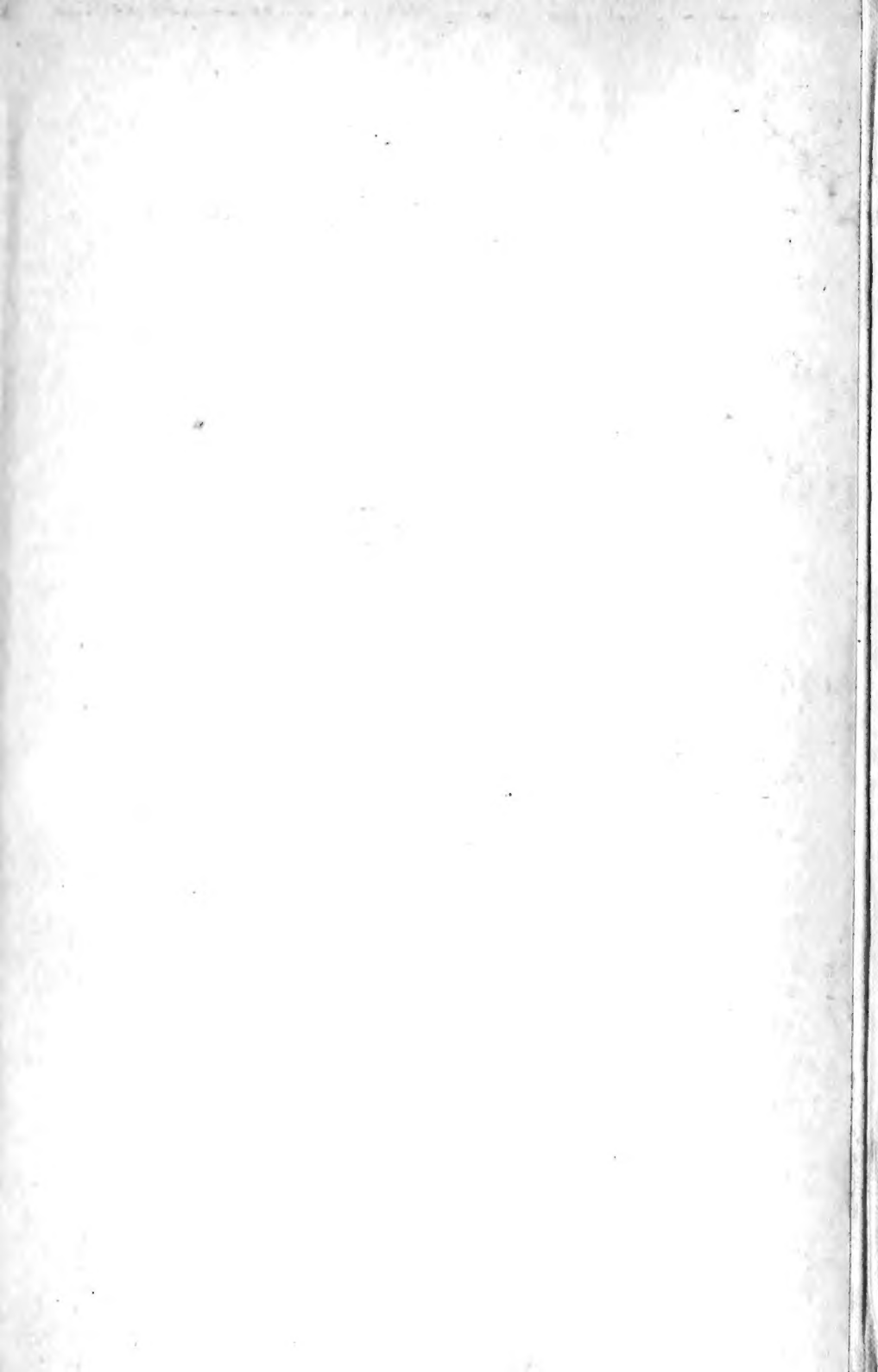
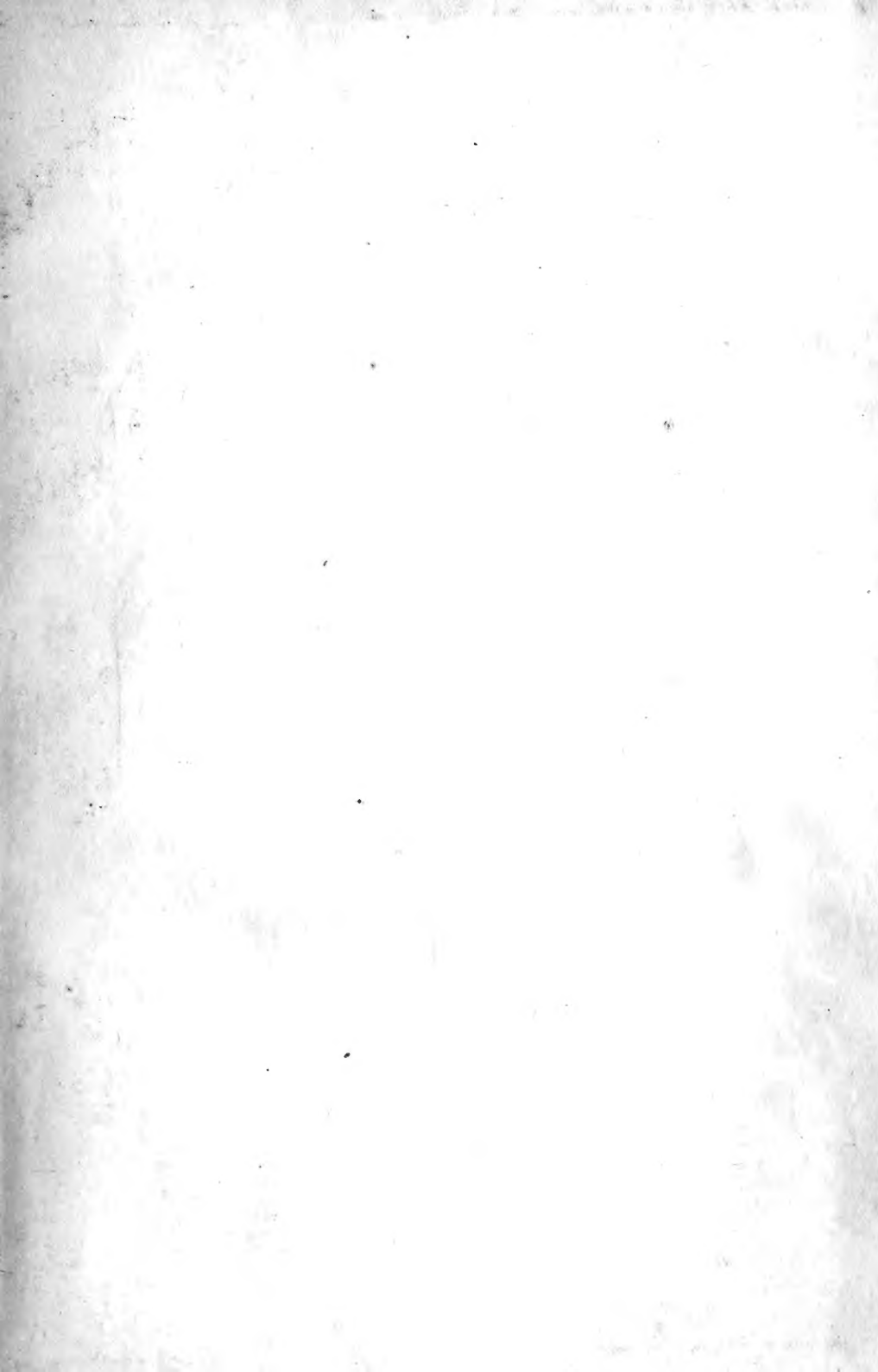


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ENDOCRINOLOGY:

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

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JANUARY, 1917

EDITORIAL ARTICLES

THE STUDY OF THE INTERNAL SECRETIONS: AN INTRODUCTION

THIS is the first number of a new medical journal, the first to be devoted entirely to the study of the internal secretions. In these days when the number of medical journals is being rapidly, and it is to be feared, sometimes needlessly, increased, it would seem incumbent upon those responsible for the appearance of another journal, to give the reasons that, in their opinion, justify its publication. And, this duty admitted, they have asked me to be their spokesman, a function that I willingly undertake since I am confident that if the high aims and purposes of the Editorial Board can be realized the cultivation of the science of medicine in one of its important branches will be stimulated advantageously and medical practice in the same domain will be improved correspondingly.

There has been, during the recent period, in no department of medicine more activity manifested than that which has characterized the study of the glands of internal secretion. The examination of the structure and functions of the endocrine glands in health and in disease has occupied a large number of careful investigators in all countries. Indeed, the interest in endocrinology has been widespread not only among alert internists and surgeons, but also among experimental pathologists and physiologists, pathological anatomists and histologists, comparative anatomists and embryologists, pharmacologists, and biological chemists. The nature of the ductless glands, previously obscure, has been recognized; and the new principle of a regulation and correlation of the functions of the different bodily organs by "chemical messengers," or "hormones" (in addition to the earlier recognized principle of nervous regulation), has been generally accepted.

As might have been expected, it has been the observations of clinical scientists that have given the initial impulse to researches bearing upon the endocrine glands. The discoveries of the relations of Addison's disease to the adrenal glands, of myxedema and of cachexia thyreopriva to the thyroid gland, of acromegaly and of dystrophia adiposo-genitalis to the hypophysis cerebri, and of eunuchism and of eunuchoidism to the sex-glands (or gonads), are instances of the fundamental contributions that the clinic can make to medical science.

Clinical scientists are ever making new observations that not only widen the perspective of their own subject, but also set new tasks to which non-clinical scientists may apply their efforts profitably.

And in the study of the whole chain of the hormonopoeitic organs (thyroid, parathyroids, thymus, hypophysis cerebri, epiphysis cerebri, chromaffin system, interrenal system, pancreas, gonads, etc.), non-clinical scientists have ably supported clinical workers and have, in addition, initiated independent lines of research that have led to discoveries of no less importance than the primary findings of the clinicians.

The bibliography of the subject of the internal secretions has grown so enormously that it has become unwieldy. Laudable and successful attempts have been made to arrange more or less systematically the results of all investigations in the form of collective reviews and of monographic presentations that simplify and facilitate an approach to the field. But each of these is out of date as soon as it is published, for new papers are appearing in widely scattered journals every week in the year.

In conjunction with the Association for the Study of Internal Secretions recently formed, it has seemed desirable that a bulletin be published in which contributions to knowledge in the domain of endocrinology may be promptly reported in summary. It is the object of the Association to promote the accumulation and diffusion of knowledge of all kinds bearing upon the endocrine glands and their functions. Papers on the subject appear, as has been said, in widely-scattered journals. There is, at present, no place in which a frequently and regularly recurring collective review of progress is accessible. Clinical reports are made in the clinical journals, pathological reports in archives devoted to pathology, and papers on structural and functional changes in the periodicals on anatomy and physiology. Valuable as these "cross-

sections" of endocrinological progress are, we need also a periodical repository that corresponds to a "vertical section" of the subject, a depot in which a review of every paper of importance, be it clinical, pathological, physiological or anatomical,—bearing upon the internal secretions, will be stored.

Workers in other domains of medical science have already recognized the value of special journals. Such periodicals have been provided already for the circulatory system, for the nervous system, and for the urogenital system—to mention only well-known instances. The interest in circulatory diseases has been definitely increased by the publication of journals like *Heart*, the *Archives des maladies du coeur*, and the *Zentralblatt für Herzkrankheiten*. There would seem to be every reason to believe that **ENDOCRINOLOGY**, the *Bulletin of the Association for the Study of Internal Secretions*, properly conducted, will also perform a real service in its special field. This bulletin will, I believe, be welcomed not only by clinical and laboratory investigators but also by our more alert general practitioners, for these men already realize the profound importance of an intimate knowledge of the ductless glands and their functions for every day work in diagnosis and therapy.

LEWELLYS F. BARKER.

THE FUTURE OF THE INTERNAL SECRETIONS

THE leading feature concerning the internal secretions which still lurks in the minds of most medical men is one that will ultimately, in all likelihood, prove to be the least important, viz., organotherapy.

Granting the far-reaching powers of the latter, when judiciously employed, and also the possibility that when organic agents will provide the actual physiological product of each gland the results obtained will far outstrip those now attainable; granting even that, as we have held, organotherapy may influence favorably some evil trends of heredity and react thereby against Nature's dastardly crime of "visiting the iniquity of the fathers upon the children unto the third and fourth generation"—eventually it will compare about as the moon does to the sun with the role of the ductless glands in the very life process itself and in disease. We are but on the threshold, through the avenues of thought it opens, of what, to the writer at least, appears as a new conception of Medicine—a Medicine befitting our dignity, our longing for logical reasoning and rationalism precisely where uncertainty and empiricism now reign supreme.

It will soon be fourteen years since the writer earnestly urged the American profession to devote some thought to this vast field, suggesting what appeared to him as fruitful avenues in the light of all the evidence then available and what personal observations, experimental and clinical, he could contribute. Time has shown that either through a happy concurrence of ideas, the teachings of experimental and clinical experience, or as offshoots, perhaps, of some of the seeds we had planted, many of the deductions therein set forth had a solid foundation. So distinctly has the trend of events sustained many of them, that it were vain to deny to-day that when Swale Vincent wrote some years ago: "Sajous apparently postulates a relationship between all the ductless glands whose functions dominate most of

the bodily activities. normal and pathological," he succinctly expressed the germ idea of what in the writer's belief, the future would demonstrate. Already it is beginning to appear that the progress of Medicine as a whole has been handicapped through the non-recognition of these structures which steadily are asserting their right to be classed with major organs, the heart, lungs, liver, etc., upon which all our labors have so far reposed. Their absence has seemed especially obscuring precisely where our role as physicians has demanded the greatest light, e. g., the pathogenesis of disease and the resources of the body to stay and offset its ravages.

In the great fields of neurology and psychiatry, to which work beyond computation and praise has been devoted, discouragement has remained the dominant note precisely where efforts on behalf of sufferers should have proved most telling. Nowhere has therapeutics remained less efficient. Indeed the growing proportion of feeble-minded and insane to the population attests to our inability to stem the tide. And yet, no single line of medical thought offers greater opportunity for development through the intermediary of the ductless glands. It may be recalled that we have long held that, in keeping with all other organs, the nerve-cell was a structure endowed with its own circulation, and that on the basis of methylene blue injections, the adrenal secretion, converted into an oxidizing ferment which was termed adrenoxidase, ascended the axis cylinder as tetano-toxin is known to do. Lichtwitz (1907-1908) likewise claimed the presence of adrenalin in nerves, though on vulnerable experimental evidence, as shown by Meltzer (1908); recently (1913), however,

Macallum and J. B. Collop, obviously unaware of the foregoing labors, also referred to a "new substance in nerve cells," particularly in sympathetic cells, which they deem "allied to adrenalin."

If the circulation of the nerve cell proves as real as present indications seem to suggest, it would open an era of inquiry and development in the neurological and psychiatric fields similar to that which followed Harvey's discovery of the circulation in the grosser tissues, for biological chemistry and histology have made possible in our time what for him was beyond reach. Indeed, with their aid Nature herself seems to prod us to see the truth by a multitude of examples. Even **red** blood may be found in the nerve ganglia of *Aphrodite aculeata*, a sea annelid, while the ganglia of certain Nemertine worms contain **hemoglobin** without red corpuscles. Briefly, if what the writer believes proves true, we must entertain the thought that colorless blood devoid of red corpuscles, the sole oxygenizing fluid in many lower forms, is as active in our nerve-cells (and other cellular elements, muscular, dental, etc.) as is the red blood which so far has captivated our thoughts. If to this oxidizing body other components of the tissues at large are also found in the nerve-cell—as ample evidence is already available to show—we cannot but hope eventually to understand morbid changes which at present can only be described. Psychiatrists will then be able to do better than declare, as in a recent text-book, that "as is true of mania, there is no known pathology for melancholia," a sentence which applies to practically the whole gamut of mental diseases. Such a development cannot but greatly enhance their therapeutic efficiency.

It is not alone the adrenal product, however, which sustains metabolism. From 1903 to 1907 we submitted evidence in support of our opinion that it did so in conjunction with the thyroid secretion (first associated with metabolism by Schiff) a trypsin-like ferment and nucleo-proteids, all distributed to tissue cells through the intermediary of leucocytes. Abderhalden (1905-1914) has independently reached very similar conclusions: "Everything points," says this observer, "to the fact that the [tissue] cell has agents at its disposal which render it capable of splitting up into their simplest units all the complicated substances which are brought to it or which it itself builds up." Again, "each separate cell, with very few exceptions, disposes of the same or similar ferments as those secreted by the digestive glands in the intestinal canal,"—those, as is well known, of the pancreas. As to the manner in which the tissue-cells are reached by these ferments, he writes: "Many facts accord with the suggestion that the leucocytes play a part in this connection." In keeping with what the writer had also held concerning the trypsin-like ferment, viz., that its proteolytic property was also the factor to which the phagocytes and the plasma owed their bactericidal and antitoxic activity, Abderhalden termed "defensive ferment" the digestive agent or agents referred to above, thus bringing "the so-called reactions of immunity into close line with processes that are normal and consequently familiar to the cells." Briefly, in keeping with what a deeper scrutiny of her methods seems to suggest, Nature, always economical in her ways and means, employs the same agencies (1) to prepare food stuffs for assimilation, (2) to convert the food and

tissue wastes into eliminable end-products, and (3) to break down pathogenic substances and organisms to convert them likewise into eliminable end-products.

If the full meaning of these few facts is apprehended, it will be seen that probably we have in the ductless glands a foundation for the solution of many questions which, though studied with utmost diligence by a host of able workers during the last seventy years, have not as yet found their solution. Indeed, experimental and clinical facts tend increasingly to show that our inability to stay death in many diseases is due to our ignorance of the role of the ductless glands in these morbid processes.

All this applies as well to another tenebrous branch, therapeutics. On a Mediterranean-transatlantic liner, some years ago, diphtheria reigned supreme in the sense that the antitoxin on board seemed to have lost its efficiency—owing probably to deficient reactive powers on the part of the obviously debilitated immigrant children affected. Night after night a child or two was buried at sea. In despair the ship surgeon sought our aid, and we suggested that calomel be given orally besides the injections of antitoxin. The burials promptly ceased. The ductless glands had reacted and poured into the blood autoantitoxin which, added to the exogenous antitoxin injected, won the day. Millions of such examples are available in the practice of our professional fathers who used calomel indiscriminately—so indiscriminately, in fact, that on the plea that since small doses did so much good, large doses should do more good, they steadily increased the dose, salivated and debilitated—and finally killed the

goose that laid the golden egg. The writer has long urged the powerful stimulating action of mercury upon the thyroid and adrenals and its remarkable property of stimulating actively through them the defensive functions of the body, mercury thus becoming what might be termed a **thyro-adrenal stimulant**, and also its pernicious influence in large doses on these glands.

Again, as is well known, digitalis, strophanthus and other agents of the same class, are supposed to owe their main beneficial influence to a direct action upon the heart. But we have long urged (1907) that these agents were **adrenal stimulants** and that their beneficial effects were due to this fact. Were it otherwise, why should Bezold and Boehm (1872) have arrested the action of digitalis by dividing the spinal cord and A. N. Richards and W. G. Wood (1915) have observed a similar inhibitive influence on the action of strophanthin and digitoxin by severing the splanchnic which is known to contain the secretory nerves to the adrenals? It has been shown also by Bedart and Mabilie (1898) and confirmed by Ewald, Macaggi and others, that we could control overactivity of the thyroid and its untoward effects by means of arsenic. We thus have in this metal a **thyroid inhibitor**, a term which might be applied to other remedies.

These few examples, to which many could be added, will suffice to show that, irrespective of agents such as alcohol, phosphorus, ergot, ether, etc., which only incidentally affect the ductless glands, there is a vast field of study available through which we may, perhaps, eventually learn to develop the main object which therapeutics should fulfill—that of **directing**

and controlling the defensive resources of the body.

Is there not ground for the hope that the internal secretions may thus fundamentally revolutionize medicine precisely where its needs are greatest, i. e., in the practical field?

C. E. DeM. SAJOUS.

ENDOCRINOLOGICAL PROBLEMS

CONSIDERABLE progress has been made in establishing endocrine syndromes. Of the thyroid gland, over-activity and under-activity; of the adrenal gland, under-activity; of the pituitary body, under-activity and over-activity both of the anterior and posterior lobe; something of the gonads, of the thymus, of the parathyroids, of the pancreas, we already know; but differentiation of a syndrome is only the a-b-c of the problem, which tells us nothing of the etiology, the knowledge of which is quite the most important requisite in dealing with a disease.

It is true that certain experimental observations do indicate the determinant of the secretory activity of certain glands. For instance, the excitation or inhibition of digestive hormone secretion under the influence of expectation or fear (Pawlow); the cytoplasmic exhaustion of various glands induced by terror, over-exertion and toxins (Crile); the out-pouring of adrenin under the influence of fear as measured by the effect of the blood from the adrenal vein upon non-striated muscle (Cannon). Still these known stimuli upon normal animals have effects which cease when the stimulus ceases.

Clinically we are far from knowing just what are the stimuli which maintain endocrine function, and

still less those which prevent it.

It may be useful to other workers to attempt orientation of some of the knowledge with reference to the etiological possibilities concerning different internal secretions as the writer envisages them. Accordingly there will be a discussion of the several endocrine syndromes from this special standpoint.

The Thyroid Problem. Even of the one gland of internal secretion the perversions of which have been most extensively and intensively studied, the thyroid, there is still the greatest uncertainty concerning the disturbing causes. Of hypotheses to account for its hypersecretion there are three classes, in support of each of which facts may be adduced.

That prolonged dread may produce thyroid hyperactivation should be a corollary of the experimental demonstration that acute fright does so; but clinical proof of this is not forthcoming: for there are many individuals chronically afraid in whom there is no hyperthyroidism. If fear then does produce hyperthyroidism, it must be only when special susceptibility exists

That heredity may furnish this susceptibility some believe on account of the fact that there are hyperthyroid families. The congenital cases, however, could be used not so much of the actual thyroid disorders as the susceptibility to its cause, if that were found.

The number of cases adduced in favor of the toxic and infectious origin of goiter is very large. Among these are its attribution to chemical alteration in the water supply (Marine and earlier observers).

Recently McCarrison has interpreted differently the belief in a water-borne etiology, and has brought

many cases in support of his view that it is infection with a colon bacillus contaminating surface water which accounts for the endemicity or apparent familiarity of goiter. Its variability of incidence he attributes to differences of individual resistance, the further assault upon immunity by an additional infection such as coryza or tuberculosis serving to render goitrous those individuals not previously so, even though already infected by colon bacilli.

Even if one of these theories is found true, the problem is not solved; for we have then to know whether the provocative agent acts upon the gland only by the medium of the sympathetic, or whether it does so directly chemically. Again we must know upon what portion of its chain the sympathetic is attacked and whether by a hormone or not. Finally it will be necessary to know whether the sympathetic is stimulated actively or whether it is not merely given free rein through interference with an antagonistic inhibitory system of nerves such as the vagal autonomic, a phenomenon the possibility of which has long been known with regard to the action of atropine upon the pupil.

TOM A. WILLIAMS.

THE PROSPECTS OF ANTERIOR PITUITARY THERAPY

FROM the time the apparently insignificant gland at the base of the brain was discovered and later called "the pituitary gland," because of its supposed direct connection with the nose and its power to produce "pituita" or mucus, this organ has been a source of considerable speculation.

It is not amiss still to attribute to this gland an element of mystery, for while our present knowledge of the pituitary is quite considerable, thanks chiefly to Cushing and his associates in Baltimore and Boston, there are undoubtedly several things yet to be learned about this really wonderful gland.

Much has appeared in the literature of the past seven or eight years concerning the infundibulum—that small portion of the hypophysis which constitutes perhaps one fourth of its total bulk and has a histological structure quite unlike that expected of a ductless “gland.” Especially have the therapeutic possibilities of the active principle obtained from the infundibulum come in for much discussion in the literature; and the range of its therapeutic utility is such as to cause no little surprise and skepticism, especially to one who is not informed of its numerous and varied therapeutic indications. When the story is told to the novice that not only will a certain remedy hasten labor in the startling manner to which most of the profession have now become accustomed, but will also prevent post-partem hemorrhage and uterine subinvolution; stimulate galactogenesis and, occasionally, abort a mammary abscess; increase heart action and raise blood pressure, thus exerting a salutary influence in shock or collapse; produce copious diuresis; act as a remarkably efficient enterokinetic and even as a “regulator” of certain functional disturbances of endocrine origin, the eyebrows are raised in astonishment and, maybe, the lips are somewhat upcurled! But all this is really so, none the less; and the posterior pituitary hormone under various names has sprung into surprising popularity because of its evident dependability in a dozen

widely differing circumstances.

In like manner the chemical agent present in the anterior or true glandular portion of the pituitary body, bids fair to establish itself as thoroughly as a useful addition to our therapeutic armamentarium; and, too, in quite a number of complicated and seemingly unrelated symptoms-complex.

Less than a year ago Brailsford Robertson and his associates in the University of California isolated from the anterior lobe of the pituitary a chemical substance which he called "tethelin." Its administration produces a striking effect upon growth; and while the majority of the experiences upon which the reports of these investigators were based were experimental rather than clinical, it is evidently quite true that "tethelin" (or anterior pituitary substance) is of prospective merit as a means of stimulating growth under suitable conditions.

Another line of investigation with the therapeutic application of this new remedy has been referred to by Richter, of St. Louis. In a report published but a few months ago (see p. 114) he states that this remedy has undoubted virtue as a means of controlling the main symptoms of Graves' disease. While Richter's cases are not numerous and their verification by others has yet to be accomplished, it seems undoubted that the heart-hurry, nervous manifestations and metabolic unrest are controlled by a course of anterior pituitary therapy. We have had occasion, personally, to prescribe this treatment in four cases of thyrotoxicosis, and in three of these the beneficial results were quite obvious. There seems to be a decided anti-thyroid influence, which shows itself by an advantageous sedative effect. While we do not

yet know just how these results are brought about, it is of interest, at least, that there are results.

In deficiency disorders in which there are signs of hypopituitarism, one might expect this remedy to be of some service, and it is; but that it is of possible utility as a remedy for epilepsy seems almost impossible, yet Spears, of Louisville, was tempted to make a trial of this remedy in epilepsy and his brief report published in the organization periodical of this Association (see p. 128), more as a request for information than anything else, is, to say the least, quite encouraging. This case is of unusual interest and so the report is repeated here:

A sailor, age 28, came for treatment for epilepsy which was of a severe and well-established type, having extended for nearly twenty-three years. Since the age of six years the attacks had appeared three or four times a week, the highest number recorded in a single week being eight and the longest interval between them being twenty days.

Two grains of anterior pituitary gland were given by mouth three times a day, and later this dose was increased to five grains. After a month of this treatment the attacks became less frequent and at the end of four months ceased. The medication, however, was continued with brief intermissions for seven months.

At the time of writing this report the man had gone over eight months with no seizure and felt so sure that this treatment had cured him that he came asking for a letter to the local recruiting office as he wished to reinlist in the Navy, from which he had been discharged ten years ago on account of his affliction.

Now this is but a single experience, yet who can say that it may not be duplicated many times or that the results obtained did not have something to do with the remedy which it is claimed worked a cure?

Since this was written our attention has been called to a favorable report by Beverley R. Tucker (see p. 99) on the same subject.

And this is not all, for the most recent report which has come to our notice directs attention to the prospective value of anterior pituitary gland in impotence in the male. Stelwagen, of Philadelphia, reports six cases of functional impotence in which two and a half grains of anterior pituitary three times a day for a varying period effected sufficient results to warrant their being outlined in a report on the subject (see p. 118). Whether Stelwagen's experiences are going to be duplicated, is not for us to say. We merely wish to call attention to the fact that the prospects of this new therapeutic measure appear to offer much of encouragement.

With the foregoing remarks in mind it is not unreasonable for us to hope that in the active principle of the anterior lobe of the pituitary body we may find as trusty a therapeutic weapon as the better known extract of its neighbor, the posterior lobe. What is now needed is concerted, clinical study of this remedy. Evidently the possibilities of harm are practically nil, at least when compared with the posterior lobe preparations.

Anterior pituitary therapy should now be thoroughly tried in "the crucible of the clinic."

HENRY R. HARROWER.

ORIGINAL COMMUNICATIONS

THE WHITE ADRENAL LINE: ITS PRODUCTION AND DIAGNOSTIC SIGNIFICANCE

By Emile Sergent, M. D., Paris, France

Physician to the Charite Hospital

WHEN during the study of a case of adrenal insufficiency I accidentally discovered the vaso-motor phenomenon to which I gave the name "ligne blanche surrenale," I indicated in my first communication on this subject the method of bringing about this phenomenon.

Little by little, I have defined the various possible causes of error, figuring them out myself or noticing them in the reports of other authors.

It is necessary to follow certain rules which I shall now outline, for only those white lines can be considered as examples of the adrenal line which appear under conditions of technical research similar to those previously indicated, and which present characteristics parallel to those which I have assigned to this particular manifestation.

To bring about this phenomenon the skin of the abdomen is selected by preference and on it is traced a geometrical figure—a rectangle, triangle or cross—thus obviating any possible confusion with lines possibly caused by scars, folds of the skin, etc. Ordinarily I outline a square around the umbilicus with a blunt object, as the rounded end of a fountain pen or, simply, the finger tip, taking special care to avoid rubbing, particularly with the nail. The figure should

be made by a simple superficial stroking, one must neither bear down nor scratch. The motion should be deliberate and never rapid. The early or premature appearance of an outline is always a sign of clumsiness, as such treatment strikes and surprises the vaso-motors, thus interfering with the reaction instead of causing it. I am in the habit of telling my students that such a procedure is likely to be a source of error.

When the tracing has been made properly, all movement on the part of the patient is prohibited and one waits a short time. Immediately following the outlining nothing is seen, provided the proper technique has been followed; but after a few seconds, about half a minute, a pale line or band begins to be noticed following the course of the finger (or pen). Gradually this becomes more and more distinct and white, at the same time becoming larger, so that eventually the line exceeds in size the actual area touched by the finger tip.

This white line attains its maximum clearness in the course of about one minute, and persists for one, two or even three minutes before being gradually obliterated. This, at least, is what is to be expected in well-defined cases of adrenal insufficiency, the only ones, in fact, in which the test has any real value.

Certain errors may and do result from improper technique. I need only mention those due to an improper degree of pressure exercised at the time of making the tracing; but I wish to direct attention to some causes of error which may be due to various insignificant circumstances.

Naturally the lighting plays an important part. In bright daylight or sunlight, or even in bright electric

light, it is sometimes difficult to see the white line. It is my custom after having made the tracing, to draw up the sheet or clothing in such a way as to cast a light shadow such as may be produced by a screen. By taking this precaution, I have demonstrated the phenomenon perfectly when a test made just before had failed to disclose it.

In like manner all factors causing a direct or indirect influence on the capillary circulation of the skin of the abdomen may modify the vaso-motor reactivity and, therefore, disturb the conditions favorable to the test. Hence it is useless to seek the line in a subject whose abdomen previous to the test was covered with a poultice, fomentation or compress. A number of minutes should be allowed to elapse after the removal of such applications before making the test. Also in subjects who are clothed one should wait a while so that pressure from the corset or underclothes can have no influence. For that matter, in ambulant cases this local pressure influence is not the only deterrent factor to be looked after, the upright position, fatigue and the effects of walking all have a certain unfavorable influence. In a word, if you desire to follow the exact technique, before making the test place the patient at rest for at least fifteen minutes, with the abdomen free and but lightly covered.

It seems advisable not merely to outline the rules of technique, but to emphasize the objective characteristics of the "ligne blanche surrenale," so that it may not be confounded with other vaso-motor conditions from which it must be distinguished. The phenomenon which I originally described must be differentiated from certain white lines accompanied by

red lines appearing simultaneously, encircling them or being encircled by them, and preceding or following them. In this connection there will be found in a recent communication by Ravaut and Kronatlinsh read before the Societe Medicale des Hopitaux here in Paris, a detailed study of these various lines.

The diagnostic significance which I have deduced from my researches is concerned solely with white lines presenting the characteristics repeatedly and accurately outlined by me—to the white line which I have called “adrenal.” In attributing to this a pathogenic quality I have considered it purely as a symptom of adrenal insufficiency. To my way of thinking it is a result of hypotension brought about by the hypoadrenia. To understand the philosophy of its production by such light stroking I have proposed the following explanation: In arterial hypotension we know that there is a peripheral vaso-dilatation; if we begin to produce a light stimulation of the skin, vaso-constriction will replace the vaso-dilatation.

I will not discuss here the objections which have been brought up—I have done it before and quite often enough. But I will reiterate some general considerations which have been previously presented by me. In pathology as well as in clinical medicine there are no pathognomonic symptoms, in the absolute sense of the term. Diseases are recognized by the presence of a group of symptoms, and these symptoms of the same disease do not necessarily show themselves in exactly the same manner in every case, for here a certain symptom may be absent, and there another. However, some symptoms are more constant and consequently of greater value than others, and this is the case with the white line in the syndrome of adrenal insufficiency.

Is it, then, sufficient ground upon which to base a diagnosis? To answer this definitely would be exceeding the scope of this paper, and going a little too far. As I have said before, and as I maintain, when I determine the presence of the "ligne blanche surrenale," my attention is quickened and immediately I begin to look for the other signs of hypoadrenia, such as melanoderma of the Addisonian type which, in turn, causes me to look for other evidences of Addison's disease. This does not necessarily prove that the melanoderma cannot be present save in a typical Addison.

Again, rose spots have a symptomatic value conceded by all clinicians in the diagnosis of typhoid fever. Does this mean that typhoid cannot exist without being accompanied by these rose spots, or that these same spots can not be found in other diseases than typhoid? Are all tachycardias necessarily of thyroid origin? Nevertheless does not the discovery of tachycardia stimulate us to look for other symptoms of the Basedow syndrome?

I wish here to warn the profession against a somewhat growing tendency to seek the absolute in clinical medicine. The clinic only permits an approximation; possessing neither an absolute sign of value, nor an incontestable diagnostic measure; but it strives rather to group signs and syndromes and to associate with them the results of functional action and reaction.

It is only with such ideas in mind that we should seek to demonstrate the "ligne blanche surrenale," and that we will be able best to appreciate its diagnostic value.

COMMENT ON DR. SERGENT'S ARTICLE

Dr. Henry R. Harrower, Los Angeles: While it is now some years since Doctor Sergent first announced the clinical test so concisely outlined above, it does not seem that the procedure has attained the degree of professional popularity that its importance warrants. In current French literature the "white line" is quite commonly referred to, and undoubtedly many clinicians know of this procedure, but few seem to be using it as a routine.

None the less it is extremely valuable, especially, for instance, in studying serious symptoms-complex accompanying the severe acute infectious diseases. Possibly the usual reason for passing by a good suggestion—insufficient information, especially of a practical nature—has been the cause of this; and if so, the minute instructions so carefully given cannot fail to revive a practical interest in a procedure, the real diagnostic value of which is most serviceable.

The test described here has the advantage of convenience and simplicity. No apparatus is required and assistance is unnecessary. Like all diagnostic procedures, it is not infallible; nevertheless it may be tried more often with profit in many cases.

The discovery of the condition of hypoadrenia and the manifestations accompanying Sergent's line, is worth much to both physician and patient, for acute hypoadrenia is common enough and sometimes responds almost miraculously to suitable organotherapy. On occasion a hypodermic of adrenalin solution, from 2 to 15 minims of the 1:1,000 solution, or the intravenous injection of, say, five minims well diluted with normal saline solution, is a life-saving procedure of the utmost value.

RECENT INVESTIGATIONS ON THE INFLUENCE OF THE ANTERIOR LOBE OF THE PITUITARY BODY UPON GROWTH, AND ON THE PROPERTIES OF THE GROWTH-CONTROLLING CONSTITUENT, TETHELIN.

By T. Brailsford Robertson, Ph. D., D. Sc.

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THE well-known clinical manifestations of hyperactivity of the anterior lobe of the pituitary body all point towards an intimate association between the physiological activity of this organ and the growth of certain tissues, particularly the bones and epidermis. If the incidence of the hyperactivity be pre-adolescent the resultant is usually some measure of gigantism, while if the incidence of hyperactivity be post-adolescent the manifestations are usually of the acromegalic type.

With the realization of these relationships which resulted from the clinical investigations of Marie and many others during the closing years of the preceding century, it was inevitable that attempts would be made to reproduce in the laboratory some of the clinical manifestations of hyperpituitarism by the administration of pituitary tissue to animals.

Many of the earlier investigations in this field were, however, vitiated by the failure to distinguish between the physiological actions of the anterior and posterior lobes. Embryologically, anatomically and functionally these two lobes of the pituitary body are totally distinct organs. It is now well understood that the posterior lobe secretes a very powerful hormone, somewhat analogous in its actions to adrenalin and ergot, and it is obvious that such a substance,

especially when administered over prolonged periods of time, may be expected to give rise to very widespread disturbances involving growth among other functions, and that these effects are to be regarded as purely secondary symptoms of chronic intoxication, and devoid of significance as evidence of any specific action upon the growth of tissues. Thus Etienne and Parisot¹ found that repeated injections of posterior lobe extract led to permanent hypertension and hypertrophy of the heart, Franchini² observed ulceration and hemorrhages in the intestines, Thaon³ observed hyperemia and hemorrhages in the kidney, and Cushing⁴ observed extreme emaciation after repeated injections of sterile emulsions or extracts of posterior lobe tissue. According to Biedl⁵ large doses of pituitrin lead to depression and muscular weakness, followed in twenty-four hours by death.

The earlier investigations in which anterior lobe tissue, emulsion or extracts were employed yielded for the most part negative results. In the light of the more recent and positive results of Aldrich⁶, Schaffer⁷, Wulzen⁸ and myself⁹, it would appear probable that the early failures were attributable to one or more of the following factors: 1. Misapprehension of the nature of the effects to be expected. 2. An unfortunate choice of age at which to initiate administration. 3. Insufficiently prolonged administration. 4. Insufficient dosage, and 5. Preliminary treatment of the tissues or extract of such a nature as to involve partial or total destruction of the growth-controlling principle.

Hyperplasia of the anterior lobe of the pituitary body is notoriously associated with gigantism and

acromegaly. On the other hand pathological conditions resulting in partial or total destruction of the anterior lobe of the pituitary body are associated with a clinical picture of adiposity, under-development of the skin, bones, sexual organs and secondary sexual characters. An exactly similar picture may be elicited in animals by extirpation of the pars anterior, as Cushing has shown.¹⁰ It was therefore anticipated that the administration of an excess of the anterior lobe secretion to animals would lead to a condition resembling the clinical pictures of gigantism and acromegaly. Notwithstanding these expectations, however, those observers who have obtained positive results unite in reporting a decided initial retardation of growth in weight and linear dimensions when anterior lobe tissue is administered to young animals.

While at first sight these experimental results stand in striking contradiction to the clinical findings, I am of the opinion that the contradiction ultimately will be found to be apparent and not real. There is a very widespread and mistaken tendency to regard "growth" as a single process and to infer that if a given substance or condition accelerates the growth of one particular tissue at any given time, the same substance or condition will also accelerate the growth of other tissues or of the same tissue at a different physiological age. In a series of investigations, some of the results of which have been embodied in recent publications,¹¹ I have found, on the contrary, that growth is a multiplex phenomenon, and that factors which favor the growth of one particular type of tissue or the growth of the whole animal at one particular age, may actually exert the reverse action upon another tissue or at another stage

in the growth of the animal concerned. Thus cholesterol very strikingly accelerates the growth of carcinoma¹² and the rate of division of paramoecia¹³, on the other hand it equally emphatically retards the early growth of white mice¹⁴. Lecithin retards the growth of carcinoma¹² and the rate of multiplication of paramoecia¹³, while it equally markedly accelerates the growth of tadpoles.¹⁵ In the effect of lecithin upon tadpoles we have a very interesting illustration of the diverse actions of the same substance upon the growth of different tissues in the same animal, for while as stated lecithin accelerates the growth of tadpoles in weight and linear dimensions, the multiplication of the pigment-cells in the skin is inhibited, with the result that the animals which receive lecithin are very lightly pigmented in comparison with normal tadpoles of the same age.

