area a characteristic "goose-flesh" is often seen. The reaction in a thyroid patient (exophthalmic goitre or toxic adenoma) lasts for $1\frac{1}{2}$ to $2\frac{1}{4}$ hours as compared with $\frac{1}{2}$ to $\frac{3}{4}$ hour in the normal subject. Whether the reaction will be found in other than thyroid cases has not yet been determined.

In addition to the local reaction the systemic response may also be used as a criterion of sensitiveness. A hypodermatic injection of 0.5 cc. (1:1000) solution of adrenin is administered. In a positive

reaction there is usually an early rise in blood pressure and pulse of over 10 points and at times 50 points or more. In a half hour there is a moderate fall followed by a secondary rise and fall, normal being reached in about $1\frac{1}{2}$ hours. In addition various symptoms of Graves' disease may be produced or augmented, not however, in Goetsch's experience, to a dangerous degree.

The following may all or in part be found: increased tremor, apprehension, throbbing, asthenia, and in fact an increase of any of the symptoms of which the patient may have complained. Vasomotor changes may be present; namely, an early pallor of the face, lips, and fingers, due to vasoconstriction, to be followed in fifteen to thirty minutes by a stage of vasodilation with flushing and sweating. There may be a slight rise of temperature and a slight diuresis.

In order to interpret a test as positive it is regarded as necessary to have a majority of these signs and symptoms definitely brought out or increased. Thus there is at times a considerable increase of pulse rate without much increase in systolic blood pressure, but with a considerable increase or exacerbation of the objective signs and symptoms; or there may be an increase of ten points in the pulse and blood pressure and a moderate increase of the symptoms and signs; or again, there may be only slight changes in pulse and blood pressure and considerable change in signs and symptoms. These may be regarded as positive. In a word, then, one must consider the entire clinical picture produced in order to gain a correct interpretation, just as in the disease itself one cannot expect every one of the characteristic signs and symptoms to be present in order to make a diagnosis.

A considerable degree of correspondence between the severity of the disease, clinically, and the reaction has been noted. After thyroidectomy, either in cases of exophthalmic goitre or of adenoma, the sensitiveness to adrenin is materially reduced, if not entirely removed. After excision of adenomata the sensitiveness disappears quite early because here the entire offending tissue is removed. In the case of exophthalmic goitre, however, a certain degree of sensitiveness may persist because one cannot with safety remove the entire thyroid gland.

The test has been of greatest value and help in the diagnosis of that large group of borderline cases resembling in some respects Graves' disease, but without definite recognizable signs on the part of the patient generally or in the findings of the thyroid gland, which may not be palpably enlarged. Many of these cases have proved to be dependent upon the adenomatosis of the thyroid gland discovered at operation which was advised previously on the basis of the positive adrenalin test. Many small adenomata were found, however, too small to be palpated before operation. In this manner the uncertainties in diagnosis are produced by the disease. That the diagnosis in these cases is correct is shown by the histological evidence of functional activity in these adenomata and by the fact that a practically complete cure is accomplished by removal of the adenomatous tissue. The reaction has been of particular value in picking out thyroid cases from that large group of ill-defined conditions, designated as psychoneurosis, psychasthenia and neurasthenia. In several instances of this kind in which mental symptoms predominated, and in which the examination failed to

reveal any positive signs in the eye, thyroid gland or heart, there was found a mildly positive adrenin reaction and at operation multiple small adenomata were found in the thyroid gland.

For the details of technique, which are important in the successful use of the test, the reader is referred to Goetsch's original paper (7), from which a considerable part of this article is quoted.—R. G. H.

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ADRENIN AND ARSPHENAMINE

From time to time striking claims are put forth as to the therapeutic usefulness of adrenin. Aside from its value as a short lasting sympathetic stimulant many observers remain unconvinced that it has any well grounded claim to favor. This feeling is based partly upon numerous failures that have been made in attempting to utilize it in unsuitable cases or, possibly, improperly administered. The frequent claim of its efficacy when given by mouth has been contrasted with its lack of any demonstrated effect when so administered to experimental animals.

Milian has since 1913 insisted, however, that adrenin is able when properly administered to obviate or cure the disagreeable by-effects of all the arsenical antiluetics. As a routine measure he favors the administration of 2 mg. (2cc. 1:1000 sol.) by mouth one hour before an injection of arsenobenzole, repeating the dose five minutes before and one hour after the injection. In cases in which the patient is intolerant of the arsenobenzole Milian advises the administration of 1 mg. by mouth mornings and evenings for four days. To prevent crises, congestion of face, vomiting, etc., he gives five minutes prior to the arsenobenzole a subcutaneous injection of 1 mg. of adrenin and an intramuscular injection of 0.5 mg. Objective signs that the patient is sufficiently under the influence of the adrenin are an augmented arterial pressure, tachycardia, generalized tremor, and, especially, pallor of the face. Intravenous injections, Milian believes, should be reserved for emergencies and the dose should be small—0.1 mg. in 100 cc. of normal saline solution. The danger of other than

small doses intravenously should be emphasized. Cases are on record of fatal results following the use of a few drops only.

Nageli also has recently reported an instance in which adrenin proved strikingly useful. The patient was first given 150 mgs. of neosalvarsan. Within 15 minutes a marked exanthema appeared and persisted about 20 minutes. Succeeding injections of the neosalvarsan were followed by the same reaction. It was found, however, that if the injection was preceded a few minutes by a dose of adrenin hypodermically administered no cutaneous reaction followed. The dosage of adrenin required varied with the amount of neosalvarsan. One-half milligram (0.5 c.c., 1:1000 solution) was sufficient when 300 mgs. of the arsenical was given, while for 600 mgs. twice as much adrenin was required.

In American and British practice the use of adrenin in conjunction with arsenobenzole has apparently received little attention. In view of the desirability of putting hormone therapy upon a firm basis it is to be hoped that a conclusive series of papers will be forthcoming and the degree of usefulness,—or uselessness,—of adrenin in forestalling ill effects of arsenical antiluetics be established beyond peradventure.

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ABSTRACTS

343. (ADRENAL, CHLOROFORM POISONING) Recherches anatomo-pathologiques dans un cas de mort par surrénalite aigue et insuffisance hépatique post-chloroformiques. (Morphological studies in a case of suprarenal and hepatic insufficiency following late chloroform poisoning). *Lancelin (R.)*, Bull. de la Soc. Méd. des Hôpitaux (Paris), 1917, 3. s., 41, 550.

The author claims on the basis of his case, that the hepatic intoxication as a cause of death in late chloroform poisoning has been over emphasized, and that a considerable part of the clinical characteristics appear referable to suprarenal deficiency. This he concludes from a study of the degenerative changes in the suprarenal glands.—A. L. T.

344. (ADRENAL DYSPEPSIA) La dyspepsie surrénale. Loeper, Beuzard et Wagner. Bull. de la Soc. Méd. des Hôpitaux (Paris), 1917, 3. s., 41, 903. Also Progrès Méd. (Paris), 1917, 3. s., 32, 241.

The authors state that frequently "dyspepsia" is of suprarenal origin, mostly due to suprarenal deficiency. Injections of epinephrine lead to increased gastric secretion and increased intestinal activity as shown by gastric analysis and fluoroscopy. They suggest that gastropathies and constipation in soldiers may be due to suprarenal depletion.—A. L. T.

It should be remembered that the demonstration of pharmacodynamic activity of epinephrin in any given case no more proves its suprarenal etiology than does the well known effect of cascara prove that constipation is due to "Hypocasearism." In this connection see abstract of article by Giley and Quinquand in this issue.—Ed.

345. (ADRENAL, FEVER) Un cas d'insuffisance surrénale aigue au cours de la fièvre récurrente; lésions, préexistantes des capsules surrénales. (A case of suprarenal insufficiency in the course of recurrent fever; preexisting lesions of the suprarenal glands). Portocalis (A.), Bull. de la Soc. Méd. des Hôpitaux (Paris), 1917, 3. s., 41, 545.

346. (ADRENAL, KIDNEY) Ricerche sperimentali sui potere tossico degli estratti di reni e di capsule surrenali (Toxicity of renal and adrenal extracts). Caecese (E.), *Folia medica (Napoli)* 1916, 2, 409-17.

A series of thirteen injection experiments in rabbits and guinea pigs is reported. Aqueous extracts of kidney or adrenal were employed. The usual results of indifferent organ extracts or of toxic doses of adrenin were observed.—R. G. H.

347. (**ADRENAL, NEPHRITIS**) L'altération fonctionnelle des glandes surrénales dans un cas de néphrite chronique hypertensive. (Functional alterations of the suprarenal glands in a case of chronic hypertensive nephritis.) Porak (R.), Bull. de la Soc. Méd. des Hôpitaux (Paris), 1918, p. 197.

The author injected an extract of the suprarenal glands of a nephritic individual intravenously into a rabbit. Less pressor effects were produced than by extracts of normal glands. This is taken to indicate an exhaustion of the glands which might have been due to (a) long hyperactivity and final exhaustion, or (b) exhaustion after intoxication by nephritis as in any other instance of intoxication. Porak does not believe that the nephritic high blood pressure is due to epinephrine, but is due to mechanical causes.—A. L. T.

348. (**ADRENAL PLURIGLANDULAR**) As syndromes pluriglandulaires endocrines dos decurso das infeccoes chronicas. (Pluriglandular syndromes in infectious and chronic diseases). Motta Rosende (C.) Arch. Brasileiros de Med. (Rio de Janeiro), 1917, 7, 150.

A woman of 40 with facial edema, ascites, swelling of the ankles and dry skin, showed zones of pigmentation,—in short, the symptoms of tuberculous peritonitis and, in the opinion of the author, of adrenal insufficiency.—B. A. H.

349. (**ADRENAL**) The white adrenal line: its production and diagnostic significance. Sargent (E.) Med. Press and Circ. (Lond.) 1917, 103, 509-10.

Reprinted from *Endocrin.* 1917, 1, 18.

350. (**ADRENAL THYROID**) Addisonisme et maladie de Basedow. Syndrome polyglandulaire. (Addison's disease and Basedow's disease.) Etienne (G.) Bull. Soc. Méd. des Hôpitaux (Paris), 1916, 40, 927-30.

A case report.

351. (**ADRENAL, VACCINATION**) Syndrome d'insuffisance surrénale aigue, provoqué par la vaccination antityphoïdique,

chez un addisonien latent. (Syndrome of suprarenal insufficiency in a case of latent Addison's disease induced by anti-typhoid vaccination.) Satre, A., Bull. Soc. Méd. des Hép. (Paris), 1917, 3. s., 41, 1318.

The author supports the view of Sergent that adrenal deficiency is an important factor in such cases.—A. L. T.

352. (ADRENALS) A case presenting ADDISON'S SYNDROME. Tice (F.) Med. Clin., Chicago, 1916, 2, 547.

Report of a case of Addison's disease in a woman who had shown increasing pigmentation of the skin for a period of five years. The cardinal symptoms of this disease are increasing physical and mental inertia, gastro-intestinal disturbances, and pigmentation of the skin. Tice recites a long list of pathological conditions in which pigmentation of the skin may occur without any involvement of the adrenals. Tice is of the opinion that the pigmentation of the skin in Addison's disease as well as in the other conditions which he mentions is due to a disturbance of the chromaffin system rather than to disease of the adrenals alone. "By designating the condition as Addison's syndrome we are not compelled to indicate our conception of what is present in the suprarenal capsules."—J. P. S.

353. (ADRENALS, CYSTIC) A huge hemangioma of the liver associated with hemangiomata of the skull and bilateral cystic adrenals. Major (R. H.) and Black (D. R.) Am. J. Med. Sc. (Phila.) 1918, 156, 469-483.

The feature of this case that is particularly interesting from an endocrine viewpoint is the condition of the adrenals. This is, as nearly as the authors could determine, the third case of bilateral cystic adrenals ever reported. The glands were of about equal size, 11x8x4 cm., and weighed together 350 grams. The glands were cut with difficulty on account of calcareous deposits in the walls of the numerous cysts present. The cysts were filled partly with lymph-like and partly with sanguineous fluid. They were apparently the result of congenital disturbances of growth in which connective tissue, lymphatics and blood vessels all played a role. Degenerative changes were very marked.—R. G. H.

354. (ADRENALS) De l'insuffisance surrénale dans le paludisme (Adrenal insufficiency in malaria). Puisseau and Lemaire. Presse Méd. (Paris) 1916, 24, 545-47.

Two forms are recognizable, the sub-acute and the acute. In the latter especially there are found at post mortem acute

degeneration or acute hemorrhagic infiltration of the adrenals. The authors believe that the attacks of coma, the rigid phase and the cholericiform symptoms in pernicious malaria are due to failure of adrenal functioning, as are such other symptoms as lowered blood pressure, asthenia, lumbar and abdominal pain, vomiting and diarrhea. Adrenin is accordingly recommended as an important adjuvant of quinine in the treatment of the disease.—R. G. H.

355. (ADRENALS) Enlarged suprarenals and sudden death in an infant. Pritchard (E.) Proc. Roy. Soc. Med. (Lond.) Sec. Dis. Children, 1918, 11, 35-6.

A brief note on the subject. At post-mortem no cause of death could be found. The thymus and various endocrine glands were normal.—R. G. H.

356. (ADRENALS) Focal necrosis of the adrenal gland; with remarks on adrenal insufficiency. Moseheowitz (E.) Am. J. Med. Sc. (Phila.) 1918, 156, 313-329.

The condition referred to is stated by the author to be an unusual one which has not hitherto been described as a distinct adrenal lesion. The article comprises descriptions of two new cases and a critique on adrenal insufficiency. The case descriptions include both symptomatology and blood and autopsy findings. In case I, "a man, aged forty-one years, with calculous pyelonephritis, a nephrectomy was done. Promptly after the operation the patient went into a profound shock. After an intravenous infusion he rallied so that on the following day his pulse was 112, although firm in quality. For the remaining two days of his life his temperatures were sub-normal, 93.6° to 96° F., with normal pulse rate and decreased frequency of respiration." Case II, is that of an eight-year-old girl. She was anemic, had frontal headache and vomited several times daily. There was no edema or cyanosis. Upon admission various signs of infection were present. The von Pirquet test was negative. The urine became loaded with pus and the symptoms increased in severity. Before death the patient became comatose and the pulse at times imperceptible. At autopsy only one adrenal was removed; it was enlarged slightly, but otherwise normal in gross appearance. Under the microscope many of the capillaries were found plugged with bacteria.

The critique on adrenal lesions and the symptomatology is in an article of this length inevitably inadequate. The pathology involved is more satisfactorily treated than the physiology. The obsolete adrenalin tonus theory, for example, is again announced as valid.—R. G. H.

357. (ADRENALS) Forma suprarenal do impaludismo (Adrenal form of Malaria). Fraga (C.). Acad. Nac. de Med. de Rio de Janeiro, 1917, Aug. 23.

The author accepts the necessity of granting the existence of adrenal insufficiency due to malaria, as has been described by Paiseau and Lemaire (*Presse Méd.*, 1916, 24, 545-47). For the acute form the first and best treatment is adreninized serum given by vein.—B. A. H.

358. (ADRENALS) Funktion der Nebennieren. (Function of the Adrenals.) Bauer. *Virchow's Archiv.* (Berlin) 1918, 225, 1.

An interesting study. The function of the cortex is the making of pigment from the superfluous uric acid in the blood. This pigment is transformed by the medulla into adrenalin. An increase of uric acid in the blood is found in nephritis and Addison's disease. In both diseases there is hypertrophy of the cortex. In nephritis this increase of uric acid gives rise to an increase of adrenin and a rise of blood pressure. In Addison's disease, however, where there is destruction of the medulla the formation of adrenalin is diminished.—J. K.

359. (ADRENALS) La fonction des surrénales. I. Du rôle physiologique supposé de l'adrénaline." (The function of the adrenal glands. I. On the supposed physiologic rôle of epinephrine). Gley (E.) et Quinquaud (A.). *Jour. de Physiol. et de Path. Gén.* (Paris), 1918, 17, 807.

The authors deny the presence of a "physiological function" of adrenalin, i. e., "the adrenal glands do not maintain a normal tone in the sympathetic system, as evidenced by the action of adrenalin on vasomotor tone."

The research is chiefly concerned with the relation between splanchnic stimulation and discharge of adrenalin into the circulation.

They found that there was a rise in general blood pressure on stimulation of the splanchnics, but that this result was obtained even after the adrenal gland was removed. The operation is described at length, and the precaution is given not to injure the splanchnic endings.

Other conditions which did not eradicate the rise in blood pressure after stimulation of splanchnics were as follows: (a) Caustery of medulla, (b) double adrenalectomy with reflex stimulation, (c) ligaturing of adrenal veins.

In asphyxia the rise in blood pressure occurs in adrenalectomised cats as in normals.

The above experiments seem to prove that the cardiovascular reactions dependent on the vasomotor nervous system do not depend on the adrenalin content of the blood.

The second part of the paper deals with the path of adrenalin in the general circulation.

Blood was taken from various parts of the circulatory system (a) inferior vena cava below the adrenal veins, (b) inferior vena cava above diaphragm, (c) left ventricle and was injected into a normal animal as a test for the presence of adrenalin. The blood was taken before and during stimulation of the splanchnics, directly or reflexly.

There was no evidence of adrenalin in the general circulation, especially in the left heart, in sufficient quantities to permit the theory that adrenalin causes increased vasotonus normally or during emotional excitement.—W. E. B.

360. (ADRENALS) Les Syndromes Hypoépinephriques de guerre. (Hypoepinephric syndrome of war.) Satre (A.) et Gros (P.) Progrès Méd. (Paris), 1918, —, 205.

The authors describe several types of cases which they claim to be fundamentally suprarenal exhaustion characterized by weakness, hypotension, neurasthenia and gastric disturbances. The condition is apparently immediately caused by conditions of especial stress acting upon the suprarenal glands which are competent only for common life and incompetent for the stress of active war services. Suprarenal gland extracts proved to be quickly restorative. Epinephrine is best given intra-muscularly since subcutaneous injections may give rise to localized necrosis.—A. L. T.

361. (ADRENALS) Le vomissement, symptôme d'insuffisance surrénale dans la fièvre typhoïde (Adrenal insufficiency in typhoid fever). Khoury (A.) Presse Méd. 1916, 24, 7.

The author considers severe vomiting in typhoid fever a symptom of adrenal deficiency, on the ground that after hypodermic injections of adrenin the vomiting is relieved. This conclusion is not in accord with recent work on adrenal physiology.—R. G. H.

362. (ADRENALS) Nebennierenapoplexie bei kleinen Kindern. (Hemorrhagic adrenals in the young.) Friedrichsen (C.) Jahrbuch f. Kinderheilk. (Berlin) 1918, 87, 109.

Clinical description of the symptoms of hemorrhage of the adrenals. The disease begins with extreme acuteness with high fever, vomiting, abdominal pain, and cyanosis without dyspnea.

Often purpura is to be observed. The patients die 6-24 hours after the beginning.—J. K.

363. (ADRENALS) Nebennieren bei Wundinfektionskrankheiten. (Changes of adrenals in infections.) Dietrich. *Centralbl. f. Pathol.* (Wiesbaden) 1918, 29, 169.

The author examined the adrenals in persons dying of peritonitis, sepsis and gas-gangrene and found typical changes in the cortex; the number of the lipoid vesicles was increased; there were vacuoles to be seen; the cells showed albuminoid degeneration; all symptoms of inflammation were present. The adrenals are stated to be very sensitive to infection since they normally have the function of rendering toxins harmless.

—J. K.

364. (ADRENALS) Réaction surrénale et vaccination antityphique (The adrenal reaction in anti-typhoid vaccination). Loeper (M.) *Presse Méd.* 1916, 24, 463-64.

In six months the author saw six cases in which the vaccination had resulted in severe symptoms, vasomotor and gastro-intestinal. Some of these were low blood pressure, asthenia, cyanosis, cramps in the legs and back and diarrhea and vomiting. Such symptoms Loeper considers due to suprarenal deficiency. No convincing evidence is offered, however, that such is the case. The patients responded well to adrenin treatment, but in case of this sort of symptoms the "therapeutic test" is far from adequate. It is stated that the theory was confirmed by experiments upon guinea pigs but no details are given.—R. G. H.

365. (ADRENALS—THYROID) Maladie d'Addison et goitre exophtalmique. (Addison's disease and exophthalmic goiter.) Ramond (F.) et François (A.) *Bull. et Mem. de la Soc. Méd. Hôp.* (Paris), 1917, 41, 1131-34.

In one case of Addison's disease it was observed that after a few months exophthalmic goiter symptoms began to appear with distinct improvement in general health, and recession of symptoms of Addison's disease. This led the authors to try opotherapy of Addison's disease in the form of combined thyroid and adrenal gland extracts. In about one-fifth of the cases thus treated improvement was clear and distinct.

The authors conclude: (1) that an association of thyroidism and hypoadrenalism exists; (2) prognosis of Addison's disease is less grave when associated with hyperthyroidism than when alone; (3) Adrenal-thyroid therapy is the treatment of choice for Addison's disease.—A. L. T.