Returning to the effects of pituitary issue upon growth, we find precisely analogous phenomena. Thus the subcutaneous administration of anterior lobe emulsion to rats inoculated with Flexner-Jobling carcinoma very markedly accelerates the growth of the neoplasm, while an emulsion of other issue, such as liver, does not produce any acceleration.¹⁶ On the other hand, the administration of emulsified anterior lobe tissue to young mice leads to equally marked retardation of growth in weight and linear dimensions between the sixth and twentieth weeks after birth.⁹

The multiplex character of the growth-process is very clearly revealed in the time-relations of the growth of man and other animals.¹⁷ The curve of growth does not ascend in an even sweep from its intra-uterine point of initiation. On the contrary, it

exhibits both in man and in mice, and probably in other animals as well¹⁸, no less than three perfectly definite "cycles" or periods of alternating rapid and slow growth. That the occurrence of these cycles is an essential feature of the growth of mammals is revealed by the coincidence of their number in such widely separated forms as man and the Muridae, and by the facts that in both these forms the extra-uterine portion of the first growth-cycle approximately, but not exactly, coincides with the duration of the period of lactation, and that in both forms the period of most rapid ascent of the third cycle coincides with the attainment of sexual maturity. We may infer that in the growth of mammals at least three totally different, albeit interrelated processes are involved, and in the light of the preceding results it would appear not improbable that a particular factor which is favorable to one of these processes may actually be unfavorable to another. The possibility is thus indicated that an agency which causes retardation of growth at a certain stage in the development of a mammal may actually lead to acceleration of growth at some other stage in the development of the same animal.

The experimental findings appear to lend striking support to the above deduction, for in long-continued experiments in which anterior lobe tissue was administered to mice for over a year, I have found that the initial retardation of growth is succeeded by acceleration, which in course of time (at the age of fourteen months with the dosage employed) not only makes good the deficit due to the initial retardation, but results in the pituitary-fed animals actually exceeding the normals in weight.⁹ The linear dimensions of

these animals being inferior to those of the normals, they become very solid and compact in build, and on weighing them one was continually surprised that comparatively small animals should weigh so much. This was particularly striking in the case of the animals fed with the pituitary extract, Tethelin, described below.

Similar late acceleration of growth (unpublished) was observed by Dr. Wulzen in administering anterior lobe tissue to fowls.

It has recently been shown that any retardation of growth is succeeded, on removal of the cause of retardation, by compensatory over-growth which tends to restore the normal weight of the animal, or even to result in over-shooting the mark and the attainment of a weight which is temporarily supernormal.¹⁹ It might be imagined that in the results of pituitary administration we had merely another instance of this effect; but it must be remembered that compensatory over-growth only occurs when the retarding influence (such as shock, injury, or dietary deficiency) has been removed. Now in the experiments which I have described the daily administration of pituitary tissue was continued throughout the entire duration of the experiment. The agency which produced the initial retardation therefore was not removed, and nevertheless the over-growth occurred. Furthermore, Schafer found,¹ in comparatively brief experiments, upon rats, that while the administration of anterior lobe tissue to very young rats led to retardation of their growth, at a more advanced stage of development the administration of anterior lobe tissue led to an acceleration of the gain in weight, although these animals, not having received pituitary

tissue while still very young, had never displayed any retardation due to the administration. It would appear legitimate to infer, therefore, that at a late stage in the third or adolescent growth-cycle the administration of excess of pituitary (anterior lobe) tissue leads to an acceleration of growth, while at an earlier stage in the development of animals the administration of anterior lobe tissue leads to retardation of the rate of growth.

It is not improbable that in the light of these facts our interpretation of certain clinical pictures will ultimately require modification. Thus it is quite conceivable, in the light of the above experimental findings, that pre-adolescent hypopituitarism, at a certain stage of development, might yield effects in some respects analogous to those of late post-adolescent hyperpituitarism.

Some of the reasons for the early failures to observe positive effects resulting from the administration of anterior lobe tissue are now abundantly clear. In the first place the clinical facts had led to an erroneous conception as to the nature of the results which might be expected. In the second place, the effects vary, not only in magnitude but in kind, with the age of the animals employed. Unless all of the experimental animals are of the same age and at a similar stage of development when administration is initiated increases in the rapidity of growth in some animals may very easily cancel decreases in the velocity of growth of others so that the net result is zero. The same lack of apparent effect also obviously may be encountered if administration be initiated at a period when the retardative effect is about to be transformed into an accelerative effect.

The factor of dosage is also a very important one. Early investigators were so deeply impressed by the physiological potency of the posterior lobe extracts that a similar potency was expected of the anterior lobe, and the quantity of tissue administered was often too small to elicit results. The large dosage required to elicit extreme effects was well illustrated in my experiments by a comparison of the effects of administering the isolated growth-controlling principle, Tethelin, with those elicited by administration of the whole anterior lobe.

The most potent catalysors (i. e. stimulators or retarders) of growth which have so far been found are either lipoids or closely related to lipoids in their solubilities. In seeking to isolate the growth-controlling principle from the anterior lobe I therefore paid particular attention to the lipoids. It was very shortly observed that these glands contain a most notable amount (10 mgm. per ox-pituitary or 0.7 per cent of the fresh anterior lobe tissue) of a lipoid which presents very exceptional physical and chemical characteristics,²⁰ being soluble in water to the extent of five per cent, soluble in alcohol and in ether, and yet precipitable from alcoholic solution by admixture of a definite proportion of ether; containing phosphorus and nitrogen in the proportion of 1:4, and yielding inosite on hydrolysis. So peculiar a substance, being present in relatively large amounts, necessarily fell under suspicion of being the sought-for active agent, and the effects of administration amply confirmed this suspicion.²¹

The administration of 4 mgm. of this substance (Tethelin) per day by mouth to mice from five weeks of age onward, produced a most remarkable change

in the velocity and time-relations of growth. The effect was similar in kind to that of the administration of pituitary tissue already described, that is, initial retardation followed by acceleration, but both effects were exaggerated so greatly as to involve total distortion of the curve of growth, the second growth-cycle being enormously prolonged, while the third (adolescent) growth-cycle was abbreviated and accelerated. This quantitative difference was attributable to a difference in dosage. The animals which were fed with pituitary tissue received an eighth of a gram of fresh tissue daily, corresponding to a daily dosage of between eight- and nine-tenths of a milligram of Tethelin, or one-fifth of the amount of the growth-controlling principle which was administered daily to the animals which received Tethelin.

Tethelin also reproduces exactly the effect of anterior lobe tissue upon the growth of carcinoma,²² subcutaneous administration to rats inoculated with Flexner-Jobling carcinoma producing a most marked acceleration (100 per cent) of the growth of the neoplasm.

The coats of the animals fed with Tethelin were exceptionally good, the hair being smooth, abundant and glossy at an age when normal animals have already begun to lose their hair and present a coat of shaggy, rough and discolored appearance. These phenomena were strikingly reminiscent of the hypertrophy of the epidermis and hypertrichosis which are such notable features of acromegaly, and taken together with the very striking action of Tethelin upon the growth of carcinoma, lend color to the supposition that Tethelin is a specific stimulant of the growth of epithelial tissues.

The striking acceleration of post-adolescent and carcinomatous growth produced by administration of Tethelin encouraged the belief that Tethelin might accelerate the healing of wounds or the recovery of weight lost during inanition, and experiments upon mice confirmed this anticipation. A single dose, subcutaneously administered, accelerated the recovery of weight lost during a previous period of starvation by from 30 to 50 per cent, while administrations of Tethelin at intervals of from two to three days very markedly accelerated the formation of cicatricial tissue in lesions formed by the excision of small pieces of skin.²³

Experiments by Dr. C. L. A. Schmidt, the results of which will shortly be published, show that Tethelin is non-antigenic, since after repeated administrations fixation tests failed to reveal the presence of any antibodies in the sera of rabbits. Moreover, Tethelin is incapable of taking the place of the antigen in the Wassermann reaction and one administration does not sensitise animals (guinea-pigs) to subsequent doses. It may therefore be administered repeatedly, subcutaneously or intravenously, without danger. No less a dose than 150 mgm. (the entire yield from 15 ox-glands) administered intravenously to rabbits produces no ill-effects other than a very slight and transient rise in blood-pressure and increase in the amplitude of the heart-beat.²⁰

The administration of anterior-lobe tissue by mouth or of extracts subcutaneously, has hitherto not yielded any very striking clinical result. The chemical properties of Tethelin reveal the origins of this lack of therapeutic efficiency on the part of the preparations and extracts which have hitherto been em-

ployed. Since Tethelin is a lipoid, and readily hydrolysed by alkalis, it is probably partially decomposed in the intestine by the alkaline juices, and also, possibly, by the pancreatic lipase. A large proportion of the dose administered by mouth is therefore in all probability wasted. That it is not totally wasted is shown by the remarkable effects of administration by mouth to young mice, but the reason why such large doses should be required to elicit these effects is now perfectly clear. The active constituent of the posterior lobe (beta-iminazolyethylamine or some closely related substance) being a comparatively stable substance is absorbed in great part unaltered, whether administered by mouth or by other channels. The growth-controlling constituent of the anterior lobe, on the contrary, being chemically unstable, is largely decomposed and presumably wasted when administered by mouth.

On the other hand, if we employ dried aqueous extracts of the anterior lobe and administer subcutaneously, we are faced with the necessity of previously removing proteins from the extract in order to avoid sensitising the patient to the foreign proteins. This may be accomplished by acidifying the aqueous extract and boiling it. But Tethelin is very rapidly decomposed by moisture, especially at elevated temperatures, with the result that in boiling aqueous extracts we destroy the greater part of the Tethelin which they contain. If, in order to avoid this, we seek to remove the proteins by some precipitating agent, we must first of all ascertain that this agent does not precipitate Tethelin, and then, the proteins having been removed, the problem remains of freeing the extract from the precipitating agent and then des-

sicating the extract sufficiently rapidly and completely at low temperature to insure that the Tethelin will not be decomposed, during a subsequent period of keeping, by associated traces of moisture.

Tethelin may be prepared aseptically and, when perfectly dry, may be heated to 80 deg. C. without deterioration. It is free from contamination by protein and soluble in water to the extent of 5 per cent. It would therefore appear to be applicable to a variety of experimental and therapeutic problems in which, for the reasons outlined, anterior lobe preparations have hitherto yielded disappointing results.

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COMMENT ON DR. ROBERTSON'S ARTICLE

Dr. E. Goetsch, Johns Hopkins Hospital: I have been very much interested in reading of the results obtained by Dr. Robertson in the administration of "Tethelin" to rats, particularly because the results

confirm in so large a measure those reported by me in the Johns Hopkins Bulletin, Feb., 1916, in an article entitled "The Influence of Pituitary Feeding upon Growth and Sexual Development."

It was shown in these experiments that it is the anterior lobe which is responsible for the growth and rapid sexual development and that when extracts of posterior lobe were similarly administered there was no such stimulation and in fact the impression was gained that in many instances there was actually retardation of growth. In view of this I am glad to see that Dr. Robertson finds that his growth principle is derived from the anterior lobe alone, in other words showing definitely that the posterior lobe principle is exceedingly toxic while the anterior lobe principle is tolerated quite well by experimental animals.

I am inclined to believe from my results that the variability of findings reported by different authors is to a large extent dependent upon the dosage and the activity of the extract used, for upon using a dose which was evidently too large for the young rats there was a failure to gain weight, whereas when the dose was decreased definitely there was an immediate rise in the weight curve. If the dose was thus regulated I failed to find instances of initial retardation such as reported by Dr. Robertson. Not only was there definite increased weight over the controls but also a definite increase in skeletal dimensions was determined by X-ray of the spinal column and long bones. The animals receiving anterior pituitary powder had in practically every instance longer body length and an increased length also of the long bones. The extract used was obtained from the Experimental Laboratories of Armour & Co., representing the dry extract of the anterior lobe of the ox. The most favorable dose for positive results in the rats was found to be 0.05 gm.

In the light of these findings one should not speak of a contradiction of the clinical findings, for, with pituitary over-activity in the human one finds over-

development not only of the entire body, but of the sexual glands as well. In pituitary under-activity, in cases of tumor, there is resultant under-development and genital hypoplasia if the under-activity antedates puberty. Indeed if the under-activity is post-adolescent then we find a consequent adiposity and cessation of genital function. The fact that the administration of anterior lobe tissue to very young rats leads to retardation of their growth and at a more advanced stage of their development to acceleration of the gain in weight as referred to in Schafer's work, seems to me to be explained possibly by comparative differences in dosage for it can be seen readily that a dose could well be too large or in fact toxic for a very young animal and therefore not suitable for the stimulation of growth, whereas in an older animal this same dosage might be favorable for such stimulation. In other words, to get a continuous stimulation it seems necessary to have a dosage calculated upon the ratio of gland extract to body weight. Whether this accounts for the results obtained by Schafer or not I do not know. It seems possible, however.

It is likely that in "Tethelin" we will have an active extract which will be very much more readily administered and the experimental or therapeutic activity of which also can be much better controlled than the ordinary extracts of pituitary hitherto used. Not only laboratory investigators but also clinicians will welcome the possibility of using this active principle in their work.

No mention is made but it would be interesting to know whether Robertson finds that the development of the sex glands is premature and even supernormal in fact, and whether he has made any histological examination of these glands or conducted breeding experiments to test this point. Such results would undoubtedly be obtained in view of similar findings after administration of the dry gland extract.

THE RELATION OF THE ENDOCRINE GLANDS TO OSTEOMALACIA.

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THE etiology of osteomalacia is still in doubt. Until about thirty years ago scarcely a guess was hazarded as to the cause of the condition. Until recently the theory of ovarian origin, originated by Fehling, has been generally accepted. Because of the rather frequent association with other disturbances, and because of the good results of various kinds of specific glandular therapy, other glands, singly or as a part of a pluriglandular disorder have been suspected of causing this disease.

There are three commonly described forms of osteomalacia, puerperal, rheumatic and senile, of which the puerperal form is by far the most frequent. Rickets and osteitis deformans would seem to be the result of a similar process, although the course and microscopic appearance may vary.¹

Histological and chemical investigations indicate that the process in osteomalacia consists in a replacement of normal bone that has undergone metabolism, by calcium-free or calcium-poor bone.²

Following the report in 1879 and 1880 of the good therapeutic effect on certain cases of osteomalacia, of removal of the pregnant uterus and ovaries as a complement to Caesarian section, Fehling recommended the procedure in the treatment of several cases of this disease.

Noting the good results of ovariectomy, he expressed the theory that osteomalacia was due to a pathological function of the ovaries leading to a vasomotor bone hyperemia which produces solution of the lime salts. Cristofolletti modified this view by assum-

ing that the endocrine function of the ovary lasts during pregnancy and causes a hypo-function of the chromaffin tissue. Falta⁴ regards as questionable the relation of the chromaffin tissue and metabolism.

Analysis, by McCrudden,² of the clinical results of castration in puerperal osteomalacia, indicate that whereas many cases were benefited or cured, a very large percentage of cases was not cured by the operation. While it might be suggested that the process continued even after the removal of the exciting ovaries, the return of malacia following a temporary cure after operation, the occurrence of the disease in non-pregnant women and before puberty as well as in males, speak against this hypothesis.

Although Wallart⁵ observed peculiarly marked development of the interstitial stroma cells in both pregnant and non-pregnant women, repeated, minute, histological examination of the ovaries, whether in the follicular apparatus, the germinal epithelium or the corpus luteum, has indicated no specific change.⁶

Although the theory of ovarian origin of osteomalacia appears untenable, the undoubted benefit of castration in many cases demands explanation. Castration, itself, according to most investigators, has no effect on the general metabolism.² Many cases recover spontaneously; others apparently improve as a result of varied treatment. The good results of castration are ascribed by McCrudden² to the prevention of future pregnancies. If this view is accepted the equally good result of X-ray sterilization and of normal and artificially induced labor is not surprising.

Evidence in support of Cohnheim's view that bones normally undergo active metabolism has steadily accumulated. Hanau⁷ pointed out that at ne-

cropsy, changes similar to osteomalacia are found in the pelvic bones of women apparently free from malacic symptoms. McCrudden² believes that osteomalacia is an exaggeration of a normal process, that when catabolism exceeds anabolism there is a tendency toward osteomalacia. He explains the prevalence of the disease in puerperal women as due to fetal demand for calcium. He emphasizes the occurrence of the disease usually after several rapidly succeeding pregnancies in poor women whose hygienic environment is bad. Occurring in non-pregnant women and in males, the disease is explained on the basis of increased calcium demand, from fractures, injuries, bone tumors and often from an unknown cause.

Biedl⁶ assumes that the principal role in the production of osteomalacia is played by the ovary (perhaps by the parovarium), and, judging by the incidence among men, by the testis. Male cases are relatively rare. In the castrated male patient reported by Elliott and Nadler⁸ the testes were normal upon histological examination. There was no retention of calcium or of phosphorus indicated in examination of the urine and stools of the week following operation as compared with that of the weeks preceding castration. Six months after operation pain was less marked, but chest deformity had increased. Five years after castration the process seemed at a standstill, although the bones showed no improvement upon X-ray examination.

The discovery of glandular interrelationships, especially between the ovaries and the thyroid and adrenal glands, suggested these glands in the part of pathogenic agent of osteomalacia. Hoennicke⁹ proposed a thyrogenic theory, which was amplified by

Parhon and Goldstein.¹⁰ While the evidence of abnormal thyroid function is present in many cases, it is as often absent. The insecure basis for this theory is shown by the fact that the authors have not decided whether a hypo- or hyper-secretion is responsible for the condition.

Parathyroid hyperplasia is common in osteomalacia, as it is also in normal pregnancy. Osteomalacia associated with hyperthyroidism and tetany has been reported. An association of tetany with rickets has long been recognized.

That the adrenal glands are concerned in the etiology of osteomalacia, was proposed by Bossi,¹¹ who reported the favorable influence of long continued subcutaneous injections of adrenalin. The glycosuric action of adrenalin and apparently also its action on the heart and vessels is strikingly slight in this disease.

Osteomalacia has never been reported in Addison's disease. Cristofolletti¹² collected 47 cases treated with adrenalin, 11 pregnant and 35 non-pregnant women. Of the former 45 per cent were cured and about 18 per cent. improved; of the latter 17 per cent. were cured and 40 per cent improved. Biedl asserts that there is no evidence that the adrenal cortex has a direct influence upon bone metabolism. It is not improbable that the pharmacodynamic action of adrenalin may account for the good results, which are the only evidence in favor of the pathogenic significance of the adrenals in osteomalacia.

Improvement has followed the injection of pituitrin in a few cases.¹³ Pal¹⁴ has reported improvement after the feeding of extracts of the anterior lobe.

Thymus gland, usually combined with phosphorus or other drugs, has seemed to be of value.

The view of Pommer that the central nervous system controls the development of osteomalacia, deserves, in the opinion of Falta, more attention than it has received, particularly because of the intimate relation of the central nervous system with ductless gland function.

It may, then, be said that in the present state of our knowledge, there is no real evidence that the frequent and manifold manifestations of endocrine disturbance occurring in osteomalacia, are a cause rather than an expression of the same metabolic disorder. Certainly, the action of no one gland or glands may be considered as causal factor. The conception of osteomalacia as an exaggeration of normal bone catabolism seems worthy of consideration. Further studies may indicate an influence of the endocrine glands upon such metabolism.

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COMMENT ON DR. NADLER'S ARTICLE

Dr. R. G. Hoskins, Chicago: The excellent summary of the evidence on the etiologic significance of the endocrine glands in osteomalacia, by Doctor Nadler, shows that as a mere matter of logic the commoner theories along this line are untenable. His conservative attitude is to be commended. It is a lack of such conservatism that has brought the endocrine literature into a disrepute that is, on the whole, deserved.

The fact that various of the internal secretions modify metabolic activities makes it probable that osteomalacia and other metabolic diseases are influenced by conditions in the endocrine glands. In view of this fact very definite evidence is needed to establish the existence of specific relationships in all such cases. That an operation like ovariectomy which supposedly exerts a marked influence on calcium metabolism should likewise affect the course of osteomalacia is not surprising. That other endocrine glands indirectly or directly play some part is probable. Further than this the evidence at present justifies no definite conclusion.

Dr. Frank E. Peckham, Providence, R. I.: From an orthopedist's standpoint it is clear that normally there is a metabolism going on in all bone. Growth is constantly taking place and waste products being thrown off. Bone physiology, like the physiology of all other structures in the body, is intimately associated with the endocrine organs. Some authors consider that the thyroid presides especially over the fixation of calcium and if its function is interfered with, there is an excess of elimination and hence a softened osseous system. Undoubtedly this condition is an etiological factor in some cases of scoliosis and may be relieved promptly by thyroid extract.

It is well established that the endocrine glands are very interdependent; the product of one organ stimulates the next one in line. Hence the therapeutic use of a single extract is not likely to be as effective as several given together. For the stimulation of calcium metabolism it has been shown that the adrenals exert some effect and that the thymus is also concerned with the retention of calcium by the body. Clinically good results have been obtained in the treatment of osteomalacia by giving pituitary extract.

As a matter of fact our knowledge of endocrinology is not yet what it ought to be; but theoretically, at least, pluriglandular treatment should be preferable to single gland medication; and in osteomalacia and in other disorders of bone physiology, such combined treatment is probably still the most logical at our disposition.

Dr. Charles A. Elliott, Chicago: In discussing the relationship that may exist between the endocrine glands and osteomalacia, one is forced to state at the outset that there is no demonstrated proof at present that any such relationship exists. However, the theory of such relationship is the most attractive explanation of the phenomena observed in this disease.

Osteomalacia has been demonstrated to be a disease in which there exists, as the most striking phenomenon, a disturbance in the metabolism of the alkaline earths, notably calcium and magnesium, but as to the cause of such disturbed metabolism there is no unchallenged theory. The theory, first elaborated by Fehling, that the ovaries are the causal factor in the production of osteomalacia, has been abundantly disproved, but the value of the operative procedure advanced by him, namely castration, has been demonstrated beyond a doubt for all of the cases in the puerperal group. The beneficial results of this procedure, however, do not lie in the supposed specific influence of the ovaries upon metabolism, but rather in the prevention of future pregnancies, during which time osteomalacia is prone to progress.

To my mind the best argument in favor of osteomalacia being a disease of disturbed function of the endocrine glands is found in the comparison with the analogous relationship that exists between thyroid function and metabolism in general, a matter that has been abundantly proved. If metabolism in general is regulated by the endocrine system, it seems likely that the disturbance in calcium and magnesium balance, as seen in osteomalacia, reasonably may be assumed to be due to a disturbance of a similar endocrine function.

BOOK REVIEWS

L'INFANTILISME HYPOPHYSAIRE, avec une introduction a l'etude des infantilismes et une classification des syndromes hypophysaires. By Stephen Chauvet, Laureat de l'Academie de Medicine de Paris; Membre de la Societe d'Anthropologie de Paris; Member of the A. S. I. S., etc. 1914, Pp. 333. Ill. 46. Paris. A. Maloine, Fr. 8.00.

This excellent thesis covers quite fully the subject of infantilism and the syndromes of dyspituism. It contains a splendid bibliography, covering no less than 106 pages, and sufficient illustrations to make clear the clinical phases of the author's study.

Infantilism is not such a simple condition as some have been led to believe. It exists in numerous forms and the etiology as well as the treatment differs materially. Doctor Chauvet characterizes this syndrome as an arrested development of the organism. This symptom complex dating from infancy prevents the normal pubertal development and causes the persistence for longer or shorter periods, of the morphologic characteristics of infancy, including: Short stature; infantile size and shape of the head, trunk and limbs; weakness of the muscular system; persistence of the epiphysial cartilages and absence of certain points of ossification in the bones; arrest of development of the secondary sex characteristics, etc.

With these somatic disorders one also finds what the author terms "puerilisme psychique" and the subject of the mental state in various forms of infantilism is carefully considered.

Among the several types of infantilism considered by Chauvet are the following: Nanism, infantilism of Brissaud's and Lorain's types, ateliosis, juvenilism, feminism, eunuchism, dystrophia adiposo-genitalis (Froehlich), reversive infantilism, acromegaly with infantilism, etc.

Those phases of the study of infantilism which are concerned with anthropology receive interesting attention; and from the standpoint of the neurologist as well as of the general practitioner Doctor Chauvet's well-considered monograph is worthy of warm recommendation.

Shortly after its publication this monograph was awarded the Prix Chatauvillard for 1915.—H. R. H.

ETUDES CLINIQUES SUR L'INSUFFISANCE SURRENALE 1898-1914. By Emile Sergent, Medicin de l'Hopital de la Charite, Paris, Member A. S. I. S., etc. 1914. Pp. 498. Paris, A. Maloine. Fr. 8.00.

From Sergent's first communication to the Societe de Biologie, Paris, December 24, 1898, until the current issue of this journal, he has steadfastly directed attention to the pathologic physiology of the adrenal glands and, despite opposition, has maintained his stand.

Our present information about the adrenals is largely due to four men—Sergent, Sajous, Elliott and Cannon. The clinical work of Sergent paved the way for Sajous' important communications, Elliott's demonstration of the adrenal control of the sympathetic and Cannon's recent work on the relation of the emotions to these glands.

We are indebted to Sergent for our profitable knowledge that the adrenals are involved in many disorders, acute and chronic, beside the well-described syndrome of Addison. His book is a lasting monument to his persistent interest in this subject and a vade mecum to the every-day study of this important and still somewhat unappreciated phase of clinical medicine—H. R. H.

THE LITERATURE ON THE INTERNAL SECRETIONS

GENERAL SUBJECTS

DUCTLESS GLANDS, Recent Investigations. Cannon (W. B.) Bull. Johns Hopkins Hosp. (Balt.) 1916, xxvii, 247.

The bodily changes accompanying strong emotions, such as fear and rage, are related to certain glands of internal secretion, especially the adrenals, and probably the thyroid.

When infuriated a cat's pupils are dilated, hair stands erect, heart is accelerated, the activities of stomach and intestines inhibited, and muscular fatigue lessened. There is an increased liberation of sugar from the liver, an increase of circulating erythrocytes and the coagulation time of the blood is decreased.

These changes also occur in man. Fear and rage are emotions underlying the struggle for existence and the changes noted increase the efficacy of the organism for physical struggle. Most of the phenomena noted are due to increased circulating adrenin, the adrenal glands being stimulated by the sympathetic nervous system.

The author believes the reason organs disturbed during emotional stress are not disturbed at other times is that a high neuroene threshold is interposed between the central nervous system and the visceral cells. This threshold is only crossed when great excitation is present in the central nervous system. In pathological cases the threshold is lowered from great emotional experiences and there is a frequent disturbance of these organs, causing dyspepsia, tachycardia and glycosuria.

Besides a routine function, the adrenals have an emergency function in times of great excitement. This is likewise true of the thyroid, its increased activity augmenting the metabolic processes and aiding the efficiency of the adrenin.

W. B. T.

The Functions of Menstruation, with Reference to the Internal Secretions. Shlenker, (M. A.) New Orleans Med. & Surg. Jour. 1916, lxi, 105.

Theories as to the function of menstruation are briefly discussed. The findings of Hitchman and Adler of the histological changes in the uterine mucosa during menstruation are reviewed fully. The author states that the whole endo-

crinous system elaborates hormones which influence and control menstruation. The ovarian secretion especially influences this function. The thymus, posterior lobe of the pituitary, and thyroid glands also play an important part in menstruation. There is undoubtedly a relation between the secretion of the mammary glands and menstruation as evidenced by the enlarged state of the breasts just prior to menstruation. The article is a concise resumé of our knowledge of the subject.—W. B. T.

(SYMPATHETIC) Normal Reaction of Skin to Stroking.

Tracy, (E. A.) Boston M. & S. Jour., 1916, clxxv, 197.

The normal reaction of the skin to stroking is found to be a brief vasodilation followed by a vasoconstriction lasting longer. From experimentation and reasoning it is found that the reaction of vasodilation is caused by stimuli coming over the autonomic branch of the vegetative nervous system, acting on the hormone X (the "autonym" of Eppinger & Hess) in the blood stream, and that the vaso-constrictor is due to stimuli coming over the sympathetic branch of the vegetative nervous system and acting presumably upon the adrenin in the blood stream.

E. A. T.

HORMONES in Bryophyllum. Loeb (J.) Science (Lancaster, Pa.) 1916, n. s. xlv, 210.

Hormones are often thought of as occurring only in animals. Evidence that hormone control may play a part in the growth processes in plants is offered. Stems of Bryophyllum will under certain conditions bend downward and put forth roots. Loeb suggests that both these phenomena are due to the elaboration and collection of one or more hormones in the regions of the stem affected.—R. G. H.

Endocrinopathic Inheritance. Timme (W.) Jour. A. M. A. (Chgo.) 1916, lxvi, 1438.

The history of a family of 24 members, in four generations, with evidence of altered internal secretions is described in detail. The relation of these cases to the Mendelian theory is also pointed out. In the first generation both individuals were defective. In the second generation all were apparently normal, but one married a man with an unstable endocrine system and three of the six children were abnormal and a fourth one showed abnormal tendencies; another member of the second generation who was apparently normal and married a normal individual, had three children, one of whom was abnormal, and another showing abnormal tendencies.

In the third generation all marriages were with normal individuals, but the fourth generation shows one abnormal male and two females with abnormal tendencies.—F. C. P.

PITUITARY Extract, Action of. Hoskins (R. G.) Jour. A. M. A. (Chgo.) 1916, lxvi, 733.

Hoskins calls attention briefly to the depression of tonus and peristalsis in the small intestines when pituitrin (saline extract especially) is given intravenously. Since this extract is often given clinically as a peristaltic stimulant he believes that each lot of the product should be tested by the manufacturer and its effect on peristalsis noted on the label of the container.—F. C. P.

Ductless Glands and their Relation to the Treatment Functional Gynecological Diseases. Rabinovitz (M.) Am. Jour. Obs. (N. Y.) 1916, lxxiv, 177.

A review of some of the recent literature, to which a good working bibliography is appended.—W. H. M.

(ADRENALS) Le virilisme et l'inversion des caractères sexuels. Blanchard (R.) Bull. Acad. Méd. (Par.) 1916, lxxvi, 47.

Virilism is a condition accompanied by the appearance of a beard, with increased muscular power, heavy voice, etc. in women. It usually occurs at the climacteric. The current explanation of this phenomenon is that these changes result from modifications in the adrenal glands with or without effects upon the ovaries. In this paper the subject is considered from the special viewpoint of the activities of the gonads.

Hippocrates relates two cases of virilistic transformation in women named Phoetusa and Namyxia. Ambroise Paré described certain degenerate women whom he termed *hommasses* (*viragos*) who, in losing their feminine somatic characteristics, assumed those of men, becoming also robust and bold. He ascribed these changes to suppression of the menses. Apert was the first to advance a scientific explanation of acquired virilism, viz.: the presence of lesions of the adrenal glands. It was not until later that changes in the sexual glands were held to be responsible, although these changes were alleged to be secondary to those in the suprarenals. Tuffier's celebrated case of adrenal virilism reported in 1914 left no doubt as to the nature of at least one form of virilism. The author, who is a zoologist, states that analogous behavior is seen in certain birds. As far back as John Hunter attention was attracted to the assumption by elderly female birds of male plumage. Hunter regarded the

phenomenon as teratological. The Germans have described such behavior under the term viriliscence. The pheasant seems especially disposed to this affection, the transformation, however, being incomplete. The altered hens do not cease to lay. The theory advanced of ovarian origin seems to have little formation in fact. This viriliscence has been noted in at least 24 species of birds belonging to 4 orders. All barnyard fowls seem to be included. Mammals are also subject to virilistic changes, but the subject has received but scant attention. As in birds the changes are restricted to the tegumentary structure.

(THYROID) What Goiters Demand Operation? Lahey (F. H.) Boston M. and S. Jour. 1916, clxxiv, 273.

Lahey considers the goiter question from the surgeon's standpoint. The thyroid gland is subject to the following changes, from a clinical point of view: (1) Thyroiditis; (2) Enlargement (symmetrical or asymmetrical) without toxic symptoms (simple goiter, colloid goiter); (3) Enlargement (symmetrical or asymmetrical) with symptoms of hyperthyroidism (hyperthyroidism or exophthalmic goiter); (4) Cysts; (5) Adenomata; (6) Carcinoma and sarcomata.

Thyroiditis occurs chiefly in the presence of infections elsewhere in the body. In three cases, abscess formation occurred but once, and in that case it was impossible at the time of incision to be certain that the pus was not outside of the thyroid gland. Surgical treatment will rarely be necessary here and, when so, only in the form of incision and drainage.

Symmetrical enlargement without toxic symptoms usually occurs in young girls soon after the establishment of the menses. The enlargement may be somewhat greater in one lobe than the other, and the gland upon palpation is fairly firm. Provided there are no symptoms of hyperthyroidism, this type of goiter in no way demands surgery, but should be submitted to medical treatment, and a careful watch kept for the onset of symptoms of hyperthyroidism, when an operation should be advised.

Colloid degeneration may also produce enlargement of the thyroid, which is more or less symmetrical, although one lobe is frequently enlarged more than its neighbor. The gland in this case is usually soft on palpation. The condition is the result of a retention of some of the elements of the thyroid secretion. This type of goiter may be submitted to surgical treatment because of its unsightly appearance, because of pressure symptoms, or because it has persisted for a long time.

Enlargement involving the whole gland, or, what is more common, the whole gland but more particularly the right lobe, with symptoms of hyperthyroidism, are best submitted to surgical treatment in the form of ligation or partial thyroidectomy as early as possible. The so-called cardinal symptoms of hyperthyroidism need not be and frequently are not all present. The presence of two of these symptoms with or without some of the secondary symptoms, such as nervousness, diarrhea, sweating, etc., should suggest strongly the existence of this disease and even the presence of an unexplained tachycardia should be looked upon with suspicion.

Cysts of the thyroid, when of sufficient size to be noticeable, are usually single, and should be submitted to surgical operation because of their unsightly appearance, because of pressure, because they are intrathoracic, or may become so. A very large intrathoracic cyst or adenoma may be present while there appears but a slight enlargement in the region of the thyroid gland, represented by the top of the cyst as it appears above the clavicle or sternal notch. These intrathoracic goiters may exist with but occasional interferences with respiration or circulation.

Adenomata of the thyroid may be single or multiple, and, like cysts, should be submitted to surgical operation for the same reasons and because they may at any time become malignant.

With cysts and adenomata symptoms of hyperthyroidism as a result of pressure may arise at any time and operation then be indicated.

Carcinoma and sarcoma of the thyroid gland, to be benefited to any extent by surgical measures, more than in almost any other part of the body, must be submitted to early surgical treatment, and then even under the most favorable conditions the prospect of early recurrence is great. This constitutes an argument in itself to remove all suspicious localized swellings of the thyroid gland.

Endocrine Glands, Relation to Female Generative Organs.

Timme (W.) *Am. Jour. Obs.* (N. Y.) 1916, lxxiv, 474.

Timme gives consideration to the intricate relationships of the endocrine glands in the female, showing especially the clinical importance of the pituitary, thyroid and adrenals in the regulation of the functions of the ovaries and the essential functions of sex.

Many functional disorders of the ovaries have their origin in others of the glands of internal secretion, and a study of many menstrual and pelvic disorders is made more profitable by looking for evidence of remote endocrine dysfunction.

EXPERIMENTAL INVESTIGATION

ENDOCRINE GLANDS, Studies on the Conditions of Activity in. I. Electrical Response as an Index of Glandular Action. Cannon (W. B.) and Cattell (McK.) *Am. Jour. Physiol. (Balt.)* 1916, xli, 39.

The work described in this paper is preliminary to a series of reports of studies of the endocrine glands. Stimulation of a nerve connected with a gland may have at least two direct effects, one on the gland cells and one on the smooth muscles of the blood vessels; and it may have two indirect effects, an alteration of the rate of blood flow, and the motion of secreted fluids along the ducts. These possibilities are discussed and experiments described.

The authors conclude that an electrical change accompanies the secretion of saliva, even when the blood supply is cut off, or the flow through the duct is stopped, and that the electrical change is a manifestation solely of the secretory process. The change is absent when secretion is absent, although each of the conditions attendant on secretion may be severally induced.—T. C. B.

THYROID GLAND, Secretory Innervation. II. Cannon (W. B.) and Cattell (McK.) *Am. Jour. Physiol. (Balt.)* 1916, xli, 58.

This second paper describes the histological, anatomical, electrical, etc., evidence for innervation of the thyroid, and gives the results of experiments, using the action current as a criterion of activity.

Stimulation of the sympathetic cord high in the thorax evokes an action current after a latent period of from five to seven seconds. Stimulation of the vagus trunk in a cruritized animal, and injection of pilocarpine (excitor of cranial autonomic endings) have no effect on the thyroid.

The conclusion is drawn that the non-medullated nerves to the thyroid cells belong to the sympathetic and not to the cranial division of the autonomic system, and that they are true secretory nerves.—T. C. B.

THYROID Hormone; Elaboration of Specific. Marine (D.) and Rogoff (J. M.) *Jour. Pharm. and Exp. Ther. (Balt.)* 1916, ix, 1.

Gudersnatch has shown that thyroid gland substances have a marked effect in depressing weight and accelerating metamorphosis in tadpoles. This phenomenon serves as a delicate biologic test for the thyroid hormone. Using this

method the authors have investigated the effect of administering iodine on the hormone content of thyroid gland. Augmentation of the activity of the gland could be detected within eight hours and it became well marked in twelve hours. Involutionary changes were detected histologically within twenty hours. At the end of thirty hours only a small fraction of the iodine administered had been incorporated into the active hormone although it had been fixed by the thyroids almost quantitatively. The suggestion is offered that the amount of hormone elaborated is dependent upon the available quantity of "mother substance." This mother substance is possibly a tyrosin or tryptophane derivative.—R. G. H.

THYROID Hydrolysis Products; Effects of Feeding to Tadpoles. Rogoff (J. M.) and Marine (D.) *Jour. Pharm. and Exp. Ther.* (Balt.) 1916, ix, 57.

Kendall has described a method of hydrolyzing thyroid substance and separating it into three fractions: "A" which affects general metabolism, "B" which affects particularly the skin, and an inactive "residue." The authors prepared such fractions from normal ox, normal sheep and iodine free hyperplastic lamb thyroids. The substances were tested for their hormone content by the method described in another abstract. (Tadpole test.)

Product "A" of the ox and sheep thyroids was found to be rich in iodine and to contain an active hormone, while the product "A" from the hyperplastic glands contained no iodine and was inactive. Product "B", although it contained considerable iodine in the first two cases, in all three lots was inactive. The same was true of the "residue" which contained a small quantity of iodine. Artificial iodization of fraction "A" from the hyperplastic glands failed to produce any active hormone. The iodized blood protein, "Iodalbin," was found to have a thyroid-like effect on the tadpoles. This research points toward the possibility eventually of synthesizing thyroid hormone from tyrosin or tryptophane derivatives and iodine.

R. G. H.

THYROID Gland in Vivo, Absorption of Potassium Iodide by , Following Intravenous Injection in Constant Amounts. Marine (D.) and Rogoff (J. M.) *Jour. Pharm and Exp Ther.* (Balt.) 1916, viii, 439.

This is an extension of an earlier research by Marine and Feiss on the affinity of thyroid cells for iodine. It was found that iodine administered as KI was taken up by the thyroids almost instantaneously whether perfused through the isolated organs or injected into the circulation of the intact animal. The amount of absorption was correlated with the functional

state of the gland. So rapid was the absorption that practically none of the iodine was excreted by the kidneys. Neither the liver nor spleen showed any retention of iodine.—R. G. H.

THYROID Adenomata; Physiological Activity in Relation to Iodine Content. Graham (A.) *Jour. Exp. Med.* (N. Y.) 1916, xxiv, 345.

The physiologic activity of various thyroid adenomata was tested by the tadpole feeding method. (See Marine and Rogoff., *Jour. Pharm. and Exp. Ther.*, 1916, ix, 1.) The adenomatous tissue had an effect similar to that of normal thyroid substance but was less active. The effect in both cases depends upon the active iodine content. No constant relation was observed between the activity of the tumor substance and its state of growth or differentiation. The author concludes that the thyroid substance acts not specifically but merely as a general metabolic stimulant—a conclusion in harmony with that of other investigators in this field (This conclusion suggests that thyroid substance should have an important place in practical therapeutics and indicates the rational basis for its employment.)—R. G. H.

THYROID and Parathyroid Glands; Relations Between. Tanberg (A.) *Jour. Exp. Med.* (N. Y.) 1916, xxiv, 547.

Tanberg offers further evidence bearing upon the opinions now commonly held that parathyroid extirpation in thyroid hypertrophy and that complete removal of the thyroid gland with the enclosed external parathyroids causes the remaining parathyroids to develop a thyroid-like structure.

In five cats kept for several months on an exclusive meat diet marked hypertrophy of the thyroids developed (confirming previous reports). The hypertrophy closely resembled that occurring in fragments of thyroid left after thyroidectomy. No characteristic changes in the parathyroids could be detected after the meat diet. In animals dying of acute tetany after parathyroid extirpation no changes in the thyroids could be detected. Three cats suffered chronic tetany for several months after the removal of three parathyroids. The thyroids were found to be slightly atrophic, although the animals had been on a meat diet which normally causes hypertrophy.

In another cat subacute parathyroid deficiency without chronic tetany prevented meat diet hypertrophy of the thyroids. Another cat after meat diet showed thyroid hypertrophy. Removal of one thyroid lobe and two parathyroids caused no significant change, however removal of a third parathyroid caused a loss of hypertrophy. Parathyroid deficiency therefore prevents a meat diet from causing thyroid hyper-

trophy. In three cats long-standing thyroid deficiency (total in two cases) caused no detectable change in the structure of the parathyroids. Chronic parathyroid deficiency sometimes resulted in a hypertrophy of the remaining parathyroid tissue characterized by the development of large, transparent, sharply defined cells with large nuclei rich in chromatin.

These results indicate that the thyroids and parathyroids are independent organs, but do not exclude the possibility of interaction between them. The small number of experimental animals used detracts somewhat from the significance of the results.

R. G. H.

ADRENAL Secretion; Influence on the Thyroid. Cannon (W. B.) and Cattell (McK.) *Am. Jour. Physiol. (Balt.)* 1916, xli, 74.

Injections of small doses of adrenalin (0. 1-0.2 mil., 1:100,-000) evokes in the cat an action current in the thyroid gland.

Stimulation of the splanchnics when physiologically separated from the central nervous system also evokes an action current in the thyroid, and this current does not appear if the abdominal blood is prevented from returning by temporary ligature of the inferior vena cava close to its entrance into the thorax. The electrical change does appear promptly when the blood is released. The electrical change also fails to appear after splanchnic stimulation, if the adrenals have been previously removed.—T. C. B.

THYROID Secretion; Effect on Pressor Action of Adrenalin. (IV.) Levy (R. L.) *Amer. Jour. Physiol. (Balt.)* 1916, xli, 492.

This is a continuation of the work of Cannon and Cattell, previously reported.

The object of the paper is to present evidence of the presence of thyroid secretion in the circulating blood after stimulating the cervical sympathetic, or after the injection of adrenalin, and to demonstrate that thyroid secretion increases the effectiveness of adrenalin in raising arterial pressure. Its effects on blood pressure and pulse rate are also recorded.

—T. C. B.

ADRENALS; Spontaneous Liberation of Epinephrin. Stewart (G. N.) and Rogoff (J. M.) *Jour. Pharm. and Exp. Ther. (Balt.)* 1916, viii, 479.

The authors describe an extensive series of experiments upon the output of adrenin from the adrenal glands. The secretion was collected in blind pouches fashioned from the vena cava, from which it could be liberated at will into the blood stream. This technique prevented the formation of

active substances from traumatized blood. The presence of adrenin in the blood was detected by its well-known pressor influence and by its mydriatic effect in the eye, the sympathetic innervation of which had previously been destroyed by removal of the superior cervical ganglion, an operation which causes hypersensitiveness to adrenin. The quantity discharged was determined by comparison of the pressor effect with that of a known quantity injected. Usually cats, but occasionally dogs were used. The rate of adrenin discharge was found to vary from 0.0008 to 0.0028 mgm. per minute. Cutting the sympathetic nerve paths to the adrenals abolished the evidence of secretion. A single denervated gland was found adequate to sustain life, but from it no detectable secretion was discharged except when it was massaged. Stimulation of sensory nerves and asphyxia lasting two minutes failed to cause any detectable augmentation of the adrenin discharge. The authors comment on the difficulty of applying results derived in anesthetized severely traumatized animals to normal cases. The question remains open as to whether any adrenin is secreted during quiet normal existence.

R. G. H.

(ADRENALS) Gastric Ulcers following Epinephrectomy.
Mann (F. C.) Jour. Exp. Med. (N. Y.) 1916, xxiv, 329.

Acute ulcers of the stomach have been observed in high percentages in dogs dying of adrenal deficiency. Mann undertook an investigation to determine whether the ulcers were due essentially to free acid. Four dogs were used as experimental animals and one as a control. In all five a patch of jejunum was transplanted into the stomach wall near the antrum. Thus both gastric and intestinal mucosa were exposed to the same concentration of acid. From four of the animals the adrenals were removed in two operations, resulting in death. In three animals definite ulcers of the gastric mucosa were found and the fourth showed congestion and erosion. In one of the four only was the jejunal mucosa affected; it showed pin point ulcers. Mann concludes that acid as such plays only a secondary role in producing the ulcers, as otherwise both gastric and jejunal mucosa should have been alike affected.

R. G. H.

ADRENALS; Influence on the Kidneys. Marshall (E. K. Jr.) and Davis (D. M.) Jour. Pharm and Exp. Ther. (Balt.) 1916, viii, 525.

The adrenal glands were removed from cats in two operations which permitted survival from one to seven days. The urea content of the blood was found to be increased to a marked degree while the excretion of this substance and of

creatinine was correspondingly decreased. The excretion of phenolsulphonephthalein was also somewhat depressed. The kidneys showed no noticeable histological changes after adrenalectomy, but the injection of urea, creatinine and sodium chloride caused an abnormal change of the histological picture due to an accumulation of fat. There was no marked change of protein catabolism. Renal depression occurred even while blood pressure and general vitality remained normal. The authors offer as the most probable explanation of their results a theory that the adrenal glands normally secrete some substance necessary to maintain renal functioning.—R. G. H.

ADRENIN; Effects on Distribution of Blood. I. Volume Changes and Venous Discharge in the Limb. Hoskins (R. G.), Lee Gunning (R. E.) and Berry (E. L.) *Am. Jour. Physiol. (Balt.)* 1916, xli, 513.

Adrenin injected intravenously into the intact animal generally causes in all doses a constriction of the limbs. Occasionally, however, expansion occurs. Removing the skin converts contraction to expansion.

Adrenin in both pressor and depressor dosages increases the venous outflow from muscles; it therefore causes active vasodilation in the muscles.

Adrenin causes decreased outflow of blood from the skin, hence vasoconstriction of the cutaneous vessels. Infusion or instantaneous injections are qualitatively similar. The local vasodilator effects probably account for at least part of the beneficial effect in active and fatigued muscle.

"From the foregoing observations it is obvious that in the intact animal adrenin in any general sense is neither a vasoconstricting nor a vasodilating agent. It is one or the other, depending on the vessels involved."—T. C. B.

ADRENALS; Content of Epinephrin, Influence of Emotional Disturbances. Stewart (G. N.) and Rogoff (J. M.) *Jour. Exp. Med. (N. Y.)* 1916, xxiv, 709.

This paper is largely of technical interest, but certain of the findings may be mentioned. Emotional disturbance which has been stated to cause adrenal discharge produced no detectable depletion of the store of adrenin in the glands. Morphine produced a depletion both in cats and dogs. Postoperative edema of the adrenals also caused a depletion. A diminution in the adrenin store of the adrenals was noted after severe operations. This was only partially due to the anesthesia. One adrenal was removed in rabbits. If time was given for recovery from postoperative depletion the adrenin store of the second was considerably greater than that of the first (suggesting compensatory activity).—R. G. H.

ADRENIN, Effects on Secretion of Lymph... Yanagawa (H.) Jour. Pharm. and Exp. Ther. (Balt.) 1916, ix, 75.

Yanagawa reports a systematic research on the effects of various substances including adrenin on the lymph flow in dogs. Starling has reported that stimulation of the splanchnic nerves causes augmented flow of lymph from the thoracic lymph duct. Tomazewski and Wilkeno found that adrenin, on the contrary, diminished lymph flow and antagonized the lymphagogic effect of peptone. Yanagawa injected intravenously relatively large doses of adrenin. An increased lymph flow occurred as long as the pressor effect of the adrenin lasted. The augmented flow was supposedly due mainly to an increase of capillary pressure in the intestines. (Adrenin causes augmented capillary pressure in the gut by impeding portal outflow.—H.) An increase in the solids, ash and sugar content of the lymph after adrenin administration suggests an osmotic factor also in lymphorrhea. Adrenin was found to produce no detectable diminution in the lymph flow after injection of Witte's peptone.—R. G. H.

(ADRENIN Effects.) Pharmacology of Seminal Vesicles.

Waddell (J. A.) Jour. Pharm. and Exp. Ther. (Balt.) 1916, ix, 113.

Freshly excised seminal vesicles of rats and guinea pigs were used. These (when suspended in isomotic solutions) ordinarily exhibit slow rhythmic movements. Adrenin solution, 1:800,000 to 1:200,000, stimulated the tissues to increased tone and rhythmic contractions. Waddell's results have an interesting bearing on the "stress function" of the adrenal glands. Possibly adrenin stimulation plays a part in normal seminal discharge.—R. G. H.

PITUITARY Influence on Growth and Sexual Development.

Goetsch (Emil) Bull. Johns Hopkins Hosp. (Balt.) 1916, lxxvii, 29.

It is the purpose of this report to give the results of pituitary feeding in young rats, with especial reference to the early development and the histological changes produced in the sex apparatus and to its influence on breeding and parturition. The report is founded on information derived from histological sections and close observation of the animals.

Briefly it might be said that the extract of the anterior lobe of the pituitary gland, when fed to young rats stimulates the growth of the animal, increases its activity and hastens sexual development. The posterior lobe extract has a retarding influence. Ovarian extract (corpus luteum) has a stimulating influence on the female and a retarding influence upon the male sexual development.

(THYROID) Functional Significance of Mitochondria in Toxic Thyroid Adenomata. Goetsch (Emil) Bull. Johns Hopkins Hosp. (Balt.) 1916, xxvii, 129.

In the absence of criteria of thyroid over-activity in fetal adenomata there remained the possibility that the activity of some of the cells of the adenoma might be in excess of the normal; to determine this point, sections of a total adenoma were stained to demonstrate mitochondria in the cell cytoplasm, and these sections were compared to sections of normal gland.

Mitochondria occurs in the protoplasm of all cells and probably evidence the degree of activity of the cell. It was felt that in the study of the pathological anatomy of the thyroid gland the mitochondria would prove an index of thyroid activity.

It was found that the mitochondria in adenoma were morphologically the same as in the normal gland, but they were strikingly more abundant in the adenoma.—W. B. T.

ADRENALIN; Influence on Contraction of Skeletal Muscle. Takayasu (S.) Quar. Jour. Exp. Physiol. (Lond.) 1916, ix, 347.

Solutions of adrenalin 1:1,000,000 show no distinct effect on the frog's sartorius. In stronger solutions the contractile power is diminished, the latent period is not affected. Injection of adrenalin into the dorsal lymph sac causes diminution in the amplitude of contraction, as in the case of muscle immersed in the solution.

The contractions are unlike fatigue, and unlike veratrinized muscle. They resemble more the influence of an excess of potassium, but differ, in that the latent period is less prolonged.

T. C. B.

[ADRENAL CORTEX in Delayed Death following Burns.] Lattes (L) Arch. ital. de biol. (Turin) 1916, lxiv, 123.

Concerning previous observations by Kolisko, the author finds that in animals killed in from five to seven days after the infliction of a burn, the adrenal cortex shows characteristic changes. These consist in hyperemia accompanied by hemorrhages. The lipoids, estimated by histological examination only, appear to be considerably diminished, particularly in the glomerular and fascicular zones. The neutral fats, cholesterol and cholesterol esters, have almost totally disappeared, while the phosphatids are more or less conserved. Karyokinetic figures are abundant, particularly in the external portion of the fascicular zone.

The adrenal cortices in animals killed within 12 or 24

hours after the infliction of burns reveal no abnormalities other than considerable hyperaemia and occasional hemorrhages. The adrenal cortices in animals killed from 10 to 15 days after the infliction of burns reveal no abnormalities.

The author considers that these findings lend support to the view expressed by Kolisko that delayed death following burns is due, not to primary intoxication produced by the burn, but to the adrenal insufficiency which is a secondary effect of the burn.—T. B. R.

(PANCREAS) Protein Feeding and Creatine Elimination in Pancreatic Diabetes. Rose (W. C.) Jour. Biol. Chem. (Balt.) 1916, xxvi, 331.

Protein feeding in dogs after complete extirpation of the pancreas does not lead to the disappearance of creatine from the urine as does similar feeding in normal fasting animals.

While protein feeding does not reduce the creatine output to zero, there is a slight decrease in the amount eliminated, which is attributed to the utilization by the animal of beta-glucose derived from the protein, with accompanying inhibition of the output of creatine.

The behavior of the creatine elimination in phlorhidzin and pancreatic diabetes offers additional proof of the dependence of the creatine elimination upon the carbohydrate utilization. T. B. R.

PANCREAS; Deficiency and Vasomotor Irritability. Hoskins (R. G.) and Lee Gunning (R. E.) Am. Jour. Physiol. (Balt.) 1916, xli, 79.

The evidence pro and con the "Loewi reaction" is discussed and experiments to obtain more satisfactory evidence are described. The authors conclude that their observations do not support the theory that the pancreas normally exerts a depressing influence upon the sympathetic nervous system.

T. C. B.

PANCREAS; Isolation of Growth-producing Substance from Sheep Pancreas. Eddy (W. H.) Jour. Biol. Chem. (Balt.) 1916, xxvii, 113.

Rats were fed on Mendel's casein diet, which permits maintenance but not growth. To this was added the water-soluble portion of the alcoholic extract of sheeps' pancreas. It was found that this addition induces marked increase in growth. The substance is removed from the extract without loss of power by Lloyd's reagent (colloidal hydrous aluminium silicate). It is also precipitated in the phosphotungstic precipitate of the extract. The improvement in growth is probably not due to a special combination of amino-acids in-

troduced with the extract, since Lloyd's reagent removes from the extract none of the amino-acids which it contains, but does, on the contrary, remove the growth-stimulating substance.—T. B. R.

RETROPERITONEAL CHROMOPHIL TISSUE, Active Principle of, Has Same Physiological Action as Suprarenal Principle. Fulk (M. E.) and McLeod (J. J. R.) *Am. Jour. Physiol. (Balt.)* 1916, xl, 21.

Using the "pharmacodynamical test" of G. N. Stewart, the authors find that retroperitoneal chromophil tissue of man, and numerous animals (dog, cat, rabbit, guinea pig, white rat, calf, sheep and pig), has the same physiological action on intestinal and uterine muscle as the active principle of the medulla of the adrenal glands.—T. C. B.

(PANCREAS) The Lipoids ("fat") of the Blood in Diabetes. Bloor (W. R.) *Jour. Biol. Chem. (Balt.)* 1916, xxvi, 417.

In severe diabetes the blood lipoids were all markedly increased up to 100 per cent. or more of the normal values. In mild diabetes the lipoids may be normal. In general the more severe or long standing the diabetic condition the more marked was the abnormality in the blood lipoids.

In spite of the high values the relations between the lipoids were practically those of normal individuals, indicating that the fat metabolism was essentially normal. There was a tendency, however, for the fat to accumulate in excess of the other constituents and this fact and possibly also the high lipid values, foreshadow the lipemia.

The high lipid values noted occurred entirely in the plasma, the composition of the corpuscles remaining practically normal.

The fact that cholesterol increased parallel with the fat in diabetic blood, even in severe lipemai gives further support to an earlier assumption (*Jour. Biol. Chem.* 1916, xxiv, 447) that cholesterol has a part and probably an important part in fat metabolism. For the same reason the determination of cholesterol in the plasma should give valuable information regarding the lipid content of the blood in diabetes.

In the present series no definite relationship could be found between high blood lipoids and the occurrence of acetone bodies in the urine.

Lipemia was observed in but two of thirty-six cases studied and these were not under treatment, but were on an unrestricted diet. No lipemia was found in any of the cases under treatment (fasting till sugar-free, followed by a building up of tolerance for carbohydrate and protein). Diabetic

lipemia probably originates mainly in the fat of the food and the probable reason for its appearance in the blood is a partial failure of the mechanism for dealing with fat. Cholesterol increases parallel with the fat up to eight times its normal value, while lecithin is relatively little increased. Since lecithin formation has been found to be an early stage in the metabolism of fat it is possible that the inability to form lecithin may be a factor in the production of lipemia.—T. B. R.

PITUITARY BODY Composition and Physiological Activity.

(II) Fenger (F.) Jour. Biol. Chem. (Balt.) 1916, xxv, 417.

The physiological activity of the posterior lobe of the pituitary body is somewhat higher during the growth period than after maturity. This is analogous to the conditions existing in the thyroid, the thymus and the adrenals. The infant gland contains more phosphates both in the anterior and posterior globes than glands from fully mature animals.

The uterine-contracting active principle of the posterior lobe of the pituitary body is readily extracted from the fresh glands by water and also by neutral and acidulated methyl or ethyl alcohol. The acidulated methyl alcohol extract is more than twice as strong as the water extract and somewhat stronger than pure crystalline beta-imidazolylethylamine hydrochloride.—T. B. R.

PITUITARY GLAND. Effect on Growth and Fission of Planarian Worms. Wulzen (R.) Jour. Biol. Chem. (Balt.) 1916, xxv, 625.

The rate of fission in planarian worms is increased by a diet of pituitary substance, no matter what portion of the gland is used or what the age of the worms employed.

The growth of planarian worms is accelerated by a diet of pars glandularis and pars intermedia, provided that the worms are very small when the diet is begun.

There is indication of a distinction between the substance which produces fission and that which produces growth. It is suggested that the growth-producing substances of the pars glandularis and pars intermedia leave the gland by way of the blood vessels of the pars glandularis.

T. B. R.

(PITUITARY) Cell Changes in Hypophysis of Albino Rats After Gonadectomy. Addison (W. H. F.) Anat. Record (Phila.) 1916, x, 1.

The acidophile cells remain nearly unchanged, but the large cells are enlarged and are more granular. Later these latter may vacuolize and form a colloid-like substance. Some of them may completely degenerate.—E. R. H.

PITUITARY Extract; Effect on Frog's Esophagus. Waddell (J. A.) *Am. Jour. Physiol. (Balt.)* 1916, xli, 529.

Pituitary extract depresses both the circular and longitudinal musculature of the frog's esophagus. The tone, the rhythm, and the amplitude are affected simultaneously. The depression is more marked at the gastric end. Variation in oxygen supply and temperature do not modify the depression. The depressor substance does not seem to be destroyed in the process of depressing the tissues.—T. C. B.

Hormones, Proenzymes and Enzymes; Destruction by Ultra-Violet Radiations. Burge (W. E.), Fischer (W. R.) and Neill (A. J.) *Am. Jour. Physiol. (Balt.)* 1916, xl, 426.

Hormones, proenzymes and enzymes are destroyed by exposure to ultra-violet radiation. The rate of this destruction is proportional to the amount of energy applied. The specific wave lengths causing destruction are 302 microns and 297 microns. The cholagogic activity of the bile is not affected.
T. C. B.

(THYROID) Transplantation of Ductless Glands. Manley (O. T.) and Marine (D.) *Jour. A. M. A. (Chgo.)* 1916, lxxvii, 260.

Following experiments with transplants of various organs, the authors have devoted most of their time to work with thyroid tissue. After making 289 auto-thyroid transplants in 141 rabbits, they conclude that auto-transplants uniformly "take" and grow, and the amount of growth is determined by the amount of thyroid removed and also by the administration of iodine or desiccated thyroid. The resecretory and regulatory nerves are not necessary for normal growth or functional activity of the thyroid. The results with homografts are not so satisfactory and the duration of the grafted tissue is modified by both the host and the tissue used for the grafts. These two factors may be quite independent, antagonistic or helpful to each other. In the case of the thyroid this reaction may be modified by iodine.

F. C. P.

(PITUITARY) Study of the Hypophysis in the Pig. Miller (M. M.) *Anat. Record (Phila.)* 1916, x, 226.

The entoderm as well as the ectoderm enters into formation of this gland. The ectoderm comes from the brain and oral cavity, and the entoderm from the foregut. The notocord aids in the development of the hypophysis. The anterior lobe contains the entodermal medullary portion and a cortical ectodermal part.—E. R. H.

HYPOPHYSIS; Development in Turtles. Baumgartner (E. M.) *Anat. Record (Phila.)* 1916, x, 179.

The hypophysis appears in 3 mm. embryos. The caudo-dorsal tip of Rathke's pouch develops into the superior lobe, the remainder of the pouch goes into the anterior lobe. Lateral buds form a thin layer under the diencephalon, a layer forming part of the anterior lobe. Three histologically different parts develop.—E. R. H.

(OVARY) Suggestion as to Process of Ovulation and Ovarian Cyst Formation. Schochet (S. S.) *Anat. Record (Phila.)* 1916, x, 241; 447.

It is suggested that the liquor folliculi may contain a digestive enzyme. The rupture of the Graafian follicles is due in part to digestion of the theca by the liquor folliculi.

E. R. H.

THYROID Gland; Normal Mode of Secretion. Bensley (R.) *Am. Jour. Anat. (Phila.)* 1916, xix, 37.

The secretion is indicated by the appearance of vacuoles in the outer poles of the cells. These contain a dilute solution similar to the colloid in the follicles. This is probably excreted directly into the vascular channels. The intra-follicular colloid is probably formed from the vacuoles in the outer pole of the cells. The stored intra-follicular colloid is no measure of the activity of the thyroid at the time of observation. This activity is indicated by the intracellular secretion.—E. R. H.

HYPOPHYSIS; Ablation in Frog Embryos. Smith (P. E.) *Science (Lancaster, Pa.)* 1916, n. s. xlv, 280.

About sixty successful ablation experiments were carried out in 3 mm. frog embryos. The operation resulted in a depression of growth and a failure of pigmentation of the epidermis. The thyroids of the experimental animals were about one-third as large as those of the controls and showed atrophic conditions histologically. The development of the sex glands was also much retarded. (A fuller account is to be published later.) —R. G. H.

(PITUITARY). Effect of Hypophysis-ectomy in Embryo in Growth and Development in Frog. Smith (P. E.) *Anat. Record (Phila.)* 1916, xi, 57.

The hypophysis invagination was removed from 200 frog larvae in the stage shortly after closure of the medullary plate. Sixty per cent. of the experiments were successful. The rate of growth was delayed; but there was no marked difference in their activity. None reached the adult state

because of disease. The operated larvae were much lighter in color than the controls and the pigment was decreased in the superficial layer of the ectoderm, but not in the deeper layer. The hind limb buds appeared somewhat delayed and the growth of legs was light if at all. The thyroid was very much smaller than in the controls in most cases, but not invariably. When the thyroid appeared to be normal the legs developed normally.—E. R. H.

HYPOPHYSIS (Anterior Lobe) and THYROID; Results of Extirpation in Tadpoles. Allen (B. M.) *Science* (Lancaster, Pa.) 1916, n. s. xlv, 755.

Allen's experiments with the hypophysis duplicate those of Smith. (See abstract.) From 430 tadpoles 3.5 to 4 mm. in length the anlage of the hypophysis was successfully removed. The wounds healed in 20 to 30 minutes and the animals seemed none the worse for the operation. The results were in general the same as those reported by Smith. The operated animals although showing perfect recovery were more than normally susceptible to unfavorable environment. This was not due to the operative severity, since thyroidectomy did not have a similar effect.

Thyroidectomy was successfully performed upon 336 tadpoles from 6 to 6.5 mm. in length. Growth continued normally up to the time of the appearance of the limb buds, then instead of undergoing metamorphosis the animals retained their larval condition for several weeks. Thyroid feeding was used successfully in one case to accelerate the metamorphosis.

Allen's results are in harmony with those of Gudernatsch, who found that thyroid feeding materially hastened metamorphosis. A later report is promised, which will include data on the effects of the operations on other endocrine glands.
R. G. H.

DUCTLESS Glands and Hibernation. Mann (F. C.) *Am. Jour. Physiol.* (Balt.) 1916, xli, 173.

As the changes in metabolism are so marked in hibernation, it was thought that a new insight into the functions of some of the ductless glands, or a cause for hibernation, might be found by a study of these glands in a hibernating animal. Gophers (*spermophilus tridecemlineatus*) were used. Two methods were employed: the first was a comparative histologic study of all the glands in the active and dormant animals. The second was the removal of certain glands and determining whether the animal would become torpid in the same manner as unoperated animals.

The author concludes that his "results do not justify the assumption of any theory ascribing the phenomena of hibernation to a lack of function of all or any of the ductless glands."

T. C. B.

GROWTH as Affected by Feeding Thyroid, Thymus, Hypophysis and Pineal Substance. Hoskins (E. R.) *Jour. Exp. Zool.* (Phila.) 1916, xxi, 295.

Feeding experiments were carried out with albino rats. Thyroid substance in sub-toxic doses caused no change in body weight, but there was possibly an increase in general growth balanced by a decrease in body fat. Marked hypertrophy was noted in the heart, liver, spleen, kidneys and the male adrenals. Less certainly the male hypophysis and the alimentary tract and possibly the skeleton, testes, and epididymi shared in the hypertrophy. The hypophyses of the females were smaller than normal.

Thymus feeding resulted in no constant effects on the body weight or on that of the individual organs. These results are contrary to the report of an earlier investigator that thymus feeding depresses the testes in the rat.

Hypophysis and pineal substance also produced no detectable effect on growth or organ weight.—R. G. H.

ORGAN Extracts; Effects of Subcutaneous Injection on Flow of Pancreatic Secretion. Rogers (J.), Rahe (J. M.), Fawcett (G. D.) and Hackett (G. S.) *Am. Jour. Physiol.* (Balt.) 1916, xl, 12.

A continuation of the studies the results of which were published in this same journal, volumes xxxvii and xxxix. The authors conclude that the non-coagulable portion of aqueous extracts of the pituitary, pineal, parathyroids, thymus and adrenals, as well as the liver, spleen and pancreas, contains all the material from each of these organs which directly can affect through the circulation the functional activity of any other organ.—T. C. B.

THYMUS Extirpation and Transplantation. Renton (J. M.) *Glasgow Med. Jour.* 1916, lxxxvi, 14.

In transplantations of thymus from one guinea-pig to another Renton found healthy thymus tissue up to fifty-three days after the operation. The thymus was rapidly absorbed when transplanted to the peritoneum (abdomen and tunica vaginalis) or under the skin, but grew well in the subperitoneal tissue. No symptoms were caused by transplantation of the thymus, nor was it possible to determine if the thymus transplant functionated even when it grew well. Total removal of the thymus did not cause apparent symptoms in young guinea-pigs and rabbits.

OVARIAN Extract and Uterine Contractions. Barry (D. T.) *Jour. Physiol. (Lond.)* 1916, 1, 259.

Injections of ovarian extract result in an increase in the frequency and force of the uterine contractions in the cat. Local applications cause increase in frequency and increase in amplitude of the uterine contractions.—T. C. B.

(PANCREAS). Influence on Spleen and Thyroid of Complete Removal of Pancreas, External Function. Sweet (J. E.) and Ellis (J. W.) *Jour. Exp. Med. (N. Y.)* 1915, xxii, 732.

In the course of studies upon the pancreas in which the external function of the gland was completely removed, two findings seemed worthy of remark by these writers. The first was that a noticeable simple atrophy of the spleen rapidly followed such an operation. In addition to this the thyroid apparatus of the animals showed a constant change, evidenced microscopically by a translucency which might amount to an actual transparency, microscopically an evident increase in the amount of colloid, chemically by a marked increase of the iodine content of the gland, and physiologically by a greatly delayed appearance of tetany, after the complete operative removal of the thyroids and parathyroids.

CASTRATION; Effect on Weight of Pituitary and Other Glands of Internal Secretion in Rabbit. Livingston (A. E.) *Am. Jour. Physiol. (Balt.)* 1916, xl, 153.

The experiments were made on rabbits, the primary object being to compare averages and individual weights of the pituitaries of operated and control animals of both sexes. The author concludes as follows:

There is no constant sex difference in the weight of the hypophysis. Neither sex shows a constant hypertrophy of the hypophysis after castration or spaying. There is a constant relationship between the rate of increase of body weight and the response of the hypophysis to castration or spaying. There is less hypertrophy of the hypophysis in those groups in which there is an increase in the rate of growth.—T. C. B.

(GONADS). Differential Effect of Calcium Upon the Rate of Growth of Two Sexes of Fowl. Pearl (R.) *Science (Lancaster, Pa.)* 1916, n. s. xliv, 687.

In this preliminary report Pearl reports feeding calcium lactate and lactophosphate in small doses to growing chicks. The males were not affected, but the females showed a marked augmentation of growth. Even more striking was the effect on the reproductive organs. The egg production in the lactophosphate females in unit time was about five

times as great as in the controls. When a small quantity of corpus luteum was fed along with the calcium the acceleration of growth was completely inhibited. The fact that a simple salt has an entirely different effect upon the growth processes in the two sexes furnishes another piece of evidence of the deep-seated biochemical differences which underlie sex differences. Pearl's observations coincide with various lines of clinical evidence (especially the researches of Blair Bell) which indicate that calcium plays an important role in the reproductive functions of the female.—R. G. H.

THYROID Gland; Influence of Diet and Iodides on Hyperplasia, in Opossums in Captivity. Bensley (R. R.) *Am. Jour. Anat.* (Phila.) 1916, xix, 57.

Bensley found that in opossums which were kept on a mixed diet the thyroid underwent hyperplasia. The addition of iodine produced the colloid type of gland, but did not inhibit hyperplasia. It appears that hyperplasia of the thyroid gland can be controlled by a restricted diet.—E. R. H.

(ADIPOSIS DOLOROSA) Deux cas de maladie de Dermum avec culture des tumeurs in vitro. Marinesco (G.) and Minea (J.) *Presse méd.* (Par.) 1916, xxiv, 504.

Careful clinical examination followed by histological examination of the tumors in adiposis dolorosa was carried out by these Rumanian physicians. They find that the structure of the masses varies with their volume. In small tumors the cellular tissue is mesenchymatous. Attempts were made to cultivate pieces of the tumors in human serum, rabbit serum and in a mixture of these. In this last they observed a luxuriant proliferation of the mesenchymatous cells on the third day. The growing masses contained various shaped cells, fusiform, triangular and polygonal, connected by a granular structure. In the protoplasm of these cells were granules which took the hematoxylin stain. Later as these structures developed more, the hematoxylin-staining granules underwent a change and their place was taken by drops of fat.

H. R. H.

(SECRETIN) Action de la sécrétine sur le rein. Piticarín (J.) *Presse méd.* (Par.) 1916, xxiv, 504.

Piticarín reports to the Biological Society of Bucharest his experience in the study of the effects of secretin upon the action of the kidneys. His conclusions are: 1. That secretin excites the renal secretory mechanism just as it excites that of the pancreas. 2. There is a parallelism between renal hyper-secretion and that of the pancreas brought about by secretin. 3. Variations in the origin of the secretin

do not alter this faculty. 4. The increased renal secretion resulting from injections of secretin follow shortly after the introduction of the secretin into the blood, reach the maximum in 15 to 20 minutes and gradually fall thereafter. 5. The urine is quite similar to urine secreted under ordinary circumstances.—H. R. H.

THYROID, Recent Advances in our Knowledge of the Active Constituents, Chemical Nature and Function. Kendall (E. C.) Boston M. & S. Jour. 1916, clxxv, 557.

Kendall isolated a crystalline iodine (60 per cent.) compound from the thyroid in 1914. It is locked in the protein molecule and can be obtained only under the influence of carbon dioxide. The administration of this substance gives all the effects of thyroid administration. If amino acids (which?) are injected simultaneously the pulse rate is enormously affected; otherwise not. In general it affects the growth, mentality, skin, hemoglobin, and metabolism.

G. H. H.

THYROID Gland, Conditions Affecting Secretion. Cannon (W. B.) Boston M. & S. Jour. 1916, clxxv, 562.

Using the galvanometric method, Cannon shows that the nerves of the thyroid belong to the sympathetic rather than the vagus system and that they act as true secretory nerves. The injection of adrenin, or the stimulation of the adrenal gland produces activity in the thyroid. Cannon believes that the gland is normally protected by a high neurone threshold. He fused in six cats the anterior root of the right phrenic nerve with the right cervical sympathetic strand. This increased the pulse rate, the basal metabolism (100 per cent.), caused diarrhea and made them excitable. In two that died of the disease, the cortex of the adrenals was greatly enlarged. The disease can be made to disappear by removing the lobe of the thyroid on the same side as that operated on.

G. H. H.

THYROID, Transplantation in Dogs. Goodman (C.) Am. Jour. Med. Sci. (Phila.) 1916, clii, 348.

According to Goodman highly organized tissue cannot as yet be permanently transplanted from one organism to another.

Parenchymatous organs of a more highly physiological function when transplanted into another animal undergo autolysis and are eventually absorbed or replaced by scar tissue.

The permanency of a transplant might be secured by finding ways of decreasing the recipient's immunity and of performing the transplant in the presence of an infection.

One of the difficulties was venous thrombosis. This was overcome by adopting the technique referred to in *Annals of Surgery*, December, 1914. In thirty cases under general anesthesia with twenty-five dogs the carotid artery remained free from thrombosis and the transplants retained their life for an indefinite length of time while the more highly organized tissue of a complicated physiological function will remain intact for a short time only.

In his review of the other glands of internal secretion about the same results were accomplished.—C. E. E.

PITUITARY AND THYMUS. Simultaneous Administration to Growing Chicks. Maxwell (S. S.) Univ. of Cal. Pub. in *Physiol.* 1916, v, 5.

In the early stages of the growth of white Leghorn chickens the administration of the anterior lobe of the pituitary body exerts a retarding influence, which is more marked when a larger amount is administered, and this retarding effect is not prevented by the simultaneous administration of thymus substance. After three months' administration of pituitary (anterior lobe) and thymus, post mortem examination showed the thymus to be much smaller in the birds which had received pituitary and thymus than in the controls, which received an equal amount of liver tissues. It is probable that in these experiments the retardation of growth of the thymus and in body-weight were both due to the administration of pituitary substance.—T. B. R.

(PANCREAS) Interrelation of Surviving Heart and Pancreas of Dog in Sugar Metabolism. Clark (A. H.) *Jour. Exp. Med. (N. Y.)* 1916, xxiv, 621.

An apparatus is described by which it is possible to perfuse separately a surviving heart or pancreas or to perfuse them together. Locke's solution with various percentages of dextrose was used. It was found to be essential to observe rigid aseptic precautions to avoid the effect of bacteria on the perfused sugar. Passage of the solution through the pancreas did not alter the sugar content. The pancreas apparently, however, did contribute something to the solution which caused an augmented utilization of sugar by the beating heart. This pancreatic contribution has some of the characteristics of enzymes. It is inactivated by boiling; it is unstable, rapidly becoming inactive on standing; it acts in small amounts; it causes a great acceleration in the rate of a reaction which otherwise proceeds slowly, and the rate of the reaction diminishes as the reaction proceeds. The substance thus lacks the stability and quantitative reactivity of the recognized hormones. The disappearance of the sugar

was dependent upon the activity of the heart, failing to occur when the pancreas perfusion was passed through the non-beating organ. Most of the sugar that disappeared was simply condensed to a non-reducing form and could be recovered by hydrolysis. A part, however, could not be so recovered. As to its actual fate no evidence was secured. That the substance obtained from the pancreas represents a hormone involved in the relation of that organ to sugar metabolism seems, as the author suggests, not unlikely.

R. G. H.

CORPUS LUTEUM of Pregnancy, as it is in Swine. Corner (G. W.) Pub. No. 222, Carnegie Inst., Washington.

A comprehensive consideration of the morphology and histology of this gland.—W. H. M.

THYROID Feeding, Materials Available. Rogers (J.) N. Y. State Jour. Med. (N. Y.) 1916, xvi, 232.

Owing to variability in activity of the commercial thyroid preparations and their crudity, experiments were begun several years ago by Rogers and his associates to determine more accurately something definite about the materials of therapeutic value which could be obtained from the thyroid gland. It was found that the active substances present were soluble in water and could readily be extracted from the gland by maceration of the fresh, hashed tissue in saline and expression. Since autolysis was found to alter or more or less destroy the active substance, fresh glands only should be used. By a process described in detail it was possible to separate 2 chief portions of the extract—the one containing the nucleoproteins, some of the coagulable proteins and the globulins, the other a noncoagulable soluble residue. Both portions were found to have physiological actions. The first portion could be dried and made into tablet triturates with lactose, the second may be used in the form of an aqueous solution. The tablet preparation of the proteins was found to yield most satisfactory results in cases of myxedema, often proving effective where the previous feeding of the whole gland had been without influence. The second portion of the extract when given intravenously to dogs was found to cause marked fall of blood pressure, deepened respiration, but no increase in the heart rate, and to be extremely active in these respects, although large doses failed to kill the animals. The preparation was used in man in doses of three to twenty drops from two to five times daily, alone or in combination with the thyroid proteins, and often proved markedly beneficial in the mixed cases of hypothyroidism and hyperthyroidism, in

true hyperthyroidism and in some cases of hypothyroidism when given with the proteins. Case histories illustrate the results obtained from the use of these two new thyroid extracts.

(GONADS) Effects of Suprarenal Feeding. Hoskins (R. G.) and Hoskins (A. D.) *Arch. Int. Med. (Chgo.)* 1916, xvii, 584.

Forty-eight young white rats were fed upon desiccated adrenals from one-fourth to 2 grams per day depending upon the age. The feeding continued from 2 to 8 weeks. Twenty-five control animals from the same litter were kept under identical conditions. A constant diet of cracked grain and bread and milk was supplied. The animals were killed at ages varying from 5 to 12 weeks. They were weighed and the following glands removed and weighed: Hypophysis, thyroid, thymus, heart, adrenals, spleen, kidney and ovaries or testes. The smallest organs were weighed to tenths of a milligram; the others to milligrams or centigrams depending upon the size. The organ weights were reduced to percentages of body weights. No difference in the experimental and normal series could be detected in the kidney, heart, hypophysis, thyroid, thymus or adrenals. The spleens of the experimental series were somewhat smaller than those of the controls but highly valuable. The ovaries in the few cases stated were larger in the experimental series. The testes (26 experimental, 18 control) showed hypertrophy. These results in confirmation of clinical evidence indicate that the adrenals exert a stimulating influence on the sex glands.

THYROID and PARATHYROID, Effects of Inanition on Structure in Albino Rat. Jackson (C. M.) *Amer. Jour. Anat. (Phila.)* 1916, xix, 302.

In young rats held at constant body weight the thyroid follicles and cells were relatively small and hydropic degeneration appeared. The cytoplasm in extreme cases was granular and eosinophilic, and the cells were often broken down and resorbed, leaving in view only naked pycrotic nuclei. Nuclei also underwent karyolysis and karyorrhexis. In adults after acute or chronic inanition the thyroid changes were essentially similar to those of the younger rats at maintenance. The changes described are found in ordinary animals under many different conditions and in these cases are probably due to cell inanition. During inanition the parathyroids suffered changes similar to, though less marked than, the thyroid. "Oxyphil" cells found in parathyroid glands may be atrophic rather than functional.—E. R. H.

ENDOCRINOLOGY

CLINICAL STUDY

(THYROID) Metabolism in Exophthalmic Goiter. Du Bois, (E. F.) Arch. Int. Med. (Chgo.) 1916, xvii, 915.

The metabolism in exophthalmic goiter was studied in a respiration apparatus which is also a calorimeter. Thirty-six observations were made on eleven patients with this disease, and six experiments were made on a cretin. The heat production is an index of the severity of the disease and the effect of treatment. There is an increase of 75 per cent. in very severe cases, 50 per cent. in moderate cases, while in mild cases it may be within normal limits. The tachycardia, cardiac enlargement and emaciation quite probably are due to increased metabolism.

The increase in average water elimination through the skin and lungs is closely proportioned to the increase in heat production.

Rest in bed caused a material fall in heat production. This is the only form of conservative treatment that appeared to cause a reduction in metabolism.

A cretin thirty-six years old produced half the calories eliminated by children his size. His metabolism was 20 per cent. below the normal adult level, estimated by the skin surface area. Three and a half days of treatment with thyroid extract raised his heat production to normal.—W. B. T.

PITUITARY Tumor Involving the Crus Cerebri, with Unusual Endocrine Symptoms. Timme, (W.) Jour. Nerv. & Mental Dis., (N. Y.) 1916, xliii, 505.

Tumors of the crus cerebri usually give rise to symptoms depending on the position the tumor assumes in relation to the anatomical divisions of the crus. Besides these direct symptoms, there are those arising from pressure of the neoplasm on remote cells or tracts within the crural divisions. The author reports a case in which, apart from the symptoms of oculomotor involvement with crossed paralysis, ataxia and incoordination of cerebellar type, there were added abnormally rapid skeletal growth and sexual precocity.

A boy, fourteen years old, following a blow on his head two months previous, developed symptoms of tumor of the crus, coincident with which priapism was noted. His stature increased three inches in five weeks. He became drowsy and his sight began to bother him.

Autopsy showed the presence of a glioma, not pressing on the hypophysis. The hypophysis was normal in size.

W. B. T.

OVARIAN Secretions, Practical Aspects. Graves, (W. P.)
N. Y. State Jour. Med. (N. Y.) 1916, xvi, 394.

The author considers that genital atrophy is the result of temporary or permanent cessation of ovarian functions and that it may cause abnormalities of great gynecological importance.

Circulatory disturbances of the genitals may be relieved or cured by the administration of ovarian extract, which produces a hyperemia of the external genitals. Graves used this with good success in two cases of kraurosis and in one of furunculosis of the vulva.

Ablative symptoms appear after the artificial or natural cessation of the ovarian functions; these are manifested by hot flashes, sweating, vague muscular pains and psycho-neuroses in some cases. These symptoms are markedly relieved by ovarian extract. Graves considers that little or no practical value is obtained by retaining ovarian tissue after hysterectomy, claiming that after this operation has been performed, vasomotor symptoms follow both transplantation of ovarian tissue and leaving the whole ovary in situ, similar in degree and frequency to those following total ablation of the ovary.

Ovarian extract relieves functional amenorrhea in young women, but the result is not permanent and long continued use of the extract is necessary.