366. (**ADRENALS**) *Surréalites aiguës dans les accès pernicieux palustres (Adrenal factor in symptomatology of pernicious malaria)*. Paiseau (G.) and Lemaire (H.) *Bull. d. l'Acad. Méd. (Paris)* 1916, **76**, 300-301.

A brief article developing the authors' belief that the adrenals play an important part in this disease and that adrenin is useful in the treatment. The topic is discussed at greater length elsewhere. (*Press Méd.* 1916, **24**, 468; *Abst. Endocrin.* 1917, **1**, 115.)—R. G. H.

367. (**ADRENIN**) *Adrenalin mydriasis as a somatic symptom of dementia precox and organic brain disease*. Fuller (S. C.) and Chambers (R. M.) *Dementia Precox Studies*, 1918, **1**, 30-34.

A study of the effect of adrenalin instillation into the conjunctival sac of the eye was made on 100 cases, 48 of which were cases of dementia precox; 71 per cent. of the latter gave a reaction as a result, 54 per cent. a mydriasis and 17 per cent. a miosis or so-called paradoxical reaction. The remaining 29 per cent. of dementia precox cases were negative. None of 13 cases of manic-depressive insanity gave any sort of reaction. Thirteen cases of paresis gave reactions in 46 per cent. There were no other positive reactions excepting in the case of 1 arterio-sclerotic and 2 cases classed as imbeciles whom the authors believed might be cases of dementia precox with early onset.

It is suggested that "in adrenalin mydriasis a valuable, though not absolute, clinico-diagnostic test for differentiating dementia precox from manic-depressive insanity is available."

L. G. K.

368. (**ADRENIN**) *Adrenalin vasodilator mechanisms*. Hartman (F. A.), Kilborn (L. G.) and Fraser (L.) *Am. Jour. Physiol. (Balt.)* 1918, **46**, 502-520.

In this investigation the response of the blood vessels of the hind limb to adrenalin was studied at varying intervals after denervation, both with the normal circulation and when the limb was perfused with Ringer's solution, the adrenalin being then introduced into the perfusion fluid. The effect of adrenalin on the cat's limb was studied at hourly intervals after denervation for as long as thirty-three hours. It was found that during the first five or six hours, i. e., while the limb is dilating, adrenalin produces an increase in volume with difficulty, but that while the limb is recovering its tone the dilator effect of adrenalin begins to reappear. After denervation of

greater duration, however, the dilatation occurs from a greater range of doses of adrenalin than is the case in the normal limb. During perfusion the peripheral dilator action in both normal and denervated limbs becomes similar, and dilatation under these circumstances also occurs with a greater range of doses.

It was shown, too, that depressor doses of adrenalin can cause dilatation of a limb by acting on the ganglionic mechanism only. (See abstract in *Endocrin.* 1918, **2**, 160 (Abst. 91), but dilatation can be produced by the action of adrenalin on either the ganglionic (sympathetic and dorsal roots) or on the peripheral mechanism.

On this subject see also abstracts of articles by Gruber, *Endocrin.* 1918, **2**, 164 (Abst. 105), and by Dale and Richards in this number.—L. G. K.

369. (ADRENIN) Apoplexie séreuse du néo-arsenobenzol guérie par la méthode milian a l'adrénaline. Saupher. *Presse Méd.* 1916, **24**, 6.

A patient very ill as a result of neo-arsenobenzole medication was treated with adrenin. The outcome was very satisfactory. Saupher believes that the patient's life was saved.

—R.G.H.

370. (ADRENIN, AUTONOMIC N. S.) New researches on striated and smooth muscles of homeothermic animals. X. Action of various substances, especially pilocarpine and atropine, on some smooth muscle organs. Bottazzi (F.) *Atti r. accad. medico-chir. (Napoli)* 1917, 33 page reprint; *Physiol. Abstracts*, 1918, **3**, 103-104.

Pilocarpine increases the tone of intestinal muscles, especially those of the dog's small intestine; atropine always completely annulled this effect. The action of these alkaloids on the retractor penis muscle and the uterus was irregular. Adrenalin, *p*-hydroxyphenylethylamine, β -iminazolylethylamine, and hypophyisine acted on the uterus in a regular manner; the first 2 compounds caused relaxation of the non-pregnant and contraction of the pregnant uterus of the bitch, and always produced contraction of the uterus of the cat. *Chem. Abst.* **18**, 1897.

371. (ADRENIN, GLYCOLYSIS) L'épreuve de la glycémie adréalinique chez les soldats suspects d'affections hépatiques. (On the use of epinephrine hyperglycemia in soldiers suspected of having hepatic disturbances). Loeper (M.) et Verpy (G.), *Bull. Soc. Méd. Hop. (Paris)*, 1917, —, 730.

The authors suggest the use of epinephrine as an aid to study of the liver in disease, with particular reference to the glycogen-glucose equilibrium.—A. L. T.

372. (ADRENIN, HEART) L' epreuve de l'adrenaline dans l'appréciation de la résistance cardiaque. (On the use of epinephrine for the determination of cardiac resistance). Loeper (M.), Wagner (C.) et DuBois-Roquebert (H.) Bull. de la Soc. Méd. des Hôpitaux (Paris), 1918, 3. s., 42, 90.

The authors determine the cardiac response to epinephrine by fluoroscopy. In this way a dilatation or contraction of the heart can be observed according to the normality or abnormality of the cardiac mechanism in response to increased peripheral resistance to be overcome.—A. L. T.

373. (ADRENIN, HEART) L' action de l'adrénaline sur le cœur étudiée par la radioscopie. (Study of the action of epinephrine on the heart by the use of radioscope). Loeper (M.), DuBois (H.) et Wagner (C.) Progres Méd. (Paris), 1918, 33, 83.

(Same article as above). See also *Endocrin.* 1918, 2, 160, Abst. 90.—A. L. T.

374. (ADRENIN) Neutralizzazione dell'adrenalina col sangue normale (Neutralization of adrenin in normal blood). Manfredi (L.) *La Clin. med. ital.* (Milan) 1916, 55, 6-24.

The article consists largely of a review of some of the Continental literature on the relations of endocrine glands to the adrenals and particularly of an assumed antagonism between the pancreas and adrenin. The experimental part of the paper consists of a determination of the threshold dosage of adrenin necessary to cause glycosuria in the rabbit. About 0.5 cc. "adrenalin" per kilo body weight was required. Meltzer's work on this problem was overlooked.—R. G. H.

375. (ADRENIN PITUITRIN) Acción antagónica de la adrenalina y de les extractes hypofisiaries sobre les bronquies. (Antagonistic effect of adrenin and pituitrin in the bronchi). Houssay (B. A.) *Rev. Asoc. Med., Argentina*, (Buenos Aires), 1918, 28, 433.

The author demonstrated in 1911 that hypophyseal extract is bronchoconstrictor. He showed by experiments on guinea pigs that its action is always antagonistic to that of adrenin,—never synergetic. The adrenin effect is much the more intense.

The satisfactory results obtained in asthma with the two together is to be explained by the marked predominance of the adrenin.—Author's Abst.

376. (ADRENIN-PITUITRIN, ASTHMA) La médication adrénalino-hypophysaire de l'asthme. (Adrenin-pituitrin treatment of asthma.) Bensaude (R.) and Hallion (L.) Presse Méd. (Paris), 1918, 20, 185.

The authors call attention to the clinical value of epinephrine-hypophysis extract medication in acute asthmatic attacks. They suggest some autonomic disturbance as a causative factor in bronchial asthma.—A. L. T.

377. (ADRENIN, TYPHUS) Pression artérielle et insuffisance surrénale, dans le typhus exanthématique. (Arterial pressure and suprarenal insufficiency in exanthematous typhus.) Danielopolu (D.) et Simice (D.), Arch. d. Mal. du Cœur (Paris), 1918, 11, 1.

The authors find a diminution or total absence of vascular and cardiac response to epinephrine in cases of exanthematous typhus. In convalescence, the reaction reappears. They suggest that the reasons for the phenomenon may be either a hyosecretion of epinephrine or that toxins prevent the peripheral responses, or both.—A. L. T.

378. (ADRENIN) Prolonged constriction of the blood vessels by subcutaneous injection of adrenalin into the ear of a rabbit. A demonstration. Auer (J.) and Meltzer (S. J.) Proc. Soc. Exp. Biol. and Med. (New York) 1916, 14, 54-55.

The prolonged constriction obtained was attributed to the slow destruction of adrenin by the tissues of the rabbit's ear.
—L. G. K.

379. (ADRENIN) The antagonistic action of epinephrin to the fatigue produced by the perfusion of acid sodium phosphate. Gruber (C. M.), Am. Jour. Physiol. (Balt.), 1918, 47, 185-188.

Adrenalin was found to counteract the fatigue produced by the perfusion of acid sodium phosphate, as tested by the changes in the height of muscular contraction, in the same way as when lactic acid or acid potassium phosphate was used. See abstract of article by Gruber and Kretschmer in this number.—L. G. K.

380. ADRENIN, The character of the toxic action of. Loew (O.) Biochem. Ztschr., 1918, 85, 295-306; J. Chem. Soc. (Lond.), 114, I, 281.

When in the form of its salts in neutral solution, adrenaline has only a very slightly toxic action. The free base, however, and its first red oxidation product, are extremely toxic and this action can be readily demonstrated on the nucleus of *Spirogyra*. Loew ascribes the toxicity to the lability of the H-ions in the molecule, which is specially marked in alkaline solution.

—Chem. Abst., **12**, 2096.

- 381. (ADRENIN) The effect of adrenalin upon the fatigue produced by the injection of the fatigue products, lactic acid and acid potassium phosphate.** Gruber (C. M.) and Kretschmer (O. S.), *Am. Jour. Physiol. (Balt.)*, 1918, **47**, 178-184.

The tibialis anticus muscle in the cat was perfused with Ringer's solution, and stimulated 84 times a minute with maximal make and break induction shocks, the tendon of the muscle being attached to a lever. Fatigue was induced by the addition of acid potassium phosphate, lactic acid or sarcosolactic acid to the perfusion fluid. When adrenalin (0.5 c.c. to 1 c.c. of a 1:1000 solution) was added it was found to counteract the induced fatigue in identically the same way as it does the fatigue produced normally in active muscles.—L. G. K.

- 382. (ADRENIN) The treatment of nephritis by adrenalin.** Harris (I.) *Med. Press and Circ. (Lond.)* 1917, **103**, 528-53.

Most of the author's cases have done well on adrenin and those which have not done so had not responded well to any treatment. The urine is increased and ascites and edema as well as albuminuria decreased. Two cases are described with tabulated details of the results secured. In one adrenin was given, 10 m. once or twice daily, hypodermically, and in the other 10 or 15 m., four times daily. The diuretic effect of the drug does not depend upon any pressor effect. Harris' findings are in opposition to the trend of more recent experimental work (as Gunning, 1918, Abst. No. 104, p. 164). In rabbits, however, diuresis from adrenin has been recorded.—R. G. H.

- 383. (ADRENIN) The vasodilator action of histamine and of some other substances.** Dale (H. H.) and Richards (A. N.). *Jour. of Physiol. (Lond.)* 1918, **52**, 111-165.

Among the "other substances" is adrenaline, whose action is closely related to histamine, which makes this paper of endocrine interest. Cats under ether were used under normal circulatory conditions and also with artificial perfusion of the limb with hirudinized cat's blood, or oxygenated Ringer's solution containing 6 per cent. gum arabic.

Discussing Mautner and Pick's theory of "shock" by histamine, said to be due to obstruction in the liver (in the capillaries opening into the intralobular vein) the authors maintain that if the above be true, the latency of result should be shortest if the injection be made into the portal vein. Their results show least latency when injected into arterial system, intermediate when into inferior vena cava, and longest when into portal. Its action can not be in liver or lungs. The vasodilator action occurred when the vessels to the liver, spleen, stomach, etc., were ligatured.

Small intravenous injections of histamine, adrenaline and acetyl choline cause marked dilatation in hind limbs 16 days after complete denervation, suggesting that the nervous connection is not necessary.

In normally innervated hind limbs of cats small doses of histamine (0.01-0.02 mgm.) and adrenaline (0.001-0.005 mgm.) produce variable results, i. e., constriction or dilatation. With adrenaline the constrictor response is more common than with histamine. These substances then have a double action depending on doses and existing conditions in the tissues. Acetyl choline (0.001-0.01 mgm.) on the other hand has only a dilator effect.

The immediate effects of nerve section are: dilatation of arteries of leg, due in part to cessation of impulses from vasoconstrictor center, and partly to the direct stimulation of vasodilator fibres; large increase in amplitude of volume pulse.

The administration of histamine and adrenaline in above doses after denervation causes intensified dilatation. The authors criticize Hartman and Fraser's results as being in evidence only in rare cases when the constriction the former claim may be accounted for by a general fall in blood-pressure.

The dilator action of acetyl-choline is due to inhibition of tone to arterial muscle; when this tone is lost to some extent by nerve section the dilator action of acetyl choline is not so much in evidence. The authors demonstrate this.

In cats with unpigmented pads it was shown that on the denervated side there was an increase of temperature accompanied shortly by a pallor, the former due to increased blood flow, the latter to a recovery of tone in the capillaries. During this stage there is an exaggerated dilatation after injection of histamine and adrenaline and a decreased dilatation after injection of acetyl-choline.

Cocainization before denervation causes increased dilatation after acetyl-choline showing the prevention of loss of tone in the arteries by direct stimulation of vasodilators.

Anemia and cold suspend the dilator action of both histamine and acetyl-choline. The latter is recovered more quickly.

These conditions affect the capillaries more severely than the arteries, hence the histamine is said to act upon the capillary tone.

Histamine applied locally causes capillary dilatation and increased exudation of lymph.

In perfusion experiments, if adrenaline (1-10 million) is not present in the perfusion fluid histamine produces a vasoconstriction; otherwise a vasodilatation. Histamine seems to act on some part of the circulatory system that has a large effect on volume and little on flow. The presence of minute quantities of adrenaline is necessary for this effect to become manifest.

A discussion of the importance of capillary tone in normal circulatory conditions is included.

Traumatic conditions changing the metabolic rate produce histamine-like substances which may cause dilatation in the capillaries producing "shock" or peripheral stagnation.

—W. E. B.

384. (**ADRENIN**) Über die Wirkung des Adrenalins auf die Blutverteilung beim Menschen (Influence of adrenalin on the distribution of the blood in man). Rosenow (G.) Deutsches Arch. f. klin. Med. (Leipsie) 1918, 127, 136.

After an intramuscular injection of adrenalin in man the volume of the forearm as measured by the plethysmograph increases. After this very often the volume diminishes. The effect is due to the contracting of the abdominal blood vessels to a greater degree than those of the periphery. These observations in man parallel those of Oliver and Schaefer in animals. Rosenow suggests that this may prove to be a good method to test the functional condition of the splanchnic vessels, e. g., in cases of arteriosclerosis.—J. K.

385. **BANTI'S DISEASE** in children, progress and treatment of. Graham (E. E.) Am. Jour. Obst. (N. Y.) 1916, 74, 548.

Of no direct endocrine interest.

386. (**CORPORA LUTEA**) Etiopatogenia del embarazo extrauterino. (Pathogeny of ectopic **PREGNANCY**.) Piccardo (T.), Semana Méd. (Bs. Aires), 1918, 26, 90.

Piccardo has found that in many women operated upon for ectopic pregnancy, the tubes show no injuries of the mucosa (macroscopically). He believes in accordance with Ancel and Bouin, Moreaux and Katz and other observers that the smooth

muscle of the tubes brings about fixation of the ovule, fecundated or unfecundated, under the influence of the corpus luteum, and that ectopic pregnancy is due to early formation of the trophoblast. This in turn is occasioned by physical or anatomo-pathological disturbances of the corpus luteum.

This theory is subject to much criticism. In fifteen pages no histologic evidence is offered to prove that the mucosa is normal. The nearness of the intestines renders infection probable. To conclude that the corpus luteum is responsible for the ectopic pregnancy without histological or macroscopic study of the structure is scarcely permissible. And finally, it is not inherently probable that the muscularis plays such a relatively large part and the ovum itself such a small one.—G. P. G.

387. CORPUS LUTEUM and the periodicity in the sexual cycle. Loeb (Leo) *Science* (N. Y.) 1918, n. s. **48**, 273-277.

A discussion of the author's previous work on this subject.—F. A. H.

388. (CORPUS LUTEUM) Etiopatogenia del embarazo extra-uterino (Etiopathogeny of extra-uterine gestation.) Picardo (T.) *Semana Méd.* (Buenos Aires) 1918, **25**, 91.

The author thinks that the premature fixation of the ovum is due to the ability it possesses to develop precocious trophoblasts. It is probable that this capacity is derived not merely from the ovary but that the corpus luteum also contributes.

—B. A. H.

389. CORPUS LUTEUM, Soluble extract of. Beach L. E. *Maryland M. Jour.* (Balt.) 1916, **59**, 198-200.

A superficial report of six cases of menstrual disorders treated by a soluble extract of corpus luteum. The results were favorable. The corpus luteum preparation was not identified.—R. G. H.

390. CORPUS LUTEUM, The therapeutic use of the extract of. Happel (H. E.) *Med. Rec.* (N. Y.) 1917, **91**, 848.

After describing the origin, development, appearance and structure of the corpus luteum, Happel takes into consideration function, indications, and reports of cases in which the extract has been employed. The corpus luteum elaborates an internal secretion which (a) determines the development of the secondary sex characteristics, as growth of the breasts; (b) controls menstruation; (c) is essential to the uterine

changes connected with implantation of the ovum and its maintenance during the early stages of pregnancy; (d) retards ovulation during pregnancy; (e) aids in maintaining the nervous equilibrium and normal metabolism.

The extract obtained from pregnant animals is more potent than that from the non-pregnant. It is useful in the treatment of functional dysmenorrhea and amenorrhea, scanty or irregular menstruation of young girls. Thyroid extract and extract of corpus luteum are exceedingly valuable in the treatment of the scanty or irregular menstruation of young women who have a tendency toward obesity. It is useful in some cases in nausea and vomiting of pregnancy. The neuroses of the natural, artificial, and premature menopause are relieved by its administration in adequate doses. The extract should be prescribed soon after operative removal of the ovaries. Asthenia, inability to concentrate, nervousness, scanty or irregular menstruation, the symptom complex of ovarian insufficiency are alleviated by the extract. It has also been recommended in the treatment of hyperemesis gravidarum, sexual asthenia sterility, and repeated abortion not due to pathological lesion.

The dosage must be adapted to the needs of the patient, increased until the effect is produced, and the treatment continued for a sufficient length of time. If the symptoms recur, it should be prescribed again.—W. H.

391. DIABETES and INFANTILISM, Case of. Parkinson (J. P.) Proc. Roy. Soc. Med., Sec. Dis. Children. 1917, 10, 26-7.

The author describes briefly a typical case of diabetes in a 10 year old girl. She has grown very little for the past five years during which period the diabetic symptoms have continued. There is no specific evidence of endocrine gland defects except the diabetes. The infantilism is of the Lorain type.—R. G. H.

392. (DIABETES) Besteht beim Diabetes mellitus eine Steigerung der Zuckerbildung oder eine Störung des Zuckerverbrauches? (Is sugar destruction diminished or sugar formation increased in diabetes mellitus?) Bernstein and Falta. Deutsches Arch. f. klin. Med. (Leipsic) 1918, 127, 1.

In light cases the fraction CO_2/O_2 (respiratory quotient) is often normal. When a patient is kept on a carbohydrate-free diet and this is followed by one high in carbohydrate the fraction at first does not undergo a change because glycogen is formed; after a time in light cases the fraction increases on

account of oxidation of the sugar. Normally an intravenous injection of sugar causes an increase in the respiratory quotient; in diabetes such an injection is followed by glycosuria but not by an increase in the quotient. Injection of adrenalin or pituitrin has in diabetes no influence on this quotient. In serious cases of diabetes it is impossible to increase the quotient; in cases the prognosis of which is fatal the quotient even diminishes and glycosuria increases. Although it is not possible to prove that in diabetes more sugar is formed it is, according to the authors, certain that the oxidation of sugar is largely diminished.—J. K.

393. (DIABETES BLOOD GLYCOLYSIS.) Het suikersplitsend vermogen van het bloed in zyn beteekenis voor het wezen der suikerziekte onderzocht. (The glycolytic power of the blood and its significance in diabetes). Hekman J. and Van Heeteren (A.) *Nederlandsch Tijdschrift voor Geneeskunde*. (Haarlem) 1918, **62**, 497.

The authors have worked out a new, exact method for determining the glycolytic power of the blood. Contrary to previous workers the authors always found the glycolytic power increased. They always used, however, the whole blood instead of only the serum, which procedure permitted a comparison of their values with those reported in the literature. In diabetes the results are not always uniform. In serious cases the glycolytic power was very low, but in other cases it was often increased. Lépine has previously reported a marked reduction after experimental pancreatectomy; but the authors, on the contrary, found a marked augmentation of glycolytic activity after this operation. Similar results were obtained from the blood in acute pancreatitis. In hyperthyroidism the glycolytic power was found often to be slightly diminished, in myxedema, often increased, in Addison's disease, absolutely normal and in acromegaly markedly diminished.—J. K.