Extracts of the whole ovary are more efficacious than extracts of the corpus luteum, which latter he has found to be less constant in their action and more likely to produce digestive disturbances.

It must be determined what animals produce a secretion most favorable for the human organism. It is not unlikely that secretions from different elements of the ovary may be adapted to certain pathological disturbances.—M. B. G.

HYPERTHYROIDISM, a Cause of Irritable Heart in Soldiers. (White, (P. C.) and Hernaman-Johnson, (P.) Lancet. (Lond.) 1916, cxc, 78.

Soldiers from the front often suffer from so-called "irritable heart." These individuals are always found to have been subjected to great strain. Three case histories are given. The symptoms are palpitation, slight elevated temperature, enlarged thyroid gland, rapid pulse, breathlessness, tremor, sleeplessness, irritability, and loss of weight. The author believes irritable heart which is now so common in Europe is a "sort of pre-Graves' condition." The treatment is rest and exposure to the X-rays.—W. B. T.

[ACROMEGALY with Psychic Manifestations.] Salomon (J.) Bull. soc. clin. de méd. mentale (Par.) 1913, 359.

The patient presented, had suffered three distinct attacks of mental depression. There were present manifest symptoms of acromegaly, but neither the radiograph nor the examinations of the eye grounds indicated any hypophysial tumor. Under treatment with pituitary extract, the symptoms were decidedly aggravated, but with the administration of thyroid extract the headache, vertigo and vomiting disappeared and the mental symptoms improved. Each glandular extract was again administered with the same results.

E. M. A.

PITUITARY [Familial Localized Acromegaly, Digito-Palpebral Type]. Sicard (J. A.) and Haguenu. Bull. mem. soc. méd. d. hôp. Par. 1914, xxxvii, 1238.

A case of hypertrophy of the tarsal cartilages, localized in the hands and feet. The phalanges showed thickening throughout their soft parts and the occlusion of the eyelids necessitated a resection of the hypertrophied cartilages. A brother of the patient was similarly affected. The radiograph showed enlargement of the sella turcica and destruction of the clinoid processes, allowing one to attribute the syndrome of disturbance of the pituitary secretion.—E. M. A.

PITUITARY TUMORS, Cobblewich, (A. S.) Lancet, (Lond.) 1916, cxc, 1262.

Four cases of pituitary tumor were reported, all occurring in women, three of whom were over sixty years of age. All of the cases were far advanced and all suffered from visual defects. Autopsy of the first case revealed a cystic tumor the size of a walnut. The other three cases were myxedematous and one suffered from diabetes. No especial treatment is mentioned and the chief value of this article is in the description the symptomatology of the severe cases.—W. B. T.

ENDEMIC GOITER. The Effect of Typhoid Inoculation. Nicholson (M. A.) Lancet. (Lond.) 1916, cxc, 275.

The author, following a suggestion of McCarrison that endemic goitre was an infection due to a water borne organism, prepared a typhoid vaccine and used this to treat the goiter in the Lawrence Military Asylum. The treatment consisted of two inoculations at ten days' interval. It was carried out on a large number of patients, the author arriving at the conclusion that it had no effect on endemic goiter, either as a curative or prophylactic agent.—W. B. T.

EXOPHTHALMIC GOITER. Ochsner, (A. J.) *Ann. Surg.* (Phil.) 1916, lxiv, 385.

The important features are discussed from the standpoint of the clinical surgeon. Adolescent hyperthyroidism is mentioned, the author believing that the symptoms will subside with rest and proper diet, provided the heart is not injured. The same may be said of the hyperthyroidism of pregnancy. Another form is discussed occurring in individuals residing in regions where goiter is endemic, who show no symptoms of the disease until they go to a community where water does not contain goiter-producing substances, then, due to the absence of the irritating substances, the symptoms of goiter appear.

The author has examined microscopically every thyroid gland removed in his clinic during the last six years. Every gland showed structural changes which accounted for the condition.

Surgical treatment should only be considered after internal medicine has failed. Before operation it is essential to get the patient in the best possible condition. One should never give these people thyroid extract, iodine or digitalis.

The extent of the operation should depend on the severity of the disease and the patient's condition. Less ether will be required, if, after the patient is anesthetized, the head of the table is elevated. Gastric lavage should follow the anesthetic. The operation may be performed under local anaesthesia to advantage. If ether is used, always give morphine and atropine previous to operation. A transfusion of 400-600 mls. of normal blood prior to the operation will increase the margin of safety enormously. All blood vessels should be cut between hemostats, and the wound should be drained after operation.

The post operative treatment should consist of diet and rest. The importance of drinking much water is stressed.

W. T. B.

(THYROID) Surgical Treatment of Goiter. Porter (M. F.) *Ann. Surg.* (Phil.) 1916, lxiv, 395.

It is possible to improve on the results heretofore achieved in the surgical treatment of goiter. Judicious surgery will do this. It should be the rule to remove all permanent goiters whether they produce symptoms or not. A larger portion of the thyroid should be removed than is usually done, even at the risk of producing hypothyroidism, in order to prevent recurrence and achieve more complete relief.

A liberal incision should be made, the whole gland exposed before commencing removal. This usually enables

the operator to distinguish the normal from the abnormal portion of the gland. The hyperactive portions are lighter in color and not as firm as the normal gland tissue. One should endeavor to remove all the pathological tissue possible.

The co-existence of nephritis or diabetes with hyperthyroidism should be an argument for, not against, the operation, since these other morbid conditions often disappear after the operation.—W. B. T.

EXOPHTHALMIC GOITER, Result of Operative Treatment.

David, (V. C.) *Ann. Surg. (Phil.)* 1916, lxiv, 400.

Of two hundred successive cases of exophthalmic goiter operated at Presbyterian Hospital, Chicago, five and a half per cent. died in the hospitals. The condition of sixty-five patients one year after operation was as follows: 38 patients were cured and 40 per cent. were improved. Of thirty-five patients having exophthalmos before operation only 37 per cent. were relieved from it. The duration of symptoms before operation in the patients cured was sixteen months, in those benefitted twenty-three months, in those not improved thirty-three months.—W. B. T.

HYPOPHYSIAL DISORDER in Mammary Cancer and its Relation to Diabetes Insipidus. Sekiguchi, (S.) *Ann. Surg. (Phil.)* 1916, lxiii, 297.

Polyuria often occurs in cancer of breast without renal disorder. The author thought a disturbance of the hypophysis cerebri might be responsible. He investigated thirty-five pituitary glands in cases of mammary cancer. In two of these metastasis to the posterior lobe of the hypophysis was found. There was no metastasis of the cancer to the third ventricle. The author believes the lesions of the hypophysis are probably responsible for the polyuria occasionally noticed accompanying mammary cancer.—W. B. T.

(PANCREAS) Glycosurias. McLester (J. S.) *Southern Med. Jour. (N'ville.)* 1916, ix, 99.

McLester discusses the glycosurias from an experimental and clinical standpoint, dividing them into two classes—first, the diabetic, which is an important part of a clearly defined disease complex; second, the non-diabetic, which is due to a metabolic disorder of the liver, kidneys, alimentary tract or nervous system. The diabetic organism possesses a peculiar inability to handle sugars. To the diabetic, sugar is a diuretic, while to the non-diabetic it is anti-diuretic. The liver has long been held responsible for various glycosurias, even diabetes mellitus, but experimental knowledge tends to place

much of the blame elsewhere, especially upon the nervous system. The adrenals, thyroid, parathyroids and hypophysis all have a part in the production of glycosuria. Hyperfunction of the adrenals is usually accompanied by transient glycosuria; while hypofunction, as in Addison's disease, is claimed to produce increased sugar tolerance. These glands, with the pancreas, bear a synergistic and antagonistic action to each other. The thyroid, adrenals and hypophysis hasten metabolism and stimulate the sympathetic fibers, while the pancreas and parathyroids conserve metabolism and stimulate the autonomic nerves. The pancreas is the only organ of internal secretion that has been definitely proven to be concerned in the production of diabetes.—L. F. W.

(PINEAL) Virilisme Epiphysaire. Sicard (J. A.) and Hague-neau. *Rev. Neurol. (Par.)* 1914, xxii, 858.

[BASEDOW'S DISEASE with Mental Depression and Extreme Emaciation.] Trenel and Capgras. *Bull. soc. clin. méd. mentale (Par.)* 1913, 342.

This is a report of the case of a woman of 41 years of age, with Basedow's disease, in whom the mental depression, accompanied by extreme emaciation, cleared up after four years' duration.—E. M. A.

[BASEDOW'S DISEASE and Mental Disorders.] Arsimoles et Legrand. *Ann. medico-psychol. (Par.)* 1914, 154.

In which the authors consider a type of mental disorder similar to manic-depressive insanity as due directly to thyroid intoxication.—E. M. A.

DYSPITUITARISM in a Girl of 15 Years. Stephenson (S.). *Brit. Jour. Child. Dis. (Lond.)*, 1916, xiii, 149.

The author reports a case of a girl of 15 years who was inclined to stoutness, had prominent eyes, had not yet menstruated, and who did not present any pubic hair.

He makes a diagnosis of dyspituuitarism on the following: (1) A bilateral simple optic atrophy, otherwise unexplained; (2) loss of the temporal field in the left eye (temporal hemianopsia); (3) x-ray evidence of enlargement of the sella turcica; (4) the general appearance of the girl.

Large doses of thyroid extract (four grains a day) were given, but without any particular benefit.

Stephenson thinks surgical treatment is demanded especially since there is a possibility of blindness developing.

M. B. G.

PITUITARY FOSSA, Surgical Methods of Approach, Cope, (V. Z.) *Lancet*, (Lond.) 1916, cxc, 601.

The aim of this paper is to discuss various routes of surgical approach to the pituitary fossa and to determine which is the best. The morphology and development of the gland in man, as well as the normal and abnormal anatomy of the fossa, are thoroughly reviewed. Detailed descriptions are given of four methods of approach. To Schloffer's nasal method the objection is found that it favors infection and often leaves a deformity of the nose. Horsley's temporal route is quite dangerous and impracticable. There are two fairly satisfactory operations, the Hirsch-Cushing submucous-nasal method and the fronto-orbital method of Frazier, the last being in Cope's opinion the more suitable in a majority of cases. In the author's three cases this method was successful. Two of his cases were markedly improved by the operation; the third was not benefited. He urges an early operation for patients with oncoming blindness due to pressure on the chiasma.—W. B. T.

(GONADS) Pseudo-Hermaphroditism; Remarks on Abnormal Function of Endocrine Glands. Quinby, (Wm. C.) *Bull. Johns Hopkins Hosp.* (Balt.) 1916, xxvii, 50.

A case of female pseudo-hermaphroditism of the external type is reported, showing unusual accentuation of the secondary sex characteristics of the male.

Sex aberrations are related to the endocrine system. The proper development of the sexual attributes depend on normal activity of endocrine glands.

The adrenal cortex has an important bearing on sex. It, like the sex gland, develops from the Wolffian ridge, and secretes a hormone influencing growth, nutrition and sexual development.

The sexual changes seen in acromegaly furnish evidence that the pituitary exerts an influence on sexual characteristics.

The author believes his case represents an endocrinopathy of the adrenal cortex, surely; possibly also of the pituitary body.

W. B. T.

OVARY, Relation of Angiogenesis to Ossification. Moschcovitz (Eli.) *Bull. Johns Hopkins Hosp.* (Balt.) 1916, xxvii, 71.

The study is based on five cases of calcification and ossification of the ovary, three cases of calcification and two of ossification. The process in each instance involved a corpus albicans. According to this writer 4 stages are recognizable:

- (1) An early multiple deposit within a healed corpus luteum.
- (2) A circumscribed deposit of lime within a corpus albicans.
- (3) Haversian canals appear in the lime deposits.
- (4) True bone formation occurs.

These bony structures in the ovary are not blastomatous. The tissue dies, calcification occurs, and this is followed by ossification. The development of new blood vessels affords the key note in terms of cellular ontogeny of the process of ossification.

W. B. T.

(ADRENAL) Le Virilisme Surrénale. Tuffier (E.) Rév. d. thérap. méd-chir. (Par.) 1914, lxxxi, 399.

A woman is described who exhibited a heavy black beard and moustache, baldness and very muscular limbs, typically masculine in type. She had on the forearms and hands almost confluent yellow spots. On examination of the external genital organs, there was found hypertrophy of the clitoris which measured 4 centimeters in length and was covered with a well developed prepuce. All these manifestations had appeared since the menopause. During a hysterectomy for the relief of metrorrhagia, it was observed that on either side the kidney was enveloped in a large mass of fibro-lipomatous tissue. The removed uterus showed no fibroma but was hypertrophied. The right ovary showed a tumor of the size of a large nut. The case is a remarkable example of the hirsutism of Apert or the virilism of Gilbert Ballet.

Observed especially in the infants of the female sex, these signs are of a remarkable constancy. Hypertrichosis of the masculine type is the most common symptom, having been noted in thirty of thirty-two cases, and a muscular hyperesthesia is likewise the rule among the adults. Hypertrophy of the genital organs occurred in forty of the sixty-five cases. This hyperfunctioning of the adrenals is manifested differently according to the age of the patient, activating the growth of the infants to unlikely proportions; in the case of Dun, an infant of five years appeared to be fourteen years of age and showed a hypertrichosis over the back and about the genitalia; in Walker's case, a girl of seven years of age had the figure of a man of twenty years of age, with hair of masculine distribution over the body; in the observation of Herbert, an infant of eighteen months developed hypertrichosis. The development is different in the adult especially after the menopause, the metabolism then affecting only certain organs producing hypertrichosis, hyperesthesia and hypertrophy of the genital organs.—E. M. A.

(THYROID) Energy Metabolism of a Cretin. Talbot (F. B.), *Am. Jour. Dis. Child (Chgo.)* 1916, xii, 145.

The author reports the case of a male cretin aged 3 years, 8 months, whose mental development was that of a four to six-months-old infant. The metabolism of this cretin was compared with that of two healthy infants, the one being 8½ months old and the other 10 months.

The results obtained showed that the metabolism of the cretin was at least 25 per cent. lower than that of the two infants. It was evident that he was living on a very low plane and that his energy metabolism was considerably lower than what one would expect for a child of his age. These results, while inconclusive, because of the scarcity of material for comparison, are consistent with the findings of Du Bois and others.—M. B. G.

(THYROID) Instabilité choreiforme et insuffisance thyroïdienne. Remond (A.) and Savage (R.) *Ann. medico-psychol. (Par.)* 1914, v, 385.

A report on three cases, individuals manifesting seizures of a choreiform nature, which were apparently cured by the administration of thyroid gland—E. M. A.

(THYROID) Greffe de la glande thyroïde d'un singe à un enfant atteint de myxœdème. *Medicine prat. (Par.)* Vornoff (M.) 1914, x, 106.

A clinical report before the Paris Academy of Medicine, of a child developing myxœdema, subsequent to measles, at eight years of age. At the age of fourteen the thyroid gland of an ape was transplanted to the cervical region of the child with subsequent disappearance of the myxœdematous symptoms. The author attributed his success to rigid asepsis, the brief interval of the transplantation and the vascularity of the tissue into which the transplantation was made.—E. M. A.

(THYROID) La pigmentation cutanée dans le syndrome de Basedow. Sainton (P.) and Fayolle (P.) *Bull. méd. (Par.)* 1914, xxviii, 667.

In which the authors consider the varieties of brownish pigmentation observed in Basedow's disease as resultant upon alterations in the adrenals and sympathetic system occurring in this disease.—E. M. A.

(PITUITARY) A Case Illustrating the Occasional Resemblance Tabes Dorsalis to Disease of the Pituitary Gland. Cadwalader, (W. B.) *Jour. Nerv. & Mental Dis. (N. Y.)* 1916, lxiv, 150.

PITUITARY DISEASE Causing Infantilism. Climenko, (H.)
 Jour. Nerv. & Mental Dis. (N. Y.) 1916, xlv, 352.

OPTIC NERVE Affections and Ductless Glands. Schirmer,
 (O.) Jour. Nerv. & Mental Dis. (N. Y.) 1916, xlv, 358.

PINEAL GLAND, Probable Diagnosis of Tumor. Dercum,
 (F.) Jour. Nerv. & Mental Dis. (N. Y.) 1916, xlv, 147.

A case presented before the Philadelphia Neurological Society of a man 28 years old who began four years previously to lose his vision. A year ago he began suffering from headache. The genitalia are infantile in appearance. There is an absence of hair on face, breasts or pubis. There was a double optic nerve atrophy. The X-ray shows a shallow and flattened sella turcica. There was present an internal hydrocephalus. Dr. Dercum concludes that there was undoubtedly present a tumor of the pineal gland. (Pituitary?)
 W. B. T.

Sull' achondroplasia. Massalongo (R.) and Piazza (C.) *Rif. medica* (Naples) 1914, xxx, 676; 703.

It seems plausible to these investigators that the ordinary infections and intoxications may be the primary causes of the glandular disturbance producing the achondroplasia.
 E. M. A.

[ACROMEGALY, Tumor of the Hypophysis, etc.] Cauvin.
Arch. d'Ophthalmol. (Par.) 1914, xxxiv, 657.

A case of tumor of the hypophysis is discussed in which the author draws attention to the importance of examination of the visual fields in diagnosis and the later disappearance of the symptoms produced by the tumor under suitable glandular and radiotherapy.—E. M. A.

(MONGOLISM) Ancore sull'idiozia mongoloide. Provinciali
 (U.) *Pediatria* (Naples) 1916, xxiv, 392.

Two cases of mongolism are reported. Thyroid treatment was inefficacious and antisiphilitic treatment proved a failure. The thyroid treatment, however, seemed to benefit the invincible constipation present.

(MONGOLISM). Contributo alla etiopatogenesi dell'idiozia mongoloide. Di Giorgio (G.) *Pediatria* (Naples) 1916, xxiv, 403.

Sixteen cases of mongolism from Sicily are collected and the etiology and pathology discussed by Di Giorgio. He believes that the basal cause of this disease is a pluriglandular insufficiency. There was a history of some chronic infection

or emotional shock among the parents as a rule. The mother of one was of a nervous temperament and the news of her husband's shipwreck reached her during this, her seventh pregnancy. The Wassermann reaction was positive in one or both parents in four cases; one of the mothers had a goiter, and three were tuberculous; one had had malaria during the pregnancy, and three of the fathers were hard drinkers, while a neuropathic taint was known in four of the families. The Abderhalden test for thyroid was positive in two cases and improvement under prolonged thyroid treatment was evident in two cases.

SEX GLAND Implantation. Lydston (G. F.) *Jour. A. M. A.* (Chgo.) 1916, lxvi, 1540.

The author reports four cases of sex gland implantation and from this and previous experiences concludes that sex gland implantation increases physical efficiency, especially physiosexual efficiency; also that when the technic and material are right and the recipient properly selected, preservation of hormone production by the implanted gland is certain at least for a prolonged period. He is further strongly inclined to believe that permanent physiologic and therapeutic advantageous results are equally certain.—F. C. P.

(ADRENALS) The Syndrome of Toxemia. Pottenger (F. M.) *Jour. A. M. A.* (Chgo.) 1916, lxvi, 84.

In discussing this syndrome the author states that toxemia acting on the sympathetic nervous system and hence by way of the splanchnics, on the adrenal glands, and perhaps on other internal secretory organs, causes prolongation of the toxic symptoms.—F. C. P.

Internal Secretions and Mental Diseases. Ruggles (A. H.) *Providence Med. Jour.* 1916, xvii, 240.

This article delineates the close relationship between mental disease and certain disorders of internal gland secretions. It also shows some of the proof that is brought forward concerning the interaction of the various glands' secretions. A brief description of the mental symptoms, occurring in connection with disorders of thyroid, pituitary, adrenal and sex glands, is given. Ruggles quotes from Eppinger and Hess' work and also from Cannon's studies showing how important a part is played by the interactivity of the sympathetic nervous system and the glands of internal secretion.

An outline of six cases is reported. Two of these cases showed evidence of pituitary gland disturbance associated with the mental symptoms. Three were cases of myxedema

associated with persecutory delusions and a beginning dementia. The last case was one of exophthalmic goiter in which lobectomy gave only temporary relief of symptoms and at autopsy an enlarged persistent thymus was found.—A. H. R.

(THYROID). Struma en depressie. Kappenburg (B. D. G.) *Ned. Tijdschr. v. Geneesk.* (Amsterdam) 1916, ii, 1187.

In his paper on the relation of goiter to mental conditions Kappenburg reports that 20 per cent. of the fifty-six persons with goiter at the Utrecht Hospital presented more or less pronounced mental impairment while only 4.4 per cent. among 437 other inmates showed anything of the kind. Of the 11 goiter cases referred to nearly all were of the manic-depressive or melancholia types of psychosis, while this was true of only 1.1 per cent. among the others. The thyroid gland seems to be affected more than other endocrine organs by emotional influences. It is the "glande de l'émotion" as it has been called. He compares the various theories as to the pathogenic influence of the thyroid and its connection with psychic depression. One thing is certain, he declares, namely, that such an influence exists, and the figures he presents sustain this assumption.

ATELEIOSIS. Weber (F. P.) and Stebbing (G. F.) *Brit. Jour. Child. Dis.* (Lond.) 1916, xiii, 200.

A report of a case of ateleiosis, a somewhat rare condition of general and symmetrical dwarfism and infantilism with which is associated a more or less complete bodily and mental arrest of growth and development. It is not confined to any portion of the body. The whole body is affected. These dwarfs differ according to the period at which relative or absolute arrest of growth and development has occurred. It is probably of endocrine origin. The sex glands are usually hypoplastic and defective. The family history of the case reported is negative, both as regards the mother's and the father's family. Thyroid extract was given without improvement; in fact, its administration seemed to make the patient worse mentally.

EXOPHTHALMIC GOITER; A Minor Symptom of. Cyriax (R. J.) *Lancet* (Lond.) 1916, i, 1148.

In a letter to the editor of the *Lancet* Cyriax draws attention to a peculiarity exhibited by some patients suffering from exophthalmic goiter—namely, a tendency to wash their hands with a frequency out of all proportion to necessity. He attributes this phenomenon to hyperidrosis of the hands, especially of the palms, in a certain number of cases; how-

ever, the statement is made that these symptoms occur in cases in which there is no excessive sweating of the hands. The patients complain that their hands always feel dirty. In this latter type it is possible that these individuals are suffering from a neurosis.

The author attaches importance to this symptom as it sometimes appears in comparatively early cases. He reports seven cases of exophthalmic goiter—all women—in which this symptom occurred.—W. B. T.

GOITER. Dowd (C. N.) Jour. A. M. A. (Chgo.) 1916, lxvi, 480.

The author summarizes the results of one hundred and thirty-seven cases of goiter treated by surgery.—F. C. P.

HYPOPITUITARISM, Infantilism. Climenko (H.) Am. Jour. Dis. Chil. (Chgo.) 1916, xii, 596.

A girl of 12 years was stunted in growth, and was but 7 years by the Binet-Simon test and, therefore, backward in school. The subcutaneous adipose tissue was excessive.

An x-ray examination showed that the sella turcica was encroached on by bony projections from its anterior and posterior clinoid processes, as well as from the base, necessarily producing a pressure upon the pituitary and interfering with its function or, if these projections were embryological in nature, hindering the development of the gland.

The patient showed a high sugar tolerance, both to glucose and adrenalin. This with the anemia, the lack of ossification of the long bones, the absence of distinct myxedematous symptoms and signs, the absence of any response to thyroid medication, but a distinct amelioration after the administration of pituitary extract (entire desiccated gland) led the author to consider this a case of infantilism due to hypopituitarism.

M. B. G.

[THYMUS Histology in So-called "Mors Thymica."] Hammar (J. A.) Svenska Läkares. Handl. (Stockholm) 1916, xlii, 867.

Judging from some histological research work on a number of cases, it is Hammar's opinion that the so-called "thymus death" is not of thymic origin. His present communication confirms in every respect his former statements on the subject. Two years ago he published a report of the thymus findings in fourteen cases of sudden death from internal causes. One was an adult, and the others were children varying in age from 9 days to 6 years. Hammar has also a report in the press on the thymus in twenty-five cases of ex-

ophthalmic goiter. His present exhaustive article gives the microscopic findings and other minute data of the thymus from sixteen children from 3 weeks to 15 months old. The findings are analyzed and compared with similar data from an equal number of apparently healthy children of approximate ages killed by accident or dying from other external cause. The thymus in the cases of sudden death from internal causes differed in no respect from the thymus in the healthy children. Not even in two cases of typical "thymus death" included in this series could anything be found to incriminate this gland, in fact it compared favorably in every respect with the thymus from the accident cases.

(PARATHYROID) Rachitisme syphilitique chez un enfant; spasme du glotte et convulsions généralisées, etc. Marfan (A. B.) *Nourrisson* (Par.) 1916, iv, 291.

Marfan reports the case of a child of two years with hereditary syphilis. It suffered from tetany, the manifestations of which included spasm of the glottis, contractions of the facial muscles and general convulsions.

A careful histological examination of the parathyroid glandules did not evidence any obvious structural change.

(PANCREAS) Zur erblichen Diabetes. Heiberg (K. A.) *Deut. med. Wchnschr.* (Berl.) 1916, xlii, 268.

Heiberg of Copenhagen details his findings in the study of several cases of familial diabetes and reports the autopsy findings in two members of the same family who died with diabetes at 15 and 42 years respectively. The microscopic examinations of the pancreas did not show any noticeable change in the anatomic structure as compared with normal specimens examined simultaneously.

ADDISON'S DISEASE; Acute Onset, Rapid Recovery. Ticken (T.) *Am. Jour. Med. Sci.* (Phila.) 1916, clii, 422.

Ticken reports the case of a young man with an infection of both kidneys showing the symptoms of Addison's disease. After clearing up his kidney infection the symptoms of Addison's disease disappeared also. Ticken's explanation is that the function of the adrenal glands was interfered with by an inflammatory exudate. This extended from the pelvis of the kidneys into the surrounding tissues and involved especially the medullary portion of the adrenals and closely associated sympathetic ganglia

The unusual features of this case are:

1. Sudden onset of pain, chills, fever and sweats.
2. Bilateral involvement of the adrenals, as manifested

by the marked tumor masses palpable in both lumbar and hypochondriac regions with positive urinary findings for bilateral renal pelvic involvement.

3. The early and rapidly progressive pigmentation of the skin.

4. The rapidly developing asthenia, reaching the point of helplessness in seven days.

5. The extremely low blood pressure coming on so early in the disease.

6. The rapidly advancing anemia; 2,240,000 red cells and 35 per cent. hemoglobin in 7 days, in a previously robust young man.

7. The rapid improvement which followed when once the patient had conquered the acute infectious process which was crippling his adrenals.

8. The complete recovery of the patient and continued good health for a period of two years after his dismissal from the hospital.

C. E. E.

THYROID Disease, Clinical Value of Metabolic Studies.

Boothby (W. M.) Boston M. & S. Jour. 1916, clxxv, 564.

Boothby finds that practically all patients in the Peter Bent Brigham Hospital that show more than 10 per cent. variation from the DuBois standard for basal metabolism have some endocrine disturbance. Each ductless gland sends into the blood stream an autacoid (Schäfer) and these control the rate of activity of the various body cells. This suggests the value of the study of the basal metabolism in suspected endocrine disorders, especially those of the thyroid. His case histories show the need of operative removal of the thyroid when the metabolism is above normal and the possibility of using the expectant plan when it is normal. The metabolic values will serve to determine also when enough of the gland has been removed.

G. H. H.

(THYROID) Relationship of Pathological Histology and the Iodine Compounds of the Human Thyroid.

Wilson (L. B.) and Kendall (E. C.) Am. Jour. Med. Sci. (Phila.) 1916, cli, 79.

After a thorough study of 566 cases in the Mayo Clinic, the authors conclude that "the iodine in the glands exists in two independent forms of combination, only one of which, the **a** form, is toxic." The **a**-iodine compound is present in the actively hyperplastic glands of advanced hyperplastic toxic goiters in only 1-20 to 1-15 the amount in which it is present in normal thyroids. This is due not to a reduced production of the toxic substance, but as a result of its greatly

increased diffusion from the gland into the blood stream.

The amount of the iodine parallels the clinical grouping (by Plummer).

The authors are continuing their studies and seeking the key to the relationship between the pathology and chemistry of the thyroid and the clinical manifestations of thyroid dysfunction.

G. H. H.

DIABETES MELLITUS, Beeinflussung durch den Krieg.

v. Noorden (C.) Med. Klinik (Berl.) 1916, xii, 991.

This is a comprehensive and most interesting exposition of the influence of the war on patients with diabetes before the war and those who have developed it during the war. He has examined about 100 diabetic officers and men in the last two years, but does not include these in his discussion, limiting it to fifty-four diabetic patients who stayed at his clinic for several weeks or months. Of this number, about a third were long known as diabetics, but in 37 the symptoms have come on since the war began. Four of the old diabetics were officers between 35 and 42 who had kept their severe diabetes under control and did garrison duty efficiently. Under the stress of war, they collapsed entirely in the course of a few months. Those with mild diabetes, after a period of exacerbation, found that their tolerance for carbohydrates was higher than ever before the war, but the sugar content of the blood kept high, and by the end of three months the collapse came. The interval was longer in officers, and up to a year or longer in those never on service on the firing line. All those officers who held out longer than three months at the front were over 40, and thus had passed the age when diabetes is most liable to a malignant course. In few instances was there any tendency to exacerbation of the diabetes by wounds incurred, but an intercurrent infectious disease was often followed by aggravation of the diabetes. This is readily explained by infectious-toxic injury of the pancreas islands. Diabetes seems to protect against acute nephritis; there were no cases of acute nephritis among the diabetics although this disease is occurring with exceptional frequency during this war.

In 37 cases of diabetes developed for the first time during active service, 17 exhibited a severe form in from three to eighteen months. In 3 of the 17 severer cases and in 7 of the 20 milder ones, other members of the family had diabetes. In the mild cases the sugar disappeared from the urine under a few days of rest and dieting, but in all the groups the sugar content of the blood kept high. v. Noorden emphasizes that hyperglycemia is of far greater import for the treatment and prognosis than glycosuria in these mild cases. When the

blood sugar remains high it shows that the sugar metabolism is deranged much more than would be surmised from the urinary findings and general condition. In many cases in which others had diagnosed harmless alimentary or neurogenous glycosuria, his diagnosis from the sugar content of the blood had been "true and progressive diabetes." and it had always been confirmed by the later course of the case. This applies with special force to the "war diabetics" with hyperglycemia of 50 or 100 per cent. higher values.

In these and all cases of diabetes he warns against dropping dietetic restrictions at once when the sugar disappears from the urine. This is the very time when systematic, long continued dietetic restrictions have done the most good with the least possibility of harm. He is convinced that diabetes develops only in those predisposed from birth or with acquired injury of the pancreas. Infectious-toxic changes in the Langerhans islands are probably responsible for it more frequently than is generally recognized. This is liable to occur with any infectious disease.

Nervous stress alone is scarcely able to elicit diabetes although it may transiently increase the glycosuria and entail complications by whipping up the adrenals to excessive functioning. The experiences of this war, with its enormous demands on the nervous system, will solve the question—like a natural experiment on a huge scale—whether there is ground for assuming the possibility of chronic neurogenous and traumatic diabetes. Neurogenous impulses may reach the pancreas indirectly: central nervous system—sympathetic—adrenals—blood—liver. and the excess of hormones thus produced may in time exhaust a substandard pancreas.

J. A. M. A.

Vagotonus and Sympathicotonus in Scarlet Fever in Children.

Moltchanow (W. I.) and Lebedeff (D. D.) Rousky Vrach (Petrograd) 1916, xv, 457.

This is a comprehensive discussion of the latest teachings regarding the two divisions of the nervous system—the somatic and the vegetative, the latter comprising the sympathetic and the so-called autonomous nerves. Each organ supplied by the vegetative nerves receives sympathetic as well as autonomous fibres. Functionally, these groups of nerve impulses are characterized by their antagonism. Thus, if one group carries impulses which excite activity, the other transmits inhibitory impulses. For instance, in the eye the autonomous oculomotor nerve contracts the pupil while the sympathetic dilates it. In the heart the autonomous vagus shows the heart's action, while the sympathetic nerve increases it.

In the stomach and intestines the vagus increases peristalsis, while the sympathetic inhibits it.

The different behaviour of these nerves can be demonstrated by the action of certain drugs. Thus adrenalin excites the sympathetic nerves, having no action on the autonomous. Pilocarpine, on the other hand, has no effect on the sympathetic system, but excites the autonomous nerves. Atropine paralyses the same fibres of the autonomous system as are excited by pilocarpine. As these nerves have to do with internal secretions and metabolism, their study in acute infections is of considerable interest. This can be accomplished by the pharmacological tests devised by Eppinger and Hess. The author applied the tests to ten children, varying in age from six to twelve years, during the second and third weeks of scarlet fever. The following method was employed: Twenty-four hours before the test, the patient was given 50 to 100 grams of glucose on an empty stomach, in the morning, and each portion of urine voided during the 24 hours was tested for the presence of sugar. If no sugar appeared an equal amount of glucose was given on the following morning, and one to one and a half hours later from 0.7 to 1 mil. of adrenalin, 1 to 1000, administered subcutaneously in 15 to 20 mils. of normal salt solution. In one to three days later the pilocarpine test was applied by administering subcutaneously from 0.004 to 0.01 gram of pilocarpine. A few days later atropine was injected in doses of 0.0004 to 0.001 gram, according to age. The blood pressure and pulse were determined before and after each experiment. The effect of adrenalin was determined by the appearance of glycosuria, redness of the skin, and the state of the pupils. The pilocarpine and atropine reactions, by the salivation, perspiration, and lacrymation. In some cases Aschner's sign was looked for, namely, decrease of pulse rate on pressure on the eyeball.

Analysis of the results obtained by the authors shows that only one of the eight patients who received adrenalin showed a slight glycosuria. Three did not react at all, while the others showed either a rise in blood pressure or increased pulse rate, or both. All ten reacted to pilocarpine in varying degrees. All reacted to atropine although not to the same extent. These results show that if there is an increased tonus in one division of the vegetative system there is a lowered tonus in the other. In eight of the patients a vagotonus was observed, and in one a balance of both systems. Applying these results to conditions found in scarlet fever, the authors conclude that the cardiovascular disturbances and eosinophilia are due to a vagotonus. The white

dermographism which they observed in all cases they attribute to local changes in the vessel walls and the inflammatory process in the skin.—N. Y. M. J.

Insufficiencia Pluriglandularis. Krabbe (K. H.) Ugeskr. f. Læger (Copenhagen) 1916, lxxviii, 1399.

The subject of this comprehensive report is an imbecile, now 18 years old, presenting numerous symptoms characteristic of deficiency of the internal secretion from a number of the ductless glands. These include pigmentations, sclerodactylism, microcephaly, retention of teeth and senile changes in the teeth, cryptorchidism, aphasia, achylia, atrypsia, renal diabetes and latent tetany, with various other metabolic, nervous and trophic disturbances, including scanty growth of hair and a decidedly senile aspect. This list of anomalies includes some we are accustomed to see from insufficiency of the thyroid, of the parathyroids, adrenals, testicles, and perhaps from the pancreas, but the picture of insufficiency is not complete for any of these organs. The special feature of the case is the combination of the infantile and the senile.

Krabbe discusses the conditions at length to illustrate the necessity for examining the function of each of the ductless glands in suspicious cases: the growth of hair, the skin, the genitals and the conditions of growth, roentgenoscopy of the hypophysis, examination of the teeth, the epiphysis lines, the bones of the wrist, microscopic examination of the blood, the blood pressure, sugar in the blood and in the urine and, finally, the electric responses of the muscles and their excitability and the mental status.

By determining early enough any deviation from normal in these findings, we may be able to initiate useful treatment in time to prevent irreparable damage. Although at present, according to Krabbe [though there seems quite a little evidence to the contrary in the literature.—Ed.] only thyroid and ovary extract has given unmistakably favorable results in therapeutics, yet there is reason to suppose that time will enlarge the list of effectual therapeutic agents of this kind, both for monoglandular and for pluriglandular insufficiency. The way to hasten this is by careful and concerted study of numerous cases showing these syndromes.

THYMUS Tumors. Ewing (J.) Surg. Gyn. & Obs. (Chgo.) 1916, xxii, 461.

Ewing observes that general pathological conditions affecting the thymus include aberrancy of thymus tissue in the thyroid; simple hyperplasia in status lymphaticus, Graves' disease, and simple lymphadenoma; exfoliation of reticulum cells in leukemia and infections; cysts; and neoplasms. Cysts

arise from persistent embryonal epithelial canals, from the branchial and ventral ectoderm, from distended softened Hassall's corpuscles, and from lymphangiomas.

Neoplasms include round-cell growths, commonly classed as lymphosarcoma, and tumors composed of flat or cylindrical epithelium. The so-called round-cell tumors, properly called thymomata, are derived from the epithelial stroma cells, and may be distinguished from true lymphocytomata of lymph-nodes. The cells are not round lymphocytes, but polyhedral, or cylindrical, or giant derivatives of the stroma cells. The same variations in structure are observed as in Hodgkin's granuloma and reticulum-cell sarcoma of lymph-nodes.

The clinical course of these tumors of the thymus also varies from the character of a progressive granuloma to that of a highly malignant locally aggressive neoplasm which may produce widespread extensions and metastases. A notable feature is perforation of the chest wall. Thymic carcinoma includes those tumors composed of pavement, cubical, or cylindrical epithelium; but there is no sharp dividing line between the two groups, and both arise from the reticulum cells. The parallel existing between thymic granuloma and thymoma on the one hand, and lymphatic Hodgkin's disease and reticulum-cell sarcoma on the other, suggests that in both organs an infectious agent initiates an infectious process which often runs into a neoplasm.

The cases reported by Ewing include a rapidly progressive febrile case with very extensive invasion of the neck, chest, and axillae by a tumor of diffuse structure; a perforating sternal tumor of two years' progress, structurally resembling Hodgkin's granuloma, retrogressing under the X-ray; and a slowly progressive thymoma of granulomatous type, limited to the mediastinum, and showing polyhedral reticulum cells and Hassall's corpuscles.

**EXOPHTHALMOS (originally due to Exophthalmic Goiter),
Postmortem Findings.** Mackinnon (R.) *Brit. Med. Jour.* (Lond.) 1916, ii, 488.

Mackinnon had the opportunity of performing an autopsy on an individual, dying from pneumonia, in whom there was an exophthalmos of long standing which was originally due to exophthalmic goiter. The other symptoms of this disease had long since disappeared, but the exophthalmos remained to a marked degree. The thyroid was normal in size, colloid appeared rather deficient. The two chief abnormal features recognized in microscopic sections of the gland were a marked vascularity and an increase of the glandular tissue at the expense of the colloid. The acini varied a good

deal in size, and were lined with cubical or columnar cells, both being represented in one acinus in many places. The cubical cells predominated, and the columnar cells stained more heavily with hematoxylin and had the appearance of more recently formed elements. The thymus was persistent but small. The spleen was normal, and a small accessory spleen was found. The pituitary and adrenal glands showed no macroscopic lesions, and were normal in size and texture. There was no enlargement of the lymphatics, and the cervical ganglia showed no change. The heart was normal, and there was no thickening, hardening, or dilatation of the blood vessels. On removing the supraorbital plates nothing unusual was found. Owing to the protrusion of the eyeballs, the retro-orbital space was abnormally deep. It was filled with fat.

[**THYROID Disease, Blood Changes.**] Sandelin (T.) *Finska Läkares. Handl.* (Helsingfors) 1916, lviii, 1076.

Carefully made blood studies in exophthalmic goiter and thyro-toxicosis do not indicate that the findings are of special value. Thirty-two cases were examined, the counts being made under uniform conditions (early morning, fasting, etc.) and the technic was carefully checked. Numerous second specimens were examined after operations on the thyroid, but with practically no diagnostic profit.

THYROID Gland, Acute Atrophy. Eve (F. C.) *Brit. Med. Jour.* (Lond.) 1914, ii, 583.

A woman aged 40, had had goiter for 5 years. It was greatly aggravated each spring after influenza, with exhaustion and high fever. There was great variability of the symptoms throughout. The blood pressure ranged from normal to 240 millimeters, and the pulse from 100 to 200 per minute. The weight was inconstant and the catamenia irregular. There was intermittent exophthalmos, headache and pigmentation of the skin. The sleep and strength were very variable. This was accompanied by alternating diarrhea and constipation. Two days before death the thyroid which was four inches in diameter, began to undergo autolysis and on his last day was impalpable.

The reporter compares this with a similar phenomenon which he has observed before death in lymphadenoma, with another case of obscure fever in a woman with a large goiter which atrophied rapidly during the last week of life and with still another case, of Graves' disease, which died two months after an attack of diarrhea, fever and severe wasting, during which the goiter vanished entirely.—T. A. W.

THYROID in the Insane, Weight of Gland. Kojima (M.)
Brit. Med. Jour. (Lond.) 1915, i, 804.