394. DIABETES, Pathogeny of, and fecal disinfection. Palacios (G. D.) *Med. Rec.* (N. Y.) 1916,**89**, 543-51.

Develops a theory that "the primitive phenomenon of the pathogenic mechanism of diabetes mellitus is to be found in an excess of ammoniacal and acid fermentation of the large intestinal contents." The starvation treatment, according to this theory acts by relieving the intestine of its fermenting content.—R. G. H.

395. **DIABETES**, The dietetic treatment of, complicated by nephritis. Stark (H. S.) Med. Rec. (N. Y.) 1916, 89, 987-91.

Of technical interest.—R. G. H.

396. **DIABETES INSIPIDUS** in children. Moffett (R. D.) and Greenberger (M.) Med. Rec. (N. Y.) 1917, 92, 487-95.

This article comprises a detailed report of a case together with an excellent review of the literature. A careful study was made of the results of reduction of sodium chlorid and of water. The results were not satisfactory. Pituitrin in half c.c. doses two or three times daily reduced the urine from 7000-8000 c.c. to 1500-2500 c.c. daily. The authors believe that the pituitary is primarily at fault in this disease. The article concludes with a valuable bibliography of 166 titles.—R. G. H.

397. **DIABETES MELLITUS**, Acute. Elmer (E. O.) Med. Rec. (N. Y.) 1917, 92, 987.

A brief report of a case which developed and ended fatally within a period of three days.—R. G. H.

398. **DIABETES MELLITUS**, The diet in, as modified by considerations of nitrogenous metabolism. Cornwall (E. E.) Med. Rec. (N. Y.) 1916, 89, 907-10.

Cornwall emphasizes the benefit to be secured by regulating the quality and quantity of protein food to favor protein metabolism.—R. G. H.

399. **DIABETES MELLITUS**, The present treatment of, Moses (H. M.) Med. Rec. (N. Y.) 1916, 90, 1069-72.

A readable general review of the most approved modern therapeutic practices useful to any reader desiring an epitome of these.—R. G. H.

400. **DIABETES MELLITUS**, The relation of prognostic factors to treatment in. Foster (N. B.) Med. Press and Circ. (Lond.) 1916, 101, 193-95.

The author emphasizes that every case demands careful study not only of the diabetic state but of all conditions influencing health. Infections must be kept in mind as a constant danger. Early cases should be kept sugar-free to augment resistance and avoid acidosis. Restricted low diets are the means of accomplishing this. In advanced cases glycosuria

must be controlled to regain normal weight and vigor. The chief difficulty is the necessity of long-continued constant vigilance.—R. G. H.

401. DIABETES MELLITUS, *Syzygium jambolanum* in the treatment of. Kramer (A. S.), *J. Am. Inst. Homeopathy* (N. Y.) 1918, 10, 1489-95.

From experiments in vitro and on dogs, and humans, it was concluded that *Syzygium* retards diastatic activity, stimulates the pancreas to increase the oxidation of glucose in the muscles, and decreases the amount of glucose in the urine of diabetics unless the blood has been greatly dealkalinized. In the latter case, prior to administration of *Syzygium*, NaHCO_3 (contained in a double gelatin capsule to prevent its neutralization by the gastric HCl) should be given, or else calcium lactate if the urinary phosphates are excessively high. *Syzygium* is less efficient in glucosuria of renal (phlorphizin) origin and in that due to purely nervous conditions, and is not indicated in glucosuria produced by pituitary overactivity. *Chem. Abst.* 18, 2003.

402. DUCTLESS GLANDS, Diseases that can, with assurance, be referred to absence of, or derangement with function of. Root (A. S.), *Arch. Ped.* (N. Y.), 1918, 35, 401.

The writer thinks that the only diseases which can, with assurance, be attributed to an absence of, or derangement of function of the ductless glands are those referable to the thyroid, i.e. myxedema, hyperthyroidism and exophthalmic goiter. There is some evidence to support the view that Frölich's syndrome is due to a derangement of function of the pituitary gland. The clinical evidence in favor of giving pituitary gland in cases of diabetes insipidus is sufficient to warrant its administration. Prescribing preparations of the endocrine glands for obscure disorders cannot be too strongly condemned. A plea is made for the early recognition of cretinism, in order that the best end results may be obtained, i.e., from early thyroid treatment.—M. B. G.

403. (DUODENUM) Extirpation of the duodenum. Dragstedt (L. R.), Dragstedt (C. A.), McClintock (J. T.) and Chase (C. S.) *Am. Jour. Physiol.* (Balt.) 1918, 46, 584-590.

As a result of the controversy as to whether the complete extirpation of the duodenum is fatal or not the authors performed a series of experiments in which the duodenum or varying lengths of the jejunum or ileum were removed. Several

dogs so treated survived from one to three weeks, and one lived for three months without a duodenum. None of them exhibited any symptoms which could not be explained by the loss of the bile, pancreatic and duodenal juices, and death was really due to starvation from inability to digest food. The upper intestinal tract then can not be classed with the adrenals or parathyroids as essential to life.

It was also found that when the intestinal juice was allowed to empty into the abdominal cavity no toxic effects were produced. When bacteria were excluded from the lumen of the intestine, various pathological changes even to complete occlusion of the blood supply to an isolated piece of intestine with resulting autolysis and reabsorption, occurred without the elaboration of sufficient toxic substances in the cells themselves or in their secretions to kill the animal. Nor was the duodenal juice found to contain any substance (hormone) necessary to the life or the function of the intestine lower down, since animals survived for as long as twelve days when a fistula was made which drained all the duodenal and pancreatic juice as well as the bile to the exterior.—L. G. K.

404. (**ENDOCRINE GLANDS** A case of pluriglandular disturbance; **Organotherapy; Cure.** Timme (W.) Arch. of Ped. (N. Y.), 1917, 24, 901.

A boy of 7½ years had the digits of both hands and feet erythematous and pustular; great fatigability; slowness in physical growth, sluggish mentality and uneven temperament were noted. The condition had continued a year and was steadily growing worse. A very complete history of the case, past and present, pointed to an endocrine disturbance, the hereditary factors pointing in the same direction. Pituitary medication was begun at once in the form of whole gland capsules administered twice a day, one hour after meals. Together with these, three drops of adrenalin in salt solution were given by the mouth three times daily, after meals. During the next two weeks the patient slowly improved, blood pressure rising to 92 mm. He had more initiative, was less irritable and more amenable to direction; weight remained stationary, extremities about the same, but less painful.

At one time during the pituitary treatment, the patient complained severely of frontal headaches, a symptom frequently attending pituitary treatment. The headaches in this case promptly ceased when the administration of the gland was stopped. They did not return, even after beginning again with the gland. The quantity was diminished thereafter, the intervals between doses being increased to whole days and even to two days.—W. H.

405. (**ENDOCRINE GLANDS**) **A new syndrome.** Block (S.)
Med. Rec. (N. Y.) 1916, 90, 984-86.

The author sets off one group of the border line endoerine-neurotic cases as presenting a new symptom-complex. The procedure appears to the reviewer as being merely verbalism.
R. G. H.

406. (**ENDOCRINE GLANDS**) **Dementia precox.** Ernst (J. R.)
Med. Rec. (N. Y.) 1917, 91, 942-3.

In a general article the author points out the paucity of reliable data on the relation of the endocrine glands to this condition and emphasizes the need of extensive systematic researches on the problem.—R. G. H.

407. (**ENDOCRINE GLANDS**) **Dysmenorrhea.** Shaw (J. C.)
Internat. J. Surg. (N. Y.) 1916, 29, 321-24.

An interesting general discussion of the etiology of this condition. Endocrine dysfunction is regarded as an important factor.—R. G. H.

408. (**ENDOCRINE GLANDS**) **Fibromas del útera (Uterine fibromas).** Castaño (C. A.)
Semana Méd. (Buenos Aires) 1918, 25, 69.

Castaño believes that uterine fibroma is due to depressed thyroid and augmented ovarian and hypophyseal functions. He thinks that endocrine disorders are often produced by syphilis. No definite proof of the assertions is offered.—B. A. H.

409. (**ENDOCRINE GLANDS**) **PEPTIC ULCER, The probable endocrine origin of.** Friedman (G. A.)
Jour. A. M. A. (Chgo.) 1918, 71, 1543-48.

A somewhat uncritical review of the literature is offered. The reliable data as well as some dubious physiology and pathology are treated. The conclusion is reached that the endocrine glands play a predominant role.—R. G. H.

410. (**ENDOCRINE GLANDS**) **Precocity.** Cautley (E.)
Med. Press and Circ. (Lond.) 1917, 103, 141-43.

An interesting general discussion of this topic and of the part played by the endocrine glands. No new data are offered.
R. G. H.

411. (ENDOCRINE GLANDS) The ductless glands in dementia praecox. Dereum (F. X.) Arch. of Diag. (N. Y.) 1917, 10, 38-45.

The various glands of internal secretion of patients with dementia praecox suffer in the course of the development of the organism so that their functions are subsequently imperfectly performed. It is probable that the entire ductless gland chain is involved in most cases. Certain glands, especially the sex glands, may dominate the picture; in some patients it is the thymus, in others the system of pituitary, thyroid and adrenals. The symptoms which would point to thymus involvement are considered in detail.—L. F. W.

412. ENDOCRINE GLANDS, Some observations upon the. Cobb (I. G.) Med. Press and Circ. (Lond.) 1916, 101, 466-69.

A vigorous general article of interest particularly from a standpoint of practical endocrine therapeutics.—R. G. H.

413. (ENDOCRINE GLANDS) The bone changes occurring in Von Recklinghausen's disease. Gould (E. P.) (Based upon an investigation carried out in the Laboratory of Prof. Ludwig Pick, Friedrichshain, Berlin.) Quart. J. Med. (Lond.), 1918, 11, 221-27.

Von Recklinghausen's disease is more than a disease of peripheral nerves and skin. A frequent symptom is softening of the skeleton. This softening is microscopically and macroscopically the same as osteomalacia. Osteomalacia being probably a disease of the glands of internal secretion, these glands must be studied in von Recklinghausen's disease.—Chem. Abst., 12, 2213.

414. (ENDOCRINE GLANDS) The causation and cure of certain forms of insanity. Farrant (R.) Brit. M. J. (Lond.) 1916, 1, 882-3.

Reviewed elsewhere in this issue under the caption "The endocrine glands in the insane," page 452.

415. (ENDOCRINE GLANDS) Relationship of the ductless glands to arterial disease. Daland (J.) Arch. of Diag. (N. Y.) 1917, 10, 32-38.

Experimentation and accumulated evidence secured at the bedside clearly prove that overfunctioning thyroid and adrenals produce arteriosclerosis, more especially when the hyper-

function is long continued or recurs frequently. The method whereby sclerosis is produced is not known. It is probably a secondary process and no doubt varies in different patients. Overwork, mental or physical, throws an added strain on the ductless glands. Daland believes that worry, fear, and "strenuous living" account for the great increase of this condition in recent years.—L. F. W.

- 416. (ENDOCRINE GLANDS)** The ductless glands in gynecology. Bandler (S. W.) *Am. Jour. Obstet.* (N. Y.) 1917, **76**, 644-673.

"The influence and action of the endocrine glands are evidenced by somatic, mental and psychic changes. If we can fathom and understand what the ductless glands have done to an individual up to the stage of puberty, we may appreciate why the individual develops as he does. If we can reason out what these ductless glands have done to that individual from puberty on, we may understand why that individual is what he is and why so many changes have occurred in him. If we can eventually fathom what hereditary and accidental intercurrent factors are responsible for these gland changes and for the consequent somatic, mental and psychic factors, then medicine will have accomplished a glorious work." The article is an essay of 30 pages in which this statement is engagingly amplified. It is a general article impossible to abstract satisfactorily.—W. H., R. G. H.

- 417. (ENDOCRINE GLANDS)** The relation of the glands of internal secretion to gynecology and obstetrics. Ehrenfest (H.) (Collective abstract) *Interstate Med. Jour.* 1917, **24**, 627-30.

This paper is a very interesting review of the symposium on ductless gland disturbances recently held by the American Gynecological Society. The author remarks upon the increasing interest towards this subject shown by the general profession.—L. F. W.

- 418. ENDOCRINE neurasthenia.** Williams (T. A.) *Med. Rec.* (N. Y.) 1917, **91**, 623-27.

A general discussion of the endocrine basis of various manifestations of neurasthenia, including several case reports in which hormone therapy was successful:

a. Thyroidism with marked vasomotor symptoms alleviated by adrenin and "adrenal residue" which materially lowered blood pressure.

b. Adrenal deficiency ("vagotonic") treated with dried adrenal gland with some success but not so great as when small quantities of thyroid, pituitary and gonad substance were added.

c. Preadolescent hypopituitarism treated with marked success by pituitary gland substances.

d. Pluriglandular type, treated with "mixed hormones and organic phosphorus."

Such papers as this serve to point out the need for an extensive program of systematized studies of endocrine therapeutics. That some successes occur can not be doubted, but what is needed particularly now is more knowledge of the indications and limitations in this field.—R. G. H.

- 419. ENDOCRINE ORGANS, Studies on, of dementia precox.**
Kojima (M.) Proc. Roy. Soc. Med., Sec. Psych., 1917, 10, 88-99.

Data elsewhere reported. See Abst. in this issue.

- 420. ENDOCRINE ORGANS, Studies of, of dementia precox.**
Kojima (M.) Dementia Precox Studies (Chicago) 1918, 1, 92-98.

Describes the microscopic appearance of the endocrine organs from two patients, one a male and the other a female.

The glands are, on the whole, small, especially in the female. There appeared to be hypofunction of the thyroid in the male and hyperfunction of the same gland in the female. The sexual glands were very small in the female. The ovaries appeared to be undergoing an early involution. The testes of the male showed very slight spermatogenesis. This seems to be a report of the same cases recorded previously, Proc. Roy. Soc. Med., Sec. Psych. 1917, 10, 88-99.—F. A. H.

- 421. FAT DYSTROPHIES of endocrinous origin.** Beck
(H. C.) Northwest Medicine (Seattle), 1917, 16, 1.

A discussion of the dystrophies which are more or less common to all the ductless glandular disturbances with special emphasis on the fat dystrophies, under the following heads: (1) Thyrogenic obesity, hypothyroidism, due to suboxidation; (2) Eunuchoidism, Hypogenitalism; (3) Hypoadrenia; (4) Pancreaticogenic obesity in the preglycosuric stage of diabetes mellitus; (5) Hyperpinealism; (6) Hypergonadism; (7) Hypopituitarism.—J. P. S.

422. **GIGANTISM**, Case of. Smith (W. M.) Proc. Roy. Soc. Med. (Lond.) Sec. Dis. Children, 1916, 9, 74-6.

A short case report illustrated with photograph and cranial skiagram of a girl $12\frac{3}{4}$ years old, $5\frac{1}{3}$ feet in height and weighing 245 lbs. ("17 st. 7 lb.") Pubic hirsuties and menstruation were present. The sella turcica shows in the skiagram as well developed but there is no definite evidence of tumor.—R. G. H.

423. (**GONADS**) Über Hypogenitalismus und seine Abgrenzung von Infantilismus. (Hypogenitalism and infantilism.) Borchart (L.) Berliner klin. Wchnschr. 1918, 55, 348.

Although it is of course possible that the conditions of hypogenitalism and infantilism may co-exist in the same patient, there is no causal relationship between them.—J. K.

424. (**HORMONES**) Ductless gland cell control. Moellig (R. C.) 1st Lieut. M. R. C., Monograph, 75 pp. Published privately.

In a highly speculative article the author attempts to analyze the endocrine functions on an embryologic basis. No new data are offered. While much thought and ingenuity have been expended in elaborating the thesis it is doubtful if this type of activity can be further justified in the present state of the endocrine literature.—R. G. H.

425. (**HORMONES-SPLEEN**) The hormone equation of the psychoses. Carpenter (C. R.) Med. Rec. (N. Y.), 1916, 90, 843-46.

The writer expounds some novel theories of endocrinology but without adequate evidence to support them. He believes that spleen material used therapeutically is efficient in malaria but occasionally produces mental derangements.—R. G. H.

426. (**HYPOPHYSIS**) A case of pituitary tumor. Clogg (H. S.) Proc. Roy. Soc. Med., Sec. Neur. 1917, 10, 40.

A brief report of a case having positive Wasserman reaction, failing sight, increasing weight and impotence.—R. G. H.

427. (**HYPOPHYSIS**) A comparison of the activity of extracts of the pars tuberalis with extracts of other regions of the ox pituitary. Atwell (W. J.) and Marinus (C. J.) Am. Jour. Physiol. (Balt.) 1918, 47, 76-91.

A "pars tuberalis" differing histologically from both the pars intermedia and the pars anterior propria is described in the bovine hypophysis. Extracts were made of the pars tuberalis, probably contaminated with small amounts of neural stalk, and the action of these was compared with the effects produced by extracts of pure pars intermedia and pure neural stalk.

Extracts of pars tuberalis were found to be very inferior to extracts of the pars intermedia and of the neural stalk in producing contractions of the isolated uterine segment or in raising the blood pressure of the dog. The authors believe that the effects displayed by the pars tuberalis extracts were due to the inclusion of small amounts of the neural stalk substance, and that the pars tuberalis itself contains no active principle. The intravenous injection of extracts of pure pars intermedia produces pressor effects in both the dog and the rabbit. An extract of the pure neural stalk also causes a rise in blood pressure in the dog. This fact removes one objection to the possibility of the secretion of the pars intermedia passing into the neural lobe and then, via the neural stalk, into the third ventricle.—L. G. K.

428. (**HYPOPHYSIS**) **Carcinoma da hypophyse.** Moraes (E. de) *Brazil Medico* (Rio de Janeiro), 1917, **31**, 206.

A case of hypophyseal tumor was considered during life as a syndrome of Gradenio because there were present suppurative otitis, paralysis of the right rectus externus muscle of the eye and pain which required trephining the mastoid and curetage of the cells,—the latter without satisfactory result. The exact diagnosis was made at autopsy.—B. A. H.

429. (**HYPOPHYSIS**) **Cases of acromegaly.** Weber (F. P.) *Proc. Roy. Soc. Med. (Lond.) Clin. Sec.* 1917, **10**, 20-22.

Three brief case reports including serologic, urine, perimeter and skiagram findings. Nothing particularly striking is brought out.—R. G. H.

430. (**HYPOPHYSIS**) **Case of pituitary cyst: death from adrenal hemorrhage.** Catarinich (C.) *Med. Jour. Australia* (Sydney) 1916, **3**, 73-74.

A brief case report including gross pathological findings.—R. G. H.

431. (**HYPOPHYSIS**) Case of dystrophia adiposa genitalis, with congenital lues. Langmead (F.) Proc. Roy. Soc. Med. (Lond.) Sec. Dis. Children, 1917, 10, 25-6.

A brief case report. Nothing very striking except the association of the disease with congenital syphilis. This, the author states, "cannot be merely fortuitous," but no convincing evidence on the point is presented.—R. G. H.

432. **HYPOPHYSIS cerebri**, A case of sarcoma in the region of the. Pinchin (A. J. S.) West London Med. J., 1916, 21, 138.

A brief report of a case with description of the operation by which an attempt was made to remove the tumor. Nothing of interest to the endocrinologist.—J. P. S.

433. (**HYPHOPHYSIS CORPUS LUTEUM**) On the effects of feeding pituitary body (anterior lobe) substance, and corpus luteum substance to growing chicks. Pearl (R.) Proc. Nat. Acad. Sc. (Washington) 2, 50-53.

Details published elsewhere. Both substances were found to retard growth.—R. G. H.

434. (**HYPOPYSIS**) Diabete insipide et hypophyse (Hypophysis and diabetes insipidus). Lereboullet (P.) Anales de la Facultad de Med., Montevideo, 1917, 2, 712.

Observation of three cases of diabetes insipidus with hypophyseal syndrome in which the polyuria was diminished by injections of hypophyseal extracts.—B. A. H.

435. (**HYPOPHYSIS DIABETES INSIPIDUS**) Hipopituitarismo de origen sifilitico. Diabetes insipida. Trofoneurosis a tipo esclerodérmico de las extremidades inferiores. (Syphilitic hypopituitarism, diabetes insipidus and sclerodermic trophoneurosis of the lower extremities). Castex (M. R.) Prensa Med., Argentina, 1917, . . ., 39.

A man of 45, showing senile changes, had great ulcers and scars on the legs, scleroderma, polyuria of 4 to 7 litres, negative Wasserman, no lymphocytosis, . . . and normal sella turcica. The author mentions that Oppenheim and Nonne have observed cerebral syphilis (of the base) with considerable polyuria but, influenced by Marañón, considers that this condition is of hypophyseal origin. The researches, however, of Camus and Roussy as well as those of Houssay (which the

author does not mention) have demonstrated the existence of a polyuria independent of the hypophysis and have marked out a zone at the base of the brain, injury of which produces this condition. (See *Endocrin.* 1918, **2**, 94.)

This observation permits a remark that both the genital atrophy and the polyuria described by Castex might be due to a basal cerebral lesion. This has been demonstrated clinically and, by Camus and Roussy and Aschner, experimentally. The reviewer, however, has not been able to produce genital atrophy experimentally in this way.—B. A. H.

436. (HYPOPHYSIS—DIABETES INSIPIDUS) The effect of injections of pituitary solution on the urinary output in a case of diabetes insipidus. Clausen (S. W.), *Am. J. Dis. Child.* (Chgo.), 1918, **16**, 195.

Clausen made a study of the urinary output of a 9½-year-old boy suffering from diabetes insipidus, as influenced by injections of pituitrin. Following injections of from 0.25 to 1 c.c. of surgical pituitrin, there is a marked diminution of the urine volume. This diminution persists for from 5 to 6 hours, sometimes much longer. The volume of night urine is reduced when pituitrin is injected at any time on the preceding day. The hourly rate of elimination of chlorids is always reduced after injections of pituitary solution. The hourly rate of elimination of urea is usually only slightly, if at all, reduced and the hourly rates of elimination of creatinin and uric acid are only slightly reduced by injection of pituitary solution. The hourly rate of elimination of titratable acids in the urine is only slightly influenced by these injections. The hourly rate of elimination of no substance studied is increased by injections of pituitary solution. When the hourly ingestion of water and sodium chlorid or urea is maintained at constant high level, the urea elimination is quite uninfluenced by the injection of pituitary solution, whereas, the chlorid elimination is considerably diminished, and the water elimination very much diminished. Pituitrin injections in diabetes insipidus control urine output primarily and thirst secondarily.—M. B. G.

437. (HYPOPHYSIS) DIABETES INSIPIDUS Zur Lehre vom. Oehme (C.) and Oehme (H.) *Deutsches Arch. f. klin. Med.* (Leipsic) 1918, **127**, 261.

The effect of pituitrin on the secretion of the kidney is first an increase in the secretion of water and chlorides followed by a diminution of the secretion of water. The effect is not changed by cutting the nerves to the kidneys. Pituitrin

acts on the kidney itself. An injection of pituitrin into the ventricle of the brain has no effect. In normal cerebrospinal fluid substances are found which in a dilution of 1:10,000 to 1:200,000 have the same action on the blood vessels as does pituitrin. When pituitrin is injected very slowly the increase in the secretion of water and chlorides is not observed and at once the secretion of water is diminished. Diabetes insipidus is certainly not caused by a hyperfunction of the hypophysis. Most probably the concentrating power of the kidney is normal but, according to the authors, there is an increased irritability of the organ.—J. K.

438. (HYPOPHYSIS) Dystrophias hypophysiarias. Barros (F.) Rev. dos Cursos (Porto Alegre) 1918, 4,, (No. 4.)

A case report of a tumor of the hypophysis with adiposity and diabetes insipidus.—B. A. H.

439. (HYPOPHYSIS) Extirpación de la hipófisis en el perro. (Hypophysis extirpation in the dog.) Houssay (B. A. First National Congress of Medicine, Buenos Aires, 1916.

Between 1908 and 1916 the operation was performed upon 120 dogs, using a modification of Cushing's technique. The operation carried out without actual ablation of the gland did not cause death nor any appreciable change in the animal after the first effects had worn off. The extirpation of the gland, an easy procedure, produced a very high mortality. The dogs, whether the gland was removed at the operation or not, showed in the first few hours tachycardia, oliguria (adults), polyuria (puppies), shallow respiration, marked diminution in weight, transitory glycosuria and marked elimination of nitrogen.

The death of the animals after hypophysectomy ordinarily occurred in 20 to 48 hours, although the recovery from the anesthetic was prompt. Several dogs lived 7, 9, 10, 12 days, but with progressive indisposition and weakness. Young dogs endured the operation better than old.

Slight lesions of the gland provoked few or no symptoms, but with more extensive lesions or actual ablation the symptoms were more marked. In the young dogs there was complete arrest or retardation of growth in general and especially of the teeth, genitals and hair. In all cases marked adiposity developed in a month or two after the operation. This did not yield to opotherapy. It did not develop parallel with the genital atrophy. In adults there was testicular atrophy in all cases of ablation or extensive lesion of the whole gland or of the an-

terior lobe alone. In some dogs there was a subcutaneous infiltration of the tissues with a mucoid substance, the ears becoming large like those of a pig; also atrophy of the prostate and internal genitals, of the seminiferous tubules of the testes and of the interstitial cells. In the young dogs the process of ossification was retarded or arrested. Checking of growth was the only effect on the teeth. In the blood the red cells and hemaglobin were diminished.

Several adult dogs were able to take without developing glycosuria large doses of sucrose (350 gms.) maltose or lactose. Adrenin glycosuria was difficult to produce. No thermal reaction followed the injection of extracts of anterior lobe.

The thyroids in two dogs killed several months after the removal of the hypophysis showed changes from the normal. There was an excessive accumulation of colloid, flattening of the epithelium and, in some instances, degeneration of the cells. The parathyroids were normal or enlarged. Significant changes were not seen in the pancreas, liver, kidney, spleen or adrenals. None of the above mentioned changes followed the mere operation without actual removal of the hypophysis.

The part of the hypophysis that is physiologically important is the anterior lobe.—Author's Abstract.

440. (HYPOPHYSIS) Insufficiencia hipofisiaria—Distrofia adiposo-génitale de origen syphilitique. (Hypopituitarism—Dystrophia adiposo-genitalis of syphilitic origin.) Castex (M. R.) Prensa Med. Argentina, 1917, Suppl. 4, No. 11.

A patient, 42 years of age, had been syphilitic since the age of 23 and had had nephritis for 4 years. Then followed adiposity, sexual impotence, headache, and increasing weakness. The sella turcica was normal, the Wasserman reaction positive, the pupils unequal, the spleen enlarged and the lymphocyte count high. The author believes that the adiposo-genital symptoms are of hypophyseal origin. From the description this conclusion does not necessarily follow. The symptoms might well all be due to meningeal syphilis.—B. A. H.

441. (HYPOPHYSIS) Sobre un caso de síndrome de Froelich. (A case of Frölich's syndrome). Lagos Garcia (C.) Semana Méd. (Bs. Aires), 1918, 26, 21.

Lagos Garcia described the case of a boy, eight years old, with female distribution of fat, without cerebral and visual disturbances, but with destruction of sella turcica. He believes the condition due to a pituitary tumor, but proposes at first to give pituitary organotherapy.—G. P. G.

442. HYPOPHYSIS) Interrelationship of the female sex glands and the pituitary body. King (J. E.) *Am. Jour. Obst.* (N. Y.) 1917, **76**, 964.

Following the suggestion that the pituitary gland is one of far reaching influence in many vital processes, the author remarks upon the opposite effects which hyper- and hyposecretion of this gland produce upon metabolism, growth and mental characteristics. If the pituitary be removed from a young animal of either sex, before the secondary sex characteristics have appeared, the sexual organs will retain their infantile type. In case of an adult animal, retrograde changes take place, the genitals reverting to their infantile type. In diseased conditions of the gland causing a hyposecretion there will result either failure of the sex changes to take place or reversion to the infantile type, depending upon the age of the patient. The author remarks that the phenomena of puberty cannot be entirely attributed to the pituitary, but are due to its interrelation with the sex glands, citing as proof the results of castration.

The pituitary enlarges during pregnancy, and a number of investigators agree that this hypertrophy is the result of an enormous increase in what have been termed "pregnancy cells." What effect this hypertrophy has upon its secretions is not clear. Whether there is an increase, a decrease, or only a change in the character of the secretion, has not been determined. The remarkable effect of injection of pituitary extract in producing strong uterine contractions suggests several plausible theories by which the occurrence of labor has been explained.

In the child-bearing life of the woman pituitary disturbance will result almost uniformly in menstrual disturbance, and this is often the first symptom which the patient notes. In the analysis of any suspicious case, the ever close interrelationship of all the ductless glands must be kept in mind. Study of the clinical types is far from complete and their classification still depends upon the accumulated evidence of many observers.

In young women of from sixteen to twenty years of age and in whom menstruation began late, then stopped completely after a few irregular, painful and scanty periods, are found undoubted instances of mild hypopituitarism in childhood which results in the deficient development of the sexual organs, and which becomes apparent only at and following puberty.

Pituitary disturbance occurring after puberty, may find its expression after marriage by the appearance of amenorrhea, sexual indifference, drowsiness, etc.

The next type of hypopituitarism includes certain women who have an intense longing for children and who, when the menses cease are convinced of their pregnancy. The predominating obsession of pregnancy makes it possible to place these subjects in a distinct group, and in order to indicate the origin of their disorder, and at the same time to express the dominating feature the term "Pseudocyesis of Hypophysial Dystrophy" is suggested.—W. H.

443. (HYPOPHYSIS) *La hipófisis y el aparato dentario (Hypophysis and teeth)*. Erausquin (R.) *Comunic. al Congreso Dental Panamericano de Chili*, Oct., 1917.

The hypophysis was removed from two dogs, brothers of which served as controls. In the operated dogs were observed: a reduced volume of the skull and corresponding reduction in the size of the teeth; in the tooth form no change in the coronal portion but retarded calcification in the roots; partial persistence of the deciduous teeth; augmentation of the root pulp cavity and of the apical foramina. The histological structure was normal. The hypophysis extirpations were made by Dr. Houssay.—B. A. H.

444. (HYPOPHYSIS) *Metabolism study of a case of Froelich's syndrome (dystrophia-adiposo-genitalis)*. Rosenbloom (J.) *Interstate Med. Jour. (St. Louis)*, 1917, 24, 475-80.

A carefully prepared metabolism study of a case of dyspituitarism.—L. F. W.

445. (HYPOPHYSIS) *On the presence of albumoses in extracts of the posterior lobe of the hypophysis cerebri*. Abel (J. J.) and Pineoffs (M. C.) *Proc. Nat. Acad. Sci. (Balt.)*, 1917, 3, 507-517.

All commercial preparations of the pituitary gland that were examined were found to contain secondary proteoses and possibly peptones. The "Hypophysin" of the Farbwerke-Hoechst Company is not, as claimed, a solution of the isolated active substances of the pituitary gland, but a mixture of proteoses with varying amounts of active and inactive constituents of the gland. The proteoses present account fully for the chemical reactions (Biuret and Pauly reactions and the laevo-rotation) which are stated to characterize the pretended active principles. The proteoses separated from the pituitary extracts are devoid of action upon the uterus.—L. G. K.

446. **HYPOPHYSIS, Perithelioma of the, with report of a case.** Jackson (H.), *Tr. Chicago Path. Soc.*, 1915-16, 10, 110.

Report of a case of tumor of the hypophysis with description of the gross and microscopic appearance of the growth. No clinical symptoms are mentioned except gradually increasing blindness. The diagnosis of perithelioma was based upon the presence of a well defined perivascular space about the abundant blood vessels and the characteristic endothelial cells of the tumor mass. Jackson was able to find only one similar case in the literature.—J. P. S.

447. (HYPOPHYSIS) Pituitary extract. Nordin (G. T.)
Jour. Lancet (Minneapolis) 1918, **38**, 35.

In primiparas pituitrin should never be used during the first stage of labor, even in small doses. In multiparous women where the cervix is soft and easily dilatable, a small dose of pituitrin will in about 80 per cent. of the cases convert a slow, tedious labor, into a progressive one. During the second stage, where secondary inertia sometimes sets in, pituitrin in small doses will, usually, set up strong rhythmical contractions, and a normal labor will result. In any condition which tends to produce atony of the uterine muscles pituitrin is of value. According to Bandler, any form of uterine hemorrhage is benefited by pituitrin, except where malignancy is the cause. It is also of especial value in bleeding after curettage. Although pituitrin is of little value in bringing abortions on, it is of decided value in completing them when so far advanced that they cannot be prevented and in expelling the membranes and placenta.

The details of nine cases are reported, and the following conclusions drawn:

1. That the pituitary extract is of benefit wherever there are atonic involuntary muscles to deal with.
2. That in obstetrics one should always look out for contra-indications to its use, and in their absence start with small doses.
3. That manipulation in obstetrics and gynecology, with their dangers of hemorrhage and infection, can be eliminated, or at least minimized, in a large proportion of the cases, by cautiously using pituitrin.—W. H.

448. (HYPOPHYSIS) PITUITRIN in nocturnal incontinence of urine. Mikhailow (N. A.). *Urol. and Cut. Review* (St. Louis), 1917, **21**, 561. *Abstr. Brit. J. Child. Dis.* (Lond.), 1918, **15**, 143.

In most cases of incontinence, the essential cause is atony of the bladder accompanied or not by local changes such as

hyperemia of the base and neck of the bladder, anemia and slight edema of the mucosa. Mikhailow uses pituitrin in such cases and finds that after 3 or 4 subcutaneous injections, given once a week, the incontinence disappears. He records 19 cases, 10 of which were in children from 5 to 10 years of age who were cured by doses of pituitrin ranging from 0.2 to 1.0 c.c.—M. B. G.

449. **(HYPOPHYSIS)** Presentation of a pathological specimen of a large tumor of the pituitary gland. Lynch (R. C.) Laryngoscope (St. Louis), 1917, 27, 847.

Nothing of interest to the endocrinologist.—J. P. S.

450. **(HYPOPHYSIS)** Report of a case of adiposis dolorosa. Nice (C.M.) Med. Rec. (N.Y.) 1916, 90, 65.

The case presented the typical features, extreme adiposity (262 pounds in a young woman 5 feet 3 inches tall) and persistent severe pain. Thyroid treatment was without effect. Daily injections of pituitary extract, however, soon brought about amelioration which continued to a point permitting normal work.—R. G. H.

451. **HYPOPHYSIS, Sensory elements in the human cerebral.** Bryant (W. S.) Anat. Rec. (Phila.) 1916, 11, 25-27.

The author has found in human hypophyses certain ciliated epithelial cells in the linings of the clefts. These he interprets as sensory in nature although no convincing evidence on the point is cited.—R. G. H.

452. **(HYPOPHYSIS)** Some properties and actions of tethelin, the active constituent of the anterior lobe of the pituitary body. Robertson (T. B.) Cal. S. Jour. Med. (San Francisco) 1917, 15, 491.

A general exposition of the author's views on growth and of the properties of "tethelin."

453. **(HYPOPHYSIS)** Study of dystrophy adiposa genitalis in women. Schumann (E. A.) Am. J. Obst. 1918, 78, 428.

The syndrome resulting from the effects of deficient pituitary secretion upon the female system may properly be divided into three clinical groups, according to the age epoch affected: (1) Hypopituitarism in childhood and before puberty; corresponding to Froehlich's syndrome with an infantile

uterus and ovaries and almost rudimentary external sexual apparatus. (2) Hypopituitarism becoming manifested only after sexual activity has developed either during adolescence, or beginning during the period of betrothal and reaching its height in the months immediately following marriage. The history of such a case is usually of a young girl of good health maturing at 12 to 14 years, menstruating regularly after that and showing no signs of any disorder until she becomes engaged. At this point, she rather suddenly develops amenorrhea, gains weight and becomes chlorotic. She remains so for 2 to 5 years, when her condition improves and her menstruation returns, the adiposity disappears and pregnancy may supervene, or, on the other hand, her condition may become more marked, her mentality impaired, and she degenerate into the adipose infantile type of fat women. (Amenorrhea of obesity.) (3) This type generally gives a history of a woman who matured normally, menstruated regularly, had married and had borne one or more children. After the birth of the last child, she undergoes lactation atrophy or superinvolution of the uterus. Menstruation may be suppressed or be irregular and scanty. There is a marked deposit of fat and a carbohydrate tolerance which becomes excessive; there is no impairment of the sexual desire and no external sexual changes, but there is an atrophic condition of uterus and ovaries. Pseudocyesis commonly occurs.

Treatment of all three groups consists in general measures and empirical use of glandular extracts. The writer avails himself of the systolic pressure as an index of what gland to use. In cases with low blood pressure, he administers anterior pituitary extract and in those with high blood pressure, thyroid extract.

The prognosis must be guarded in all cases as to recovery, but is favorable in direct ratio with the age of the patient.

He cites three cases as examples of each group.—M. B. G.

454. (HYPOPHYSIS) The action of pituitary extract on the kidney. Knowlton (F. P.) and Silverman (A. C.) *Am. Jour. Physiol.* (Balt.) 1918, **47**, 1-12.

Using the method of Barcroft and Brodie the authors measured the blood flow and oxygen consumption of the kidneys of cats before and during the diuresis induced by pituitary extracts. They found that the oxygen consumption was not increased during such diuresis, and therefore conclude that there is no evidence that pituitary extract stimulates the renal cells. Throughout the experiments increased blood flow was an invariable accompaniment of pituitary diuresis. From their evi-

dence they believe that it is possible to explain the diuretic action of pituitary extract entirely on the basis of the vascular changes and increased filtration pressure obtaining in the kidney.—L. G. K.

455. (HYPOPHYSIS) The clinical possibilities of the pharyngeal pituitary. Bryant (W. S.) *Med. Rec. (N. Y.)* 1916, 90, 441-445.

This article describes the anatomy of the pharyngeal hypophysis—a small bit of tissue left behind in the migration of the anterior lobe to its post-embryonic position. The organ is stated to occur constantly in man. A bibliography of some 30 titles is included. A theory is developed that therapeutic post-pharyngeal irritation produces wide effects through stimulation of the pharyngeal pituitary.—R. G. H.

456. (HYPOPHYSIS) The effect of injections of pituitary solution on the urinary output in a case of diabetes insipidus. Clausen (S. W.), *A. J. Dis. Child.*, 1918, 16, 195.

Clausen made a study of the urinary output of a 9½-year-old boy suffering from diabetes insipidus, as influenced by injections of pituitrin. Following injections of from 0.25 to 1 c.c. of surgical pituitrin, there is a marked diminution of the urine volume. This diminution persists for from 5 to 6 hours, sometimes much longer. The volume of night urine is reduced when pituitrin is injected at any time on the preceding day. The hourly rate of elimination of chlorids is always reduced after injections of pituitary solution. The hourly rate of elimination of urea is usually only slightly, if at all, reduced by injection of pituitary solution. The hourly rates of elimination of creatinin and uric acid are only slightly reduced by injection of pituitary solution. The hourly rate of elimination of titratable acids in the urine is only slightly influenced by these injections. The hourly rate of elimination of no substance studied is increased by injections of pituitary solution. When the hourly ingestion of water and sodium chlorid or urea is maintained at a constant high level, the urea elimination is quite uninfluenced by the injection of pituitary solution, whereas, the chlorid elimination is considerably diminished, and the water elimination very much diminished. Pituitrin injections in diabetes insipidus control urine output primarily and thirst secondarily.

—M. B. G.

457. HYPOPHYSIS, The extract of the posterior lobe of the. Chenerson (M.) *Arch. Mens d'Obstet et de Gynecol. (Paris)* 1918, 7, 22.

The indications for the employment of this extract "pending the period of dilatation" are said to be very variable. The remedy was administered sometimes by intravenous and sometimes by subcutaneous injection, the maximum dose being 0.2 gm., at times 0.1 gm. was sufficient, while upon other occasions as much as 0.3 to 0.4 gm. was required to bring about the desired results. When injected intravenously, it is well to dilute the extract with 5 c.c. of physiological serum. Success was obtained in 26 cases of simple uterine inertia out of 40 cases treated. In 18 cases in which this remedy was employed to combat prolonged and difficult expulsion, 16 were successful; these comprised 11 multiparas and 7 primiparas. In 9 cases of malpresentation, 4 of the face and 5 breech, administration of this remedy was followed by success. Four out of 5 cases of postpartum hemorrhage were successfully treated.

All accoucheurs who have employed this extract during the "period of expulsion" according to the author have obtained good results. In only 3 cases out of 25 was it found necessary to use forceps.

The results obtained by the present author and a dozen others whom she mentions in "provocation of labor" were for the most part negative. As a remedy for postpartum retention of the urine the author found it successful in 29 out of 35 cases, administration being preferably by the intravenous method. The article concludes with a brief consideration of the inconveniences and dangers which accompany this form of therapy as well for the mother as for the child.—W. H.

458. (HYPOPHYSIS) The use and abuse of pituitary extract.
Kosmak (G. W.) Jour. A. M. A. (Chgo.) 1918, 71, 117-19.

This paper, like several others of recent date, is largely a warning against the careless use of pituitrin in obstetrical practice. Kosmak regards it as a valuable drug, but as safe for use only in cases of simple inertia, particularly in multiparas, when there is no obstruction to the passage of the child, no exhaustion, and when the presenting part is engaged. Doses of more than 5 minims should not be used and should not be repeated until the effect of each has passed. Pituitrin should not be used to induce labor nor as a substitute for forceps.—R. G. H.

459. (HYPOPHYSIS) Trastornos hipofisiarios en ginecología. (Hypophyseal disorders in gynecology.) Guardado (J.) Soc. de Obstetr. y Ginecol. de Buenos Aires, Oct. 31, 1917.

In two patients suppressed menstruation was re-established after injections of extracts of posterior lobe of hypophysis. In

the second of the cases the woman was 28 years of age, married and had suffered from amenorrhea for two and a half years. Ovarian opotherapy, by mouth and hypodermatically produced no effect but after nine pituitary injections menorrhagia followed.

The author would deduce from these observations that the hypophysis was etiologically involved.—B. A. H.