Kojima weighed the thyroid glands obtained at autopsy in numerous cases, and found that the average weight in the non-insane individuals was about 22 to 25 grams. In insane persons, however, the average weight was much less, approximating 16.5 grams in the male and 16.87 grams in the female. Attention was called to the great variation in weight of the thyroid among different classes of the insane, especially in females.—T. A. W.

ADIPOSIS DOLOROSA, Contribucion al estudio... Pizarro
(R. G.) Sem. Medica (B. Aires) 1916, xxiii, 347.

Pizarro suggests that clinical experience seems to indicate that syphilis is a likely etiological factor. In a case carefully outlined here, it was found not only that the patient was syphilitic but that suitable antisyphilitic treatment caused an almost complete disappearance of the pain and later of the adipose masses.

MYXEDEMA and the Nervous System. Pitfield (R. L.) Am.
Jour. Med. Sci. (Phila.) 1916, cli, 409.

The administration of thyroid does not always yield the same effect, e. g., in one woman it brought on an increase in weight and depressed the libido sexualis. In myxedema it fails to bring back complete mental acuity and well being.

Athyrosis is always accompanied by anemia, nervous depression, and weakness. It may stimulate neurasthenia, pernicious anemia, and dropsical nephritis. It may induce cardiac decompensation and glycosuria.

Women who have borne children, and women at the climacteric are most frequently affected. Often a history of thyroiditis, scarlet fever, or hereditary syphilis has been obtained. The best results are obtained with women under 45.

Pitfield reports five cases to illustrate his theses.

G. H. H.

PHARYNGEAL PITUITARY, Clinical Possibilities. Clinical Relation of Naso-pharynx to Hypophysis-System. Bryant
(W. S.) Med Record (N. Y.) 1916, xc, 441.

Bryant states that there is a pharyngeal hypophysis present in the pharynx of all individuals. It is located in the median line of the pharynx in close association with Luschka's tonsil. In the adult the average size of this body is about 5 mm. long, from 1-4 to 3 mm. wide, and from 1-5 to 1 1-2 mm. thick. This he believes to have the same function as the cerebral pituitary. In the proof of this Bryant gives the

following data: The pharyngeal pituitary is a part of the hypophysial system representing the lowermost extremity of Rathke's pouch, the hypophysial pedicle of the embryo, which, failing to emigrate through the cranium, has not disappeared through retrogression, but has become organized, in man, into a true glandular body in the pharynx. The phylogenetic history of the hypophysial system shows that in the lowest vertebrates, the glandular lobe, itself a portion of the primitive pharynx, is in open communication with the pharynx. This communication is usually lost in the ascending scale, by the chondrification of the base of the skull, but remnants of hypophysial tissue remain along the route traveled by the embryonic hypophysis from the cotodermic unlage to the brain.

The pharyngeal pituitary resembles the glandular portion of the cerebral pituitary. Cetelli has found indirect circulatory connections between the pharyngeal hypophysis and the cerebral hypophysis, through a venous plexus in the sphenoid body. In cases of atrophy of the cerebral hypophysis, the pharyngeal hypophysis very significantly is sometimes found to be in a state of hypersecretion. Bryant believes that its physiological significance is explained by its relation to Waldeyer's ring. Consequently in infections of the naso-pharynx the function of the pharyngeal pituitary is interfered with, and on treatment of the naso-pharynx—either by removing the tonsils and adenoids in a chronically inflamed throat or by medical treatment—with the clearing up of the infection the patient gets the pituitary effect, namely, more rapid growth and improved nutrition as well as the local improvement. He found that stimulation of the pharyngeal pituitary by chemical means and injection of hypophysial substance into the system gave similar remedies.

C. E. E.

THYROID-PARATHYROID Apparatus, Function of. Kendall (E. C.) *Jour. A. M. A. (Chgo.)* 1916, lxxvi, 811.

The author first calls attention to the hypotheses of Plummer, viz: 1. In thyroid disturbances the effects are due to a change in the rate of normal function. 2. The stimulating effect of increased thyroid activity is not felt in any particular set of organs or tissues alone, but the stimulus is active throughout the body. 3. The stimulating action is intracellular.

Kendall then suggests the possible formula, di-iodo-dihydroxy-indol for the crystalline substance obtained from thyroid gland and possessing the physiological activity attributed to the gland. He here suggests, as the result of his

studies, that the function of the parathyroid is to convert ammonium carbonate into urea, and states that we may conclude that the function of the thyroid is to furnish a catalyzer which regulates the rate of deamination.—F. C. P.

HYPOTHYROIDISM a Factor in Certain Uterine Hemorrhages. Salzman (S) Am. Jour. Obs. (N. Y.) 1916, lxxiv, 812.

Salzman believes that certain uterine hemorrhages are the result of an alteration or lack of one or more of the hormones which control the normal uterine flow. He believes that uterine hemorrhage in which there is no discernible pelvic disease or pathology (and in which there is no evidence of the so-called "hemorrhagic states") is due to a deficiency in the secretion of the thyroid gland.

Accordingly such a hemorrhage should be controllable by the judicious exhibition of thyroid gland and this author reports six cases of hemorrhage of this character which substantiate his opinion.—W. H. M.

THYROID, Goitre exophthalmique développé à la suite d'un violent traumatisme de l'épaule. Duplant (M.) Presse Méd. (Par.) 1916, xxiv, 333.

Duplant reported to a recent Réunion Médicale de la Ire Armée the case of a young soldier, 21 years old, suffering from digestive troubles and also manifesting characteristic symptoms of Graves' disease which resulted from a fall while doing some carpenter work. His clavicle was fractured. The tachycardia appeared first, later the goiter and finally a well-marked exophthalmos. Added to this there was a typical trembling, the whole constituting a complete Graves syndrome. Duplant believes that the shock on the shoulder and the base of the neck caused a lesion of the cardiac nerves which was really the origin of the malady since the various other factors were carefully ruled out.

HYPOPITUITARISM, Dystrophia adiposo-genitalis, etc., with Positive Wassermann. Fearnside (E. G.) Proc. Roy. Soc. Med. (Lond.) 1915-16, ix, Sec. Neurol. 50.

Fearnside believes the syphilis is a not infrequent etiological factor in pituitary disease and reports a case with Froehlich's syndrome in which the serum reacted positively to the Wassermann test.

HYPOPITUITARISM, Its Relation to Epilepsy. Tucker (B. R.) Va. Med. Semi-Mo. (Richmond) 1916, xxi, 1.

A clinical paper, containing nine case reports tending to show that the pituitary may be a factor worthy of consideration in certain cases of epilepsy. According to Tucker, "the

study of hypopituitarism in its relation to epilepsy is a distinct advance as it separates a class of helpable epilepsy."

A number of cases were fed pituitary substance with noticeable changes in the number and frequency of attacks. In several instances discontinuance of the extract prompted a return of the symptoms.

The preparation used was an anterior lobe extract, the dose ranging from 10 to 30 grains a day.—H. R. H.

(THYROID) Scleroderma with Graves' Disease. Sequeira (J. H.) *Proc. Roy. Soc. Med. (Lond.)* 1915-16, ix, Sec. Dermat., 66-68.

Sequeira reports a case of hyperthyroidism in which typical scleroderma was present.

(GOITER) Endemischen Kropf im Königreich Bayern. Weichardt (W.) and Wolff (M.) *Münch. med. Wchnschr.* 1916, lxxiii, 309.

As a result of extremely painstaking investigation, proof is offered by these writers that geologic conditions have no influence whatever upon the incidence of endemic goiter in Bavaria.

(PITUITARY) Hypophysistumoren. Josefson (A.) *Klin. Monatschr. f. Augenheilk. (Stuttgart)* 1915, lv, 636.

This is a clinical consideration of the pituitary tumors and deals particularly with the eye findings—bitemporal hemianopsia, and other evidences of intracranial pressure such as choked disc, optic atrophy, and eventually total blindness.

(THYROID) Influence of Tonsil and Adenoid Abnormalities on Health. Clevenger (W. F.) *Lancet-Clinic (Cincin.)* 1916, cxv, 549.

Chronic tonsillar disease is a frequent cause of thyroid hypertrophy and also torticollis in childhood, and obviously the effective treatment of thyroid disorders must necessarily involve a careful examination of the mouth and tonsils and the treatment or removal of these organs if seriously diseased.

HYPERTHYROIDISM, a Cause of Death. McGuire (S.) *Va. Med. Semi-Mo. (Rich.)* 1916-17, xxi, 27.

Of the last hundred thyroid operations performed by Stuart McGuire, there were five fatal cases, despite anociassociation, the division of the operation into several stages and the utmost care and gentleness. This writer is somewhat pessimistic, stating that his mortality is steadily increasing since in his first series of one hundred he had no deaths. He be-

lieves that he is getting a larger and larger number of bad risks.

The paper is accompanied by a consideration of the pre- and post-operative procedures and a discussion of the various measures at present being used in the treatment of this disease. Unfavorable opinions regarding the X-ray are being changed by the introduction of the Coolidge tube, and McGuire now relies more on the X-ray than on any other one factor save rest.

(PITUITARY) Pathogenesis of Some Confusional States.

Williams (T. A.) *Internat. Clinics.* (Phila.) 1916, ser. 26, ii, 173.

Among the numerous causes of confusion considered in this paper is disordered internal secretion. Of this pathogenesis there are reported a number of cases:

(1) A case of narcoleptic confusion in an adolescent boy (17) possibly of pituitary origin and causing suspicions of dementia precox but recovering fully after some years.

(2) Clear cut narcolepsy from hypopituitarism in a young woman of 25, complaining of pain in the back and dragging of the legs, absent-mindedness, marked amnesia, heavy headaches sometimes of a "bursting" character deep and low in the head, and torpor, often extreme and sudden enough to cause a fall. Intoxicated feelings with singing and absurd speech, blurring of vision, great adiposis with tenderness (weight gained in 3 months was 53 pounds), asymmetry of limbs, increased reflexes, visual field contractions and a deep sella turcica. Radiotherapy relieved the narcolepsy, headaches, visual fields and amnesia, but not the adiposis.

(3) Preadolescent hypopituitarism. A girl of 11, lost interest in her lessons, grimaced, fibbed to avoid duties, became gluttonous and very stout, later corpulent. Three hundred grains of levulose produced no glycosuria. Recovery ensued upon pituitary feeding which was dispensed with at puberty. She is now well, five years later.

(4) A woman age 32, suffering from undue anxiety causing exhaustion and confusion with tremor. Prominent eyeballs, congested lids, tachycardia, Moebius' sign. All symptoms aggravated by hormotone. Recovery while taking secretogen. Allusion is also made to the confusion of hyperthyroidism, but it is not considered in detail.—T. A. W.

GOITER and Life Expectancy. Mayo (C. H.) and Plummer (H. S.) *Lancet-Clin.* (Cincin.) 1915, cxiii, 649.

Of the simple goiters including the thyrotoxic (non-hyperplastic) type, there were 934 operations performed on 926 patients with 5 deaths, all of which occurred in patients

with thyrotoxic degenerations. Of the exophthalmic goiters there were 386 patients given operative treatment; of these there were 22 injections with hot water, with two deaths, 19 double ligations without mortality, and 388 single ligations, with two deaths.—J. D.

THYMUS Disturbance in the Adult. Hoxie (G. H.) N. Y. Med. Jour. 1916, ciii, 676.

This writer relates the history of a number of cases in which the condition had been diagnosed as neurasthenia or myasthenia. This group of cases has in common enlargement of the thymus, shortness of breath and extreme weakness, but shows no gross pathological changes. Variability of the pulse and blood pressure, subnormal temperature, and atony of the gastrointestinal tract, in patients showing no evidence of organic disease, are additional symptoms pointing to the endocrine dysfunction. The dullness is usually noticed when percussing the manubrium sterni. If the dull area extends out a half inch or more on either side of the manubrium, and if the manubrium is duller than the corpus, one should proceed with differential tests. Gentle percussion rather than the stronger type is necessary to bring out a body so closely adherent to the posterior surface of the bone. Under such ordinary percussion the dull area is that of a triangle with its base just below the interclavicular notch and its apex between the junctions with the sternum of the second and third ribs. The aortic dullness does not reach as high as the center of this area and does not lie as symmetrically under the sternum. An intrathoracic thyroid might give a similar dull area, but this could usually be found to extend above the interclavicular notch and move with the act of swallowing. Aneurysms of a size sufficient to cause substernal dullness would give also a thrill of pulsation. The fluoroscope should be used to verify all cases in which the percussion would indicate thymic enlargement. In making this examination, when one sees a mass in the sternum, one should keep in mind the questions: "Does it have a movement of its own? Does it have a definite form through which the bones are seen more indistinctly?" The treatment of the condition demands rest and forced feeding, with attention to the emunctories and the environment. The medical treatment calls first for the use of arsenic in heavy doses. It would seem as if the thyroid gland furnished the best material to permit the thymus to sink back into quiet. This the author has worked out by trying the various glandular extracts. He says one would suppose that the adrenal extracts were of particular value, but thus far this has not been clinically verified.

PITUITARY and Renal Function. Motzfeldt (K.) Boston M. & S. Jour. 1916, clxxiv, 644.

Certain cases of diabetes insipidus treated with pituitary extract and observations on normal individuals lead to the conclusion that the pituitary controls both the quantity and certain of the solids of the urine. In the cases of diabetes insipidus, posterior pituitary therapy reduced the excessive amount of urine and increased its concentration. In the absence of radiographic findings in the sella turcica Motzfeldt supposes that the essential disorder is a hypofunction of the posterior lobe.

A number of experimental injections of pituitrin in healthy individuals caused changes on the urine both as to amount and total solids. According to Motzfeldt the effect of the posterior lobe of the pituitary on renal function may be explained in part by a direct effect upon the kidneys through the circulatory system and part by an influence upon the sympathetic nervous system and, perhaps, in part by an influence upon the other glands of internal secretions.

(THYROID) Traumatichem Morbus Basedow. Schulzinger (E.) Münch. med. Wchnschr. 1916, lxiii, 473.

A clinical consideration of Graves' disease following wounds of war

(ADRENALS) Traumatichem Morbus Addisonii. Leszcziner (H.) Virchow's Arch. (Berl.) 1915, ccxxi, 67.

A comprehensive consideration of Addison's disease the result of localized trauma.

(GOITER) Etiologia del gozzo endemico e del cretinismo; ipotesi di lavoro. Arcangeli (U.) Rivista Osped. (Rome) 1916, vi, 33.

The author agrees with other writers, notably Kutschera (Münch. med. Wchnschr, 1913) that endemic goiter does not originate from water, nor is it hereditary. His hypothesis is that it is really an infection, due to a transmissible protozoa carried by some intermediary host which, according to Arcangeli is probably the bed-bug.—H. R. H.

(PITUITARY) Morbid Somnolence and its Relation to the Endocrine Glands. Dana (C. L.) Med. Record (N. Y.) 1916, lxxxix, 1.

A clinical consideration of somnolence as a not infrequent manifestation of endocrine disorder. Several cases of pituitary disease in which this symptom was prominent are discussed.

THERAPEUTIC EXPERIENCES

(THYROID) Ueber die Behandlung der weiblichen Unfruchtbarkeit. v. Fellenburg (R.) Cor. Bl. f. Schw. Aertze. (Basle) 1915, xlv, 1409.

It is believed that in certain cases of sterility in the female, the chief disorder is connected with the endocrine glands. Because of the intimate physiological relationship of the thyroid and the gonads, von Fellenburg administered thyroid extract to a number of cases of sterility with no apparent cause. Conception followed in several of these. It is also remarked that this form of treatment brought about good results in cases of habitual abortion. Those to whom this treatment is given should be kept under close observation, the heart being watched and blood counts made from time to time.—H. R. H.

(ADRENALIN) Cura della nefrite con l'adrenalina nella pratica di condotta... Borelli (G. B.) Il Policlinico (Rome) 1916, xxiii, 574.

Three cases of nephritis, two acute and one chronic, were treated with adrenalin per os with remarkable benefit. One case, a child of 5, received one mil. of the 1:1000 solution daily in four doses. Two adults, aged 50 and 62 respectively, received two and a half mils. in five equal doses suitably spaced.

This confirms the experiences reported five years ago by Ercolani, who was among the first to recommend adrenalin by mouth for the treatment of nephritis and to emphasize its convenience and harmlessness.

EXOPHTHALMIC GOITER, Radium Treatment. Aikins (W. H. B.) Med. Record (N. Y.) 1916, xc, 334.

It is pointed out that in many refractory cases of exophthalmic goiter that do not respond satisfactorily to other methods of treatment, radium is of benefit.

Aikins' own clinical experience showed that when radium was applied over the thyroid the more penetrating radium rays diminished the vascularity and reduced the size of the gland.

Dawson Turner thinks that radium has two definite advantages as compared with the X-rays, namely: 1. The possibility of giving definite doses. 2. The fact that it can be applied without noise or excitement while the patient remains quietly in bed.

C. E. E.

GRAVES' DISEASE. Treatment by Roentgen Ray. Seymour (M.) Boston M. & S. Jour. 1916, clxxv, 568.

Of the 80 cases under treatment at the Massachusetts General Hospital all showed improvement except 7. Five of these showed no change. Of the 80 cases 8 were completely cured of their symptoms. They use a dose of 4H (equals 4 Holz knecht, or 10x Kienbock, or 1B Sabouraud-Noire). This produces a slight erythema, but no skin irritation. The target is 10 inches from the skin with a filter of 4 mm. of aluminum and 1 thickness of sole leather. The dose is not repeated within 3 or 4 weeks. Seymour also finds the evaluation of the basal metabolism of distinct value as an index of thyroid activity. Five cases of extra-cervical ribs were found in the 144 cases studied but no symptoms could be traced to this abnormality.

G. H. H.

EXOPHTHALMIC GOITER, Roentgen Treatment. Pfahler (G. E.) and Zulick (J. D.) Penn. Med. Jour. (Athens) 1915-16, xix, 661; *ibid.* Am. Jour. Roentgenol. (Detroit) 1916, iii, 63.

After a very complete review of the literature of the subject, the authors point out that although many cases of exophthalmic goiter have been treated by Roentgen rays, conclusions as to the efficacy of the treatment are risky owing to the great variability in the technic employed.

The authors believe that the X-ray has a field of distinct usefulness in the treatment of this form of goiter. A preliminary roentgenogram of the chest should be made in all cases in order to obtain some information as to thymic size and as to substernal extension of the goiter. When the thymus is not found enlarged, a single dose directed through the sternum will be sufficient. When it is enlarged, the rays should be passed through two fields on either side of the median line below the clavicles, including the first, second and third spaces.

The dosage must be carefully regulated so that the total amount given the patient is known. The series decided upon should not be repeated inside of three or four weeks. Sometimes it is advisable to divide the treatment so as to give a dose through only one or two fields at a time. After there is a distinct improvement in the symptoms, the interval should be prolonged, for there is danger of reducing the secretion of the gland to the extent of producing the symptoms of hypothyroidism.

The authors conclude their study as follows:

We believe that the trial of treatment for one series with an interval of waiting of one month is justifiable in all

cases, for if operation is decided upon nothing is lost, and many operations in this way can be avoided.

Treatment should be directed toward both the thyroid and the thymus glands.

An increase in weight and a decrease in pulse rate are the first signs of improvement and are practically always found.

Treatment must not be prolonged over too great a period or hypothyroidism may be produced.

The goiter and the exophthalmos are the last to show improvement, and in many cases show no change.—A. J. S.

THYMUS Hypertrophy, Roentgen Therapy. Cook (P. H.)
Boston M. & S. Jour. 1916, clxxv, 483.

Cook reports three cases of enlarged thymus in small children, which were affected favorably by X-ray treatment. His conclusions are based on deductions of Lange, which he endorses: Roentgen irradiation of the thymus produces artificial involution of the gland. X-ray therapy is the method of choice in cases of enlarged thymus in children, whether the symptoms be mild or urgent. Urgent cases should receive repeated massive doses. Recurrences due to regeneration of the gland are to be looked for and controlled by further treatment. Children whose physical or mental development is retarded should, if suspicion is directed toward the thymus, receive tentative X-ray treatment even though a positive diagnosis cannot be established. X-ray therapy as a precautionary measure, or preoperative treatment may enable children of the so-called lymphatic type to withstand intercurrent disease or anesthetics, which would otherwise prove fatal. Preoperative exposure of older children and adults, where there is a suspicion of enlarged thymus, might lessen operative mortality. Routine preoperative X-ray treatment in cases of hyperthyroidism should be resorted to with a view to lessening operative mortality. X-ray exposure of the thymus gland has proved harmless, whether in normal or abnormal subjects; a therapeutic test with the X-ray is, therefore, always permissible.

PARATHYROID Treatment of Paralysis Agitans. Berkeley (W. N.) Med. Record (N. Y.) 1916, xc, 105.

Further clinical experience by Berkeley appears to justify the opinion previously expressed, that parathyroid gland is not a "cure" for paralysis agitans, but that 60 to 70 per cent. of the sufferers from this disease who have given the remedy a fair trial for a minimum of from three to six

months have been greatly benefited, and that in such patients the progress of the disease has been arrested, or very materially retarded.

One patient, an elderly man, has taken the capsules for seven years (also the hypodermic solution at times), and he is still in fairly good condition, but lapses into helplessness within a few days when the medicine is omitted.

Another recent case, a woman fifty-two years old, has done very well. Her agitation has been entirely arrested, and the rigidity greatly relieved. She had suffered with the disease for two years before Berkeley saw her, and had spent all of her money on osteopathic and electrical treatments; so that, if suggestion had anything to do with her case, she certainly had ample opportunity for full exercise of her imagination before undertaking the parathyroid medication.

There are no other internal secretions which have any specifically beneficial effect whatever—either alone or in combination—in paralysis agitans. Among the older patients pineal gland is a useful stimulant to functionally failing mental activity, and there is now on the market one extract of pancreas which is valuable in the peculiarly obstinate constipation these patients are afflicted with. But this writer cannot too strongly deprecate promiscuous dosing with thyroid, and pituitary, and others of the internal glands. Thyroid, especially, does serious harm; even massage of the neck over the thyroid gland sometimes liberates enough of the thyroid secretion to make the patient quite uncomfortable.

Like most chronic diseases, paralysis agitans does not do well in institutions, for reasons which are sufficiently obvious. The most successful cases have been in private practice, where cheerful surroundings, occasional opportunities for travel, and a varied diet contribute to the patient's comfort, and increase his resisting power. But a fair proportion even of the almshouse poor have been greatly helped.

Berkeley still believes, as he has done for a long time, that paralysis agitans is caused by a deficiency of the parathyroid glands, and that further and more diligent study of the complicated chemical processes involved will make it ultimately possible to cure paralysis agitans with parathyroid in just the same way in which cretinism is cured with thyroid.

PITUITRIN. Cogburn, (H. R.) *New Orleans Med. & Surg. Jour.* 1916, lxxviii, 738.

This writer discusses the clinical value of pituitrin and then emphasizes its possible dangers if administered in too great dosage and too early in the course of labor. If used intelligently it is a remarkable remedy.—W. B. T.

(PITUITARY) Ueber Kachexie hypophysären Ursprungs.
Simmonds (M.) Deut. med. Wchnschr. (Berl.) 1916, xlii, 193.

Two cases of cachexia at autopsy were found to have total destruction of the pituitary body as the sole discoverable cause of the condition preceding death. One case originated from an old embolic process and the others from new growths. (Simmonds also refers to several pituitary cases discussed in a previous paper). It is suggested that empirical pituitary medication might properly be given in cases manifesting progressive cachexia in which no well-defined cause can be discovered.

(THYROID) Sindrome da insufficienza tiro-paratiroidea familiare. Laureati (F.) *Pediatrics* (Naples) 1916, xxiv, 411.

This writer agrees with the belief of Concetti that there is a normal physiologic insufficiency of the thyroid in the newly born. It gradually is overcome either by the development of the child's thyroid or by its getting in the mother's milk the products of her sound thyroid. If the mother or wet nurse has thyroid insufficiency, the child may suffer from lack of thyroid secretion and fail to thrive unless given to another woman to nurse. The infant may present symptoms of thyroid deficit or thyroid excess, or there may be abortive forms or a subphysiologic thyroid state. One young woman had no symptoms suggesting thyroid trouble until she became pregnant when she gained 44 pounds in weight. Her weight dropped back to normal after the birth of the child, but she was not able to nurse it long, and suffered from tremor and insomnia. The child did not thrive until a wet nurse was provided, when it began to gain at once and was soon placid and sturdy. In another pregnancy the woman had the same temporary increase in weight.

Laureati thinks there can be no doubt that thyroid insufficiency was responsible for the abnormal conditions in both mother and child. He remarks that Concetti noticed that thyroidectomized goats were unable to suckle their young adequately, but produced more milk under thyroid treatment. Their milk production dwindled again when the thyroid treatment was suspended. Laureati relates that a woman developed an incomplete type of exophthalmic goiter at the close of the last three of her six pregnancies. The disturbances persisted for three months and her nursling during this period became restless and lost flesh, with digestive disturbances and debility. Under phosphorus and thyroid treatment, with bromids, for the mother and artificial feeding for the child, the trouble was soon broken up. By the tenth month the child's progress was normal in every respect. In

both these cases the infants presented symptoms of the same type as the mother.

In another family, the first four of the six children of a healthy country couple grew abnormally in length and weight during the first months of life, and had laryngospasm when 4 or 5 months old and two died in convulsions. After weaning, the children became normal in weight and growth generally. As term approached in the sixth and seventh pregnancies, Laureati gave the mother a course of thyroid treatment and the children developed normally and had all the appearance of health. The right lobe of the mother's thyroid is somewhat hypertrophied, but she has never presented any symptoms suggesting exophthalmic goiter. The convulsions and tendency to tetany in this family suggest that the parathyroids in the infants were insufficient. Schiffer has reported the case of a family with five children all of whom had tetany in infancy when they were given artificial feeding but not while they were nursing their mother. Her milk evidently supplied antibodies which maintained the proper balance. When this was withdrawn, tetany manifested itself. Thyroid treatment is not only useful in warding off or curing the syndrome from thyroid and parathyroid insufficiency, but it serves also as a touchstone to reveal the true cause of abnormal development of nurslings and prove its direct dependence on the internal secretion of the thyroid gland in the nursing woman. Measures to restore thyroid functioning to normal tend to restore the balance in the endocrine system.

J. A. M. A.

TESTICLE Grafting. Unexpected Results. Morris (R. T.)
Jour. A. M. A. (Chgo.) 1916, lxvii, 741.

The patient, aged 27, lost both testicles from a complication of mumps at 13 years. He was alert and mature mentally, but physically somewhat undersized and youthful in appearance and voice. The prostate gland could not be found to be present. The scrotum was shriveled and apparently quite empty. The penis was small, the skin wrinkled and the pubic hair sparse.

The graft was taken from a hernia patient, 54 years old, and consisted of a wedge-shaped segment of testicle. It was sliced into three parts, each about 3 mm. in thickness, and one was placed beneath the sheath of the left rectus abdominus, another into the right rectus and the third was introduced into the right side of the scrotum by an incision down to the remains of the testicle, of which there was barely a trace. In the left scrotum was placed a celluloid testicle to produce an effect of mass on that side.

The patient did not observe any immediate effect and the portion inserted into the right scrotum began to undergo absorption. With its disappearance, however, the vestige of the original testicle began to enlarge and is now grown to be one-third normal size and apparently still growing. It is softer than normal, but besides the growing testicle there is a growing epididymis and an enlarging spermatic cord on that side. Another graft was made last March, and this afforded a chance to observe that the newly developing testicle was quite normal in contour, with normal appearing tunic and vessels. Coincident with the development of the testicle other evidences of its presence gradually became more marked and the patient has recently consulted in regard to marriage. The morning erections are full, normal and frequent. The wrinkled skin of the penis has changed to a normal smoothness, with increased size of the organ. There is apparently a little line of prostatic tissue to be made out at the site of the prostate gland; but as yet there is no change in the voice.

The unique feature of this case, and the one which introduces perhaps an entirely new principle, is the fact of stimulation of the vestigial testicle into development. It is possible that this resource may be employed on other patients who have lost testicles from mumps, and perhaps on patients who have undescended testicles after the latter have been placed in the scrotum by some operative procedure. Another question also arises. It is possible, says Morris, that in some cases of ovarian grafting the ovum has been furnished not by the graft, but by latent cell rests in the broad ligaments, which have been stimulated to activity by its influence.—F. C. P.

(ADRENALS) *L'asystolie surrénale.* Josué (O.) Paris Méd. 1916, vi, 7.

Autopsies made in four cases of sudden death from cardiac insufficiency showed the myocardium much hypertrophied and apparently strong, not at all the aspect of a muscle that had given out from weakness, and nothing in the vicinity could be found to explain the heart failure. On the other hand, the adrenals were always extremely small or diseased in these cases, and so Josué presumes that the heart was suffering from lack of physiologic stimulus for its contractions supplied normally by the adrenals. This adrenal asystoly, as the resulting syndrome is termed, is characterized by a large heart with low arterial pressure. Drawing the finger or a stick along the skin leaves a white mark instead of the usual red mark. There is often complete arrhythmia and auricular fibrillation, with more or less dyspnea.

Digitalis has little effect in these cases, but adrenal extract had a manifest beneficial action. Early and systematic treatment with it may ward off or retard the otherwise inevitable fatal termination.

Josué details three such cases showing the marked improvement under adrenal treatment. The white line disappeared in two or three days and the blood pressure rose. It seems that the adrenals are exhausted by their efforts to supply the physiologic stimulus to the enlarged heart, but tuberculosis is probably also a frequent factor in the hypoadrenia. Three of his seven patients with adrenal asystoly had tuberculous lesions. In treatment it is necessary to distinguish which of the symptoms are to be ascribed to adrenal incompetency and which to cardiac incompetency and then give adrenal treatment or digitalis accordingly. Extract of the total gland seems to act quicker and better than adrenalin alone. It was given by mouth, 0.4 gm. a day, in two doses, or by subcutaneous injection of 1 mil. a day. This treatment not only supplies the lacking physiologic stimulus for the heart but also aids the adrenal glands to recuperate.

ADRENALINE, Action dans le blocage complet du coeur.

Danielopolu (D) and Danulescu (V.) *Presse méd.* (Par.) 1916, xxiv, 503.

The experimental research of these writers was carried out in Bucharest and reported last May before the Biological Society of that city. They gave adrenalin following accidents resulting from cerebral anemia due to heart block. The effect of this remedy is not so good in cases with complete dissociation as in incomplete block. The dosage should be sufficient to produce a rapid effect and for this the authors recommend one or two milligrams of the chloride of adrenalin, by subcutaneous injection.—H. R. H.

(ADRENAL) Réaction surrénale et vaccination antityphique.

Loeper (M.) *Presse méd.* (Par.) 1916, xxiv, 463.

Accidents in connection with the antityphoid inoculation of many thousands of French soldiers do not seem to be common. One in every 400 or 500 is perhaps a generous figure. These occasional cases, however, usually suffer from acute adrenal insufficiency with varying degrees of collapse, hypotension, etc.

Sufficient cases have been studied by Loeper and others to advance some suggestions regarding etiology and treatment. Certain individuals acquire a lowered resistance as a result of the experiences of trench life—their “résistance capsulaire,” as Loeper calls it, is reduced. When the anti-

typhoid inoculation is made, such individuals are unduly sensitive and acute hypoadrenia may supervene. In such cases adrenalin is both prophylactic and curative; and to obviate these rare but disconcerting experiences Loeper recommends the following procedure:

1. Take the blood pressure as often as possible before vaccination.

2. Do not inoculate tired or worn-out individuals, until they have had a good rest.

3. Give such cases (with lowered tension) a preliminary dose of adrenalin some hours before the vaccine.

4. Watch the post-vaccinal tension in suspicious cases, and give more adrenalin to those with a "secondary hypotension."—H. R. H.

ADRENALIN in Collapse following Antityphoid Vaccination. Jour. A. M. A. (Chgo.) 1916, lxxvii, No. 11.

In the Paris Letter to the Journal of the American Medical Association is reported the communication of Lian made to the Réunion médicale de la IV-e Armée in which he outlined two accidents resulting from mixed antityphoid and antiparatyphoid vaccination. There was a general syndrome of an acute adrenal insufficiency, namely, fever, headache, vomiting, profound depression, vertigo, faintness, very low arterial pressure, Sergent's "white line," and in the more serious one, hiccough, epigastric and lumbar pain, oliguria and albuminuria. These troubles disappeared in four days in one patient, and in twelve in the other. Although the appearance of this intolerance is difficult to explain in these two patients (there being no contraindication and no marked reaction in other subjects treated with the same vaccine), the clinical character of these manifestations is not surprising. It is a rule to see typhoid and paratyphoid infection accompanied by profound depression and very marked arterial hypotension. One can, therefore, understand that in case of intolerance of injection of sterilized cultures of typhoid and paratyphoid bacilli, there should occur a syndrome of acute adrenal insufficiency. For these reasons, Lian is inclined to believe that in this exceptional reaction of intolerance to typhoid and antityphoid vaccines, there is a great fall of arterial pressure, and he recommends in such cases, if the pulse is small and easily obliterated, the subcutaneous injection of adrenalin chloride solution (from two to four injections of 0.5 mg. in 24 hours). It is to be hoped that this treatment will give as good results in such cases as in the analogous but more serious and more frequent accidents accompanying the intravenous injection of salvarsan and neosalvarsan.

In the discussion which followed Levy stated that he had observed in a man, aged 35, as the result of an injection of antiparatyphoid vaccine, threatening collapse, a temperature of 40.2 C. (104.4 F.) pulse uncountable and cyanosis of the extremities. In this case, the administration of adrenalin gave the happiest results. Nevertheless, Levy is of the opinion that to attribute these symptoms entirely to adrenal insufficiency may be going a little too far.

(THYMUS) Corea minor. Aetiologie og pathogenese. Haneborg (A. O.) Norsk Mag. f. Løgevid. (Christiania) 1916, lxxvii, 1040.

Haneborg gives the details of sixty-nine cases of chorea, and then discusses the views of various writers as to its etiology. He believes that the hysteric form is rare and is accompanied by other signs of hysteria, and that it often occurs from imitation. One feature peculiar to chorea minor is that it begins exclusively in children. Adults can develop acute rheumatism, but never chorea. The chorea age, it is emphasized, is from 2 to 16, and this age is just the period of activity of the thymus gland. May it not be possible that chorea is the result of deficient or perverted functioning of the thymus gland? Does the thymus gland contain substances which have a tranquilizing influence on the nervous system, so that any deficiency in its internal secretion may leave the nervous system in the young free to behave abnormally? The adult nervous system has acquired a stable balance so that it does not suffer from lack of thymus functioning.

According to Haneborg it seems plausible to assume that with acute articular rheumatism or any other acute infectious disease the thymus may suffer. It need not inevitably suffer but, if it does, its secreting function may be impaired and the unstable nervous system of the child may feel the lack of the normal restraining influence from the thymus. The nervous system is thus left free for exaggerated reflex irritability, and we have the clinical picture of chorea. Thymus extract seems to have a sedative influence on the nervous system. Vetlesen has been giving it systematically to patients with exophthalmic goiter, finding it decidedly beneficial, and Haneborg has given it with good effect to control convulsions. He mentions the case of a congenital idiot who had had for years from fifteen to thirty convulsions a day, rebellious to all measures, until they subsided under a course of thymus treatment. They returned later, but milder, and only one or two a day. After a second successful case of convulsions subsiding under thymus treatment, this writer

began to treat chorea with thymus, and the clinical histories here reported show the abrupt turn for the better when this was done. Sixteen hospital patients were given the thymus treatment and several in his private practice. The results were most satisfactory, both in the infectious and in the hysteric form of chorea, even in cases of many months' standing. The choreic movements returned in one case when the treatment was suspended after a week, but subsided anew when it was resumed.

It is not presumed that the thymus is the only etiological factor in chorea, but that an insufficiency in the functioning of this gland may be the drop that makes the cup spill over—upsetting the unstable balance of the immature nervous system, and allowing the play of uncoordinated, choreic movements. There is much to sustain the assumption that an infection is the primary factor, perhaps an infectious encephalitis. But this alone does not bring on chorea, as otherwise chorea might occur in adults. The additional factor which imprints the chorea stamp on the clinical picture is thymus insufficiency, and thymus treatment may do away with this factor. He advises the salicylates at first for two days if there are rheumatic pains and fever; otherwise not. At the same time he gives from three to six thymus tablets daily—a child of 10 getting four or five a day. He suspends the thymus treatment when the jerking movements have ceased.

In two cases of pregnancy chorea, the jerking movements subsided under thymus, without other measures, as he expected, but in two cases of tic convulsif, a purely nervous affection, no effect was apparent.—J. A. M. A.

(THYROID) Opoterapia tiroidea en retracciones tendinosas post-reumaticas. Pizarro (R. G.) Sem. medica (B. Aires) 1916, xxiii, 445.

A girl of fifteen had suffered three severe attacks of acute articular rheumatism, the last of which left a contracture of the tendons of both hands, rendering them useless. When various anti-rheumatic remedies and physical measures proved ineffective, after ten days Pizarro substituted thyroid therapy with no associate treatment whatever. After six days of this treatment the benefit was apparent and at the end of three weeks the normal condition of the hands had been fully restored.—G. P. G.

(ANTERIOR PITUITARY) A New Treatment for Graves' Disease. Richter (G.) Med. Herald (Kansas City) 1916, xxxv, 307.

Four cases of ambulatory Graves' disease are reported as having been materially benefited by the administration over

a period ranging from several weeks to some months of desiccated anterior pituitary gland. All the cases exhibited well-marked characteristic symptoms of the disease and all, because of their circumstances, were forced to forego the advantages of complete rest and suitable hygienic treatment. Despite this remarkable improvement was obtained and such cardinal symptoms as tachycardia, nervousness, and even the exophthalmos were modified. The dosage recommended is fifteen to forty grains of anterior pituitary, in five grain tablets, per day.—H. R. H.

(ADRENALS) Surrénalites aiguës dans les accès perniciose palustres. Paiseau (G.) and Lemaire (H.) *Presse Méd.* (Par.) 1916, xxiv, 468.

In a report to the Academy of Medicine (Oct. 17, 1916) these authors discuss certain serious symptoms liable to show themselves in pernicious malaria. The complete syndrome includes arterial hypotension with no disturbance of cardiac rhythm, vomiting, diarrhea, lumbar and abdominal pain and severe asthenia. The "white line" of Sergent is usually present.

Three cases came to autopsy and extensive lesions of the adrenals were found and the malarial organism was found in the altered adrenals(?).

The authors consider how the adrenal syndrome may persist after the parasite is completely controlled by quinine, and while helpful conclusions are not yet drawn, it is of considerable value to know that the serious "algid" stage of pernicious malaria properly may be treated not only with quinine but also with adrenalin.—H. R. H.

GOITER, Considerations in its Medical Treatment. Anders (J. M.) *N. Y. Med. Jour.* 1916, civ, 773.

According to Anders the medical treatment of goiter depends entirely upon the form of the disease present. The non-toxic variety responds to iodine and thyroid extract, while this treatment would be decidedly pernicious in the toxic type. After having discussed the differential diagnosis of the various forms of goiter, Anders outlines quite fully his ideas of the medical treatment of Graves' disease. If rheumatism appears to be connected with the causation, a course of salicylates is advantageous. If toxemia of alimentary origin is present (quite a common cause, by the way) large rectal injections of oil to remove impacted feces and other suitable treatment to prevent coprostasis, are of much service. Careful regulation of the diet is essential. Efforts directed at the prevention of intestinal stasis and toxemia—mineral oil, periodical enemata and intestinal antiseptics (be-

tanepthol, salol and guaiacol carbonate)—have distinct values.

Certain hygienic measures are vastly more important than many drugs or organotherapeutic remedies. Active exercise and travel is contraindicated and rest, both of body and of mind, is all essential. Early in this treatment massage and passive exercise may replace active exercise with advantage. Later gradual resumption of exercise is permissible, care being taken to prevent all evidences of fatigue. Hydrotherapy may be useful, but no invigorating or exhausting measures should be prescribed. Environment is important, all depressing or exciting influences being removed as far as possible.

Cardiac stimulants are often in order; the writer mentions digitalis and strychnia. Two remedies are "worthy of elaborate mention"—quinine hydrobromide and antithyroidin (Moebius). The former is given in five grain capsules three, and later (if well borne) four times a day; the latter in doses ranging from ten to sixty minims, two or three times daily. "The relief afforded to the distressing nervous symptoms by antithyroidin, and its apparent harmlessness, combine to stamp this as a sovereign remedy in exophthalmic goiter."

H. R. H.

(THYROID) Complete Cretinism with Normal Mentality (After Treatment). Hoag (W. B.) *Am. Jour. Obs. (N. Y.)* 1916, lxxiii, 1152; *ibid. Med. Record (N. Y.)* 1916, lxxxix, 755.