460. HYPOPHYSIS, Tuberkulose der. (Tuberculosis of hypophysis.) Froboese. *Centralbl. f. Pathol.* (Weisbaden) 1918, 29, 145.

A woman of 32 years died in coma. At the post-mortem examination the hypophysis was found nearly absolutely destroyed and replaced by granular tissue. Tubercle bacilli were not found but the histological examination gave the classical structure of tuberculous tissue. The case proves once more that destruction of the pituitary body causes coma. It is very remarkable that tuberculosis of the pituitary body is seen only in women.—J. K.

461. (HYPOPHYSIS) Un caso de distrofia genital. Schweitzer (F.) *Soc. Argentina de Pediatría*, Sept. 22, 1917.

A boy of 16 was presented with disseminated choroiditis and atrophy of the optic papillae, very marked accumulation of fat in the abdominal wall. . . ., arrest of genital development and of sexual function and enlargement of the sella turcica; there was no glycosuria ("experimental"). The case was classified as Fröhlich's syndrome. As to treatment, after mercury (Wasserman negative) hypophyseal opotherapy is suggested.—B. A. H.

462. (HYPOPHYSIS) Vorderlappens, Atrophie des, und hypophysäre Kachexie (Atrophy of the anterior lobe of the hypophysis and cachexia). Simmonds (M.) *Deutsche med. Wchnschr.* (Berlin) 1918, 44, 852.

Report of four more cases of cachexia in which the only pathological finding was a destruction of the anterior lobe of the hypophysis. (See *Endocrin.* 1917, 1, 108, 264.)—J. K.

463. (HYPOPHYSIS THYROID) dell' importanza iodio tiroideo nella funzionalita ipofisaria (The relation of thyroid iodine to pituitary functioning). Pellegrini (R.) *Pensiero Medico* (Milan) 1916, 6, 289-94, 301-03, 313-16, 325-28.

The article comprises a report of the morphological and chemical features of 17 cases together with a discussion of the

pertinent literature. No relation was discovered between the volume of the hypophysis and the amount of thyroid iodine. The same is true as regards microscopic evidence of functional activity, relative size of the lobes of the hypophysis or frequency of occurrence of the various cellular elements. There was noted a marked lack of pigment in the neural lobe in cases in which the iodine was decreased. For numerous technical details the original should be consulted.—R. G. H.

464. **INFANTILISM, Case of.** Cautley (E.) *Proc. Roy. Soc. Med. (Lond.) Sec. Dis. Children*, 1916, **9**, 72-3.

A short case report. No definite endocrine etiology could be recognized.—R. G. H.

465. **(INFANTILISM) Neotenie und Infantilismus.** Hart (G.) *Berliner klin. Wchenschr.* 1918, **55**, 612.

Includes nothing new.—J. K.

466. **(INFANTILISM) Sobe un caso de enanismo senil (Progeria). (A case of progeria).** Orrioco (J.) *Prensa Méd. Argentina (Buenos Aires)*, 1918, **5**, 133.

A patient of 19 had a height of 113 cm. and a weight of 15 k. Right hemiplegia and aphasia were present. The general appearance was typical of progeria. Neither alimentary nor adrenalin glycosuria could be elicited. Positive v. Pirquet and Wasserman reactions and lymphocytosis were observed as were marked cutaneous pigmentation, wrinkling of the skin and emaciation. The author concluded in the light of the available literature that the condition was of endocrine origin, adrenal disturbance predominating. Mercurial and opotherapeutic treatment (with adrenalin and thyroidin) gave negative results.—B. A. H.

467. **INFANTILISM, With two cases of the Brissaud and the Frölich types, respectively.** Griffith (J. P. C.), *Am. J. Dis. Child. (Chgo.)*, 1918, **16**, 103.

Griffith gives a very good clinical description of a case of the Brissaud type of infantilism in an Italian girl who at 7 years of age has the weight of a child of 10 months and the height of one of 20 months. Her hair was rather short and slightly dry and harsh, her lower extremities were bowed, the abdomen pendulous with a distinct costal flaring; mentality was apparently normal. She was given thyroid extract and then pituitary with a resulting slight increase in size. The

writer does not indicate what ultimate results were obtained in the use of these agents. The case was apparently due to hypothyroidism.

The second case was in a boy of 11 years, who gave a history of having had a fall when 14 months old, but in whom an inclination towards obesity was first noticed at the age of 11 months. He was exceedingly obese, weighing 251 pounds and having the following measurements: Height, 5 feet, 1 inch; circumference at nipples, $45\frac{1}{2}$ inches; at umbilicus, 47 inches; at anterior superior spines, 51 inches; thigh, 34 inches. In brief, this boy of 11 had the height of a boy of 14 or 15 and a weight beyond that of a normal man. The abdomen was very pendulous, penis was small, testicles descended, no trace of pubic hair. Mentality was normal for his age. The sella tureica was definitely smaller than normal, indicating a small pituitary body.—M. B. G.

468. INTERNAL SECRETION and malocclusion. Helman (M.) *Dental Cosmos* 1916, **58**, 191.

The author in enumerating the possible etiological factors of malocclusion, quotes at length and points to the mouth, teeth and jaws of the cretin, i. e., thick lips, faulty tooth formation and malposed irregular dental arches, supernumerary teeth, missing dental germs and the late retention of deciduous teeth. The so-called "Rickety Teeth" present the enamel not properly developed, showing transverse furrows and small hole-like defects which make sets of parallel lines running along the incisors and cuspids. Thymectomy (in dogs) results in small skull, undeveloped jaws, delayed, small teeth and delayed exfoliation.

In hypophysectomized dogs the deciduous dentition persists to the end of a year or throughout life. Aeromegaly, on the other hand, causes over-growth of the mandible, large dental arches and teeth often in proportion. Castration has a somewhat similar effect.—V. J. P.

469. INTERNAL SECRETION, Studies of, in their relation to the development and condition of the teeth. Gies (W. J.) *Dental Cosmos* 1917, **59**, 238.

A very interesting concluding report (abstract) of work done by the author and his collaborators. In young white rats, extirpation of the thymus had no effect on dentition; excision of the thyro-parathyroid tissue diminished dental calcification. The results suggest that the thyroid normally induces subnormal calcification, and the parathyroids normally induce supernormal dental calcification.—V. J. P.

470. **INTERNAL SECRETION**, The possible role of the glands of, in problems of **PSYCHIATRY**. Carmichael (F. A.) Kansas State Med. Soc. (Lawrence), 1918, 18, 98.

A theoretical discussion based upon the literature. The author believes that inasmuch as the glands of internal secretion act upon tropic innervation, they are also intimately concerned in the maintenance of mental stability. The delicate balance of nutrition of such highly organized units as the cells of the central nervous system would be the first to respond to derangements of the secretory function of the endocrine glands.

—J. P. S.

471. (**INTERNAL SECRETIONS**) *Concepto de las secreciones internas. Su valor en fisiología, pathología y terapéutica* (The internal secretions in physiology, pathology and therapeutics). Bové y Piqué (D. E.) *Rev. valenc. de cienc. med.* (Valencia) 1916, 18, 17-23, 42-46, 49-56, 102-110, 115-123, 136-143.

A somewhat extensive general discussion not amenable to abstracting.—R. G. H.

472. **INTERNAL SECRETIONS**, The. Chemical factors in the regulation of the organism. Stiles (P. G.) *Scient. Am. Suppl.* (N. Y.) 1917, 84, 51. (Reprinted from *Science Conspectus*.)

An interesting popular discussion of the topic.—R. G. H.

473. **INTERNAL SECRETIONS**, The relation of, to cutaneous disease. Foerster (O. H.) *Jour. Cutan. Dis.* (Boston) 1916, 34, 1-14.

The article opens with an excellent general exposition of the classical subject matter on the internal secretions. Then the relation of the thyroid and thymus to the skin and its diseases is considered. In Graves' disease the skin is thin, readily congested and perspiration is excessive, pruritus, urticaria, dermatitis pigmentation and alopecia are common. In myxedema more characteristic skin changes are found. It is pallid, cold, dry, wrinkled and infiltrated. Dryness and premature grayness of the hair are common. The eye-lashes and eye-brows often fall out. Carious teeth and brittle nails are also characteristic. It is probable that scleroderma is due partially at least to thyroid disease. No very definite relation of the parathyroids and thymus to the skin has been established.—R. G. H.

- 474. INTERNAL SECRETIONS, The relation of, to cutaneous disease.** McEwen (E. L.) Jour. Cutan. Dis. (Boston) 1916, **34**, 15-23.

The author concludes: A direct or indirect relationship may be considered as existing, or possible of existence, between the endocrine glands and the following skin diseases: Pigmentation of Addison's disease, of neoplasms of the skin, and, probably of pregnancy and from pelvic tumors; dermatoses secondary to excess of body fat; skin disturbances of puberty and the climacteric; hypertrichosis in women; alopecia in certain instances and dermatoses that are etiologically related to hypo-and hyper-activity of the glands of the skin.

—R.G.H.

- 475. (INTESTINE) The antigenic property of closed intestinal loop fluid.** Dragstedt (C. A.), Dragstedt (L. R.) and Chase (C. S.) Am. Jour. Physiol. (Balt.) 1918, **46**, 366-374.

Isolated closed loops of duodenum, duodeno-jejunum or beginning jejunum of rabbits were found to contain after forty-eight hours a quantity of bloody, foul-smelling fluid. The coagulum obtained from this by heating to 70° C. over a water bath was injected at intervals into healthy rabbits for varying periods. When compared with normal animals these did not exhibit any increased but rather a decreased tolerance to subsequent injections, nor was the presence of an antitoxin in the serum of the treated rabbits demonstrated. No indications of anaphylaxis were observed during the experiments, and it was therefore concluded that the toxic principles of closed loop fluid are not of a protein nature. However, the symptoms following the injection of large doses of the loop fluid into rodents very much resembles the anaphylactic shock which can be produced by the administration of β -iminazolethylamine, a substance present in the intestinal mucosa. It was suggested that this may be the important constituent of closed intestinal loop fluid. This research casts further doubt upon the theory that the intestinal mucosa produces a hormone which figures in death from intestinal occlusion.—L. G. K.

- 476. LIPODYSTROPHIA progressiva.** Weber (F. P.) Proc. Roy. Soc. Med. (Lond.) Sec. Dis. Children, 1917, **10**, 81-93.

An interesting general discussion of this condition and a review of a considerable part of the literature. The article is illustrated by a photograph. The data are published elsewhere. [Quart. Jour. Med. (Oxford) 1917, **10**, 131.] See also Abst. No. 141, Endocrin. 1918, **2**, 176.

No definite conclusion is reached except that the condition is not necessarily progressive. An endocrine etiology is regarded as probable.—R. G. H.

477. (**LIVER**) *Le foie, glande a sécrétion interne (The liver as an endocrine gland)*. Benoit (E. P.) *Union Méd. du Can.* (Montreal) 1916, **45**, 255-65.

A general discussion. No new data recorded.—R. G. H.

478. **MENOPAUSE**, *On the physiology and pathology of the*. Richter (G.) *Med. Rec.* (N. Y.) 1917, **91**, 446-50.

A general discussion of endocrinology with special reference to the symptoms of the menopause. No new data are offered.—R. G. H.

479. (**MENSTRUATION**) *Fistula m. del abdomen en una antigua laparatomizada (Menstrual fistula in old laparotomy)*. Tagliavache (N.) *Semana Méd.* (Bs. Aires), 1918, **26**, 19.

Not of endocrine interest.

480. (**MENSTRUATION**) *Material lost in menstruation of healthy women*. Gillett (L. H.), Wheeler (L.) and Yates (A. B.) *Am. Jour. Physiol.* (Balt.) 1918, **47**, 25-28.

The authors' data show that there is no pronounced periodicity in the output of phosphorus and calcium in women and that the amounts of these elements lost in menstruation are not sufficient to make the nutritive requirements of women for these elements materially different from those of men of the same weight. The loss of iron however is considerable, and this factor should be considered by women in choosing their daily diet.—L. G. K.

481. **MYATONIA congenita**, *Report of a case of*. Neustaedler (M.) *Med. Rec.* (N. Y.) 1917, **90**, 181-82.

Of no endocrine interest.—R. G. H.

482. *Note sur l'hypothermie chez les militaires. (Note on subnormal temperature in soldiers)*. Merklen (P.) *Bull. Soc. Méd. Hôpitaux* (Paris), 1917, **41**, —. (Oct. 18.)

The author suggests the possibility of hypofunction of the suprarenal glands with or without intestinal disturbances which may at times be responsible for subnormal temperatures.

—A. L. T.

483. **OVARIES, First 85 cases of tumors of the uterus and.** La Roque (G. P.) *Internat. J. Surg. (N. Y.)* 1916, **29**, 101-3.

Of no direct endocrine interest.—R. G. H.

484. **OVARIES, Histological examination of the, in mental disease.** Forster (Laura) [With comments by Mott (F. W.)] *Proc. Roy Soc. Med., Sec. Psych.* 1917, **10**, 65-87.

This paper is an interesting report of possible correlation between mental diseases and ovarian function. Ovaries were studied from 100 cases including those diagnosed as dementia precox, mania, melancholia, general paralysis of the insane, epilepsy and imbecility. As controls ovaries from women and children dying in London institutions were used. These, as Mott mentions, were not entirely satisfactory, being more or less abnormal themselves.

Results: Dementia precox, early involution with great scarcity of Graafian follicles; imbecility and epilepsy—nothing definite; melancholia, mania, general paralysis—diminution of follicles.

The author concludes that mental disease in general is associated with early cessation of ovarian function. She could detect no evidence of secretion in any part of the ovary, including corpus luteum, unless it be in the Graafian follicle itself; nothing resembling the "interstitial cells" of rabbits was found. The findings are tabulated and illustrated with 8 microphotographs. Mott in commenting upon the report agrees with the conclusion of a relationship existing between mental disease and ovarian depression. He emphasizes the desirability of further careful cytological study of the problem.—R. G. H.

485. **(OVARIES) Histological examination of the ovaries in mental disease.** Forster (Laura) *Dementia Precox Studies (Chicago)* 1918, **1**, 79-91.

Data previously reported elsewhere. See abstract in this issue.

486. **(OVARIES) Ovarienbefunde bei Kreigsamenorrhoe. (The ovaries in war amenorrhoe.)** Köhler (R.) *Centralbl. f. Gyn. (Leipsie)* 1918, **42**, 250.

In two cases of war amenorrhoe the ovaries were examined histologically. Distinct changes were found in them. Fischer has explained this amenorrhoe as a chronic intoxication with ergotoxin, caused by the bad German bread. Köhler does not accept this theory since the signs of tetany which never fail

in ergotoxin were not to be seen in his cases of amenorrhœa. They were caused by anatomic changes in the ovaries.—J. K.

487. (OVARIES) Two cases of primary ovarian pregnancy. Lockyer (C.) Proc. Roy. Soc. Med., Sec. Obst. and Gyn. 1917, 10, 158-182.

Of no direct endocrine interest.—R. G. H.

488. (OVARY) Hat die Ovarientransplantation praktische Bedeutung? (The practical importance of ovarian transplanting). Unterberger (F.) Deutsche med. Wehnschr. (Berlin) 1918, 44, 903.

Includes nothing new.—J. K.

489. OVARY, Internal secretion of the. (Collective Abstract.) Williams (J. T.) Interstate Med. Jour. (St. Louis), 1918, 25, 16-22.

The author presents an excellent review of the literature. He believes the internal secretion is produced by the corpus luteum and the interstitial cells. The corpus luteum controls the menstrual cycle and presides over the development of the decidua and the formation of the placenta. The interstitial cells probably produce a secretion which controls the development of the secondary sexual characteristics. The ovarian secretion has some relation to the nausea and vomiting of pregnancy.—L. F. W.

490. (OVARY) Menstruation and internal secretion. Schlenker (M. A.) New Orleans Med. and Surg. Jour., 1916, 69, 105-14.

Discusses recent work that has been done to show the relationship between menstruation and the internal secretion of the ovary.—L. F. W.

491. (OVARY) Nausea and vomiting of pregnancy treated with ovarian extract. Carter (P. J.) New Orleans Med. and Surg. Jour. 1917, 70, 234-7.

Reports twenty cases of pregnancy complicated by vomiting, relieved by the use of ovarian extract.—L. F. W.

492. (OVARY) Ovarian transplantation—Report of cases. Phillips (W. D.) New Orleans Med. and Surg. Jour., 1917, 70, 73-6.

Reports fifteen cases of autoplasmic ovarian transplantation in the human; in ten of these the operation was followed by

menstruation. Details are given of the technic found most satisfactory.—L. F. W.

- 493. (PANCREAS) Die Abhängigkeit der innere Sekretion des Pankreas vom Nervensystem (Influence of the nervous system upon pancreatic endosecretion).** de Corral (J. II). *Ztschr. f. Biol.* (Munich) 1918, **68**, 395.

In the vagus nerves of dogs are found fibres the stimulation of which causes an increased production of pancreas hormone. This can be proved by the fact that stimulating electrodes applied to the nerves below the point of egress of the cardiac fibres and after destruction of the fibres to the liver cause diminution of the blood sugar. The effect is so prompt that one is forced to the belief that it is due to the action of an increased quantity of pancreas hormone causing destruction of sugar in the tissues or in the blood itself. When the operation is gone through but stimulation of the nerves omitted the blood sugar increases.—J. K.

- 494. (PANCREAS-DIABETES) Discussion on the treatment of diabetes mellitus by alimentary rest.** Leyton (O.), Spriggs (E. I.), Ryffel (J. H.), Brown (W. L.), and Cammidge (P. J.) *Proc. Roy. Soc. Med.* (Lond.) Sec. Therap. and Pharm., 1916, **9**, 63-94.

The article does not lend itself well to abstracting. It includes more or less general discussion of the theory and principles of treatment of the disease for which the original should be consulted. The general trend of the discussion was favorable toward the Allen method. Several case reports are included.—R. G. H.

- 495. (PANCREAS INFANTILISM) El infantilismo pancreática.** (Byron Bramwell pancreatic infantilism). Bullrich (R. A.) *Rev. de la Asoc. Med.*, Argentina. (Buenos Aires), 1918, **28**, 303.

A patient at 16 years of age weighed 87 kg. and had a height of only 1.28 M. (4 ft.) He had grown well until eleven years old, then he began to grow thin and developed glycosuria (3.8 to 4.5% sugar). Toward the end of his life he had a very dry skin, like that of an old man, and the hair was sparse. A negative Wasserman reaction was obtained. Clinical tests (stools) showed deficient pancreatic secretion. He had suffered from severe diarrhoea—20 movements a day. The patient died of meningeal hemorrhage. At autopsy only insignificant lesions were found in the pancreas but the thyroid and anterior lobe

of the hypophysis showed sclerosis. The case was apparently then to some degree a polyglandular insufficiency. The reviewer attributes the infantilism to the lesion of the hypophysis but it must be considered a very complex case.—B. A. H.

496. **PANCREAS** in relation to **DIABETES MELLITUS**, Some recent work on the. Berkeley (W. N.) Med. Rec. (N. Y.) 1917, 91, 355-57.

The theory that diabetes mellitus is due essentially to deficient pancreas hormone is widely accepted. No method of isolating such a hormone has hitherto been successful. Berkeley reports that by a special method, the details of which are omitted in the article cited, a pancreatic extract has been secured which is very useful in alleviating the symptoms of the disease.—R. G. H.

497. **PANCREATITIS**, Acute, with a report and discussion of a case. Levy (L. H.) Med. Rec. 1917, 91, 721-2.

Not of endocrine interest.—R. G. H.

498. **PARATHYROID** gland, Treatment of paralysis agitans with. Berkeley (W. N.) Med. Rec. (N. Y.) 1916, 90, 105-6.

The article is largely a review of well-known subject matter. The beneficial effect of aetie extract of fresh gland is emphasized.—R. G. H.

499. (**PARATHYROID**) Observations upon the calcium content of the blood in infantile tetany and upon the effect of treatment with calcium. (Abst.) Howland (J.) and Marriott (W. McK.) Johns Hopk. Hosp. Bull. (Balt.) 1918, 29, 235-39.

The authors consider the theory regarding the parathyroid etiology of infantile tetany dubious but possibly valid. A new technique for the determination of calcium in small quantities of blood was evolved. It was found that the Ca. content of adult serum was 9 to 11 mg. per 100 c.c. In rachitic children the average was 9.4 mg. In active tetany the average in 18 cases was 5.6 mg., a reduction of approximately 40 per cent. In 5 cases of convulsions not due to tetany the Ca. varied from 8.9 to 11 mg. per 100 c.c. serum. It was found possible by continuous administration of Ca. in the food to restore the Ca. of the blood. Calcium chlorid in the experience of the authors was more efficacious than lactate.—R. G. H.

500. (PARATHYROID) TETANY as a sequel to gynecological operations and as a complication of pregnancy. Stein (A.) Interstate Med. Jour. (St. Louis), 1916, 23, 1078-85.

Reports a case of tetany which persisted for six weeks, following a gynecological operation (euretting) and was not relieved by the usual treatment. Fifteen other cases that have appeared in literature are reviewed. The author believes a disturbance of the endocrine glands is responsible for the tetany that appears during pregnancy or following it. These cases are usually relieved by administering thyroid extract and calcium.

—L. F. W.

501. (PARATHYROIDS) Contribución al estudio de la anatomía normal y patológica de las glándulas paratiroides. (Normal and pathological anatomy of the parathyroids). Strada (F.) Rev. Universidad de Córdoba (1917), 4, No. 6.

In an anatomical study of 168 cases Strada found 4 parathyroids in 86 cases, less than 4 in 76 cases, 2 in 5 cases, 3 in 7 cases and more than 4 in 10 cases. Details as to size, location and gross and microscopic structure are given. In this important report a certain number of pathologic-anatomical data are included.—B. A. H.

502. (PARATHYROIDS) Sobre parastruma. (Parathyroid tumor). Strada (F.) Rev. Universidad Nac. de Córdoba (1917), 4, No. 6.

A tumor the size of a thumb was removed from the side of the neck five years after its earliest appearance. In some regions the appearance of parathyroid "chief" cells was preserved, but in other regions evidence of malignancy was observed.—B. A. H.

503. PINEAL body, Hyperplasia of the. Bell (H. H.) Jour. Missouri M. Assoc. (St. Louis) 1916, 13, 239.

A very brief discussion of two cases.—R. G. H.

504. (PINEAL) Studi sulla ghiandola pineale. III. I fenomeni secretorii ed i lipoidi. I risultati della colorazione vitale alla Goldman (Secretory phenomena in the pineal gland studied by vital staining). Biondi (G.) Rev. ital. di Neuropath., Psich. ed Elet. 1916, 9, 303-321.

The article includes a review of the literature and a well-illustrated account of the author's cytological studies. It is

not suitable for abstracting. No conclusion is reached as to the function of the pineal gland.—R. G. H.

505. PITUITRIN and ADRENALIN injections, Treatment of asthma by. Zueblin (E.) *Med. Rec. (N. Y.)* 1917, **91**, 364-67.

Reports the satisfactory use of this combination. In view of the fact that adrenin causes dilatation of the bronchioles through its action on the sympathetic neurocellular terminations and that pituitrin causes contraction by a direct action upon the bronchial muscles, the combination would seem irrational. Houssay, who has made a special study of the problem, regards the beneficial effect as due to the adrenin overcoming the harmful influence of the pituitrin.—R. G. H.

506. PITUITRIN and EPINEPHRIN, Treatment of hay fever and asthma by. Zueblin (E.) *Med. Rec. (N. Y.)* 1917, **92**, 10-12.

A case is reported in detail in which the remedy was successfully used. The author regards weakened heart action as often an important factor in such cases. It is toward the heart that the pituitrin is addressed. Its constricting effect upon the bronchioles would seem to contraindicate its use, some other heart stimulant being substituted.—R. G. H.

507. (PITUITRIN, APPENDICITIS) Utilité de l'emploi de l'extrait hypophysaire dans le traitement des paralysies intestinales consecutives aux opérations d'appendicite a chaud. (Hypophyseal extract in the treatment of intestinal paralysis following appendicitis operations). Kirmesson (E.) *Bull. de l'Acad. de Méd. (Paris)*, 1918, **79**, 82.

Favorable results on intestinal and renal activity are reported.—A. L. T.

508. (PITUITARY) A study of one hundred cases of pituitary disease. Abrahamson (Q.) and Climenko (H.), *Jour. A. M. A. (Chgo.)*, 1917, **69**, 281-282.

The authors conclude that the middle and posterior lobes of the pituitary secrete a substance (or substances) which does not influence sugar metabolism, but controls the salt content on which the electrical conductivity of the blood depends. This control is not exercised through the nervous system. Diseases of the posterior and intermediate portions of the pituitary gland disturb the fixed ratio of the salt content of the blood.

Slight disturbances result in polyuria, if there is renal sufficiency, or in water logging of the tissues if there is renal insufficiency.—L. G. K.

509. PITUITRIN, The prophylactic use of, in nose and throat operations under local and general anesthesia. Solinger (S.) *Am. J. Surg. (N. Y.)* 1918, **32**, 124.

This study was made upon 48 individuals, supplementing a previous similar study of 100 cases. The effect of the drug upon blood pressure, coagulation time and post-operative bleeding was observed. Hypodermic injections of 1 c.c. to adults and 0.5-1.0 c.c. to children was administered. In all but one case the blood pressure was increased, avering 10 mm. systolic and 6 mm. diastolic. In 60 per cent of the cases the augmented pressure persisted as long as 18 hours. The coagulation time was reduced by $\frac{1}{2}$ to 5 minutes. Thirteen of the 48 cases developed moderate primary hemorrhage and 35 only a slight bleeding, results which the author regards as more favorable than normal and hence as indicating the usefulness of the drug. Uterine contractions amounting to cramps in some cases occurred.—R. G. H.

510. PITUITRIN, The use of small doses of, for inducing and shortening labor at term. Stein (A.) and Dover (H.) *Med. Rec. (N. Y.)* 1917, **92**, 238-40.

The article particularly emphasizes the desirability of small doses. The conclusions are that the best mode of administration is intramuscularly in 2 to 4 minim doses. It is useless for the induction of premature labor. With castor oil, however, it can be used successfully to induce labor at term. After the onset of labor it is useful to strengthen uterine contractions. It can be used as an efficient adjuvant of the bougie method. The judicious use of harmless small doses serves to reduce the number of forceps deliveries.—R. G. H.

511. PLACENTAL EXTRACT, Tissue-stimulating effect of. Frank (R. T.) *J. Cancer Research (Balt.)* 1917, **2**, 515-6.

The extract is standardized by 4 successive injections in 8 days into immature rabbits, followed by comparison of the uterus with a control with respect to length, thickness and weight. The extract produces histological changes in the uterus and increases the water content of that organ. Stimulation of the uterus occurs in the absence of the ovaries, even in atrophic uteri 16 months after castration; it also occurs in animals "deprived of their thyroid, adrenal, or pancreas, or of their thyroid and adrenal." The stimulation influences the breast, in-

creasing its area and causing development of its ducts, acini, and nipples. Uterine stimulation takes place in rabbits, cats, guinea pigs, and rats; breast stimulation is less distinct in the last 2 animals. These conclusions are drawn from the research: The animal organism contains growth substances, which exert a stimulating effect on 2 groups of organs, one derived from Müller's ducts, the other from the skin and its appendages; epithelia, connective, and muscular tissue cells of both groups respond to the stimulus. Transplanted tissues respond to stimulation; and transplanted stimulated tissue has greater vitality in its new environment than unstimulated controls. Growth may be stimulated after advanced and prolonged atrophy, but not beyond normal (i. e., pregnancy) limits. Finely divided cells tend to a marked degree to reconstruct along normal groupings and configurations. *Chem. Abst.* 18, 1893.

512. (SEX) **A propos de la cause du virilisme (The cause of virilism).** Baudoin (M.) *Bull. d. l'Acad. Méd. (Paris)* 1916, 76, 296-97.

A brief article noting a case of sex inversion in a bird, due to diseased ovaries.—R. G. H.

513. (SEX) **Further experiments on the sex of parthenogenetic frogs.** Loeb (J.) *Proc. U. S. Nat. Acad. Sci. (Washington)*, 1918, 4, 60-62.

This is a continuation of Loeb's well-known earlier experiments in which unfertilized frog's eggs were made to develop by pricking. With careful precautions to avoid accidental semination of the eggs and with adequate controls the experiments were repeated. Twenty leopard frogs parthenogenetically produced have lived from 10 to 18 months. In nine of these which had reached adult size the sex was determined. Seven were males and two females.—R. G. H.

514. (SEX GLANDS) **Luteal cells and hen-feathering.** Boring (A. M.) and Morgan (T. H.) *Jour. Gen. Physiol. (Balt.)* 1918, 1, 127-131.

Other work has shown that in the ovary of the hen there are groups of cells (luteal cells) which produce a yellow pigment reacting similarly to the luteal pigment of the corpus luteum of the mammal. These cells are absent in the testes of the adult male fowl. Removal of the ovaries leads to the assumption of full male plumage by the female. In the present paper similar luteal cells are demonstrated in the testis of the Sebright cock which is feathered like the female (hen-feath-

ered). Castration of the Sebright cock causes him to assume the plumage of the ordinary male fowl. It was concluded therefore that the secretion of the luteal cells suppresses in the hen and in the Sebright male the characteristic cock-feathering.—L. G. K.

515. (**SEX GLANDS**) Multiple neurofibromatosis (von Recklinghausen's disease) and its inheritance: with description of a case. Preiser (S. A.) and Davenport (C. B.) *Am. J. Med. Sc.* (Phila.), 1918, **156**, 507-540.

An elaborate study of the topic is presented with the autopsy findings of a father together with a description of the disease in his son. An interesting feature in the latter is a delayed sexual development such as has been reported in several other cases of this disease.—R. G. H.

516. **SPLEEN** extract, A further note on the therapeutic value of. Harrower (H. R.) *Med. Rec.* (N. Y.) 1916, **89**, 1000-1001.

Reiterates a belief that it is of value in tuberculosis and malnutrition.—R. G. H.

517. **STATUS LYMPHATICUS**, Military aspects of. Ewing (J.) *Jour. A. M. A.* (Chgo.) 1918, **71**, 1525-30.

The article comprises a discussion of the anatomic characters, occurrence, clinical manifestations, pathogenesis and clinical diagnosis of this condition. Being of a general nature the paper does not lend itself to abstracting. The author believes that status lymphaticus is much more common than is generally recognized. It is suggested that in the adrenal hypoplasia characteristic of the condition lies, possibly, the key to its symptomatology. The cases described are suggestive of one stage of Timme's Syndrome. (See *Endocrin.* 1918, **2**, 209.)

Ewing concludes: "The present conditions in the military service in America, when numerous races and classes are brought under the draft, seem to offer quite unique opportunity of determining the economic and military importance of definite status lymphaticus and it is to this aspect of the subject, rather than to its possible ramifications, that the present note is directed."—R. G. H.

518. **STATUS THYMOLYMPHATICUS**. Mohr. *Berliner klin. Wchnschr.* 1918, **55**, 519.

Patients with status thymolymphaticus upon exertion very soon show signs of fatigue. As patients with myasthenia show

the same symptoms, Mohr examined at autopsy the thymus glands of certain cases of myasthenia. He always found pathological changes in the thymus and a "status lymphaticus" even when, during life, no trace of a disease of the thymus was to be detected.—J. K.

519. (TESTES) Störungen der inneren Sekretion bei Eunuchoiden. (Endocrine condition in eunuchoidism.) Voelkel (E.) Berliner klin. Wchnschr, 1918, 55, 345.

A man forty years of age exhibits adiposity and aplasia of the testicles. The other endocrine glands are normal. The article includes a speculative discussion of the etiology of the condition.—J. K.

520. (TESTIS) La radiotherapy des néoplasmes intra-abdominaux d'origine testiculaire (Testicular neoplasm successfully treated with radiotherapy). Bécclere (A.) Bull. d. l'Acad. Méd. (Paris) 1916, 76, 72-81.

Of slight endocrine interest. The author shows that testicular neoplasms share with the gonad cells in their sensitiveness to radiations.—R. G. H.

521. TESTIS, Pathology and physiology of the interstitial cells of the. Freiberg (H. B.) Lancet-Clinic (Cincinnati), 1916, 116, 320-27.

An interesting review of the literature concluding with a brief study of a case each of cryptorchidism, feminism in a male and senility. The microscopic picture in the testes of each indicated that secondary sex characteristics depend upon the interstitial cells.—R. G. H.

522. (TESTES) Síndrome GASTROINTESTINAL del hipogenitalismo. (Gastro-intestinal syndrome of hypogenitalism). Hardoy (P. J.) Communication Asociacion Médica Argentina, Aug. 5, 1918.

Certain subjects with hypogenital stigmata present modifications of appetite, gastric dilatation, "heart burn," vomiting and constipation. Amelioration of the symptoms can be brought about by thyroid medication. The author theorizes to the effect that a lack of testicular hormone brings about a vagal hypothyroidism. (That the results secured are due merely to a non-specific general metabolic stimulation would be a more tenable hypothesis.—Ed.)—B. A. H.

523. **TESTIS, The pathology of the retained.** Doolin (W.) Med. Press and Circ. (Lond.) 1917, 103, 369-372.

A general discussion.—R. G. H.

524. **(THYMUS.) A demonstration of an enlarged thymus with an anomalous vena innominata.** Falls (F. H.), Tr. Chicago Path. Soc., 1915-16, 10, 57.

Report of case of an infant that lived only four hours. The thymus measured \pm cm. broad by 5.5 cm. long. The left innominate vein passed over the anterior surface of the thymus instead of occupying its normal position posteriorly. The trachea was compressed by the enlarged thymus. The adrenals and hypophysis showed no gross nor microscopic lesions and were normal in size.—J. P. S.

525. **(THYMUS) Centributo allo studio e all terapia dell'ipertrofia timica (The therapy of thymus hypertrophy).** Gismondi (A.) Gaz. d. Osped. e d. Clin. (Milan) 1916, 37, 1634-37.

The author discusses at some length the mechanical features of thymus hypertrophy, including tracheal compression and also compression of the veins of the head, neck and arm, leading to congestion of the thymus itself, congestion of the bronchial mucosa and, by interfering with pulmonary flow, leading to partial asphyxia. From this cause a fatal asphyxia may develop at any time. Painting the skin with iodine has been successful in the author's experience in causing a retrogression of the hypertrophy. In older children the X-ray is very useful but should be employed with caution, 5 or 6 H. units being a maximal single dose, and 20 a maximal total. An aluminum filter should be used. The favorable results of Franchetti and Penele with adrenin or adrenin and pituitary extract are mentioned.—R. G. H.

526. **THYMUS death.** Law (F. M.) Am. Atlas Stereoroentgenol. (Troy, N. Y.) 1916, 1 (i) 29.

A remarkably fine skiagram of the thorax of a three year old child who died under anesthesia. Thymus enlargement is well shown.—R. G. H.

527. **(THYMUS) Die Funktion der Thymusdrüse. (On the function of the thymus.)** Hart (C.) Jahrbuch f. Kinderheilk. (Berlin), 1917, 84, 318.

Atrophy of the thymus causes retardation of growth. The development of the thymus is dependent on the general devel-

opment of the body. In chronic paedatrophy the thymus is generally very small. Regeneration of an atrophic thymus is never seen.—J. K.

528. **THYMUS.** Eine neue Funktion der inneren Secretie der Tymusdrüse. (A new function of the internal secretion of the thymus.) Del Campo (E.) Ztschr. f. Biol. (München) 1918, 68, 285.

Muller has proved that a fatigued muscle of a frog acquires new vigor after being injected with thymus extract. Del Campo has repeated these experiments with mammals and obtained the same results. If the nervus ischiadicus of a rabbit is stimulated every four seconds and the contractions of the musculus soleus are registered the contractions soon become smaller. They reach their original height again after an injection of thymus extract into a vein. It was proved that this extract does not act on the muscle directly but on the nerve, for when stimulation of the nerve does not cause further contraction, stimulation of the muscle still gives rise to a strong contraction. Therefore Del Campo concludes that exhaustion of a muscle is caused by exhaustion of the nerve and not of the muscle itself, hence the action of thymus extract is on the nerve. The author points out that these facts may prove of some clinical value, for we know that extirpation of the thymus in animals causes myasthenia.—J. K.

529. **THYMUS enlargement, Report of two cases of.** Skagus (C. S.) Lancet-Clinic (Cincinnati) 1916, 115, 246-7.

A brief discussion of the condition with superficial case reports.—R. G. H.

530. **(THYMUS) Further proof of the existence of a specific tetany-producing substance in the thymus gland.** Uhlenhuth (E.) Jour. Gen. Physiol. (Balt.) 1918, 1, 33-36.

The condition of tetany produced in salamander larvae by an exclusive diet of thymus, was shown to be due to a specific tetany toxin and not to a dietary deficiency, since tetany also developed in those animals that received earthworms in addition to thymus gland in their food. Thymus feeding also does not retard metamorphosis, as some believe, the retardation in such experiments being due to the restricted diet.—L. G. K.

531. **(THYMUS) Grave osteoporosi infantile associata a sclerosi del timo (Grave osteoporosis associated with sclerosis of the thymus).** Lanzarini (F.) Riv. di clin. pediat. (Florence) 1916, 14, 393-418.

Abstracted from La Pediatria, Endocrin. 1917, 1, 540.

532. (THYMUS) On the role of the thymus in the production of tetany. Uhlenhuth (E.), Proc. Nat. Acad. Sci. (Balt.), 1917, 3, 517-518.

Salamander larvae fed exclusively on thymus invariably developed tetany, the symptoms being the same as those produced in mammals by parathyroidectomy. It is suggested that the thymus contains the substances which cause tetany and that it excretes them into the body, from which they are removed by the parathyroids. Extirpation of the latter would thus cause tetany. Tadpoles, which develop parathyroids a few days after hatching, have never been known to develop tetany when fed with thymus. Since salamander larvae have no parathyroids they at once exhibit symptoms of tetany on feeding with thymus, but at metamorphosis when parathyroid glands appear, the tetany ceases. Tetany was never obtained in metamorphosed salamanders, even when kept on an exclusive thymus diet.—L. G. K.

533. (THYMUS, PARATHYROID) The antagonism between thymus and parathyroid glands. Uhlenhuth (E.) Jour. Gen. Physiol. (Balt.) 1918, 1, 23-32.

Salamander larvae of several species were fed exclusively on calf's thymus. After a certain development stage, supposed to correspond to the establishment of secreting power in the animal's own thymus gland, tetany appeared in all the larvae. But at a later period, corresponding to the development of the parathyroid glands, all tetanic symptoms disappeared. It was concluded therefore that mammalian thymus gland contains a substance which is capable of producing tetany when fed to the larvae of salamanders. When the parathyroids develop they remove the symptoms of tetany, but in addition to these the salamander possesses another mechanism which during the larval period inhibits the production of tetany by the animal's own thymus gland. In one species (*Ambystoma tigrinum*) this mechanism is sufficient to prevent tetany even when the larvae are fed with thymus.—L. G. K.

534. (THYMUS) The cause of sudden death in status lymphaticus. Symmers (D.), Am. J. Dis. Child. (Chgo.), 1917, 14, 463.

Symmers thinks that sudden death in status lymphaticus may be brought about in at least two ways. The first and most frequent cause is of the nature of an anaphylactic reaction due to sensitization of the body by a specific nucleoprotein formed in the lymph nodes as the result of necrosis of numbers

of germinal follicles. Before the so-called anaphylactic incubation period has expired, the tissues are again subjected to the action of the same protein formed in the same type of tissue in response to an apparently trivial injury and in this way the anaphylactic reaction is completed. The second cause of sudden death is spontaneous rupture of a hypoplastic cerebral vessel, or rupture following trivial injury, the deficiency in the vessel wall being more noticeable in the muscular coat.

(The anaphylactic theory has not as yet been substantiated.—Reviewer).—M. B. G.

535. **(THYROID) A case of hyperthyroidism.** Jamison (S. C.) New Orleans Med. and Surg. Jour., 1917, 70, 805-7.

Reports a typical case.—L. F. W.

536. **(THYROID) A case of recurrent acute thyroiditis.** Sherris (C.) Guy's Hosp. Gaz. (Lond.) 1916, N. S. 30, 34.

A very brief case report.—R. G. H.

537. **THYROID and PARATHYROID glands, The.** Cobb (L. G.) Med. Press and Circ. (Lond.) 1916, 101, 516-19.

An interesting general discussion not amenable to abstracting.—R. G. H.

538. **THYROID and THYMUS enlargement, X-rays in the diagnosis and treatment of.** Quimby (A. J.) and Quimby (W. A.) Med. Rec. (N. Y.) 1917, 91, 13-16.

The authors regard the association of the two glands in enlargement as so common that both should always be considered in case of treatment of either. In the young the X-rays should be used with caution. No dogmatic rules as to dosage are practicable. The response to radiation may be very prompt. The various goiters often are markedly benefited. Malignant neoplasms may be helped. In the latter the treatment should be vigorous. Much care should be devoted to protecting the skin from unnecessary exposure to the rays. For various practical details the original should be consulted.—R. G. H.

539. **(THYROID) Antero and retro-active amnesia following thyroidectomy.** Davis (D. L.) Med. Herald (St. Joseph, Mo.) 1916, 35, 388-91.

Davis describes at some length the case of a woman of 56 who, following a thyroidectomy, developed amnesia. This out-

come was thought by the author to be due to liberation of an unusual amount of thyroid secretion through operative trauma. A considerable amount of theorizing is included.—R. G. H.

540. (THYROID BLINDNESS) *Ceguera en hipotiroidea—mejoria por glandotrina. (Hypothyroid blindness—amelioration by glandothyrene.)* Mussio Fournier (J. C.) *Rev. Méd. del Uruguay* (1918), —, —. (July.)

Diagnosis of ophthalmia and optic neuritis was made by exclusion and by brilliant results of treatment with glandothyrene. Only restricted vision of the left eye remained. After treatment the visual acuity increased from one-fifth to one-third.—H. R.