The patient, a girl 5½ years of age, first came under Hoag's observation when she was 3½ months old. At that time she had all the typical characteristics of cretinism. Her extremities were the shortest he had ever seen. Her head was covered with a thick mass of coarse, flaxen hair, her nose showed no development, her tongue protruded, her skin was dry, and her flesh showed no resiliency. She showed no animation, even hunger apparently forming no part of her desires. At the present time the girl stood 40 inches in her shoes and she weighed 43 pounds five weeks ago, which was more than the normal weight and height of the average child of her age. There was apparently nothing abnormal in the condition of the child at the present time; she played and talked just as any other child. The absence of the thyroid could not be attributed to trauma, since there was nothing abnormal at the time of birth except that the labor was rather precipitate. Hoag inaugurated thyroid medication at the time he first saw the child, 1-4 grain of thyroid extract having been given twice daily. This amount was gradually increased until for a time, when she was about four years of

age, she took 5 grains daily. Under this amount she developed the typical signs of excess of thyroid. For some months she had been getting 3 grains daily. Very soon after beginning the thyroid treatment her hair came out in great masses and her skin came off in sheets, two or three inches coming off in one piece, and the child was practically made over in a few weeks. Hoag thought this case was worth presenting (to the New York Academy of Medicine) as demonstrating the thorough results thyroid medication together with persistent and careful attention on the part of the mother. The case showed that if one was able to treat a 100 per cent. cretin early and administered approximately the amount of thyroid that nature intended the child to have, one could get a perfectly normal child, provided the child had no other defect in any other endocrine secretion.

ADRENALIN, Intraspinal Injections in Acute Poliomyelitis.

Lewis (P. M.) *Med. Record* (N. Y.) 1916, xc 540.

In this paper is reported the results of 77 cases of infantile paralysis treated at the New York Nose, Throat, and Lung Hospital with adrenalin. There were 18 deaths, of which only 5, or 6.9 per cent., were due to straight poliomyelitis under the adrenalin treatment.

The treatment was as follows: The bottle of 1,000 solution was placed in a bath of boiling water to drive off the .5 per cent. chlorotone content, and the solution was used undiluted after cooling. The child's body was flexed over a six inch glass bottle to increase the interspinous spaces, the skin was painted with tincture of iodine before, and dressed with moist boric acid dressings after the injections. A medium sized aspirating needle was found to be the best and the punctures best made between the four and fifth lumbar vertebrae. Intraspinal pressure was relieved and 2 mls. of the 1:1,000 solution of adrenalin was injected, repeated every six hours day and night until the temperature was normal, unless kept up by some cause other than the poliomyelitis. No local anesthetic was found to be necessary.

PITUITARY Extract in Obstetrics, Results from, with Report of Case of Rupture of Uterus. McNeile (L. G.) *Am. Jour. Obs.* (N. Y.) 1916, lxxiv, 432.

This author reports his own case and collects 15 others from literature. In these 16 cases of rupture of uterus following the use of pituitrin, there were 13 deaths and 3 recoveries. This author advises against the indiscriminate use of pituitary extract, claiming that it has no use in normal obstetrics. The most recent literature on this subject is appended.—W. H. M.

ADRENALIN, Oral Administration. Harrower (H. R.) N. Y. Med. Jour. 1916, ciii, 893.

Harrower first refers to the generally accepted and often repeated statement that adrenalin is not effective when given by mouth. He then quotes a number of clinical reports showing the effective administration of adrenalin by mouth and expresses his opinion that—"the favorable experiences with total adrenal gland therapy, by mouth of course, is additional proof that the position of those who have contended that the oral administration of adrenalin is useless, is fallacious."

J. D.

ANTERIOR PITUITARY Therapy in Impotence in the Male, a Preliminary Report. Stelwagen (T. E., Jr.) N. Y. Med. Jour. 1916, ciii, 879.

This writer gives his clinical experience with a number of cases of impotence treated by the administration of desiccated anterior lobe of the pituitary body. The first case was 43 years of age, suffering from complete impotence. A five-grain tablet of the remedy was given three times a day after meals. Prostatic massage was given twice a week. A complete cure was brought about after three months of this treatment and persisted at the time of writing (one year after). A similar result was obtained in a man aged 54 years after four and a half months of this treatment. In the case of a man of 35 the report was equally encouraging. No untoward symptoms have followed the use of this preparation, except perhaps a slight gastric hyperacidity.—J. D.

PITUITRIN in Evacuation of Uterus in Early Pregnancy.

Bubis (J. L.) Am. Jour. Obs. (N. Y.) 1916, lxxiii, 673.

It is stated that it is possible to empty the uterus in the early stages of pregnancy in a few minutes with the aid of pituitrin and a curette, with very little loss of blood and without shock or collapse even in the most severe cases. No hot irrigations are required to assist in the expulsion of the fetus or placenta, nor are any irrigations or packing employed after evacuation of the uterus. Preliminary packing of the cervix and vagina to induce softening of the cervix and excite uterine contractions is likewise usually not required. The injection of one mil. of pituitrin is given after the cervix has been dilated, while the patient is under the anesthetic. Sometimes the curette is unnecessary, strong pains beginning within a few minutes and entirely expelling the uterine contents. Where the uterus is unable to evacuate itself, the curette is used to separate the adherent placenta from the uterine wall, a procedure which causes practically no bleeding, even if the placenta is removed piecemeal, owing to the firm, hard

condition of the uterine wall due to the drug. The uterine cavity is wiped dry with gauze and swabbed with 5 per cent. iodine solution; it decreases in size as rapidly as its contents are removed. With this procedure Babis has been able rapidly to empty many uteri in the fourth and fifth months of pregnancy in which a diagnosis of dead fetus had been made, but the cervix was closed.—N. Y. M. J.

THYROID Substance, Prescribing. Goodall (A.) Brit. Med. Jour. (Lond.) 1914, ii, 1351.

Variability of therapeutic effect from various pharmaceutical preparations should not be attributed to idiosyncrasy until the character of the preparation is ascertained. For instance, Thyroideum Siccum (B. P.) is supposed to be a concentration of 5 parts of fresh gland in 1 of dry. While the analysis of Martin showed 5.7, and that of Guyer 3.6 as the proportion. It is suggested that the difference may be due to the amount of trimming of fat and fibrous tissue. (Difference of age, breeding and feeding of the sheep may be of importance in this connection.)—T. A. W.

(PITUITARY) Glandular Therapy and the Epileptic Syndrome. Joughin (J. L.) N. Y. Med. Jour. 1916, ciii, 693.

This author starts his consideration of the subject by emphasizing that the recognition of the fact that a uniglandular symptomatology does not exist, that a pluriglandular symptomatology, dominated perhaps by the preponderating disorganization of one or more glands, always exists, is a great step in the right direction.

He cites, in detail, the case of a young girl, 16 years of age, presenting an epileptic syndrome which commenced with the first menstrual period. 8 to 10 grains of pituitary extract were given daily and following the initiation of this treatment there was marked improvement within two weeks. The treatment was continued for some time and now, according to Joughin, the major convulsive seizures have never recurred and she has remained free from all manifestations of epilepsy until this date, two years after the administration of the first dose of pituitary extract.—J. D.

LUTEUM EXTRACT in Menstrual Disorders. Leighton (A. P.) Am. Jour. Obs. (N. Y.) 1915, lxxii, 878.

This author reports his experience with corpus luteum in amenorrhea, dysmenorrhea and in the troublesome symptoms of the menopause. His explanation of the cause of dysmenorrhea, that it is due to a lessened or hypofunction of the ovary, is interesting, but does not agree with the majority of

endocrinologists. It has usually been supposed that ovarian dysmenorrhea was caused by an hyperfunction of the internal secretory apparatus of the ovary, hence ovarian extract in any form was contraindicated, lest one aggravate the condition already present. A good discussion was given this paper.

(ADRENALIN) Some Observations on the Treatment of Dysmenorrhea. Block (F. B.) Am. Jour. Obs. (N. Y.) 1915, lxxii, 945.

The subject of dysmenorrhea is discussed exhaustively by this author. He divides or classifies the various types as obstructive, secretory or ovarian and vagotonic. As endocrinologists, we are concerned with the second division only, keeping in mind, of course, that dysmenorrhea is not due in every case to an hyperactivity of the internal secretory apparatus of the ovary. In outlining the treatment of ovarian dysmenorrhea, Block states that one must either inhibit the ovarian hyperactivity or neutralize the elaborated ovarian secretion. The former is produced by a modification of the method of Fliess by painting the so-called "genital spots" on the nasal mucosa with adrenalin choride, 1-1,000 instead of a solution of cocaine as advised by Fliess. The neutralization of the ovarian secretion already in the blood is done by adrenalin 0.0001-0.0005 grams in sterile salt solution, injected hypodermatically. This is a very valuable contribution to this important subject.—W. H. M.

THYROID Extract in Malignant Uveitis. Bordley (J.) Jour. A. M. A. (Chgo.) 1916, lxxvii, 412.

The author reports two additional cases in which the use of iodothyrene seems to have cured malignant uveitis.

(PARATHYROID) Tetania da insufficienza paratiroidica sperimentale nella gravidanza ed eclampsia. Massaglia (A.) Gaz. deg. Osp. e d. Clin. (Milan) 1916, xxxvii, 577.

Massaglia removed three parathyroids from each of two female puppies, and they grew and thrived. When they reached maturity and became pregnant each developed tetany. Each was benefited by parathyroid therapy. According to Massaglia and a number of other Italian investigators this condition of hypoparathyroidism is similar to that which obtains in eclampsia, and the inference is drawn that here parathyroid extract is good treatment.

The condition of parathyroid insufficiency remains latent until the toxemia of a pregnancy overturns the balance and the results of parathyroid deficiency quickly become evident. This showed itself as tetany in the animals experimented upon and as eclampsia in women.

Both of the parathyroidectomized dogs had several litters and tetany appeared in each one and in all pregnancies but it was less marked in the later pregnancies. It did not appear at any time save during pregnancy and was controlled in every instance by parathyroid injections.—G. V.

GOITER Problem. Sloan (H. G.) Cleveland Med. Jour. 1916, xv, 453.

Sloan states that since thyroid disorder is quite prevalent in certain localities in which there seems to be a deficiency of iodine in the food, such as the Great Lakes region, it is well to prescribe small amounts of iodine for children as they approach and go through puberty, and a similar plan is advisable in pregnant women. For this purpose it is enough to give 0.3 mil of the syrup of the iodide of iron after meals for one month out of every three. This preparation also supplies a small amount of iron which is beneficial.

In any case of goiter one should make a careful physical examination to locate any foci of infection. If found, these should be eradicated before any form of treatment may be expected to give fully satisfactory results. Such examinations should include the teeth, nasopharynx and sinuses emptying into it, uterus, prostate, and similar regions likely to be overlooked. The condition of the alimentary canal should also be investigated and if there is any reason to suspect toxic absorption from stasis or fermentation, measures should be taken to secure proper regular evacuations. Sloan frequently prescribes capsules containing 0.3 gram of thymol, one to be taken after each meal. The regular use of buttermilk and the administration of small doses of iodine should be combined with these measures in Graves' disease, but we must be on the watch to control the dose of iodine, so as not to produce an increase in the symptoms. Usually after four to six weeks of regular administration of iodine, the gland will begin to diminish in size and become firmer. The patient must be placed at complete rest in bed for a month or more, if Graves' disease is present, and if at the end of that time there has been no decided improvement, it is then appropriate to consider surgery.

(PANCREAS) Diabetes Mellitus, Observations on Diagnosis and Treatment. Brown (M. M.) Boston M. & S. Jour. 1916, clxxiv, 317.

Clinical experiences with the use of drugs or special remedies for diabetes have been unsatisfactory to Brown. One preparation only is recommended. According to Brown the continued and intelligent use of trypsinogen (pancreas)

in certain selected cases of pancreatic diabetes exerts a beneficial influence. The pancreas content, theoretically at least, supplies needed substances and materially aids in the metabolism of the carbohydrates, and the additional remedies (gold and arsenic) seem to be a good tonic for the anemic condition. There are a number of case reports.

(PITUITARY) Hypofysetumor behandlet med organoterapi.

Magnus (V.) Norsk Mag. f. Laegevid. (Christiania) 1916, lxxvii, 1319.

Magnus reports beneficial results from pituitary medication in a case of pituitary tumor. His patient was a man of 29 who for several months had suffered from headaches and other symptoms of pituitary tumor. For the last three months he had been blind, vision being lost first in one eye. There was some improvement under a decompressive trephining operation followed by Roentgen exposures. Then a pituitary extract was given systematically by subcutaneous injection, and the tumor evidently retrogressed under it to some extent as vision returned. To restore sight to a blind man even for a few months is certainly encouraging. The man refused further operative measures and the condition finally grew gradually worse again.

PITUITARY Extract in Obstetrics. Perry (F.) Amer. Med. (N. Y.) 1916, xxii, 572.

Twenty-three cases are recorded in which pituitrin was used. The dose employed was one mil and in several cases this had to be repeated. A summary of the cases shows that labor pains were induced in from three to five minutes. They were intermittent at first, but became regular in about fifteen minutes. Delivery of the child was hastened and expulsion of the placenta was accelerated. An agreeable aftereffect of the remedy is its favorable influence on the evacuation of bladder. It should not be used in anatomical obstruction of the birth canal, nephritis with high blood pressure, or exophthalmic goiter. Where secondary hemorrhage is anticipated, it may be given late in the second stage. He advises against the early use of pituitrin. Before its administration, the cervix should first be well dilated and rigidity should be overcome.

PITUITRIN in Labor. Foulkrod (C.) Ther. Gazette (Detroit) 1916, xl, 305.

Foulkrod points out that obstetricians by no means are unanimous in their verdict, some authors being very enthusiastic in their conclusions, while others counsel care. Against the practically general opinion that pituitrin should not be used in the first stage of labor, the author cites S. W.

Bandler, who asserts that in this stage, under proper conditions, the remedy is of the greatest aid in furthering the progress of labor.

Foulkrod, however, holds that caution should be exercised when employing pituitrin, until thorough acquaintance with the possible dangers in each patient shall assure safety; this not only because the pituitary preparations vary in strength, but also because individual patients do not react to it in the same way.

Pituitary extract should not be administered by the nurse in the absence of the physician, who must not leave the patient after the latter has received a dose of it.

Foulkrod is emphatic in his assertion that the ampules at present offered hold too much of the active substance to be handled by the general practitioner, and that a whole ampuleful should never be given by him as a standard dose.

The author is extremely guarded in expressing an opinion concerning the value of pituitrin as an oxytocic, but he believes that it should be supported by some parturifacient of slower and more protracted action—ergot, for example. Still, he is very positive in declaring that pituitrin should not be resorted to unless the presenting part is definitely engaged in the pelvis and the largest diameter has passed through the plane of the inlet—and then only if the outlet has been measured carefully for any contraction of its transverse diameter.

In conclusion, it is stated, that there is a possibility of shock, on the part of the mother, and also a possibility of danger to the child, particularly if the uterine contractions excited by pituitrin are sufficiently severe to cut off the normal circulation of the fetus, through some interference at the placental site.

CORPUS LUTEUM Extract in Nausea of Pregnancy. Hirst (J. C.) *Jour. A. M. A. (Chgo.)* 1916, lxvi, 645.

The intramuscular use of solutions of the active principle of the corpus luteum is recommended by Hirst in severe emesis in the early stages of pregnancy. His report is a preliminary one, and the limited number of cases cited responded favorably to the injections. In these cases, at least, the hypodermic method is superior to the oral route.—F. C. P.

CORPUS LUTEUM Extract in Surgical Menopause. Hirst (J. C.) *Am. Jour. Obs. (N. Y.)* 1916, lxviii, 648.

Further experience by Hirst with intramuscular injections of soluble corpus luteum extract confirm his opinion of its value. In the surgical menopause results from the oral administration of corpus luteum extract have been disappoint-

ing. The large doses necessary for beneficial effects are often productive of nausea. His more recent experiences, however, with intramuscular administration of the drug, gave gratifying results. In the first case reported, after discontinuance of oral administration on account of nausea, with only slight intramuscular injections of 20 mgr. equivalent to 15 grains of fresh gland were given, at first daily for 18 doses, then on alternate days for four weeks, and later bi-weekly for a few weeks. The flashes of heat and other symptoms began to improve rapidly after about six doses, without nausea, and since the end of the treatment the patient has remained practically free of symptoms. Similar results were obtained in five other cases of supravaginal hysterectomy. Hirst believes the doses he used could be greatly increased with benefit and without harmful effect. Experience will probably show the effect of the drug to be cumulative, and that the interval between doses can be gradually lengthened and the drug then discontinued without a return to the previous symptoms.

(THYMUS) Exophthalmic Goiter, Roentgen Ray Treatment.

Simpson (C. A.) *Southern Med. Jour.* (N'ville) 1916, ix, 857.

Simpson observes that X-ray treatment will sometimes give considerable relief to the symptoms of Graves' disease. He calls attention to the frequency with which exophthalmic goiter is associated with enlarged thymus, and suggests that X-ray exposures precede the operation for thyroidectomy in all cases where an overgrowth is suspected. Excellent microphotographs illustrate the effects of X-ray on the thymus gland. The writer remarks on the inconstant findings in the blood count of exophthalmic patients and urges that they be disregarded in giving prognosis in these cases.—L. F. W.

Pedology and its Possibilities. The Study and Treatment of Children Requiring Special Attention. McCready (E. B.)

N. Y. Med. Jour. 1916, ciii, 342.

This is quite a complete consideration of the case of "children requiring special attention," or more bluntly, defectives. Much of the diagnostic as well as the therapeutic phase of the subject concerns the endocrine glands, for it is conceded that these glands are of the greatest importance in the development of the cerebro-spinal and osseous systems in early life. The adjusting mechanisms of development are more or less reciprocal, the leading role, however, is supposed to be played by the thyroid gland. As a check upon the influence of the thyroid in infancy and childhood, the thymus, the general lymphatic system and perhaps the pineal

gland become active. In due time the adrenal system stimulates sexual activity and also hastens the growth of the musculature and skeletal systems. Of great importance at this time is the action of the pituitary gland. In a hypoplastic child the clinical picture most often seen is the undersized badly nourished child with an unstable nervous system, nasal obstructions, defective vision, delayed epiphyseal union, hypotonicity of ligaments and muscles, postural defects, visceroposis and incontinence of urine and feces is frequently present. Deficiency of the eyebrows in the outer third is considered due to thyroid deficiency. The high arched palate may be produced by yielding of the palatine bones and is due to a lack of calcium.

General treatment consists of hygienic measures and very few medicines but McCready considers preparations made from the ductless glands very important. He usually gives small doses of pituitary thymus, thyroid and adrenal glands in combination. For male children testicular substance is added, for females ovarian.

(THYROID) Treatment of Nephritis. Phipps (C.) Boston M. & S. Jour. 1916, clxxiv, 73.

Phipps reports the use of thyroid in numerous cases of nephritis with, on the whole, beneficial results. One patient could not tolerate it and in one case it had to be omitted from time to time on account of its apparent toxic effect on his heart. The other cases showed rapid improvement of the edema and relief from uremic intoxication (when present). None of the cases has died.

CORPUS LUTEUM, Clinical Experience with Soluble Extract. Cuthbertson (W.) Med. Standard (Chgo.) 1916, xxxix, 178.

Six cases of menstrual disorder with or without accompanying disorders, were treated with hypodermic injections of soluble corpus luteum, each dose representing one third of a grain. The interval between injections was as much as five days. The results were said to be good and Cuthbertson recommends this treatment in three classes of cases:

(1) Young girls under-developed physically, in whom the menstrual function had been established, but was irregular and scant.

(2) Women of varying ages prior to the menopause, whose menstrual function had been fully and naturally established, but on account of high living and sedentary life menstruation had become irregular, with marked periods of amenorrhea.

(3) A large class of women menstruating irregularly and presenting a decided hysterical temperament, with little benefit from the usual treatment.

PITUITRIN in Intestinal Paresis. Colton (A. J.) Buffalo Med. Jour. 1916, lxxi, 618.

This article is built around the report of the successful treatment of a woman with double pneumonia, whose abdomen was greatly distended and tympanic, the diaphragm crowded upward, so that breathing was extremely embarrassed, and she was evidently dying. Her blood pressure had fallen forty points. One half mil. of pituitrin was injected very slowly into the median cephalic vein. "Within thirty seconds there was the most remarkable effect I ever witnessed on a human being, the expulsion of large quantities of flatus with a large liquid stool that nearly filled the bedpan. The abdomen in less than three minutes was in normal condition."

THYROID Dyscrasia, Emetine in Severe Dysmenorrhea with.

Harrover (H. R.) Pacific Med. Jour. (S. F.) 1916, lix, 306.

A case of severest dysmenorrhea in a young woman who repeatedly refused operation for what was called "membranous dysmenorrhea" is reported by Harrover. Accidentally attention was directed to the mouth by slight bleeding of the gums at the morning toilet. Emetine was given for this condition and the next period was quite different in character while the second following was almost normal. It is suggested that the alveolar condition may have been just sufficient to cause thyroid trouble which in turn (and in harmony with the writings of Dalché and others) was responsible for the pelvic condition.

(PITUITARY) Menopausa precoce; sindrome ipofisaria; opoterapia. Jona (G.) Gaz. deg. Osped. (Milan) 1916, xxxvii, 420.

A case of premature menopause is related in which the menses ceased at 29 years, after an attack of puerperal sepsis. With the amenorrhea was noted a moderate obesity, polyuria and hypertrichosis. After an interval of 12 years, i. e., at about 40, pituitary medication was commenced and after several weeks the menses reappeared with a coincident betterment of the general health. Irregular treatment was continued for over six months and at the time of writing the periods had been regular during the last five months. The interesting feature in this case is the long period elapsed from the onset of the disorder and the institution of what must be called successful treatment.

(PANCREATIN) Pathogenesis and Treatment of Epilepsy.

Cotton (H. A.), Corson-White (E. P.) and Stevenson (W. W.) N. Y. Med. Jour. 1916, civ, 532.

This is a preliminary report of clinical and experimental work done at the New Jersey State Hospital. A modification of the Abderhalden reaction, similar to that worked out by Ludlum and Corson-White in the differential diagnosis of the endocrine disorders in insanity, was used as a guide to medication; and the subjoined preliminary conclusions drawn from experiences with 69 cases of epilepsy, make this treatment of prospective interest to all who have to deal with this disease.

At least one type of epilepsy is probably a disease process dependent upon absorption of toxic or poisonous products from the intestinal canal. This stasis may be produced by an overaction of the adrenal glands.

Hyperactivity of the adrenals may be caused by (a) dysfunction of the pituitary; (b) dysfunction of the pancreas; (c) irritation of the duodenum and (d) severe fright or emotional disturbance.

Treatment by administration of pancreatin should be employed in preference to surgical procedures, though surgical procedures should be employed in long standing cases where other treatment fails.

The dosage recommended was one half a grain of extract of pancreas given by mouth three times a day—a very small amount, but evidently enough to be noticeably helpful, for “many patients while taking the pancreatin did not have convulsions. In some when the gland was stopped the convulsions returned. In others no convulsions have occurred after discontinuing the gland. . . . the administration of pancreatin has had a decided effect in stopping the convulsions.”

The explanation of this action is that pancreas organotherapy serves in some slight measure, at least, to inhibit adrenal activity. These writers also believe that it is an aid to digestion, facilitating the quicker emptying of the duodenum and allowing the proteins to be more rapidly broken down into less toxic end substances.

(THYROID) Epilepsy, with Special Reference to Treatment.

Dercum (F. X.) Jour. A. M. A. (Chgo.) 1916, lxxvii, 247.

In a general consideration of the causes and treatment of epilepsy, Dercum remarks that in some cases the administration of small doses of thyroid extract ($\frac{1}{8}$ to $\frac{1}{4}$ of a grain three times a day) for long periods has seemed to raise the patient's physiological level with marked benefit, thus per-

mitting them to respond more favorably to other treatment. Dercum insists that the diet should be so modified that the organism, already toxic, should be put to as little strain as possible, especially the liver, thyroid and other defensive glands.—F. C. P.

ANTERIOR PITUITARY Therapy in Epilepsy. Spears (L. P.) *The Link Between Members of the A. S. I. S.* (Los Angeles) 1916, i. 31.

In the organization periodical of the Association responsible for this journal there appears a note regarding a new and tentative treatment for epilepsy which is of interest. Spears reports a single case of epilepsy which seemed to be apparently cured following the administration of anterior pituitary substance.

The case was of unusual interest because it was severe and well established condition and extended for 23 years. Attacks had continued since the age of six with an average of three or four a week, the highest number in one week being eight, the longest interval between them being 20 days.

At the age of 28 he came under his care and was given 2 grains of anterior pituitary three times a day, and later the dose was increased to five grains. After a month of this treatment the attacks became less frequent, and at the end of four months he had none at all. Medication, however, was continued, with brief intermissions, for seven months. When last seen the man had gone over eight months without any attack, and felt so sure this treatment had cured him that he came for a letter to the local recruiting office as he wished to reinlist in the Navy, from which he had been discharged ten years ago on account of his affliction.

NOTE: Those writing or planning to write articles pertaining to the study of endocrinology are cordially invited to co-operate in the preparation of future issues of this journal and in the other activities of the Association for the Study of the Internal Secretions. It is requested that:

- (1) **Author's abstracts be sent in;**
- (2) **Original communications be submitted for publication and sent to any member of the Editorial Board or to the undersigned;**
- (3) **TEN copies of all previous or prospective reprints (on this subject) be donated to the Association's circulating libraries.**

Address all correspondence and secure further information from
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ENDOCRINOLOGY:

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

APRIL, 1917

EDITORIAL ARTICLES

THE GROWING INTEREST IN ENDOCRINOLOGY

NATURALLY those interested in the work and objects of the Association responsible for the publication of this periodical, are more intimately in touch with the work and literature relating to the endocrine glands than others whose particular attention may not have been drawn especially to this fascinating subject.

To those who read that part of current medical literature which either is directly concerned with endocrinology or is related to it in some way, it is very evident that the number of investigators that are occupying themselves with the numerous problems in this field, is increasing considerably. In addition to this a large share of the profession is coming to realize as never before, the intimacy of the endocrine glands with many a syndrome previously

not considered to be connected with these organs. The fact remains, nevertheless, that "the endocrinous system exerts an influence on anomalies of growth, morphogenesis and organic metabolism, on nutrition and the inherent excitability of the nervous system, and on resistance to infections and intoxications, and also that it has a preponderating influence on the causation of dyscrasias and morbid temperaments." (Quoted from a report of a special committee on the ductless glands made to the Italian Society of Medicine, Rome, October, 1912.)

It is indeed well that the attention of the medical profession seems to be veering in this direction at this time, for since these factors enumerated above cannot but be of paramount interest to every physician, and obviously are intertwined with almost every manifestation in clinical medicine, the necessity for appreciating the real and prospective relations of the hormones is made doubly clear.

The more one allows the fundamental principles brought out by the intensive study of functional pathology to influence his practice, the greater will be his respect for the endocrine glands and the methods of diagnosis and treatment which our increased knowledge of them makes possible.

Now that a concerted effort is being made by so many physicians and investigators in many lands to study endocrinology, and in these pages one may find a fairly comprehensive review of the work being done in this line, it is not unreasonable to predict still greater advances in this branch of medicine; and not the least of these will result from the clinical application of this new knowledge.

NEUROLOGICAL ASPECTS OF
ENDOCRINOLOGY

FORMAL organic neurology is of intense academic interest to those who delight in solving to the last degree intricate problems. It is a subject replete with the intensive thought and deductive reasoning necessary in demonstrating a mathematical theorem. And like it, when the demonstration is completed, the finished neurological diagnosis is a thing fit for the filing cabinet or the text-book and we can look back upon the deductive processes through which we have come as delightful mental exercises.

But it leaves the human factor—the patient—much as we found him. We have learned something, but we have helped little. The indictment that the “neurologist knows most about his patient and does the least for him” has some basis in fact. Our attitude towards neurological problems has been wrong. It has been academic. It has accepted clinical pictures as disease entities with well-known anatomical structural changes in the nervous system. And structural change in the nervous system is coterminous with incurability. Our work ceased when we had decided the extent and location and nature of this structural change. Of late, our friend, the spirochete, recognized as the instigator of much of this structural change in the nervous system, has been followed and hounded out of his retreats, and it is reported as a result that many of our cases have not only been “arrested” but have gone to cure. But how few of us have thought and inquired into the reason for this reaction of the nervous system to the spirochete? Why do not all infected with syphilis become tabetic or parietic? Why do some, exposed to the same in-

fective active source as others who acquire syphilis, remain immune? In a family of whom three adults acquired syphilis from three different sources, all three became tabetic. Is it more reasonable to assume that the strain of spirochete was the same in each instance, or that the reaction of three brothers to the spirochete was familial in type? These three brothers were all undersized, showed emotional instability, abnormal hairy distribution, and were fairly well marked dyspituitaries. They had these characteristics before acquiring syphilis. One sister, non-syphilitic, was a dyspituitary epileptic. Their father attempted suicide, one brother committed suicide, while another brother also attempted it. They were all temperamentally unfit, and maladjusted. Other authors have published the coincidences seen in tabes and in pituitary disturbance. If the nervous structure of some types of dyspituitarism has not the power of resistance to certain infective agents, notably the spirochete, can we not confer that power upon it by endocrine therapy? That is the neurological problem of syphilis,—an immunological one.

Again, the large class of muscular dystrophies has gone through the decades with each investigator adding a new sub-class, a different age incidence, a new theory. The resemblance in all classes of these dystrophies—the symptoms referable to endocrine disturbances which they all show—had almost entirely escaped comment or was dismissed as a curious coincidence; and yet here was the solution. Only within the past year has an attempt been made to give due weight to such endocrine disturbances in the pathogenesis of the muscular dystrophies.* When our ef-

*Elsewhere in this issue will be found mention of such an attempt made by the writer.

forts in this direction finally shall have attained success, an efficient therapy in this difficult class of disorders is but a little beyond.

A recent, and as yet unpublished, report of the number of endocrine cases in 1000 defective children is given as 170. To have had 17 per cent. recognized as endocrine, is in itself noteworthy. The real number is probably higher. Here is a field for the neurologist's most fruitful endeavor. The Binet-Simon age of defective children, as a result of the administration of thyroid and pituitary therapy, has been advanced by years in a few months' treatment.

To refer to the mental symptoms and reactions of individuals with disturbed endocrine systems is supererogatory. Our hyperthyroids with their incessant psycho-motor activity, their lack of mental poise; the sluggishness and torpor of the hypothyroid; the insufficiency, fatigability and depression of the hypoadrenal neurasthenic; the phobias, compulsion and anxiety neuroses of the gonad involutary period; the poise and mental power accompanying the milder hyperpituitary state,—all these need but to be mentioned to understand at a glance how the disturbances in the endocrine system make for variations in the adjustment of the individual to his surroundings and hence in his adaptability to society.

The effect, further, of the component action of the internal secretions upon the various parts of the autonomic nervous system is only now beginning to engage our attention. Surgeons operating as a cause for persistent vomiting, now for appendicitis, now for gall stone, again for stomach ulcer, and with non-success, are beginning to feel the truth of the theories put forth to account for this intractable vomiting

as the basis of irritability of the cranio-bulbar division of the autonomic system—vago-tonia. When such vomiting is treated on this pathogeny, it ceases.

Finally, hyperplastic conditions have of late received more and more attention from neurologists. There seems to be increasing evidence that stimulation of the thoracic autonomic system—the so-called sympathetic—gives rise to increase of tissue cells in the organ to which the stimulated fibre passes. Evidence gained from animal experimentation, the action of the internal secretions, especially of the hypophysis, on mouse and other tumors, increasing the rapidity of their growth, points to a nervous mechanism in control of hyperplasias stimulated by the endocrine glands. Might it be too much to hope that in the not too-distant future, hypoplasias may be similarly produced, and an inhibiting control of tumor growth arise?

So we see that in the new preventive neurology a field is broadening—due to the recognition of the effect of the internal glandular system on the various nervous mechanisms—that embraces wider and wider territory and whose limiting horizon is not yet fixed. It bears as little relation to the old narrow orthodox, formal neurology, as does modern medicine to the conception of disease entities of a half century ago.

Neurology, therefore, must emerge from its *laissez faire* position and assume the duties which endocrinology forces upon it. It must assume the place in preventive medicine that has been opened for it.

WALTER TIMME.

THE MAMMAE AS ENDOCRINE ORGANS

THAT the mammary glands have a dual function is not yet altogether accepted by physiologists or clinicians in general. Evidence, both experimental and clinical, is gradually accumulating to indicate that the mammae may have an endocrine function; but this evidence is not as concise and unimpeachable as might be desired. The whole matter still must be considered as *sub judice*.

With the growing appreciation of the internal secretory value of many parts of the body, not a few of which are well known to have a dual secretory function—both internal and external, and the intimacy of the mammary glands with other organs of internal secretion (especially the ovaries, pituitary and possibly the thyroid) it may not be amiss to recall a number of the indications that lead some to believe with us that the mammary glands are indeed a part of the endocrine system, and that this phase of their functional activities is deserving of study and the resulting knowledge of much wider clinical application.

First it is clear to all that the functional activity of the mammary glands is influenced by numerous hormonal means, for their occasional transient functional activity at birth (in the production of the so-called "witches' milk"), their growth at puberty, their frequent "sympathetic association" with the menses, their relation to the sex manifestations and last, and most important of all, their response to chemical stimuli obviously of intrauterine origin, surely constitutes a series of phenomena very similar to, if indeed not actually due to, internal secretory reactions.

Not so long ago Schil selected the manifestations

of mammary evolution and physiology as the basis of a masterly study (These de Nancy, 1912) and therein sets forth his conclusions that mammary evolution is properly divided into six stages: (1) The stage of development, divided into an organogenetic phase and a phase in which there is secretory activity (the lactation in the new-born already mentioned). This is believed to be due to a hormone passing from the mother which also probably is concerned in activating mammary secretion in the mother. (2) The prepubertal stage of functional inactivity. (3) The stage of puberty, characterized by a considerable increase in glandular parenchyma which is dependent upon the maturation of the corpora lutea and obviously the result of internal secretory activities.* (4) The gravid stage, divided into the early period during which the glands attain their full development and a "phase glandulaire gravidique" which follows complete development and is characterized by secretory activity (colostrum). It is suggested that the first part of this stage is controlled by the corpus luteum of pregnancy through a hormone produced in it, while the latter part results from a chemical messenger from the fetus itself, the placenta or possibly a myometrial gland. (5) The postpartum stage includes the period of lactation initiated during pregnancy by an endogenous stimulus and maintained by mechanical means—nursing. The phase of post-

*It has been repeatedly demonstrated that the ovaries influence mammary development. For instance Bouin and Ancel (*Jour. de physiol. et de pathol. general*; 1911, xiii, 31) showed that ovariectomy resulted in a practical disappearance of the mammae, while on the successful grafting of a piece of ovary, the lost glands reappeared. Again O'Donoghue (*Jour. Physiol.* 1911, xliii, p. xvi) and others have ruptured the ripe Graafian follicles artificially, thereby making a noticeable increase both in mammary growth and activity.

partum retrogression is merely due to an absence of stimuli. Finally there is (6) the senile stage, associated with involution, and corresponding to the period when the gonads atrophy and their stimuli no longer are active.

All these comparatively well known facts serve to emphasize the interrelation of the mammary glands with endocrine function and while this evidence is none too positive, for it does not prove these glands to have an internal secretion, at least it classes them intimately with other organs known to have distinct endocrine function.

Occasionally our knowledge of the physiological activity of a given endocrine organ has resulted from its experimental removal or, more often, from the administration of extracts of it. The internal secretory character of the pituitary was demonstrated in this manner by Schaefer and his associates in 1895. Practically all the clinical value of the adrenal medullary principle resulted from gland feeding, though, of course, much physiological work has been done in other ways. Be this as it may, mammary gland feeding is not without its influence upon the organism, and in addition to a homostimulant action which is to be expected on general principles, it is of interest to recall that the chief organs affected by prolonged mammary therapy are the ovaries.

Numerous reports indicate that mammary extract exerts an antagonist effect upon ovarian endocrine activity, and its use in hyperovarism, menorrhagia and even fibroids seems to have been accompanied by indubitable results. The writings of Bell, Shober, Feodoroff, Battuaud, Luncz, Carnot and a number of

others* seem to contain within them sufficient clinical proof that this remedy is not without clinical value. We have had occasion to prescribe it in, perhaps, forty cases and the results have confirmed our belief that there is a principle in mammary substance which antagonizes ovarian activity, reduces pelvic congestion and stops local bleeding. One case recently demonstrated this unusually well: A well advanced and inoperable carcinoma uteri, which was the source of constant hemorrhage, was treated for a short time with 30 grains of mammary extract daily. The hemorrhage was reduced to a minimum, there was a corresponding increase in strength and the patient was even led to hope that she would be cured. This influence was merely temporary, the hemorrhage returning shortly after the mammary gland was stopped; but was this proof enough that the anti-hemorrhagic effect was due to the remedy and not to suggestion, other treatment or coincidence?

Looking at this from another angle the evidence is not so complete. The breasts are rarely removed for therapeutic purposes in women early in ovarian activity; though there seems to be some proof that this operation is not without influence upon endocrine function. We know, however, that the function of ovulation may be retarded and sometimes entirely stopped by prolonged lactation, and the writer has seen a case of premature menopause in a young woman which resulted in our opinion solely from an inordinately prolonged period of lactation—four years!

Not uncommonly we find women with large mammary development whose menses are noticeably

*Including also the article by Briggs in this issue, page 188.

scanty, though this is far from a rule. On the other hand in spayed dairy cows it is well established that the period of lactation is prolonged. It is also well known that pregnant cows as a rule show a tendency to lessen their milk producing powers soon after pregnancy takes place.

There is opportunity for some animal experimentation to demonstrate the accuracy or futility of our views that the mammae have internal secretory powers; and it should not present great difficulty to remove the mammae in a number of animals and watch the functional and histologic changes in other endocrine organs, notably the ovaries. From a clinical standpoint, too, there should be numerous experiences to substantiate this position, or not, as the case may be; and it is hoped that future issues of this journal may contain scientific evidence on this subject, since it is intimately concerned with certain phases of clinical gynecology and if the endocrine function of the mammae is proved we shall have an explanation of the clinical experiences with mammary therapy already referred to.

HENRY R. HARROWER.

ORIGINAL COMMUNICATIONS

RECENT VIEWS AS TO THE FUNCTION OF THE ADRENAL BODIES

By Swale Vincent, M. D., Winnipeg

(From the Department of Physiology of the University of Manitoba)

IF we hope to gain any exact information as to the diseased conditions of the adrenal bodies, the clinical disturbances which arise from such conditions, and the rational treatment of them, it is essential that we keep in mind the most recent and the most matured observations relating to the physiology of these bodies.

No attempt will be made in this place to deal with the whole subject of the functions of the adrenal bodies. The object of the present communication is to emphasize certain broad conceptions and to discuss certain fundamental topics in accordance with the results of the most recent investigations.

It is certain that in lower vertebrates the cortex and the medulla constitute representatives of two separate and independent series of organs, and there is no reason to suspect any physiological relationship between the two. In mammals a mass of chromophil cells has become enclosed in the adrenal (or "cortex") and we have thus formed what we know as the adrenal body.*

Whether this partial coming together of the two systems in higher animals has any physiological importance we do not know. On the whole the safest

*It must be remembered, however, that even in mammals, there are outstanding portions of the original chromophil bodies and of the original cortical bodies.

attitude is one in which the assumption is made provisionally that the two portions, cortex and medulla, have separate and independent functions. At any rate 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 functions. We know nothing of the functions of the adrenal body regarded as an organ on its own account.

Modern works for the guidance of practising physicians are often very confused on this point. Thus Falta (6) says: "Already at an early period some of the chromaffin cells have broken through the complex of cortical cells to form the medulla. Through the descent of the genital organs small parts of both systems are displaced. This shows that the former complete physiological independence of both systems later gives place to a common function, at least in part (Biedl), which fact is also indicated by the previously mentioned relations of the blood-vessels. It is indispensable for the comprehension of diseases of the adrenals to consider that the two systems for a great part are functionally independent. The higher we go in the classes of animals, the greater become the complexes of the two systems that finally unite to form a single organ, the adrenal."

Now the present writer begs to submit that the fact that certain masses of chromaphil cells break into the interior of the cortex does not prove that any functional relation between the two becomes established, nor does the fact that through the descent of the genital organs small parts of both systems are displaced, bear upon the point. The same may be said of the relations of the blood-vessels. But in the next sentence it is urged that "the two systems for

a great part are functionally independent." Finally the writer returns to the idea of a single organ. Surely the matter would have been clearer if the writer had merely expressed a doubt as to any possible physiological connection between the two systems.

It seems to be well established that total extirpation of both adrenal glands will invariably cause death of the animal.* The question naturally arises whether death is to be attributed to loss of the cortex, or of the medulla, or of both of these. In the work of Falta above referred to we do not find any adequate statement of our present knowledge of this subject. The author says: "The sure knowledge that the cortical system and chromaffin system are in like manner important for life was first mentioned by later investigators (I mention only Biedl and Hultgren and Andersson)† who took into consideration the presence of accessory adrenals."