541. (THYROID) *Cause and prevention of hairless pigs in the United States.* Welch (H.) *Montana Agr. Col. Expt. Sta., Cir.* 1917, 71, 37-47.

Welch concludes from experiments made with pigs that the cause of hairless animals, including pigs, lambs, goats and calves, is goiter which is itself produced by lack of I in the thyroid glands. KI fed to pregnant females prevents goiter in the offspring, and should, therefore, be used in regions where goiter is prevalent.—Chem. Abst. 12, 2091.

542. (THYROID) *Case of cystic goiter.* Moore (I.) *Proc. Roy. Soc. Med., Sec. Laryng.* 1917, 10, 34.

No details given.—R. G. H.

543. (THYROID) *Case of sclerodermia associated with Graves' disease, and later myxedema, conspicuously benefiting by implantation of human thyroid into the bone-marrow.* Little (E. G. G.) *Proc. Roy. Soc. Med. (Lond.) Derm. Sec.* 1916, 9, 69-73.

This case is of interest both on account of the findings and because the report covers the period from 1902 to 1916. The husband had kept a careful diary of the patient's condition. In 1902 marked symptoms of Graves' disease were present. In 1907 these had partially subsided. Sclerodermia was first recorded in 1910; it soon became very marked. Thyroid medication was of relatively slight benefit. In 1911 a graft from "a case of goitre" was placed by Kocher in the tibia. Iodothyrene was also given. In 1912 a second similar graft was inserted in the other tibia. The iodothyrene treatment was continued. In

1916 the sclerodermia although not completely cured was much improved. There seemed to be in this case a definite relationship between sclerodermia and hypothyroidism.—R. G. II.

- 544. (THYROID) Cases of hyperthyroidism. (Discussion.)**
Weinberger (W. B.) *Dental Cosmos* 1917, **59**, 625-626.

Increased bone growth creates space between teeth, especially apparent in the maxillary premolar region manifesting separation of the teeth and over-development of the dental arches. There are undoubtedly a number of such cases in which orthodontists attempt to close such spaces without realizing their endocrine etiology.—V. J. P.

- 545. (THYROID CRETINISM) Entstehung des endemischen Kretinismus nach Beobachtungen in des ersten Lebensjahre.**
(Cretinism in infants.) Diviak (R.) and Wagner von Jauregg (J.) *Wien. klin. Wchnschr.* (Vienna) 1918, **31**, 149.

This is a most important article. Whether cretinism can be a congenital disease is an old question. The essays of the older authors are of no value in deciding this, since they did not know the difference between idiocy and cretinism. Diviak and Wagner von Jauregg examined all the children of a small village in Austria. In this village 8.6% of the children are cretins. They examined the children as soon as possible (i.e. 2 months) after birth and re-examined them when possible until they were four years of age. It was found possible to discover in very young infants the signs of cretinism; the most important symptoms are a flat nose and macroglossia. The growth is much retarded; the great fontanel never closes before the 13th month and is at times open even until the 36th month.

The authors are convinced that cretinism is often a congenital disease.—J. K.

- 546. THYROID deficiency, The relation of chronic infection to.** Beek (H. G.) *Southern Med. Jour.*, 1918, **11**, 492-95.

During the past three years the author has examined all patients suffering with chronic ailments, for disturbances of the ductless glands. He believes that glandular hypofunction is common in these patients and the condition is often associated with focal infections. The thyroid, adrenals, pituitary and gonads were affected in about an equal number of patients.

—L. F. W.

- 547. (THYROID) Discussion on the soldier's heart.** McKenzie (J.), Wilson (R. M.), Poynton (F. J.), Stoney (Florence A.),

etc. Proc. Roy. Soc. Med. (Lond.) Sec. Therap. and Pharm., 1916, 9, 27-60.

In this symposium the possible thyroid etiology of "soldier's heart" was referred to several times. Dr. Wilson (p. 39) observed thyroid enlargement in about one-ninth of his cases. Thyroid medication seemed to augment the symptoms. Dr. Poynton (p. 43) emphasized the probable benefit to be derived from X-ray treatment of the thyroid in any cases in which this gland might be at fault. Dr. Stoney (p. 50) laid considerable stress on the thyroid factor in these cases and on the great value of X-ray treatments of the gland. Altogether the data brought forward in this discussion and in other papers appearing more recently indicate that the thyroid does not play a major role in the condition discussed.—R. G. H.

548. THYROID disease, Ambulatory types of. Bertine (Eleanor) Med. Rec. (N. Y.) 1916, 90, 895-96.

This is an interesting semi-statistical study of the thyroid cases passing through the Cornell Thyroid Clinic in eleven months. The cases numbered 134, distributed as follows: (a) Simple goiters, 9; (b) Thyroid activity dominating the clinical picture (tremor, tachycardia, etc.), 65; (c) Depression, physical and mental, dominating, 27; (d) Mixture of activity and depression, 33. The author points out that simple changes of the quantitative aspects of secretion can not account for these findings. She regards them as indicating that other endocrine glands are involved. Jamney's recently propounded theory that so-called "hyperthyroidism" is essentially a combination of dys- and hypo-thyroidism would seem more profitable as a working hypothesis.—R. G. H.

549. (THYROID) Distiroidismo hereditaria y familiar presentandose con manifestaciones individuales contradictorias (Hereditary and familial dysthyroidism with individual, contradictory manifestations.) Ricaldoni (A.) Anales Facultad de Med., Montevideo, 1917, 2, 669.

Several instances of hereditary thyroid malfunctioning are discussed. In one family a young man, his mother and his aunt all had exophthalmic goitre. In another one brother had exophthalmic goiter and the other myxedema. In a third family it was possible to trace a pigmented retinitis and a dysthyroidism through three generations. The conditions were transmitted independently. The author believes that there is a constitutional dysthyroidism which may evolve in opposite types of thyroid malfunction.—B. A. H.

550. **(THYROID EXOPHTHALMIC GOITRE)** Deux cas de goitre exophtalmique survenus a la suite d'une commotion nerveuse. (Two cases of exophthalmic goiter following excitement). Babonneix (L.) et Célos. Bull. de la Soc. Méd. des Hôpitaux (Paris), 1917, 3. s., 41, 738.

551. **(THYROID) Exophthalmic goiter.** Bram (I.) Arch. of Diag. (N. Y.) 1917, 10, 343-61.

Discusses the comparative advantages of medical treatment for exophthalmic goiter and advocates surgical interference only in the presence of malignancy or pressure symptoms. The dangers of operative treatment and the possibilities of recurrence are considered; also the chance of postoperative myxedema and tetany. The writer maintains that improvement following the operation is probably due to the postoperative non-surgical treatment.—L. F. W.

552. **(THYROID) Exophthalmic goiter.** Cobb (I. G.) Med. Press and Circ. (Lond.) 1916, 101, 540-44.

A general discussion emphasizing the need of versatility in treating the disease.—R. G. H.

553. **(THYROID) Etiologia da polyarthrite alveolo dentaria Endocrinismo (Endocrine etiology of arthritis with pyorrhea alveolaris).** Lima (C.) Rev. dos Cursos (Porto Alegre) 1918, 4,, (No. 4.)

The author regards the arthritis in these cases as due to action of the noxious factor primarily upon the endocrine glands leading especially to depressed function of the thyroid gland.—B. A. H.

554. **(THYROID, EXOPH. GOITRE)** Goitre exophtalmique provoqué par le traitement thyroïdien. (Exophthalmic goiter induced by thyroid medication). Alfred-Khoury. Bull. Soc. Méd. des Hôpitaux (Paris), 1916, 3. s., 40, 1282.

Description of a single case.

555. **(THYROID) EXOPHTHALMIC GOITER, The new status of.** Reede (E. H.) Med. Rec. (N. Y.), 1917, 91, 450-55.

A review of recent pertinent American literature, clinical and experimental. No new data are presented.—R. G. H.

556. **(THYROID) Exophthalmic Goiter.** Sloan (E. P.) Ill. Med. Jour. (Chgo.), 1917, **34**, 155-7.

Nothing new.—L. F. W.

557. **(THYROID) EXOPHTHALMIC GOITER, Experimental lesions in the cervical sympathetic ganglia in relation to.** Wilson (L. B.) Am. J. Med. Sc. (Phila.) 1918, **156**, 553-57.

Wilson has found the goat to be an exceptionally favorable animal for the study of thyroid problems on account of the close resemblance of that gland to that of man. In 19 cases experimental studies were completed. The superior cervical sympathetic ganglia were exposed and stimulated either electrically or by injections of various sorts of bacteria. It appeared that irritation of the ganglia may produce histological pictures in the ganglia themselves and in the thyroid which parallel those found in various stages of progressive and regressive exophthalmic goiter. This evidence supports the suggestion which Wilson has previously offered that exophthalmic goiter is due to overstimulation of the thyroid gland via the nerve supply and as a result, usually, of a local infection in the cervical sympathetic ganglia.—R. G. H.

558. **(THYROID) EXOPHTHALMIC GOITER; The early diagnosis of.** Witherspoon (J. A.) Texas S. Jour. of Med. (Ft. Worth), 1917, **13**, 109-11.

Carefully reviews the early symptoms of exophthalmic goiter, and urges close observation of the so-called minor symptoms in finally establishing diagnosis. The importance of painstaking study and a complete history of each case is emphasized.—L. F. W.

559. **THYROID gland, A differential history form for enlargements of the.** Cristopher (F.) Med. Rec. (N. Y.) 1917, **92**, 985-87.

Describes an elaborate chart.—R. G. H.

560. **THYROID gland, Diseases of the.** Blain (A. W.) Internat. J. Surg. (N. Y.) 1916, **29**, 46-7.

A brief historical account.—R. G. H.

561. **THYROID gland, Embryology, anatomy, histology and chemistry of the.** Blain (A. W.) Internat. J. Surg. (N. Y.) 1916, **29**, 17-19.

Nothing new.—R. G. H.

- 562. THYROID gland, Some functions of the, and their relationship to goiter.** Peru (S.) Med. J. Australia (Melbourne) 1916, (i) 482-4.

A general article emphasizing the idea that the thyroid has a diversity of functions and that it has an important influence upon calcium metabolism.—R. G. H.

- 563. (THYROID) Goiter among the Indians along the Missouri.** Hrdlicka (A.) Science, 1916, n. s. 44, 203-4.

The author calls attention to a unique opportunity to study the etiology of goiter in a restricted locality and in a restricted group of the Sioux Indians. The incidence of the disease in this particular group is very high. It is not a tribal peculiarity; it does not extend far along the river, so far as known, nor are the white inhabitants of the same region similarly affected. Goiter among the Indians, the author concludes, is not connected with cretinism or myxedema.—R. G. H.

- 564. (THYROID GOITRE) Apropos du goître.** Roux (C.) Correspondenz-Bl. f. Schweiz. Aerzte (Basel) 1918, 48, 369.

In a very short article Roux describes the splendid effect of very small doses of iodine on goitre in children, pigs and dogs.—J. K.

- 565. (THYROID) Goitre, cretinisme et myxodéme dans les Hautes-Vosges (Goiter and hyperthyroidism in the Vosges region).** MacAuliffe (L.) Bull. d. l'Acad. Méd. (Paris) 1916, ..75, 127-29.

The author examined the school children of this district as to the condition of their thyroid glands. 2311 were examined in all. Of these, 288 had notably enlarged glands, 18 had large goiters, 3 were cretins, 2 were on the border line of cretinism, and 4 showed myxedema. No very definite evidence as to the cause of the condition was discovered except, perhaps, that rain and snow water with, of course, low mineral content was used. Hygienic conditions were good. Consanguineous marriages were infrequent. No meat, practically, except pork was utilized.—R. G. H.

- 566. (THYROID) GOITER, Pathology of.** Ellis (A. G.) Texas Med. Jour. (Austin), 1917, 33, 436-41.

The author summarizes the recent work that has been done to show the clinical relationship between the pathology and symptoms of goiter. Parenchymatous, cystic and adenomatous goiter are often but different periods in a chronic process, marked by atrophy of the essential cells and lessened function.—L. F. W.

567. (THYROID) Goiter, seventeen cases of, treated with injections of carbolic acid, iodine and glycerine. Sheehan (J. E.). *Med. Rec. (N. Y.)* 1917, **92**, 591-92.

The cases are reported very briefly. Results are regarded as satisfactory.—R. G. H.

568. (THYROID-GOITRE) Strumektomie nach de Quervain. (De Quervain's goitre operation.) Lommel. *Correspondenz-Bl. f. Schweiz. Aerzte (Basel)* 1918, **48**, 273.

The chief technical points involved are the ligation of both arteriae thyreoideae inferiores and some of the branches of the arteria thyreoidea superior followed by resection of the greater part of the thyroid gland. Only the isthmus and the arteria thyroidea ima need be left. The results seemed to be favorable.—J. K.

569. (THYROID GOITRE) Technik der Kropfoperation. (The technique of operation for goitre.) Wilms. *Munch. med. Wehnschr. (Munich)* 1918, **65**, 314.

Description of the operative technique employed in 2000 cases treated in the past four years. Of these 759 were operative cases. There were two deaths, one of acute tetany and the other of pneumonia.—J. K.

570. (THYROID) GOITER. The relation of mouth infection to. Reede (E. H.) *Washington Med. Ann.* 1916, **15**, 230-36.

The author recounts several instances in his experience in which mouth infection has been accompanied by thyroid abnormalities, particularly exophthalmic goiter, and in which marked improvement followed treatment of the infections.

—R. G. H.

571. (THYROID GOITRE TREATMENT.) Contribution a l'etude de l'etiology du goitre endémique. Le traitement du goitre par la désinfection intestinal continue au benzonaphthol. (Etiology of endemic goitre. Treatment by intestinal disinfection with benzonaphthol.) Messerli (E.). *Rev. Méd. de la Suisse Romande (Geneva)*. 1918, **38**, 248.

The author describes cases of goiter in which the administration of benzonaphthol as intestinal antiseptic has been of great service. He sustains the views of McCarrison as to the toxic origin of goiter. He advises the combination of iodine treatment with intestinal disinfection.—A. L. T.

572. (THYROID GOITRE) Vom Kropf in der Schweiz. (Goitre in Switzerland.) Hunziker (H.) *Correspondenz-Bl. f. Schweiz. Aerzte* (Basel) 1918, 48, 247.

The frequency of goitre depends principally upon the climate and upon the flora. All other theories are improbable. The author finds it necessary to try systematically the effect of very small doses of iodine on goitre. These experiments must be carried out on a great number of patients.

See Abstract No. 212, *Endocrin.* 1918, 2, 204.—J. K.

573. (THYROID) GRAVES' DISEASE and sympathicectomy. Chastier (A.) *Med. Press and Circ.* (Lond.) 1916, 101, 57-58.

A short paper emphasizing the advantages of resecting the superior cervical ganglia for the cure of Graves' disease. Two cases are reported in which excellent results were secured. The author regards the operation as the logical one on the grounds that the normal stimuli to the thyroid pass via the ganglia mentioned. As a matter of fact this is by no means an unquestioned statement; that the thyroid gland is subject largely to non-nervous control is possible if not probable.—R. G. H.

574. (THYROID) Hyperthyroidism. Morris (M. F.) *Med. Rec.* (N. Y.) 1917, 92, 895-97.

A general review.—R. G. H.

575. (THYROID) Hyperthyroidism. Clinical studies in. Watson (L. F.) *Med. Rec.* (N. Y.) 1917, 91, 411-12.

Data reported elsewhere. See *Endocrin.* 1917, 1, 178, 374, 1918, 2, 74 (No. 62).

576. (THYROID) Hyperthyroidosis associated with gynecomastia. Freeman (J. K.) *Therap. Gaz.* (Detroit) 1916, 3 s. 32, 9-14.

A description of a case, a man of 37, in whom the association occurred. A review of the literature on gynecomastia is included but references are mostly lacking.—R. G. H.

577. **THYROID in gynecology, The.** Hayć (H. E.) *Am. Jour. Obst.* (N. Y.) 1917, **76**, 958.

The purpose of the author in presenting this paper was to point out some of the conditions in the female, in which the administration of thyroid extract is of value, for the ill-determined hemorrhages in women, where the causes are obscure, until a diagnosis can be established and the best kind of subsequent treatment decided upon. Three cases are cited.

Case I. Woman, age 43, always bled freely at her periods, continuous slow loss of blood during the last ten months, excessive hemorrhages at times. Extremely pale and anemic, loud anemic murmurs and usual picture of prolonged hemorrhage. Tentative diagnosis of myxedema was made. Thyroid extract (B. W. & Co.) in increasing doses was given. Bleeding became less and strength began to return. Four weeks later a myxomatous uterine polyp was removed without anesthetic. Patient recovered quickly and is now well. Thyroid with iron continued for two weeks in 2 grain doses.

Case II. M. J., age 20, weight 237 pounds. Brief, scanty menstruation at irregular intervals of five or six weeks. No pain. No menses in the past four months. She is of good color and still energetic in her work, but of late is nervous and depressed. Thyroid, 1 gr. tablets three times a day was prescribed, increased to 5 grs. and for a time 10 grs. three times a day. Normal menstruation was restored. She has continued 5 gr. tablets for months, and has menstruated regularly for over a year. She lost 22 pounds during the first six weeks' treatment.

Case III. Miss L., spinster, age 38; diagnosis of Raynaud's disease. Nitroglycerine, 1 100 grain; no improvement; discontinued after a few weeks. 1 gr. tablets of thyroid, three times a day prescribed as an experiment. Druggist by mistake gave her 5 gr. tablets which she took for four weeks. She developed a distressed and anxious look, breathed with difficulty, pulse 130, skin cold, clammy, muscles of the face twitched, hands and legs clonic. Drug stopped and toxic symptoms soon passed away. In a few days thyroid in $\frac{1}{2}$ grain and then 1 grain doses was ordered three times daily. Nervous symptoms again developed; thyroid diminished and kept up with the smaller dose for several months. The menstrual flow decreased to normal, the affected parts became pale, and the tingling stiffness and soreness of the digits passed away. Both the hands and the feet became normal in color and function. Thyroid continued.

The results suggest the possibility of explaining Raynaud's gangrene as due to disturbance of the glands of internal secretion which causes the spasticity of the terminal vessels involved.

By the administration of thyroid a balance may be brought about, so that the circulation is restored to normal limits.

—W. II.

578. (THYROID) Injerto de tiroides en una caquexia estrumi-
priva. (Graft of thyroid in cachexia thyreoprivo.) Lenzi
(L.) *Semana Méd. (Bs. Aires)*, 1918, 26, 61.

A part of the thyroid was removed in a woman having exophthalmic goitre. Severe symptoms of thyroid and para-thyroid insufficiency developed. Lenzi then made a homograft with successful results.—G. P. G.

579. (THYROID) Manic depressive insanity or recurrent mel-
ancholia on a basis of dysthyroidism. Hamill (R. C.) *Med.*
Clin. Chicago, 1916, 2, 75. A typical case of Basedow's
disease, *Ibid.*, p. 85.

Hamill reports two cases which he contrasts as to their clinical manifestations. In the first patient, the basis of whose disease was believed to be a dysthyroidism, probably a hyperthyroidism, the manifestations of apprehension were mental in character. In the second patient, a typical case of Basedow's disease, the manifestations of apprehension were of a physical nature.—J. P. S.

580. (THYROID) MORBUS BASEDOW mit schwerer se-
kundärer Syphilis durch Salvarsan günstig beeinflusst.
(Graves' disease combined with syphilis benefitted by sal-
varsan). Stümpke (G.) *Deutsche med. Wchnschr. (Berlin)*
1918, 44, 969.

The influence of arsenic on Graves' disease is well known. In the case of combined Graves' disease and syphilis described all symptoms disappeared after seven injections of neosalvarsan.—J. K.

581. (THYROID MYXEDEMA). Sobre un caso de mixedema
congénito. (A case of congenital myxedema). Cafferata,
Semana Méd. (Bs. Aires), 1918, 26, 132.

Girl, seventeen years old. Wasserman negative. Cafferata showed two pictures of her, before and after thyroidin treatment, demonstrating marked improvement.—G. P. G.

582. (THYROID) Neurocirculatory asthenia. Robey (W. H.)
and Boas (E. P.) *Jour. A. M. A. (Chgo.)* 1917, 71, 525-28.

In this article the authors take issue with Harlow Brooks (Abst. No. 27, *Endocrin.*, 1918, **2**, 62) regarding the significance of the thyroid gland in neurocirculatory asthenia. They regard it as playing a minor role.—R. G. H.

583. THYROID operations, Recurrence after. Beebe (S. P.) *Med. Rec.* (N. Y.) 1917, **91**, 627-30.

A general discussion with citation of two specific cases.
—R. G. H.

584. (THYROID, OVARY) The changes in the central nervous system in hypothyroidism. Mott (F. W.) *Proc. Roy. Soc. Med.* (Lond.) *Sec. Pathol.* 1917, **10**, 51-59.