Now, in the first place, there is no "sure knowledge" that the cortical system and the chromaphil tissue are in like manner essential for life. There is, in fact, every reason to believe that such is not the case. Biedl, whom Falta quotes, has urged very strongly that it is the cortex and not the medulla (or the chromaphil tissue) which is essential to life. This investigator found that rabbits and dogs would survive removal of all but one-eighth part of both adrenal bodies, provided that the portion remaining consists of cortex. (4) He found also that removal of the interrenal body of elasmobranch fishes is uniformly fatal. Many years ago the present writer (18,

*A few exceptions to this rule have been recorded, but they scarcely affect the essential validity of the thesis.

†I have made minor but essential corrections in quoting.

19) attempted to solve the problem by extirpation of the corpuscles of Stannius from the eel. But the negative results which were obtained were later fully explained by the discovery of a second cortical representative. This discovery was made by Giacomini (7) who described a mass of cortical adrenal cells in the "head kidney" of teleostean fishes.

The results obtained by Biedl were recently confirmed by Wheeler,* who carried out a series of experiments in my laboratory. An attempt was made to remove the medulla of both adrenal bodies from a number of dogs, leaving the cortex undamaged. This was not precisely achieved, but it was found that the only fatal cases† were those in which very considerable damage had been done to the cortex as well as to the medulla. In some cases the abdominal chromaphil body (Vincent, 20) was removed as well as the adrenal medulla. Of course in such experiments groups of sympathetic chromaphil cells, as well as scattered cortical "accessory" bodies must be left behind. But this fact does not seriously affect the logic of the argument that it is the cortex which is essential to life. For, since removal of both adrenals is fatal, and removal of the medulla alone is not, it follows that the cortex is the essential part of the gland so far as the maintenance of life is concerned.

After the epoch-making discovery of Schafer (15, 16) that adrenal extracts raise the blood-pressure, there was a growing tendency to assume that the function of the adrenal (or, at least, of its medullary portion) is to help to maintain the normal blood-

*Results not yet published.

†At any rate among the animals which died of adrenal insufficiency.

pressure and to keep up the tone of sympathetically innervated structures in general. The present writer was one of the first to grow suspicious on this point. If the constant secretion of adrenin into the bloodstream and its action upon the sympathetically innervated vascular muscle is an important factor in the maintenance of the normal blood-pressure, then it ought to be possible by tying or clamping the veins issuing from the glands, to keep down the blood-pressure at a low level during the period of clamping or tying, and to allow it to reach its normal level on releasing the clamp or the ligature. Some writers have claimed that they have obtained this result. But Young and Lehmann (22), working in my laboratory, made an attempt in dogs to dam back any secretion which the glands may pour into the bloodstream, and, after an interval, to remove the obstruction, and allow the accumulated adrenin to flow into the general circulation. A cannula was inserted into the carotid artery, the adrenal glands were exposed through an abdominal incision, and a double ligature passed beneath the organ on each side; the ligatures were tied on each side of the gland above the vein, so as to form two pedicles. The ligatures were left in place for from ten to thirty minutes, and then released, and the blood-pressure tracing continued.

Out of eight experiments, there was no effect on the blood-pressure in three; in two there was a slight rise after releasing the ligatures; in the remaining three there was a decided rise of pressure (comparable with that which follows injection of adrenin into the circulation) lasting about three minutes. In one case the effect was repeated by tightening the ligatures a second time, and then releasing them.

It is important to note that in these experiments after tightening the ligature there was very little, if any, fall of blood-pressure. In fact the experiments merely show that adrenin is poured out into the adrenal veins.

Dr. Young (23) repeated these experiments and found that even after the lapse of several hours with the blood from the adrenal bodies absolutely excluded from the circulation, there was no appreciable fall of blood-pressure. During last winter Austmann and Halliday* at my suggestion performed a series of experiments in which the adrenals were removed or whose vessels were tied off while the blood-pressure was continuously recorded for many hours. It was found that when the experiment was continued until the animal died the blood-pressure curve was not appreciably different from that obtained from an animal simply kept under ether as long as possible. These experiments appear to show conclusively that the secretion of adrenin into the circulation is not to be regarded as a factor in the maintenance of the normal blood-pressure.

But there is another argument which militates powerfully against the theory just mentioned. It was shown by Moore and Purinton (13) that very small doses of adrenin will lower the blood-pressure, not raise it, so that the amount of adrenin which is normally poured out by the adrenal veins would tend to keep the blood-pressure down rather than up.

It is difficult, indeed, in face of the foregoing consideration, to adduce any satisfactory evidence that the secretion of the chromophil tissue is of any use

*Results not yet published.

whatever in the normal state of the animal. (Hoskins, 11.)

But the suggestion has been made that the secretion is of great service in certain emergencies. Certain experiments of Cannon and de la Paz (5) seem to show that during times of emotional stress the adrenal bodies pour into the blood sufficient adrenin to be of some service, possibly in increasing the power of sustained muscular activity. This view has received very general approval, but it would be rash to affirm that it has been firmly established. Stewart and Rogoff (17) conclude that fright has nothing to do with the results.

The experiments of Hoskins and McClure (12) taken in conjunction with others above referred to, furnish sufficient evidence to warrant us abandoning the tonus theory of adrenal secretion. But the theory is still put forward by Falta (p. 345) and is made to account for the low blood-pressure in Addison's disease.* The fact is that we have not a single physiological observation (except perhaps the effect of adrenin on the contraction of skeletal muscles†) which throws any light on the pathology of Addison's disease.

The question naturally arises, "Why is extirpation of the adrenal cortex fatal?" The answer is simply that we do not know. It is suggested by Hoskins (11) that muscular metabolism may be at fault.

*Falta's book is so extensively used by physicians and students that it is necessary to refer to its extraordinary deficiencies in the sections that bear upon physiological questions. Thus it is pointed out (p. 273) as something significant, not to say extraordinary, that extracts of the glandular portion of the pituitary body lower the blood-pressure. The Author and the Translator seem to be unaware that extracts of all organs and tissues have a similar action. (See Vincent 21, p. 24.)

†First observed by Oliver and Schafer. (15)

Some interesting experiments were carried out many years ago by Abelous and Langlois (1, 2, 3). This was in 1892, some few years before the discovery by Oliver and Schafer that adrenal extracts raise the blood-pressure. The French authors found that intravenous or subcutaneous injection of the blood of a frog dying after adrenal extirpation into a frog recently deprived of the glands, induced rapidly developing paralysis and death. The same injection into a normal frog only gives rise to slight temporary symptoms. Their theory was that death after extirpation results from the accumulation in the blood of one or several toxic substances, and that the adrenal bodies are capable of elaborating a substance which neutralizes the toxic effects of such substances. These observations were in the main confirmed by Gourfein (8, 9, 10), but have not received much attention by recent writers. The matter has recently been investigated by Hoskins (11), who finds that the blood of dogs that have just died of adrenal deficiency is in no degree toxic when administered to frogs.

That the cortex may exert antidotal properties was suggested by Myers' (14) observation that cobra poison, after being mixed with an emulsion of the adrenal cortex, was no longer toxic. There are a few other isolated records which seem to point in the same direction, but it must be confessed that the anti-toxic theory has not been substantiated.

The following is a brief summary of what, in the opinion of the present writer, represents the state of our knowledge concerning the adrenal bodies:

1. What we call the adrenal body represents the anatomical association of two elements, each one of which is derived from a separate and independent

system. The adrenal body proper or cortex is part of the "cortical" or "interrenal" system. The medulla is simply an accumulation of chromophil cells of the same nature, histologically, chemically, and pharmacodynamically, as similar but smaller masses along the sympathetic at other levels.

2. There is no clear evidence that these two systems are functionally related to one another.

3. The adrenal medulla (as well as the "chromophil tissue" generally) is derived from the sympathetic nervous system, and is alleged to facilitate this system's functions in certain physiological emergencies.

4. The cortex is derived from the germ epithelium and there is considerable evidence that it has important functions in connection with the development of the reproductive organs.

5. There is a considerable mass of clinical evidence that tumors of the adrenal cortex are frequently associated with sex abnormalities.*

6. Additional evidence in the same direction is furnished by the enlargement of the cortex during breeding and pregnancy.

7. It is possible that a final solution of the problem as to the relation between the adrenal gland and sex will only be arrived at when the wider problem of the relationships between the various ductless glands shall have been solved.

8. Feeding young animals with adrenal gland substance seems to stimulate the growth of the testis.

9. The cortex is the part of the gland which is essential to life. We do not know why its removal causes death, but it is possible that this is due to some defect in muscular metabolism.

*The association is frequent, though not constant.

10. The symptoms of Addison's disease are in no way explained by the accumulated results of investigations in the comparative anatomy and the experimental physiology of the adrenal bodies.

11. It is too early to attempt to diagnose clinically any syndromata due to hyper- or hypo-function of the adrenal bodies.

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COMMENT ON PROF. VINCENT'S ARTICLE

Prof. G. N. Stewart, Western Reserve University, Cleveland: I have no comment to make upon Prof. Vincent's excellent summary, except perhaps to add another proof, obtained by Dr. J. M. Rogoff and myself, that the discharge of adrenin from the adrenal is not indispensable for life or health.

When one adrenal is removed (in the cat) and the nerves which are concerned in the liberation of adrenin from the other divided by Elliott's operation (*Jour. Physiol.*, 1912, xliv, 374) the animal recovers from the operation and lives in apparently normal health, for an indefinite period. Nevertheless, it can be shown that the rate at which adrenin is given off under experimental conditions is very greatly reduced—to one-fiftieth or even one-hundredth of the normal rate. There are differences in the amount of the residual liberation in different experiments, these differences in all probability depending upon whether the secretory nerves have been more or less completely severed.*

But in all the animals the discharge is enormously reduced, and, in some, the test employed (denervated iris, and, on drawn blood, rabbit intestine and uterus segments) have yielded no evidence of any adrenin in the blood coming from the remaining adrenal. In one cat, for instance, it was found that there was no clearly detectable content of adrenin in the adrenal blood, although by the most delicate of the tests employed, a concentration of 1:400 millions could have been detected. This, it must be remembered, was under experimental conditions which have been supposed to increase the liberation through the nervous

*It must be remembered that Elliott's operation (section of all the fibres coming to the semilunar ganglion) has never been shown to be equivalent to section of all the fibres concerned in the liberation of adrenin. What he showed was that it protected the corresponding gland against reduction of the adrenin store under the influence of morphin, tetrahydronaphthylamine, etc. This, of course, would be quite compatible with the existence of some undivided secretory fibres, since the adrenin formed might balance the discharge.

mechanism. In the mixed blood of the right heart the concentration could have been at most one-hundredth of 1:400 millions, which the most enthusiastic upholder of the physiological importance of adrenin will probably consider below the threshold of any definite physiological reaction. Yet the animal was in good health.

Prof. R. G. Hoskins, Northwestern University Medical School, Chicago: Professor Vincent has expressed exactly my views as to the present status of the adrenal problem; but I would add that there is no reliable evidence that under normal conditions circulating blood contains any adrenin at all. It is probably significant that as the technique of investigating the problem has improved the reported dilution of the adrenin in arterial blood has constantly approached infinity. Trendelenberg, using the very delicate frog perfusion method, found that there was present in the carotid blood of normal rabbits at most no more than one part in one or two billions,—a quantity well below the threshold of vasomotor stimulation in mammals. And Trendelenberg did not wholly exclude the possibility that the infinitesimal trace of material supposed to be adrenin was actually a vasoconstrictor substance derived from traumatized blood platelets.

Much confusion has arisen from ignoring the fact that the thoracico-lumbar (sympathetic) system can itself do anything that can be accomplished by adrenin. The adrenals at most merely reinforce the effect of normal sympathetic impulses. Therefore, to ascribe promiscuously conditions of low blood pressure to adrenin deficiency as is done by various clinical writers is quite without justification. The fact that adrenin may improve such conditions no more demonstrates their adrenal etiology than does the "therapeutic test" prove that *pulsus irregularis* is due to a deficiency of circulating digitalis. When to this unsubstantiated conception of sympathetic control

by adrenin is confidently added a theory that the automatic system is similarly dependent upon the beneficent influence of a hypothetical "hormone x" actual absurdity has been reached.

It is even possible that the adrenin problem is commonly regarded from the wrong end. Perhaps it is not the discharge but the formation of adrenin that is the important thing! It may be formed merely by way of rendering harmless some precursor that otherwise would serve as a slow metabolic poison. The fact that adrenin is found in an external secretion from the skin of certain toads supports that idea. Possibly except in times of stress the adrenin of the chromaffin tissue is changed in situ to an inert form and then discharged. This hypothesis could be extended to fit the known facts better than does the theory that adrenin serves normally to maintain the tonus of the sympathetic nervous system.

ON THE CRYSTALLINE COMPOUND CONTAINING IODIN WHICH OCCURS IN THE THYROID

By Edward C. Kendall, Ph.D., Rochester, Minn.

(From the Laboratories of the Mayo Clinic)

IT is well known that desiccated thyroid gland exerts a marked physiologic activity when administered to the normal animal and man, and that the removal of the thyroid is followed by profound changes. The extremes of thyroid disturbance are seen in the two syndromes, exophthalmic goiter and myxedema; and between these are many indefinite or borderline conditions so that thyroid disturbances present a confusing mass of evidence which is not easily classified. Clinically, the cases have been classified and a basis of diagnosis established, and much light has been thrown on the progress of the disease of exophthalmic goitre.

From clinical observations the thyroid has been supposed to have a secretion which contains a substance or substances possessing certain physiologic activity; but the acceptance of such a theory in itself erects a barrier beyond which the clinician cannot go. The only passage of that barrier is by a method which will unlock the constituents of the thyroid secretion and separate the active substances in pure form. Definite conclusions could not be arrived at as long as these substances were known only by the symptoms produced by their presence or absence.

What is the substance in the thyroid that produces toxic symptoms? What is the relation of iodine to thyroid activity? Is the iodine in the gland present in a hitherto unknown substance specific for the thyroid? What is the compound in the thyroid essential

for normal life? Does the thyroid secretion contain more than one active constituent? Can the active substance or substances be separated from the gland in pure form and retain their activity? These and many more problems can be answered only by separation in pure forms of the substances in question, and by investigation of their physiologic activity.

Attempts to isolate the active principle have resulted in two classes of preparations: (1) those secured by separation of products of protein nature without decomposition or destruction of the protein molecule, and (2) those obtained by means of hydrolysis of the protein and the subsequent separation of the decomposition products. In the first class of preparations are Oswald's thyroglobulin and iodine-free nucleoprotein. Other investigators have prepared similar proteins from the thyroid. These products, which are original protein compounds unchanged in chemical nature, still retain their activity, as shown in the treatment of symptoms of cretinism and myxedema. In the second class of preparations, Baumann's iodothyron, containing about 9 per cent. of iodine, is the result of decomposition of the proteins with sulphuric acid. The iodothyron so obtained is about 4 per cent. of the total weight of the dried thyroid. Other decomposition products have been obtained by Hutchinson working with pepsin and trypsin on the thyroid proteins. Hutchinson separated in this way a product containing 3.6 per cent. of iodine.

Another means of throwing light on the nature of the iodine compound has been to prepare various iodine compounds and test their physiologic activity. Di-iodotyrosine, tetra-iodohistidine, tri-iodo-imidazole,

iodized tryptophan, and iodized phenylalanin and other organic compounds have been tested in this way, but no compound has been found which produces effects similar to those of desiccated thyroid.

The object of the writer's investigations summarized here, was to isolate in pure form one or more chemical compounds which possess physiological activity. Dialysis was used as a preliminary study of the proteins of the gland and the nature of iodine combination. Desiccated thyroid, either in suspension or dissolved in dilute alkali, was found to lose less than 5 per cent. of its total iodine by dialysis in a collodion sac against running water. Experiments were then made varying the temperature and acidity of the dialysate. These results showed that increase in temperature and acidity favored dialysis of the iodine compound, and as much as 40 per cent. could be made to pass through the sac in this way. Attempts were then made to alter the nature of the proteins to see the attending influence on dialysis of the iodine. Boiling in strong sodium hydroxide allowed 80 per cent. of the iodine to pass the dialyzing sac. Boiling with sodium hydroxide and hydrogen peroxide allowed 94 per cent. to pass.

These results showed a decomposition of the protein and a probable splitting off of iodine in the inorganic form. As such vigorous treatment would undoubtedly destroy physiologic activity, further experiments were conducted to find some treatment which would break down the complex proteins into simpler products without destruction of the compounds so obtained. Alcohol was tried as a medium for the carrying out of such treatment. Alcohol saturated with hydrochloric acid gas was tried as a hy-

drolytic agent, but no satisfactory cleavage resulted from its use. Hydrolysis with sodium hydroxide in alcohol was then tried, and it was found that this method produced a cleavage different from any of the others. Seventy-five per cent. of the iodine was dialyzable, but it was easily shown that the iodine was not split off as sodium iodide, but still existed in organic combination. After it was shown that sodium hydroxide in alcohol altered the nature of the protein to a marked degree, dialysis, as a criterion of the nature of the iodine combination, was discontinued and a detailed study of the chemical properties of these products of hydrolysis was begun.

No specific precipitant was found for the iodine compound in either an alcoholic or aqueous solution. After many attempts to find such a reagent it became apparent that the iodine was present in two different forms of organic combination. About 50 per cent. of the total iodine was soluble in acid and the rest was insoluble. As the solubility in acids affected a separation between the two apparently different iodine compounds, this treatment was used as the first step in the separation of the products of hydrolysis. Those compounds insoluble in acid are designated constituents of Group A, and those soluble, constituents of Group B.

All the constituents of Group B are easily dialyzable. Saturation of a solution of B with ammonium sulphate produces a sticky, tarry precipitate which evidently consists of amino-acid complexes and carries down with it about 80 per cent. of the iodine in B, showing that it is still present in organic combination. The iodine compound in B is precipitated to a large extent with mercury sulphate, and almost quan-

titatively with silver sulphate in the presence of magnesium oxide. A large percentage of the iodine is split off by this treatment. Oxidizing agents, even copper acetate, also easily split off the iodine from its organic combination.

A more extended study of Group A showed that the most striking chemical property of A is its acidic nature. All the constituents of A are easily soluble in dilute alkali or ammonia, and are reprecipitated by any acid stronger than carbonic acid.

Experiments with organic solvents showed that uncombined sulphur, fatty acids, and about 10 per cent. of the iodine in A is soluble in ether. The fatty acids doubtless came from the fats which were saponified by the alkaline alcohol and the sulphur probably resulted from the decomposition of cystine. Further experiments showed that the solubility of the iodine compound in organic solvents varies greatly, it being least soluble in petroleum ether. The second step, therefore, for the purification of A is the removal of fatty acids and sulphur by extraction with petroleum ether. The product thus obtained contains about 4 per cent. of iodine, and this preparation may be dissolved in alkali and reprecipitated with acids without appreciable loss of its total iodine. This treatment slowly removes some constituents containing nitrogen but no iodine, so that the percentage of iodine in A may thus be increased to about 6 per cent.

This preparation is a dark brown powder insoluble in water and acids, easily soluble in dilute alkali and ammonia. Its alkaline solution is precipitated by copper hydroxide and to a large extent by barium, calcium, and magnesium salts. It is almost entirely soluble in ethyl acetate, but by partial extraction with

this solvent it is possible to separate A into two fractions. In the ethyl acetate soluble portion of A the percentage of iodine may be increased to 13 or 14 per cent., but the ethyl acetate insoluble fraction contains only 1.5 per cent. iodine.

Except for the solubility in ether the general chemical properties of A closely resemble those of a fatty acid. By further hydrolysis of the A group the compound containing iodine has been separated in pure crystalline form. Its exact formula cannot now be stated. It crystallizes in microscopic needles that melt around 220 degrees C. It is very insoluble in alcohol, ether, water, acids, and sodium carbonate. Dilute hydrochloric acid dissolves 1 part in about 200,000. It is readily soluble in dilute alkali and ammonia.

The thyroid having been separated into several different constituents, it seemed desirable to test each one for its possible physiologic activity. These preparations were first tested with normal dogs kept in metabolism cages. Administration of Group B constituents by mouth or by subcutaneous or intravenous injection produced no apparent effect on the temperature, blood-pressure, pulse rate, nitrogen balance, or weight. Administration of Group A constituents by mouth or subcutaneous injection produced the typical so-called hyperthyroid symptoms: increase in pulse rate, slight increase in temperature, marked increase in nitrogen elimination with loss of weight, increase in nervous irritability, and, later, tremor.

These results showed that the toxic symptoms following administration of the gland can be produced by a small group of constituents which amount

to only 4 or 5 per cent. by weight of the desiccated thyroid.

Further investigations concerning the injection of Group A constituents were carried out on a large number of dogs under varying conditions. A typical result is as follows: Weight of dog 10 kilos; pulse rate during previous ten days, 90; 200 mgm. of A used for each injection. Following the injection there is no immediate effect on the temperature, pulse rate, or blood-pressure, and twenty-four hours after the injection there is still no apparent change. The substance injected seems to be inert, but at this time another injection of 200 mgm. is given and the observations continued. From thirty-six to forty-eight hours after the first injection the dog appears restless, the temperature is slightly increased, and the pulse rate has reached 120. The observations and daily injections are continued. On the fourth or fifth day the dog is in a highly nervous condition, restless, with tremor, and there is generally severe diarrhea; the pulse rate is between 200 and 250. Beside the high rate, the pulse has changed its character, becoming hard and hammer-like, with spasms of tachycardia. Although the daily injections are continued at this time, the dog rapidly becomes better, the pulse rate decreases to about 120, and the hard, pounding effect disappears. If the injections are now stopped the dog returns to normal, the pulse rate even dropping to 68 to 70 in some cases.

Having shown that toxic effects are produced by a certain group of constituents of the thyroid, attempts were made to determine the chemical nature and to isolate in pure form the toxic substance contained in this group of compounds.

The presence of iodine as a normal constituent of the thyroid has been known for twenty years. During this time many controversies have arisen out of attempts to explain the relation between the physiologic activity and the presence of iodine. From the beginning of this investigation the isolation of the compound containing iodine was held as the main objective, hence the iodine content of the various preparations of the A constituents was always determined.

By the use of A made from beef, hog, sheep, and pathologic human thyroid it was readily shown that the toxicity of A is directly proportional to its iodine content. By extracting A, containing about 5 per cent. of iodine with ethyl acetate, it may be fractionated into two parts: one containing about 9 per cent. of iodine and the other 1.5 per cent.; but, taking iodine as the standard and the effect on the pulse rate as the criterion, both these preparations produced toxic effects. This indicated that the active substance in each case was the compound containing iodine, and that this substance, combined differently in the two preparations, has differing solubilities.

The toxic effects of A were first produced by preparations containing from 4 to 5 per cent. of iodine. Later the A constituents were further broken down and a purer form, containing 25 per cent. iodine, was obtained. Injection of this under the same conditions, using iodine as the standard, produced the typical effect.

Finally, the iodine-containing compound was isolated in pure crystalline form having a constant iodine content of 60 per cent. These pure white crystals used in amount equivalent to previous injections, keeping A-iodine as the standard, produced the typical

symptoms with the same severity. We can, therefore, conclude that the substance in the thyroid responsible for the production of toxic symptoms is the compound containing A-iodin, and that this compound can be separated in pure crystalline form without loss of its activity.

To determine whether the sudden improvement in the general condition following a series of injections of A resulted from the development of a tolerance to the A compound, a dog was injected until in a highly toxic condition, and was then allowed to return to normal. To a second dog two series of injections were given, the second series being precisely similar to the first. Under the effect of the second series the dog lost weight, had severe diarrhea, became nervous, and appeared to react as severely as during the first series except in regard to the pulse rate. At no time was the rate as high, and it did not develop the hard, pounding property to such a degree. The other symptoms followed much the same course as during the first series. To a third dog three series of injections were given, the previous conditions being observed. Again, the dog reacted as before, but after the third series appeared less capable of throwing off the toxic effects. While the pulse rate was not high, there were spasms of tachycardia when the rate reached 280 to 300; but when quiet and not under excitement the rate was about 150.

These and other results indicate that the A-iodin compound does not work in a rapid and direct manner, and that some form of tolerance is produced. Further experiments are being carried out to explain more fully the factors involved.

The physiologic results on dogs established the

general toxicity of A and the non-toxic effect of B sufficiently to warrant the use of these preparations for therapeutic purposes in cases of thyroid disturbance, and during the past five years many patients have been treated.

As repeated injections over long periods are impracticable in man, the split products were always given by mouth. The results obtained may be briefly stated to be entirely in accord with the preliminary tests on dogs. No toxic effects have ever been produced by the B constituents, although more than 200 patients have been treated; but the A constituents, even in small amounts, produce toxic effects.

The severity of the condition following administration of A to normal individuals varies greatly, but in general it is as follows: If to a normal individual with a pulse rate of about 75 and a weight of about 75 kilos sufficient A is given per day to contain 3 mgm. of A-iodin, on the day following the first dose there is no apparent change except a slightly increased pulse rate. If the same daily dose is continued the patient slowly reacts, and in the course of eight or ten days nervous symptoms develop, the pulse rate is from 130 to 140, there is a tendency to perspire more freely on exertion, and the patient may be short of breath and easily tired. At first appetite is increased but later is lost, and nausea, and sometimes diarrhea develops. During this time the patient usually loses weight, from 1 to 5 kilos (idiosyncrasy?). If smaller doses are given the severity and course of symptoms are modified, but the patient will react to very small amounts of A. If large doses are given there results a serious condition in which the above symptoms are exaggerated.

As in the tests on animals, the therapeutic results on the human being were first obtained with preparations of A containing about 4 to 5 per cent. of iodine. Later they were repeated, using the purer form of the compound that contained 25 per cent. of iodine, and, finally, the typical effects with the same severity were obtained by using the pure crystalline compound containing 60 per cent. of iodine.

These results brought out a great difference in the sensitiveness of dog and man to the toxic iodine compound. To produce effects in dogs, about 1 mgm. of A-iodine per kilogram weight of dog is required for a daily dose. In the human being severe symptoms follow the administration of as little as 1-75 to 1-25 of 1 mgm. per body weight per day. Furthermore, the nervous system seems to respond much more quickly and strongly in the human being than in the dog. Why the minimum dose required to produce toxic effects in people varies greatly is now being investigated.

In addition to observations on the pulse rate and general condition, electrocardiograms were taken of several cases. In every case a change appeared by slow and regular steps, so that a series taken on fourteen or twenty-one successive days showed a great difference between the first and last, but the change between any two days was hardly noticeable.

It has long been known that the growth of cretins is materially influenced by administration of desiccated thyroid. It was therefore interesting to determine the effects of A and B on growth and mental activity.

Case 1, a cretin, aged nine years, weight 16.8 kilos, height 93 cm., was given B alone for ten weeks. Observations on her pulse rate, weight, and height showed no appreciable change

during this period, although certain other conditions, which are discussed later, were relieved. At the end of the ten weeks a small amount of A (0.5 mgm. A-iodin) was included in the daily dose. As there was a rapid response, the pulse rate increasing to 140, the dose was reduced to 1-3 mgm. of A-iodin per day, and this amount has continued. Her weight and height were taken on the following dates:

Dates.	Weight kilos.	Height cm.
January 4, 1915.....	16.30	92.5*
January 27, 1915.....	16.10	95.0
February 27, 1915.....	16.70	95.0
April 2, 1915.....	17.30	97.5
May 5, 1915.....	16.90	97.5
June 24, 1915.....	17.10	99.5
July 8, 1915.....	18.60	102.0
August 5, 1915.....	18.86	105.4
September 4, 1915.....	18.86	106.0
October 16, 1915.....	19.43	106.0
November 13, 1915.....	20.45	106.7
January 16, 1916.....	20.68	109.2
February 15, 1916.....	20.0	109.9
March 17, 1916.....	20.68	111.1
April 16, 1916.....	19.54	111.1
May 16, 1916.....	20.91	111.8
June 18, 1916.....	21.36	112.1
July 14, 1916.....	21.13	113.0
August 16, 1916.....	21.59	114.9
September 17, 1916.....	22.04	115.6
December 5, 1916.....	22.95	116.2

Although no apparent effect was produced with the B constituents in respect to growth, administration of A-iodin was followed by rapid and continued increase. At the same time the mentality was markedly improved. Formerly she was phlegmatic, not easily aroused, did not play with other children, and was backward in talking. She has greatly changed in appearance, manners, and desire to play and talk.

In this case so little A-iodin was given that no toxic symptoms were produced and only a tonic effect resulted. The cretin is abnormal because of the absence of something. This deficiency can apparently be supplied by the administration of very small amounts (1-180 grain per day) of the A-iodin compound.

Another patient, case 2, similar to this one in respect to the effect on the mentality was observed with an adult suffering from myxedema. For six months this patient was treated with B alone. At the end of that time, although entirely relieved of subjective symptoms, she was still greatly troubled

*The observations on January 4, July 8, 1915, and December 5, 1916, were taken at the Mayo Clinic. The other measurements were made at the home of the patient.

with inability to keep awake. She would fall asleep in street cars, while resting on a park bench, etc., and had great difficulty in remaining awake even a few hours a day. When in this condition, small daily doses of A produced immediate and striking relief. Within a few days the patient's whole appearance changed, her naturally bright and witty personality was fully restored, and the desire for sleep was reduced to normal.

Case 3. A boy 10 years of age. Had not been treated with thyroid. Condition was typical of cretinism, dry, scaly skin, poorly nourished, distended abdomen, feeble mentality. After six months treatment with the A-iodin compound there was very marked improvement, normal skin, distention of abdomen had been relieved. There was also marked improvement in mentality. There was a rise in hemoglobin and the general condition was excellent. The daily dose for the six months was one-eighth of 1 mgm. of A-iodin.

Case 4. Young woman 20 years of age. When entering Clinic her condition was one of extreme hypothyroidism, dry, scaly skin, cold hands and feet, even in summer, great apathy and sluggish mentality. Hemoglobin 20 per cent. This patient responded very rapidly to the alpha-iodin compound and in less than three weeks showed very marked improvement. The condition of the skin was relieved, hemoglobin rose rapidly and steadily to normal, sensation of cold no longer felt in hands and feet. Mental activity was greatly increased and all evidences of edema relieved. The entire amount required to produce this change was less than one-third of 1 grain of A-iodin.

Case 5. A woman 47 years of age. During previous ten years her activities declined until she was almost in a state of helplessness. Had been diagnosed dementia praecox elsewhere and given a hopeless prognosis. Had received desiccated thyroid without effect elsewhere. Patient was extremely resistant to A-iodin, requiring enormous doses to bring about a primary change. In about three weeks the patient had reacted, the skin condition was changed to normal, mental activity was greatly increased, apathy was relieved, edema was entirely reduced, patient left Clinic so changed that her children no longer recognized her. After having reacted to the thyroid hormone her daily dose had to be reduced to 8 mgm. per seven days. If patient increases or decreases this amount unpleasant subjective symptoms follow.

The question as to whether the thyroid contains more than one physiologically active substance cannot be answered definitely at this time, but there is

evidence that at least one other substance besides the compound containing A-iodin produces physiologic effects under certain conditions. The acid-soluble group of constituents, designated B, produces no apparent effect when given to normal dog or man, but certain symptoms of myxedema and some conditions of the skin appear to be relieved by the administration of B alone. The symptoms in myxedema relieved by B alone are burning sensations of the skin, with smarting, itching areas, soreness of bones and joints, and cramps of the muscles. No stress is laid on the relief of these symptoms, but they are mentioned in the possibility of drawing attention to the condition in other cases. They are present only in the more severe types of myxedema.

Also, a dry, scaly skin with absence of perspiration in cases diagnosed myxedema is relieved by B alone. Engman has treated a number of such cases, and among them two patients suffering from dermatitis exfoliativa. In practically all cases improvement has been noted, and in no case have there been any toxic symptoms produced. At our clinic, 92 cases have been treated with B constituents, and in no case have there been any toxic effects noticed. Twelve cases of cretins and mongols have been treated over thirty days with large doses of B. Pulse rate, respiration, temperature, and weight were taken for the entire period. While there were individual variations the average results showed no apparent toxic effects.

This non-toxic effect of the B group of constituents is in strong contrast with the A group, since they both contain iodine. The iodine-containing compound in A has been isolated and its toxicity shown; the iodine in B is in organic combination, but the

nucleus to which it is attached is unknown and no relation of iodine to activity is evident. While no definite proof of the relation of the iodine compound in the B constituent compound had been isolated in pure form it seems highly probable that the iodine compounds in B are intermediate stages in the elaboration of the A compound from iodine taken with the food. The chemical identity of the iodine compound in A is established and although a pure crystalline substance, its structure is extremely complex, having a molecular weight of 586. It is theoretically impossible to pass by one operation from inorganic iodides taken in with the food to the completely elaborated A-iodine compound. Intermediate products must exist and it seems undoubted that these are found in the B group of constituents. The amount of the total iodine in the gland which may exist in the A form, that is, insoluble in acids, varies from two to three per cent. up to 40 or 50 per cent. It is highly probable that some equilibrium exists between the two forms so that in normal conditions a constant percentage of the total iodine is in the A form, the rest is retained in the gland in the physiologic inert B form. Under conditions of thyroid disturbance this relation is disturbed and in the acute stages of hyperthyroidism very little iodine is found in the gland and what there is is mostly in the B form. The percentage of the total iodine which is in the B form varies with the duration of symptoms and severity of symptoms. By the analysis of a large number of cases it is possible to follow this decrease in the total iodine as the acute symptoms develop and after the crisis has been passed it is readily shown that the iodine in the gland

increases and the percentage of the total iodine in the A form increases.

Since it has been shown to be possible to produce hyperthyroid symptoms by the administration of the A-iodine compound the small amount in the gland in the acute stages of hyperthyroidism is not to be interpreted as a cessation of the activity of the gland at this time but is more correctly interpreted as a loss of storage capacity upon the part of the gland. The production of the substance may be as great or greater than normal but it is not retained in the gland. The physiologic activity of the B group of constituents is not at all clear. It is impossible to produce toxic symptoms by administration of this portion of the thyroid and it is impossible to relieve the symptoms of myxedema, but certain indefinite skin conditions seem to be relieved by this group of substances. It is not due to the result of the activity of the iodine compound in B, because it is possible to remove this and secure the results with the iodine-free constituents.

Conclusions. 1. By an alkaline alcoholic hydrolysis the thyroid proteins are broken into many simpler constituents, which by their solubility in acids are separated into two groups. Those constituents insoluble in acid are designated group A and those soluble, group B. No definite crystalline compound has been isolated from group B, but it appears to be composed of mixtures of amino-acid complexes. About one-half the total iodine in the thyroid proteins appears among the group B constituents. The nucleus to which the iodine is attached is unknown.

By continued hydrolysis the group A compounds have been further separated and the iodine-containing

compound has been isolated in pure crystalline form, having a constant iodine content of 60 per cent.

2. Physiologic tests on animals and human beings have shown that no toxic effects can be produced by any of the constituents of group B. Group A constituents, however, produce the so-called hyperthyroid symptoms; increase in pulse rate, with tachycardia, increase of nitrogen elimination, with loss of weight, and increase in nervous irritability, etc. Further investigation showed that the production of these symptoms was proportional to the iodine content, that partial purification of A did not destroy the activity, and finally that the compound containing A-iodine produced these effects in all stages of purity up to and including the pure crystalline form.

3. The amount of the A-iodine compound necessary to produce symptoms is extremely small. One-half milligram (1-120 of a grain) per day produced marked effects in a cretin weighing 15 kilos. The susceptibility of animals and man to this compound varies greatly, but the human being responds much quicker and to a far greater degree than the dog. Some form of tolerance for the compound is produced. In very small doses the A-iodine compound exerts a tonic effect, and appears to be essential for normal growth and life.

4. Administration of A-iodine to man produces changes in the cardiogram.

5. Although B produces no toxic effects, it appears to possess physiological properties in certain conditions of the skin.

6. The toxic properties of A are due to the isolated iodine-containing compound; and there appears to be no relation between activity and iodine in B.

A BRIEF HISTORY OF THE DEVELOPMENT
OF OUR KNOWLEDGE OF THE DUCTLESS
GLANDS*

By Gustav Baar, M. D., Portland, Ore.

FOR hundreds of years the medical world believed in the "consensus partium," which means that physicians assumed a mutual influence of the activity of the various organs of the human body upon each other. This correlation was explained on a nervous basis, the correlation being supposed to be brought about by means of the centripetal and centrifugal nerves.

The "reflex phenomenon" became known through the studies of Descartes in the 17th century, and more especially in the 19th century, when this phenomenon was more clearly elucidated by the work of the Viennese physiologist, Prochaska. Of course this neural correlation of organs was not the only hypothesis in vogue. There was also the humoral hypothesis, as represented in Hahnemann's teachings ("Homoeopathy"). This latter vindicated to every individual organ of the human body a certain influence upon the juice-mixture of the whole body. The doctrine of "isopathy" went the doctrine of homoeopathy one better, for it recommended as a therapeutic means against diseases of the various organs the use of the corresponding healthy organs: for instance, the lungs of fox for lung diseases; the liver of wolf for liver diseases; the eyes of oxen for eye diseases, etc. A replica of such procedure is found in the more modern questionable advertisements of ophoterapeutic extracts.

*Read before Portland (Ore.) City and County Medical Society March 7th, 1917.

Medicine entered a new era when Harvey in 1628 discovered the circulation: the blood now was assumed as the means of communicating between the various organs. Our confreres of those times gone by knew nothing, however, of the secretions from the various body structures, secretions which enter the blood stream by other than the known secretory ducts—though we note in Swedenborg's writings a remark that the liver and the pancreas perform a much greater chemical task than one would be led to assume from their secretory ducts; furthermore, that these organs, in conjunction with the spleen, bring about the purifying of the blood.

Then came Theophile de Bordeu, from Montpellier, claiming in 1775 that every organ creates specific bodies necessary for the integrity of the whole organism, which enter the blood either by lymphatic or venous channels. He thus explained the symptoms accompanying castration, puberty, the menopause, etc., and divined the importance of secretory anomalies as a basis for some of the pathological changes in the human body.

The first one, however, who drew a line between the "secretion" and "excretion" of the various glands was Johannes Muller in 1830. Among the secretory organs he classes the spleen, thyroid, adrenals, thymus and the placenta.

The first to prove experimentally the influence exerted by the internal secretion of a gland upon the blood mixture, and through the latter upon the whole body, was A. A. Berthold, professor in Gottingen, in 1849, who transplanted the testicles of young cockerels and noted that these cockerels, in spite of being castrated, remained normal cocks as far as vocal pow-

ers, sexual instinct, desire of combat, comb growth, etc., were concerned. Thus the existence of an internal secretion of the testicles was first accurately established.

In 1855 Claude Bernard pointed out the difference between the internal and external secretion of the liver: the latter furnishing the bile, the former producing an accumulation of glycogen within the liver and its outflow into the blood as sugar.

Shortly after this came Brown-Sequard, who taught at the medical faculty in Paris, in 1869, that all glands, whether endowed with excretory ducts or not, contributed useful and necessary substances to the blood, which, when lacking, produced pathologic symptoms. This same savant, twenty years later, set the birthdate for our knowledge of the therapeutics of the internal secretions when he, at the ripe age of 72 years, reported before a memorable meeting of the Paris Societe de Biologie, June 1st, 1889, some experiments made on his own body with subcutaneous injections of testicular juice; he claimed to have observed on himself, after such treatment, a surprising increase of physical vigor, cerebral function, appetite and intestinal activity. Since that time we have found out that the ovaries, as well as the testicles, produce "hormones" that originate in parts of the glands other than those producing the external secretions; in the male they originate in the interstitial cells of Leydig, as Hanes found in 1911; in the female probably in the corpora lutea. The functions of these sexual hormones are chiefly connected with sexual life, however they also have reciprocal relations with many other organs of internal secretion (thyroid, thymus, etc.).

In the comparatively short period which has elapsed since the epochal announcement of Brown-Sequard, a new field for research in physiology, biology, pathology and therapy has developed, an era of understanding and hope. Brown-Sequard thus impressed the medical world with a view that the glandular organs, be they with ducts, like the pancreas, liver, gonads, including also the duodenal mucosa, or without ducts, like the thyroid, parathyroid, thymus, hypophysis, or adrenals, give off to the blood certain substances that are necessary for the welfare of the body as a whole. To such substances that are derived from one organ and influence another after their passage into the bloodstream, Starling later (1902) gave the name of chemical messengers, or "hormones" from the Greek, I arouse, or set in motion.

The evidence of the existence of such hormones has been furnished in three ways:

1. Substances, physiologically active, were demonstrated in the blood or lymph leaving the gland in question; such direct and conclusive proof has been furnished as yet only for one gland, the adrenal.
2. Excision of the gland produced characteristic changes in the vital processes, which could be prevented by implantation of the gland in question or by the administration of preparations of the same gland. This sort of evidence was brought out regarding the hormones of the pancreas, thyroid, parathyroid, hypophysis, adrenals and sex glands.
3. Pathologic entities of supposed hyperfunction of some glands could be imitated artificially by administering overdoses of the substance of the gland in question. For instance, the "Graves' complex" could be produced by overfeeding with thyroid gland,

or something similar to diabetes insipidus by pituitary gland injections.

Let us take up now the history of the development of our knowledge regarding the internal secretion of the different glands. In practical importance the thyroid is undoubtedly the first.