A somewhat speculative discussion of a case of myxedema with confusional insanity together with the microscopic findings in the central nervous system and various endocrine glands, as well as the general post-mortem findings. The patient died of broncho-pneumonia. The cells of the cerebral cortex, medulla, pons and basal ganglia showed a marked chromatolysis with partial or complete disappearance of the granules. The cell nuclei were often eccentric in position. The thyroid showed interstitial fibrosis and almost complete disappearance of the colloid. An unusual quantity of colloid was observed in the pars intermedia of the hypophysis. The suprarenal glands showed diminution of lipoid from the cortex cells. The ovaries were extraordinarily large and showed evidence of a high degree of reproductive activity. This case confirms the author's belief that myxedema is characterized by a condition of exhaustion of nervous energy, correlated with which is a marked deficiency of Nissl granules throughout the nervous system.—R. G. H.

585. (THYROID) Paralisis en una hipotiroidea. (PARALYSIS in a HYPOTHYROID.) Mussio Fournier (J. C.) *Rev. Méd. del Uruguay*, 1917, **20**, 617.

A patient of 47 years gave a family history of hypothyroid disturbances, such as headache, somnolence, sensitiveness to cold, mucio-tegumentary edema and antecedent apoplexy. The same conditions were noted in the patient himself. During an intense exacerbation of the symptoms paralysis of the extremities and of the face and rectus internus, together with ophthalmogenic migraine appeared. The absence of other demonstrable etiology, the paroxysmal character of the symptoms coincident with accentuating the hyperthyroidism manifestations

and amelioration under thyroid medication led to the conclusion that the hypothyroidism caused the paralysis. Some further theorizing is offered.—H. R.

586. (THYROID) Post-mortem findings in a case of exophthalmos of long standing originally due to Graves' disease. Mackinnon (R.) Brit. M. Jour. (Lond.) 1916 (i), 488-89.

The retro-orbital space was deep and filled with fat. Nothing specific was found bearing upon the causation of exophthalmos.—R. G. H.

587. (THYROID) Prophylaxie du goitre. Roux (Y.) Rev. Méd. de la Suisse Romande (Geneva), 1918, 38, 317.

Discusses iodine administration as a prophylactic measure.
—A. L. T.

588. (THYROID) Queratocono y secreciones internas (Keratoconus and the internal secretions.) Amoretti (E.) First International Congress of Medicine, Buenos Aires, 1916, 3, (fase. II) 426.

The author described four cases of which three presented symptoms of hyperthyroidism and one, of hypothyroidism. Amelioration followed the use of anti-thyroidine and thyroidine, respectively. The Abderhalden reaction was positive with thyroid and with thymus. The author believes that keratoconus is due to malfunctioning of the thyroid supplemented by that of the thymus.—B. A. H.

589. (THYROID) Radium therapy in hyperthyroidism with observations on the endocrine system. Aikins (W. H. B.) Can. Pract. and Rev. (Toronto) 1918, 43, 235-249.

Cases are cited in which hyperthyroidism was relieved by radium treatment. (See abstract in *Endocrin.*, 1918, 2, No. 2.) The greater part of the article consists of a discussion of the interrelations of the thyroid with the sex glands, and contains nothing new.—L. G. K.

590. (THYROID) Recherches sur le metabolisme minéral dans la maladie de Basedow. (Mineral metabolism in Graves' disease.) Kummer (R. H.) Rev. Méd. de la Suisse Romande (Geneva), 1917, 37, 439.

Kummer drew the following conclusions from an extended study of a typical case of exophthalmic goiter: (1) There ex-

ists a well marked lability and increase in mineral metabolism on a constant milk diet. (2) There is great fluctuation in mineral output in spite of a steady diet. These fluctuations parallel the clinical symptoms. (3) Variations occur in calcium, chlorides and phosphates, which are notably increased in the feces, while the urinary phosphates are about normal in amount. Calcium is increased in feces and about normal in the urine, which leads to a negative balance in calcium. The phosphate in the feces is alone equal to the phosphate in the food, while the phosphate in the urine is approximately normal, consequently the urinary phosphate must have come from metabolism leading to a phosphate depletion—assuming that phosphates in feces come from unabsorbed phosphates. An injection of iodide of calcium subcutaneously led to a temporary calcium equilibrium or even to a slight positive balance.—A. L. T.

591. (THYROID) Reumatismo crónico tiroideo. (Chronic thyrogenetic rheumatism). Servetti Larraya (J.) *Rev. Med. del Uruguay* (Montevideo), 1916, **19**, 829.

A rheumatic patient, 42 years old, had tophi. It was remarked that thyroid medication eased the pain and facilitated certain movements.—B. A. H.

592. (THYROID) Roentgen treatment of exophthalmic goiter. Nordentoft (S.) *Ugeskrift for Laeger* (Copenhagen), 1918, **80**, 1331, 1371.

Nordentoft reports fifty cases of exophthalmic goiter given roentgen treatment, and discusses the participation of the thymus. The roentgen exposure was made for from forty to sixty minutes, at one sitting. Two or three exposures generally sufficed, with intervals of from four to eight or six weeks. The subjective improvement was marked from the first, the restlessness, tremor and subjective heart disturbances subsiding first, the goiter and exophthalmos more gradually; the tachycardia last of all. Even in the most favorable cases, the patients still display an unstable pulse and tendency to tachycardia on slight provocation. In several cases the desired effect was realized with a single exposure. This method of a few large doses with long intervals may prove to be better adapted for certain cases than for others. In any event, it is far more convenient for all concerned than a larger number of smaller doses. His fifty patients were given a total of ninety-nine sittings; in eighty-four the thymus was exposed as well as the thyroid, as he is convinced that the thymus is a factor in certain cases of exophthalmic goiter. He cites a number of cases from the lit-

erature in which with exophthalmos and tremor, etc., the thyroid was of normal size while the thymus was much enlarged and the thymus under other conditions seem to have enlarged, and marked improvement followed thymectomy. The antagonistic action, but with exophthalmic goiter they seem to work in concert.

He presents series of data which sustain the assumption of a "thymus Basedow" and a "thymogenous exophthalmic goiter." If the thymus is mainly responsible, then removal of the thyroid would have little effect on the disease. The thymus is the organ that should be removed in such a case. This might entail spontaneous retrogression of the thyroid. These assumptions throw light on the 20 per cent. of failures reported in the larger statistics of thyroidectomies. He describes several cases of probable thymus origin, one in a man of 50 who had been under treatment for exophthalmic goiter two years before. The tachycardia, palpitations, slight exophthalmos, tremor, and Graefe's symptom, but no Moebius' symptom, were not accompanied by goiter, but they were so severe as to incapacitate him completely. His thyroid and thymus were given a single roentgen exposure, and within two months apparently complete health was regained and has persisted during the five months since.

Such experiences teach the necessity for applying roentgen treatment to the thymus as well as to the thyroid, or possibly to the thymus alone at the first sitting. Operative removal of the thyroid should not be done until after the failure of roentgen treatment, which Nordentoft says will be of rare occurrence. He queries whether it is not our duty to expose the thymus to the roentgen rays before any operation on the thyroid. In Solling's postmortem examination of eighteen exophthalmic goiter cases he found a persisting thymus in sixteen. The question also arises whether the cases of exophthalmic goiter that respond most promptly and favorably to roentgen treatment may not be those of thymogenous origin. Thymectomy is a dangerous operation, but the thymus is exceptionally sensitive to the roentgen rays. The effect begins to be apparent in about twenty-four hours. He reports some cases of spasm of the glottis with hypertrophied thymus, cured by roentgen exposure of the thymus. In conclusion he cites statistics showing 13 per cent fatal cases of exophthalmic goiter among 1,300 given medical treatment alone, and 25 per cent in the seventy-five cases at the Frederiks Hospital. In contrast to this is the zero mortality in Fischer's ninety-four and his own fifty cases given roentgen treatment. The full details of his fifty cases are tabulated. More or less benefit was realized in all and the improve-

ment has persisted to date; only a few have been lost track of.
Quoted.—*Jour. A. M. A.*, 1918, **71**, 1702.

593. (THYROID?) SCLERODERMIA, Case of edematous. MacLeod (J. M. H.) *Proc. Roy. Soc. Med., Sec. Derm.* 1917, **10**, 60-62.

A brief case report of a woman of 46 who a year previously had begun to show menstrual irregularities and, following their cessation, swelling of the face, arms, legs and later, feet and hands. The swelling disappeared to be followed by a progressive sclerodermia very widely diffused. Pigmentation about the axillae, elbows, groins and neck has more recently appeared. The hair in the regions affected by sclerodermia had partially fallen out. The case is regarded as one suitable for thyroid treatment.—R. G. H.

594. (THYROID) Sclerodermia occurring in a case of myxedema while under thyroid treatment. Sequeira (J. H.) *Proc. Roy. Soc. Med. (Lond.) (Dermatological Section)* 1915-16, **9**, 41-43.

A woman of 58 had been successfully treated for myxedema with thyroid medication for 15 years. She then developed sclerodermia, a disease for which, as the author points out, thyroid treatment has been strongly favored.—R. G. H.

595. (THYROID [?] SCLERODERMIA) Congenital sclerodermia and sclerodactylia. Coekayne (E. A.) *Proc. Roy. Soc. Med. (Lond.) Sec. Dis. Children*, 1916, **9**, 62-3.

A short report of a case in which thyroid medication was of no apparent utility.—R. G. H.

596. (THYROID) Sclerodermia with Graves' disease. Sequeira (J. H.) *Proc. Roy. Soc. Med., Dermatological Sec. (Lond.)* 1916, **9**, 66-7.

This case is of interest in that sclerodermia is often ascribed to thyroid deficiency whereas this patient showed marked evidence of "hyperthyroidism." It might serve as an example of "hypothyroid manifestation" in Graves' disease and cast some further doubt upon the theory that this disease is actually due to hyperthyroidism proper.—R. G. H.

597. (THYROID) Sobre atireosis. (Congenital myxedema). Strada (F.) *Rev. Universidad de Córdoba*, 1917, **4**, No. 6.

Strada reports the result of a detailed postmortem examination of a four-year-old myxedematous cretin girl who had died of bronchopneumonia. Complete absence of the thyroid, cystic tumor at the base of the tongue and four parathyroids of normal structure were noted. In the hypophysis (Wt. 0.8 gm.) the intermediate cleft was filled with colloid. Microscopically no alterations were seen in the neurohypophysis, which, however, was large. In the pars intermedia a colloid cyst was found. There were some chromophile cells in the anterior lobe of which the mass was made up of voluminous cells with clear protoplasm, sometimes slightly granular, pale in color, with vesicular nuclei lightly stained and round or oval in shape. The cell outlines were not sharp. Their appearance suggested the so-called "gravidic" cells. Skiograms of the bones showed an obscure line below that of the epiphysis. This, however, had not hindered growth when thyroid was administered.—B. A. H.

598. (THYROID) Sul morbo di Flajani—Basedow (Graves' disease). Mantella (G.) *Pensiero Med. (Milan)* 1916, **6**, 221-23.

A general discussion of the symptomatology and treatment is followed by a brief report of four cases treated with anti-thyroid serum. In three of these the results were favorable.
—R. G. H.

599. THYROID, Surgery of. Gatch (W. D.) *Jour. Indiana S. Med. Assn.*, 1918, **9**, 13-17.

Discusses the surgical treatment of goiter and emphasizes the importance of a careful study of each case. The Goetsch test (Adrenin cutaneous reaction) is especially valuable to determine the degree of toxicity. Operation should be discouraged in the presence of pulmonary tuberculosis, edema of the feet, ascites or mania.—L. F. W.

600. (THYROID) Surgery of the thyroid gland. Porter (C. A.) *Boston M. and S. Jour.* 1916, **175**, 551-557.

An interesting discussion of the technique of thyroidectomy together with indications for and results of the operation. Several instructive cases are discussed. The article does not lend itself to abstracting.—R. G. H.

601. THYROID, SYPHILIS of the. Thompson (L.) *Am. Jour. Syphilis (St. Louis)*, 1917, **1**, 179.

Review of the literature and report of a case. This is a rare condition but would probably be more frequently recog-

nized if looked for more systematically. It appears to be more common in women than in men, and may occur at any age. It may accompany either congenital or acquired syphilis. The histologic picture of early stages has not been described; later stages closely resemble tuberculosis of the gland. The clinical picture may present nothing but tumefaction of the gland, or there may be tachycardia and exophthalmos.—J. P. S.

602. THYROID, The alleged detoxicating power of. Bassinger (H. R.) *Jour. Infect. Dis. (Chgo.)*, 1917, **20**, 131.

Bassinger injected diphtheria and tetanus toxins directly into the thyroid gland. He was unable by this procedure to demonstrate any detoxicating action on the part of the thyroid.
—J. P. S.

603. (THYROID) The differential diagnosis of mild thyroid toxemia and incipient pulmonary tuberculosis. Jennings (C. G.) *Med. Press and Circ. (Lond.)* 1916, **101**, 423-24.

A general discussion. No new data.—R. G. H.

604. (THYROID) The etiology of the exophthalmos in hyperthyroid goitre. O'Day (J. C.) *Internat. J. Surg.* 1916, **29**, 312-13.

A theory is offered that the exophthalmos is due to stasis in the ophthalmic veins, due in turn to "tetany of the ventricles." No new evidence is offered.—R. G. H.

605. (THYROID) The hypothyroidic eye. With some notes on Napoleon's myxedema. Jacobson (A. C.) *Med. Times (N. Y.)* 1916, **44**, 207-209.

The author believes that such a term is desirable to describe the somewhat inconspicuous appearance of the eye in myxedema and cretinism as contrasted with the prominent eye in Graves' disease.—R. G. H.

606. (THYROID) The influence of certain factors on the incidence of endemic goiter. Mackay (N. D.) *Caledonian Med. J. (Glasgow)* 1916, **10**, 254-63.

A general discussion of the relative importance of geological conditions, species, race, heredity, age, sex, occupation and social state as factors in the incidence of endemic goiter.

—R. G. H.

607. (THYROID) The irritable heart of soldiers. Wilson (R. McN.) Brit. Med. Jour. 1916, (i), 119-20.

The author is somewhat skeptical of the theory that the thyroid plays a significant role in this condition.—R. G. H.

608. (THYROID) The isolation in crystalline form of the compound containing iodine, which occurs in the thyroid: its chemical nature and physiological activity. Kendall (E. C.) Tran. As. Am. Physicians (Phila.) 1916, 30, 420-49.

Data published elsewhere. See abstracts Endocrin., 1917, 7, 18, also 1918, 2, 81-93.

609. (THYROID) The life history of the thyroid apparatus. McCarrison (R.) Med. Press and Circ. (Lond.) 1917, 103, 307-9.

The article being itself a summary of existing knowledge—and probable hypotheses—is impossible to abstract satisfactorily. Among the points emphasized is that the human infant is dependent during the normal suckling period upon the mother's milk for its elaborated thyroid hormone, a fact which is not true of the calf, hence artificial feeding of infants with cow's milk necessarily leaves a thyroid deficit. If McCarrison's point is well taken, the addition of minute quantities of thyroid material to the milk of such infants should be made as a routine measure. The close relation of the thyroid with all phases of sex life is emphasized.—R. G. H.

610. (THYROID) The relation of the thyroid gland to epilepsy. Harrower (H. R.) Lancet-Clinic (Cincinnati) 1916, 116, 100-104.

The author believes that the thyroid gland because of its intimate relation to detoxication and to metabolism in general should be considered as a possible factor in the etiology of epilepsy. In cases in which evidence of thyroid deficiency is noted thyroid therapy can be expected to act as an effective adjuvant to other measures directed toward the epilepsy.

—R. G. H.

611. (THYROID) "The soldier's heart" and its relation to thyroidism. Barr (J.) Brit. M. Jour. (Lond.) 1916, (i), 544-46.

Barr regards the thyroid as being largely at fault in this condition. The influence of the gland is exerted primarily upon the calcium metabolism which in turn affects the action

of the heart. The condition first appearing is likely to be "hyperthyroidism" followed by hypothyroidism. Calcium preparations together with iodine and thyroid tablets are favored by way of treatment.—R. G. H.

612. **THYROID**, The relation of the to the other ductless glands. Kendall (E. C.) *Jour. Lancet* (Minneapolis) 1917, 37, 768.

Data reported elsewhere. See *Endocrin.* 1918, 2, 81-93.

613. **(THYROID) Tiroides aberrantes.** Jorge (J. M.) *Semana Méd.* (Bs. Aires), 1918, 25, 542.

Jorge presents two cases: (1) A woman having an aberrant thyroid at the base of the tongue between the muscles of the floor of mouth; (2) a girl having a similar gland in the muscles, between the lingual V and the epiglottis. The glands were extirpated.—G. P. G.

614. **(THYROID) Treatment of certain types of goiter with guinine and urea injections.** Watson (L. F.) *Texas M. J.* (Austin) 1916, 82, 153-158.

Data reported elsewhere. See *Endocrin.* 1917, 1, 178, 376.

615. **(THYROID) Trichomonose intestinal: cura pelos enteroclymas iodicosi Myxedema consecutivo; cura pelos thyroidina.** (Trichomoniasis intestinalis cured by iodine enteroclysis, followed by myxedema cured by thyroid medication). Ribeiro da Silva, *Brazil Medico* (Rio de Janeiro), 1917, 31, 24.

The first treatment was given successfully to cure a severe diarrhoea due to trichomoniasis, but it was followed by marked facial edema. This was ascribed to hypothyroidism. Upon instituting thyroid medication the edema in the course of a month cleared up.—B. A. H.

616. **THYROID tumor, An intrathoracic. Report of a case with autopsy findings.** Moses (H. M.) *Med. Rec.* (N. Y.) 1917, 92, 1025-26.

The tumor measured 14x8x6.5 cm. The patient had generalized arteriosclerosis, dying from a ruptured blood vessel of the colon. The thyroid played no apparent part in the symptomatology except as possibly interfering with the action of a poorly nourished heart.—R. G. H.

617. (THYROID). *Zur Joddarreicherung bei Kropf.* Crumme. *Correspondenzbl. f. Schweiz. Aerzte (Bern)*, 1916, **46**, 494.

Crumme claims that the administration of iodine benefits patients with endemic goiter, but does harm to those with Basedow's disease. Regions in which goiter is endemic are usually free from exophthalmic goiter. Crumme therefore believes that endemic goiter is due to a lack of iodine in the food. He recommends that Switzerland import sea-fish in abundance so that it may become generally used as a food. He believes that the rich iodine-content of this food would greatly reduce the incidence of goiter in Switzerland. The ancient Greeks recommended sponge charcoal, which is rich in iodine, in the treatment of goiter. Crumme warns against the use of iodine in those patients who show a tendency to Basedow's disease. Even eating sea-fish aggravates exophthalmic goiter.—J. P. S.

618. **THYROIDECTOMY, Partial.** An operation for transplanting and anchoring the remaining lobes of the thyroid gland. Hubbard (E. V.) *Med. Rec. (N. Y.)* 1917, **92**, 842-47.

Of technical surgical interest.—R. G. H.

619. (TONUS) Some attempts to produce experimentally conditions of sympathicotonus, vagotonus and hyperthyroidism. Troell (A.) *Surg. Gyn. & Obst. (Chgo.)* 1916, **22**, 81-92.

With certain modifications, Troell repeated the experiments of Cannon (1914), who reported that it was possible to obtain, through a "hyperstimulation" of one sympathetic brought about by fusion of the anterior root of the phrenic of a cat, with the cervical sympathetic nerve, the same symptoms that characterize Graves' disease in human beings. Troell united in the neck the proximal end of the phrenic nerve with the sympathetic or vagus. In order to escape the disturbing influence of the vagus fibres on the heart he made the anastomosis of the nerves in the thorax near the diaphragm.

In several individuals phrenic and one sympathetic were severed and then sewed together, so that proximal end of the former was connected with the distal end of the latter, immediately under or at the superior cervical ganglion; phrenic impulses of central origin would then influence chiefly the smooth muscles of the orbit of the eye. A second series of operations in the thorax consisted in cutting off the proper nerve-trunks and uniting the proximal end of the phrenic with the distal end of the sympathetic or vagus.

No unquestionable symptoms indicative of sympathicotonus, vagotonus or hyperthyroidism were found. Loewi's adrenalin test was negative in the five cases in which it was made. In the eyes no other symptoms were found than the customary effects (paralysis) on the operated side.

Equally unsatisfactory were the macroscopic and microscopic findings in the organs on autopsy. Numerous firm adhesions and strands of connective tissue were present; the intestines showed occasional saclike extensions and the mesenteric glands were enlarged, indurated and pigmented.—W. H.

620. VAGATONIA. Tonus problem und Vagatonie. Schmidt (R.) *Ztschr. f. klin. Med.* (Berlin) 1918, **84**, 89.

The author contributes a critique on the theory of vagatonia. If one is to believe in the theory of Eppinger and Hess, it is concluded, he should not know too much of clinical medicine, physiology and pharmacology. Most of their principles have never been demonstrated and some are demonstrably not valid.—J. K.

The abstracts in this number have been prepared by the staff assisted by:

W. E. Blatz, University of Toronto.

W. Harrison, Detroit.

L. G. Kilborn, University of Toronto.

V. J. Pollina, Boston.

Hector Rosello, Montevideo, Uruguay.

J. P. Simonds, Northwestern University, Chicago.

A. L. Tatum, Chicago.

L. F. Watson, Chicago.

With the permission of the editors, certain abstracts have been quoted from "Physiological Abstracts" and "Chemical Abstracts."

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