THYROID. While Schiff was the first to attempt to combat thyroid deficiency by transplantation experiments in dogs in 1859, it remained for Reverdin and Kocher in 1882 to publish their observations on patients from whom the thyroid had been removed (*cachexia strumipriva*), and thus call the attention of the medical world to the importance of the gland. Within a few years it was recognized that the underlying cause of *cachexia strumipriva*, sporadic and endemic cretinism and myxedema (Ord in 1882 thus named the condition which Sir William Gull described five years before him), was the same in all, viz., the deficiency or absence of the thyroid; on the other hand, hyperfunction of the thyroid gland produced Graves' disease (*exophthalmic goiter*), though conclusive demonstration of an excess of thyroid secretion in the blood of those patients has not been furnished. In 1915 Cannon demonstrated that hyperthyroidism may result from stimulation of the nerves leading to the thyroid gland.

PARATHYROIDS. These glands were first described by Sandstrom in 1880; it was soon found that tetany developing after thyroid operations was due to the accidental removal of the parathyroids. The syndrome accompanying parathyroidectomy is characterized by an increased irritability of the peripheral neuron, muscular tremor, convulsive seizures, particularly in the hands and feet, Trousseau's phenom-

enon (pressure on the brachial nerve causing contraction of the hand) and Chvostek's phenomenon (tapping on the facial trunk causing facial twitching). MacCallum and Voegtlin showed in 1909 that the tetany is due in part to a loss of calcium from the tissues, the injection of calcium salts relieving the symptoms, due largely to their depressing the excitability of the motor nerves. Apparently the parathyroid glands exert some influence upon the retention of calcium by the nerve tissues. A disturbed calcium metabolism has been assumed, since it occurs in diseases often associated with tetany: in rickets osteomalacia, pregnancy and lactation.

THYMUS. This gland has an important relation to the sex glands, to bone growth, and also to the thyroid. Bartel and Herman reported in 1911 that they had frequently found enlarged ovaries in the so-called status lymphaticus, a condition consisting of enlarged thymus, hypertrophied tissues elsewhere in the body, constitutional hypoplasia of the aorta and of the chromaffin tissues, which is not uncommonly responsible for sudden death. Our knowledge of the function of this gland is as yet very unsatisfactory.

HYPOPHYSIS or Pituitary Gland. In 1889 Rogowitsch noticed hypertrophy of the hypophysis after extirpation of the thyroid. In the same year Marie discovered an association between acromegaly (an entity characterized by enlarged hands and feet, thick lips, protruding lower jaw, lower incisors extending beyond the upper, increase of hair in various part of the body, enlarged sexual organs, but loss of sexual function, glycosuria) and anatomical changes in the hypophysis.

In 1895 Oliver and Schafer announced that extracts from the pituitary gland caused a rise of blood pressure when injected intravenously through their constricting effects upon the blood vessels. In 1898 Howell ascribed the origin of these substances to the posterior lobe (nervous lobe) of the hypophysis.

In 1901 Froehlich described a syndrome under the name of "dystrophia adiposo-genitalis" (obesity about the abdomen, buttocks and breasts, giving a feminine type of figure, retardation of skeletal growth, with short extremities, small hands and feet and sexual infantilism); all these symptoms are due to the hypofunction of the pituitary gland (probably of the anterior epithelial lobe secretion).

In 1907 Paulesco reported death after total extirpation of the gland, whereas partial extirpation is followed only by very characteristic effects upon growth and development. In 1909 Cushing and Homans showed the gland's relation to carbohydrate metabolism. Pituitrin is the therapeutic booty resulting from all these researches. This extract of the posterior lobe is used chiefly for its constricting effects upon non-striated muscles, especially those of the uterus, blood vessels, gastro-intestinal tract, smooth muscle in the mammary gland and bladder.

ADRENALS. Next to the thyroid gland, our knowledge of the adrenals has found most promising development. Attention was first called to the importance of the chemical influence of these glands by the classical paper of Addison, published in 1855, in which he described a disease characterized by muscular and cardiac weakness, low blood pressure, subnormal temperature, apathy, vomiting and diarrhea, bronze pigmentation of the skin and mucus mem-

branes, and a progressive cachexia leading almost always to death. The majority of these patients show a tuberculous degeneration of the adrenal glands.

In 1895 Oliver and Schafer discovered the fact that extracts of the medulla of the adrenal glands, when injected intravenously, caused a rise in blood pressure. The chemical researches of Abel, Takamine and others resulted in the isolation of epinephrin or adrenalin, a definite chemical compound. The effects of the administration of this drug are essentially the same as those which follow the stimulation of the sympathetic nerves. The output of adrenin from the adrenals is increased as a result of violent emotion, fear or anger (Cannon, 1911), bringing about functional changes in the body such as cessation of gastro-intestinal movements, broncho-dilatation, increase of blood pressure and glycosuria—symptoms which can be experimentally produced by the intravenous injection of adrenalin. Elliott (1912) demonstrated that essentially the same results could be produced by sympathetic nerve stimulation.

Eppinger and Falta proved that the thyroid has an intensifying effect upon the action of adrenin.

There are other glands, like the pineal gland, mammary gland, pancreas, which are not mentioned for lack of time, and our knowledge about their internal secretions is still comparatively meager.

As Sajous has said, "the progress of medicine has been handicapped through the non-recognition of these structures which steadily are asserting their right to be classed with major organs," and this progress will be still more handicapped if we physicians fail to inform ourselves of the true progress in the science of endocrinology.

A METHOD OF CONTROLLING HYPERTHYROIDISM

By Leigh F. Watson, M. D., Chicago, Ill.

ABOUT four years ago I observed the effect of a concentrated solution of quinine and urea which was injected into an angioma of the tongue, that had been repeatedly cauterized with carbon dioxide snow without reducing its size or vascularity. Injections of a 50 per cent. solution caused the tumor to disappear completely; the tongue assumed its normal size and color and there has been no return of the condition since.

Shortly after treating the angioma, I used the quinine and urea injection in a severe case of toxic exophthalmic goiter. The patient was too ill to stand even the slight operation involved in ligating the superior thyroid arteries; the improvement following the injection was more decided than I have ever seen following ligation. Since my preliminary report, I have used quinine and urea injections in over one hundred cases of goiter with no unpleasant effects.

I recommend the method only to relieve hyperthyroidism and not to remove the goiter. It is often true that in small toxic and atoxic goiter, the inflammatory reaction following the injection is sufficient to cause the disappearance of the tumor; but the process is slow, usually covering several months, and when used for this purpose alone, the results are liable to be disappointing.

The injection must be employed with discretion; I have used it four years, the length of time being too short and the number of cases too limited, to draw

conclusions. It is suitable for use only in a hospital by men skilled in goiter work.

Too often toxic goiter is regarded as a disease of the thyroid gland alone, while in reality all the glands of internal secretion are more or less involved. For instance, I have found glycosuria in 85 per cent. of severe cases of hyperthyroidism.

Rautmann, who has recently reported the findings from autopsies on patients dying of exophthalmic goiter, states that an enlarged thymus very frequently accompanies hyperthyroidism; the adrenals and ovaries are involved in a majority of cases; the hypophysis, parathyroids, and islands of Langerhans are less frequently affected. He states further, that the changes in the thyroid, parathyroids, thymus, and hypophysis are of a hypertrophic hyperplastic nature, while the changes observed in the adrenals, ovaries, and islands of Langerhans are of a pronounced atrophic hypoplastic type.

Barker believes that a focus of irritation or infection is often present in some part of the body aggravating the hyperthyroidism; the most common conditions associated with exophthalmic goiter are chronic tonsillitis, sinusitis, nasal polyps, chronic appendicitis, pulmonary tuberculosis, gall-stones, urogenital lesions, pyorrhea alveolaris. The association of thyroid disorder and uterine disease is often observed, and has been variously estimated as representing from fifteen to twenty-five per cent. of all cases. It is not uncommon for these patients to observe that their hyperthyroidism is worse when the pelvic lesions are aggravated.

Hertzler states that the physiologic relationship between thyroid and pelvic organs suggests that the

latter are particularly liable to be the source of irritation in producing or continuing the symptoms of hyperthyroidism. Relief of the pelvic lesion is occasionally followed by subsidence of the hyperthyroidism, and vice versa. Halsted maintains that the most puzzling cases of exophthalmic goiter are explained by the discovery of the influence of the thymus. The association of the thymus should be thought of in all cases of goiter presenting marked tachycardia and psychoneurotic disturbances with lymphocytosis. Thymus involvement is probable in cases presenting dyspnea, diarrhea, and slight enlargement of the thyroid with exophthalmos and tachycardia absent.

From time to time in the course of this study it has been necessary to conduct a series of experiments. The dog's thyroid was selected because of its freedom from pathological changes.

The thyroids of several dogs were injected with different percentages of quinine and urea solution and removed at varying intervals to show the changes that take place in the normal thyroid after injection. All injections were made under ether anesthesia and the strictest aseptic technic was observed in every case. The findings may be summarized:

The injection of weak quinine and urea solution has little effect. In three or four weeks the glands are practically normal in appearance, the destruction of thyroid cells and colloid always occurring after the concentrated solutions are injected.

The injection of concentrated solutions of quinine and urea into muscle produces an intense inflammatory reaction, resulting in the muscle being completely replaced by connective tissue.

From a study of two human toxic goiters removed

for cosmetic reasons after injection, the following conclusions may be drawn:

1. In each of these cases there was a noticeable absence of adhesions around the gland; the operation was not made more difficult because of the previous treatment.

2. It is more difficult than one might suppose, to destroy a sufficient amount of thyroid to relieve hyperthyroidism, merely by making several injections through the skin.

3. The weak solutions of quinine and urea injected into thyroid tissue are productive of only a temporary fibrinous exudate, which is rapidly absorbed with more or less accompanying hyperemia. The reaction following the strong injection is more intense and results in extensive inflammation with round cell infiltration, connective tissue proliferation and necrosis of the thyroid cells with a loss of staining properties of colloid and thyroid.

I have noticed that a number of small injections of quinine and urea produce more necrosis than a single massive infiltration.

The diagnosis of hyperthyroidism is difficult at times, especially when there is no exophthalmos or decided enlargement of the thyroid. These symptoms are of little importance and may be absent in the very severe cases that have a sudden onset. Exophthalmos is present only in a small per cent. of the cases of moderate hyperthyroidism, and not demonstrable in every case of severe toxic goiter. When exophthalmos and thyroid enlargement are absent, the heart and nervous symptoms are often treated without recognizing the underlying cause of the disease. The first symptoms noticed may be slight insomnia,

nervousness, accelerated heart action or increased exertion. Often the onset can be traced to an accident, sudden fright, parturition, grief, or great emotional strain.

Too frequently the hyperthyroid patient is not regarded as a sick person. Because her symptoms may not be severe enough to compel her to stay in bed, the physician is liable to be lax in insisting on close medical supervision. Surgeons and internists agree that any procedure for the treatment of hyperthyroidism must be based upon a period of rest, with medical, dietetic and hygienic measures suited to the needs of the individuals.

The hyperthyroid patient will usually do best away from home, removed entirely from surroundings suggesting mental and physical exertion. Inquiry will frequently disclose some particular factor of work or worry that has contributed to the symptoms or perhaps caused the disease, and which should be corrected as far as possible. Sympathetic friends and relatives should be excluded, thus giving the patient an opportunity for repose, as complete as can be, in a cheerful atmosphere.

Organotherapy. Organotherapy has an established place in the treatment of hyperthyroidism. It is necessary to make a careful study and examination of each patient to determine which ductless glands are contributing to the symptoms, and if their action is one of hypofunction or hyperfunction. If the condition is found to be one of decreased function, glandular extracts should be administered; if it is a disturbance of hypersecretion, a nucleoprotein serum may be given in selected cases.

Hygienic. A patient suffering from severe hyper-

thyroidism should have a rest of several months, on an open veranda, or in a bright, cheerful room, carefully isolated from seriously ill or noisy patients. For the first few weeks he must lie down the whole or greater part of the day. The more favorable the climatic conditions, the better for him.

Dietetic. Body weight can be increased best by a simple nourishing diet, with plenty of carbohydrates, milk, fats, vegetables, and a little meat.

Medicinal. The administration of drugs is usually not necessary and should be avoided as far as possible. The treatment of symptoms as they arise is the best rule rather than any routine medication. It is not my purpose to condemn the operation for goiter. Anyone with experience in the disease can not doubt its value as a therapeutic procedure, and in many cases it is the only treatment from which the patient may derive benefit. It is my opinion, however, that only in exceptional cases should it be the first step taken to effect a cure.

Quinine and Urea Injections. In selected cases, I believe hyperthyroidism can be relieved by means of injections of concentrated solutions of quinine and urea into the thyroid.

A study of thyroids removed after infiltration has demonstrated the difficulty of destroying even a small portion of the gland by injections through the skin. As one becomes experienced in the technic, it is possible to give each injection into tissue that has not been previously infiltrated; thus destroying the greatest amount of thyroid with the smallest number of injections.

For the injection I use an all glass syringe of 1 or 2 mil. capacity, fitted with a slip needle so that the

syringe can be readily attached and detached without traumatizing the thyroid. I prefer a fine platinum needle $1\frac{1}{2}$ inches long.

After the usual aseptic precautions, the site of the injection is anesthetized with a 0.1 per cent. cocaine or 0.25 per cent. novocaine solution infiltrated into the skin, subcutaneous tissues and muscles, down to the gland. The syringe is now detached and the needle is thrust carefully into the body of the goiter. After ascertaining that there is no fluid in the thyroid and that no blood or air comes through the needle, the syringe is attached and the infiltration slowly made.

In cases of hyperthyroidism, I usually give from 1 to 4 mils. of a from 30 to 50 per cent. quinine and urea solution at a treatment, repeating the injections about every third day, depending on the progress of the patient. Eight to fifteen infiltrations are usually necessary to produce a marked improvement in the general symptoms and the disappearance of the bruit over the superior thyroid arteries.

The method is recommended only to relieve hyperthyroidism and not to remove the goiter. It is sometimes true that in small toxic and atoxic goiters the inflammatory reaction following the injection is sufficient to cause the disappearance of the tumor; but the process is slow, and when the injection is used for this purpose alone, the results are liable to be disappointing.

The procedure is one that is surrounded by certain dangers, immediate and remote. One inexperienced is liable to puncture the trachea or one of the large bloodvessels, or to make the injection into the soft tissues of the neck. Injections that are too ex-

tensive will produce the same symptoms of myxedema that follow the removal of too much thyroid by operation. For this reason, it is necessary to discontinue injections before symptomatic relief is secured.

The necessity of minimizing the slight pain from any injection by the use of local anesthesia can not be too strongly emphasized.

Preliminary injections into the thyroid gland of a few minims of a sterile salt solution, followed by injections of sterile water, are necessary to raise the patient's threshold of stimuli, thereby preventing an acute attack of hyperthyroidism which might otherwise follow the slight pain of the first quinine and urea infiltration. As soon as no hyperthyroid reaction follows the water injections, their usefulness is at an end. The use of quinine and urea injections without this preliminary precaution is likely to be disappointing if it is not disastrous.

The above treatment is suggested only to relieve the symptoms of hyperthyroidism and is not recommended as a means of removing the tumor in simple goiter.

Much depends on a proper selection of cases; the necessity of preventing pain from any injection, by the use of local anesthesia, is of vital importance, if acute attacks of hyperthyroidism are to be prevented, preliminary injections of sterile salt solution, followed by sterile water, will be found valuable.

The method is suitable for use only in a hospital by men experienced in the difficulties of thyroid surgery. The danger of destroying too much of the gland must always be borne in mind.

I believe the greatest field of usefulness for the

injection method which I have advocated will be found in those cases of beginning hyperthyroidism not severe enough to justify operative treatment, and as a preparatory measure to partial thyroidectomy in chronic cases of toxic goiter in which the patient is too ill to warrant any form of immediate operative procedure.

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COMMENT ON DR. L. F. WATSON'S ARTICLE

Dr. Harry G. Sloan, Cleveland, Ohio: We have been impressed with the value of quinine and urea injected in a concentrated solution into the thyroids of patients who show toxic goiter symptoms.

We use this solution as the mildest of all methods for diminishing the amount of secreting gland substance in the very gravely ill patients. I think as a rule these are found in the acute exophthalmic goiter, in children and at the time of puberty, it being a well recognized fact that this type of patient stands opera-

tion least well. We have found that in regard to age, patients in the third decade of life stand operations for acute exophthalmic goiter better than at either extreme of life, i. e., in the young and the very old. This fact corresponds to the ability of patients in general to withstand either hemorrhage or infection because in middle life the natural reserve of the central nervous system is more markedly developed.

Quinine and urea injections seem to give better results in the severely ill cases than hot water from the fact that the absorption of necrotic tissue caused by the injection is more slow in the case of quinine and urea than with hot water. The broken down tissue caused by hot water injections is more rapidly absorbed and undoubtedly gives rise to greater toxic action.

We graduate our dosage of quinine and urea, using 25 per cent. solution in quantities of from 1 to 5 mils.

The injection is made without general anesthesia, the skin and deep structures being perfectly blocked by novocain 1-400. In the severe cases from five to ten injections are necessary with varying periods between injections of from one week to three days.

At this stage they are able to bear ligation of the superior thyroid artery. Following this the opposite superior artery is ligated. We do not consider that these people are in a state to recover from the disease until four-fifths of the thyroid has been removed by operation and even then they must carefully observe a prolonged period of mental and physical rest of from one to two years.

A THEORY AS TO THE CAUSATION OF UTERINE FIBROMYOMATA, WITH SOME REMARKS ON THEIR PREVENTION AND CONSERVATIVE TREATMENT

By W. A. Briggs, M. D., Sacramento, Cal.

UTERINE fibromyomata occur in more than 50 per cent. of women between the ages of 40 and 60. This is a frequency greatly in excess of that of tumors homologous to any other tissue of the human body. The comparative size of these growths is commensurate with their frequency. The causes of the exaggerated size and frequency of these tumors, as compared with similar tumors elsewhere, must be inherent either in this organ itself, in some external organ, function or condition exercising on it a very powerful influence or in a combination of these.

From a histological standpoint, besides dilated lymphatics and blood-vessels, uterine fibromyomata consist essentially of pathologic reproductions of the normal uterine tissues chiefly muscular, fibrous and glandular, often seen to be in process of undergoing various forms of degeneration. The tumors inherit not only the structure of the parent organ but its characteristics also—a unique capacity for great and rapid development and an even more rapid involution. This explains, perhaps, their potential size but not their actual frequency.

That the causes, at least the exciting causes, of these growths, are not resident solely or even chiefly in the structure of the uterus itself is further indicated by the extreme frequency with which fibromyomata originate during the reproductive period and the extreme rarity with which they originate either before or after—a rarity approaching if not equal-

ling that of fibroids elsewhere in the human body, a rarity so great that until recently their existence had escaped the attention, personal as well as statistical, of more than one reputed authority.

The exciting causes of uterine fibroids, so frequently originating during the reproductive period and so rarely before or after this period, therefore, must be sought elsewhere than in the structure of the uterus itself. May they not be connected with the physiologic uterine hyperemia of menstruation, often pathologic in degree, frequency and duration; in the absence of the physiologic suspension of this hyperemia of pregnancy and its physiologic antagonism by mammary activity during lactation and in the pathologic congestion due to metric and parametric infections, uterine retrodisplacements, pelvic adhesions, colonic stasis and the universal corset?

That these causes may be so found is suggested by the following generally accepted facts: Uterine fibroids generally cease growing and are often partially or completely absorbed (a) after the menopause (b) during pregnancy (c) during lactation (d) after X-ray inhibition of ovarian function and (e) under the ovarian inhibitory influence of mammary extract: the uterus itself atrophies (f) during lactation and (g) during periods of ovarian quiescence and the entire female reproductive system normally atrophies after the menopause: in uterine fibrosis, ovarian activity, as manifested by profuse or prolonged menstruation, is so frequent as to be generally considered (h) its first and most important symptom and as often (i) maintained beyond, not rarely far beyond, the normal period: (j) uterine fibroids develop more often in women whose ovarian function is not normally interrupted by pregnancy and lactation.

In short all of the conditions, whether ovarian or otherwise, which antagonize, moderate, suspend or destroy the uterine function of the ovaries, either delay the growth or promote the absorption of uterine fibromyomata. If, then, as we have long known, these conditions produce atrophy of the uterus itself, why should they not also produce the same effect upon these adventitious growths within it which depend for their sustenance on the same sources both nervous, nutritive and hormonal?

From this array of facts the conclusion would seem inevitable that the exciting cause of uterine fibrosis, whether focal or diffuse, is in some way dependent on the functional activity of the ovaries.

In what does this influence consist? Hyperemia is the essential uterine expression of the periodic ovarian function. Normally it precedes the menstrual flow by several days, continues during the flow and then rapidly subsides. The uterus is thus more or less, often acutely, hyperemic for a third, not rarely even a half of the reproductive period of the sterile woman's life. In the normal married woman pregnancy and lactation suspend this recurring hyperemia for varying periods but, in our artificial modern life, with growing infrequency. Moreover the function of the ovaries like that of other endocrine glands is subject to depression and exaltation—in otherwise healthy women more often the latter as manifested by too frequent, profuse or prolonged menstruation, by abortive intermediate menstruation—the so-called "mittelschmerz" of the Germans—and occasionally by a seemingly continuous uterine hyperemia. When we add to this physiologic hyperemia, often present in a pathologic degree, the purely pathologic pelvic congestion due to acute and to chronic metric and

parametric infections, to pelvic adhesions, to uterine retrodisplacements, to colonic stasis and the modern corset, we have a sum-total of uterine hyperemia and congestion commensurate with the size and frequency of uterine fibromyomata.

Does not this conception of the causation of uterine fibromyomata lend itself to a rational and practical prophylaxis? Whether or not we have here traced the true pathogenesis of uterine fibromyomata certain it is that functional activity of the ovaries is a *sine qua non* not only of menstruation but also of the origin, and generally the growth, of these tumors. The control or regulation of ovarian function, then, as it relates to the uterus, would seem to be the first step in such prophylaxis.

Fortunately in the mammary gland, we have a powerful physiologic remedy which either antagonizes or neutralizes the ovarian hormone or inhibits its production or possibly acts more directly on the uterine circulation and nutrition. Whatever its mode of action it seems to be by far our most effective remedy in controlling or regulating excessive or perverted ovarian function as shown by menorrhagia in its various forms. Since it was proposed for this purpose by Robert Bell, of Glasgow, in 1896 a sufficient amount of clinical and experimental work has been reported to demonstrate its value beyond question. It would be impossible directly to establish the prophylactic power of mammary extract except by the careful observation of a considerable number of cases for a long period, but we may reasonably infer that it has some such action from the fact that, in a large majority of cases receiving mammary extract, menorrhagia is effectively controlled and under its

continued use large uterine fibroids often disappear even during the early reproductive period.

It should be the duty of the family physician, therefore, to correct disturbances of ovarian function as expressed by frequent, profuse, prolonged or intermediate menstruation.

Illustrating some of the results that may be accomplished in such conditions the following cases may be cited:

Case 1. Miss R., 26 years of age, otherwise in good health, complains of pelvic pain with slight vaginal discharge tinged with blood, coming on regularly nine or ten days after the cessation of normal menstruation—a typical but rather severe "mittelschmerz." No pelvic abnormality was discoverable. Mammary extract (gr. x, q. i. d.) was prescribed Feb. 2, 1916, and continued until June 10, 1916, when patient reported complete relief, continuing to the present date of both intermenstrual pain and discharge.

Case 2. Miss B., 43 years of age. Her menstruation, previously normal, has, for the past fifteen months, been nearly continuous—rarely ceasing for more than four or five days before the following period; uterus double normal size but no definite fibroid could be made out. Mammary extract (gr. xv, q. i. d.) was ordered March 5, 1916, and continued until Sept. 3, 1916, when patient reported that menorrhagia had been gradually relieved and that the last two periods had been normal in time, but scant in quantity.

Case 3. Mrs. A., 32 years of age. Severe menorrhagia; has been curetted three times with only temporary relief; had asserted that a double oophorectomy was performed five years ago for cystic ovaries, with no relief of the menorrhagia. March 20, 1916, mammary extract (grs. x, q. i. d.). Sept. 15, 1916, menstruation regular, but scant since May 12, 1916.

Besides the correction of excessive ovarian function and the consequent excessive uterine hyperemia in the manner suggested, all causes of pelvic congestion whether mechanical or infectious should be in as far as possible removed.

From a therapeutic point of view uterine fibromyomata may be divided into three distinct categories:

1. Those cases clinically suggestive of malignant degeneration either primary or secondary, of cystic or purulent degeneration, necrobiosis, pyosalpinx, parasitism, incarceration, torsion or other serious pelvic complication. These, if operable, are unconditionally surgical.

2. Cases after the 38th or 40th year free from serious suspicion of complications of the first group and yet presenting symptoms requiring prompt and energetic treatment—cases, for instance, with menorrhagia impairing the patient's health or of large tumors producing pressure symptoms, etc. These individuals should be given vigorous treatment from the outset, and in such cases I prefer mammary extract 1 gm. four times a day, ergot extract 0.2 gm. and hydrastis extract 0.1 gm. three times a day, and irradiation of the ovaries every three weeks. The following experiences are illustrative:

Case 4. Miss C., 48 years of age. Seen June 30, 1915; profuse and prolonged menorrhagia, marked pallor, dyspnea, hemoglobin 27 per cent., uterine fibroid $3\frac{1}{2}$ by 5 inches. Treatment included irradiation of ovaries, mammary extract, hydrastis and ergot.

Nov. 29, 1915. Amenorrhoea since Sept. 25, 1915, hemoglobin 76 per cent.

Sept. 29, 1916. Continued amenorrhoea, tumor 1 by 2 inches.

Case 5. Mrs. C., 53 years of age. Seen Oct. 1, 1915; profuse menorrhagia, with an intramural fibroid, about 3 by 4 inches. Irradiation of ovaries, mammary extract, hydrastis and ergot.

January 9, 1917, tumor gone; no flow since Nov. 10, 1916.

Case 6. Mrs. B., 42 years of age. Menorrhagia, pelvic pain, uterus three times normal size, indurated, endocervicitis, cervical abrasion.

April 28, 1916, irradiation of ovaries, mammary extract, hydrastis and ergot.

Dec. 10, 1916, amenorrhoea since July 31, 1916, uterus atrophic.

Case 7. Miss P., 48 years of age. Menorrhagia, uterus retroverted, twice normal size, distinctly nodular.

Nov. 3, 1915, irradiation of ovaries, mammary extract, hydrastis and ergot.

Aug. 31, 1916, amenorrhea since Dec. 31, 1915.

Case 8. Mrs. D., 48 years of age. On Aug. 15, 1915, she reports menorrhagia of several months duration, weakness, precordial pain radiating down left arm on exertion, vertigo, hemoglobin 24 per cent., uterine fibroid, 5 by 8 inches. Treatment consisted of iron, ergot, hydrastis, mammary extract and irradiation of ovaries.

Dec. 10, 1915, Hgb. 50 per cent.; amenorrhea since Oct. 29, 1915.

March 10, 1916, Hgb. 80 per cent., uterus 2 by 3½ inches; "hot flashes" annoying; stopped mammary extract and prescribed corpus luteum extract with good effect.

July 13, 1916. Uterus atrophic; continued amenorrhea.

3. Cases free from the clinical suggestions of Group 1 and the urgent symptoms of Group 2. These cases should be treated vigorously and persistently with mammary extract, hydrastis and ergot, but, in women under 38 or 40 years, irradiation of the ovaries should not be used until either symptoms of Group 2 develop or the futility of exclusively medical treatment has been demonstrated: for effective irradiation not only sterilizes the patient but also, under the age of 38 or 40, requires very large doses of the X-ray, whose remote and possibly injurious by-effects are as yet undetermined. Until these remote by-effects are revealed by time I must distrust such treatment and particularly the enormous doses advised by Gauss in his "Intensivbestrahlung"—in one reported case (No. 196) reaching in the course of three months and twelve days, the truly "kolossal" quantity of 2284 x, or no less than 228 erythema doses! A further history of these cases might be both interesting and instructive.

In addition to 25 cases of uterine fibroids treated exclusively by mammary extract, hydrastis and ergot and previously reported I have recently found an

other case whose record had been mislaid. The history is as follows:

Case 9. Feb. 12, 1907, Mrs. M., 38 years of age, menorrhagia, sterility, pelvic distress; uterine fibroid, intramural, 3 by 5 inches; mammary extract, hydrastis and ergot. May 15, 1907, menorrhagia relieved, tumor unchanged. March 7, 1909, tumor gone, patient pregnant three months. On Sept. 27, 1909, she was delivered of a vigorous male child living now, March, 1917, at the age of seven years.

Of these 26 cases 4 did not report at all; 1 reported but once, at the end of four months; 3 elected hysterectomy—1 at the end of three months because of pregnancy, 1 at the end of three months and 1 at the end of ten months, because impatient with treatment. The remaining cases, 17 in number, ranging between the ages of 26 and 56, recovered completely and three of them have since borne children—three now living at the respective ages of 7, 9 and 12 and 1 still-born one month after spontaneous rupture of the membranes.

Assuming that the child-bearing period ends, on the average, at forty-five, in these seventeen cases something more than 80 years of reproductive life have been saved by conservative treatment. In comparison with the results of surgery this record is certainly striking enough and yet it might well have been very much more remarkable had these cases been taken in their incipiency or, still better, in the pre-fibroid stage as suggested previously.

It might seem, therefore, to be the duty of the family physician to urge on his female patients the necessity of a yearly examination for the early diagnosis of uterine fibroids as well as those conditions which predispose to them.

Conclusions: 1. Fibromyomata of the uterus are pathologic reproductions of normal uterine tissues.

2. Their capacity for rapid development and involution are inherited from the parent organ.

3. Their exciting cause is believed to be uterine hyperemia of ovarian origin often abnormal in degree, frequency or duration especially when accentuated by uterine congestion of infectious or mechanical origin and when not periodically suspended by pregnancy and antagonized by lactation.

4. Their development may probably be prevented by a normal reproductive life and the removal or prevention of excessive uterine hyperemia and congestion.

5. Before serious symptoms, degenerations or complications develop, they generally may be dissipated by mammary extract, hydrastis and ergot.

6. The preventive and early conservative treatment of uterine fibromyomata here outlined would prevent most if not all of their invalidism and mortality whether the result of complications, degenerations or surgical intervention and preserve or restore, in the aggregate, a by no means negligible period of potential motherhood.

COMMENT ON DR. BRIGGS' ARTICLE

Dr. Emil Novak, Baltimore, Md.: With all due respect to the author of this interesting paper, it seems to me that what is true in it is not new, and what is new is certainly not proved. It is unfortunate that the title does not suggest that the paper is based upon a still unproved hypothesis as to the causation of uterine fibroids. Certainly no scientific proof has been brought forward by the author or, so far as I am aware, by any one else to justify the bold conclusion that "the exciting cause (of uterine fibroids) is uterine hyperemia of ovarian origin, often abnormal in degree, frequency or duration, especially when

accelerated by uterine congestion of infectious or mechanical origin and when not periodically suspended by pregnancy and antagonized by lactation."

The array of facts—(a) to (j)—set forth in substantiation of the author's hypothesis is far from convincing. For example, I fancy that few gynecologists would subscribe to the statement that "uterine fibroids are often partially or completely absorbed after the menopause or during pregnancy or lactation." How much less objectionable it would have been to conclude that "uterine hyperemia of ovarian origin" is perhaps a predisposing rather than the exciting cause of uterine fibroids.

Dr. Briggs displays a remarkable faith in the efficacy of mammary extract, which he includes among the factors which often cause partial or complete absorption of fibroids. "In the large majority of cases mammary extract effectively controls menorrhagia and under its continued use large uterine fibroids often disappear even during the early reproductive period." I am frank to say that I have never employed this therapeutic agent for such purposes, but I am reasonably sure that it has been similarly neglected by the overwhelming majority of gynecologists, and that this neglect is based upon a more or less well founded skepticism as to its therapeutic virtues.

I trust that these remarks will not be construed as superciliously critical of all medical papers which are not securely based on solid scientific facts. There can be no objection—indeed, there are many advantages—in weaving hypotheses, so long as we recognize them as such, and utilize them as a mere groundwork in our search for truth.

To sum up my personal impression of Dr. Briggs' paper, it seems to me that he has done well to call attention to the influence on the growth of fibroids of the periodic physiological hyperemia of menstruation, but I do not believe he has made out a case for his hypothesis that such hyperemia is the exciting

cause of uterine fibroids, or for his enthusiastic belief in the efficacy of mammary extract in the treatment of these growths.

Dr. S. W. Bandler, New York City: The author favors the idea that hyperemia is in some manner responsible for the development of uterine fibroids. This hyperemia among other causes is supposedly due to certain changes in the chemical function of the ovaries.

Since the ovaries exert such a trophic influence on the uterus and the other general structures, it is not without reason that some involvement of them, not alone from the standpoint of hyperemia, but from a trophic standpoint, may be in a great measure responsible for uterine fibroids. Here, especially, where perverted ovarian function is a responsible factor, mammary extract seems to be the natural drug for prophylactic purposes. Mammary extract controls the bleeding from the uterus in many cases, and since its relation to the ovary is undoubted, it is quite possible that by the use of the therapy and by diminution of the hyperemia, not alone the fibroid will develop less readily, but in all probability a retrogressive action is exerted.

Acting on this theory, the writer has conservatively treated a large number of cases associated with menorrhagia and metrorrhagia by the use of mammary extract, ergot and hydrastis and in some cases by the use of irradiation of the ovaries. The results are certainly most excellent and have in a great measure done away with a surgical treatment of these cases.

The idea of the paper is an excellent one and the result speaks for the logic contained therein. It is certainly worthy of trial, harms the patient in no wise, and if it succeeds in many instances in avoiding surgical interference, it is well worth the attention of the medical profession.

Dr. J. W. James, Sacramento, Cal.: The ovarian theory of the causation of uterine fibroids, although

lacking in positive scientific proof, is supported by an array of clinical findings which certainly countenance the belief that, if ovarian activity is not the exciting cause of uterine fibroids it has at least a great deal to do with their stimulation and growth. Very suggestive, if not quite convincing, are the facts that uterine fibroids develop chiefly if not entirely during the period of ovarian activity and that they decrease in size when ovarian activity lessens under the use of mammary extract and disappear, in some cases at least, after ovarian activity ceases either on account of the normal or artificial menopause or after ovarian radio-therapy.

Coincidence or a "lucky series" can hardly account for the reported success of the treatment outlined by Dr. Briggs in so many cases of uterine fibroids in different hands.

Experience is more convincing than argument and I therefore submit as evidence several cases which have occurred in my own practice:*

Miss K., single, age 36. Severe menorrhagia at irregular intervals for about one year; patient tubercular; uterus enlarged; three fibroid masses about size of fist. Mammary extract and ergotin were administered for nearly four months, at the end of which the patient had ceased to flow and the fibrous masses were greatly decreased in size. The patient died from the tuberculosis about one year after beginning treatment. The menorrhagia, however, was fully under control.

Mrs. D., age 46. Married, no children. Severe menorrhagia until patient had become extremely pale, hemoglobin 30 per cent. (Sahli). Uterus enlarged with a small fibroid in left fundus. Consultation advised hysterectomy. (Curettage and packing the uterus with astringents were of no avail.) Mammary extract was given for 6 months, also 10 X-ray treatments were given.

Patient has ceased flowing and has not flowed for 10 months; the uterus is very small and soft. Hemoglobin 75 per cent.

Mrs. N., age 36. Came for help for a very persistent constipation—a large fibroid the size of an orange was discovered to be pressing against the rectum and causing partial

*Doctor James also submitted outlines of seven additional cases treated successfully by colleagues.

obstruction. Three months' treatment as outlined (mammary extract with ergotin and hydrastis) has greatly reduced the size of the growth, which is now much softer; and at the same time the constipation is greatly relieved.

The above cases make the conclusion very definite in my mind that there is a relationship between the shrinking and disappearance of uterine fibroids and the administration of mammary extract, so much so that, though still inclined to operate in suitable cases, nevertheless, I would not condemn the patient to invalidism in case she refused operation, until I had first given the medical treatment suggested by Dr. Briggs a thorough trial.

A CASE OF ADDISON'S DISEASE WITH
MENTAL SYMPTOMS

By Beverly R. Tucker, M. D., Richmond, Va.

THE patient, a boy 19 years of age, entered the Memorial Hospital under the service of Doctors McGuire and Peple. He was tall, thin and ill-looking, and had been doing farm work. No surgical condition could be found.

The present trouble began about fourteen months ago. His family history revealed that his father was normal but that his mother died of abscess of the breast and had a nervous temperament, and that her people were also nervous. He has one brother that is frail, possibly tuberculous.

Examination on admission showed his nourishment was poor, he had lost twenty-five pounds in flesh and he was very weak. Perspiration was scant. He complained of vague subjective pains and sensations, none of which were typical of any particular thing. His reflexes were negative, except that the deep reflexes were somewhat diminished. There was no hand tremor and his pupillary reactions to light seemed sluggish.

The results of the mental examination were very interesting and showed hypochondriacal ideas, considerable emotionality, insomnia and a history of impulsive desires to get up and run. The latter seemed to be a relief reaction and overcame a certain amount of nervousness. We could get no evidence of convulsion or unconsciousness. Since he has been in the Memorial Hospital we have observed that his temperature has been sub-normal, running between 96 and 97 degrees; his pulse has been slow, averaging between 50 and 60 beats per minute, and his respira-

tion has been slow, averaging between 12 and 16 per minute. His blood pressure has been low, varying from 85 to 110 mm. systolic and from 30 to 60 mm. diastolic. His urine showed a trace of albumin, but otherwise was negative.

An examination of his blood showed the hemoglobin 80 per cent., leucocyte count from 10,600 to 10,800, red cells from 5,280,000 to 5,824,000. A gastric analysis was attempted but he was unable to retain a test meal at the time. His feces have been examined three times and have always been negative, except that once a trace of blood was found. There were two blood Wassermann reactions and one spinal fluid Wassermann made, all of which were negative. His spinal fluid was also negative as far as the cell count and globulin content were concerned.

Examination reveals no axillary hair and very scant pubic hair. There is no glandular enlargement except a slight enlargement of the epitrochlear glands. His skin is dry and vasomotor mottling is observed about the lower extremities, and distinct bronzing can be seen on the face, chest, abdomen, spine, knees and toes. The mucous membranes showed no bronzing. His speech is rather monotonous. An examination of his heart and lungs was negative. He gives a history of hook worm infection in the past, for which he has taken treatment. Once he vomited a round worm. Since he has been in the hospital his bowels have been irregular, alternating between spells of constipation and diarrhea. His sleep has been poor. He has complained at times of pain in the lower abdomen. For some time he refused to take food, or vomited when he took it. He also complains of shortness of breath and a choking sensation in eating, of a sense of gas on the bowels and sick

headaches. At times he has spit up a little blood after eating. This was only in streaks and occasional.

Addison's disease is supposed by some to be due to tuberculosis of the adrenal glands. No focus of tuberculous infection can be found in this case; however, the patient has a brother, whom I have never seen, who probably is tuberculous. Dock, in Osler's System of Medicine, describes reflex changes in some cases which are due to spinal tract degeneration, and also mentions that mental symptoms, especially insomnia and mental confusion, have been observed. I can find no mention of imperative ideas. It is possible that this patient's irresistible desire to run was of sexual genesis and was a replacement of a sexual impulse. He has, however, shown no sexual proclivities since he has been in the hospital. His genitals are of normal development except for the lack of hair. This body hair deficiency is distinctly a hypo-adrenal manifestation. This patient has also shown the mental symptoms of irritability, fatigue and emotional-ity. Confusion was not observed.

The boy has greatly improved but the prognosis is doubtful. The treatment has been general attention and adrenal gland extract grs. ii, three times a day.

COMMENT ON DR. TUCKER'S CASE

Dr. William Wallace Behlow, San Francisco: This very interesting case presents certain symptoms which require considerable study. The youth of the patient, his mental symptoms, and the apparent absence of any demonstrable tuberculous focus elsewhere in the body are of more than usual interest.

In considering the youth and the mental disturbance, one must remember that certain psychoses are very likely to appear during adolescence. It is there-

fore possible that the mental deterioration may be merely an associated condition. On the other hand, Addison's disease frequently presents cerebral symptoms, either in mild or severe form .

It is now believed by many physicians that the adrenal glands in this disease are congenitally abnormal and are therefore more likely to be affected by any infectious process than would be the case were they normal organs. If we accept this conception of the disease, it is not difficult to believe that other organs may be the site of congenital disturbances, and if such be the case, it is possible to consider the mental signs as merely a manifestation of deficient cerebral function.

Viewing the case from a different angle, we know that in this disease the entire gland frequently suffers from the degenerative process. Remembering the relation between the development of the adrenal cortex and that of the brain, we may consider that these two distant parts of the anatomical structure, have some interrelated functions. If, therefore, the adrenal cortex is in a state of hypofunction, it is not unlikely that certain exciting or inhibitory influences on the brain are lacking.

The apparent absence of tuberculosis elsewhere in the body is important. It is unfortunate that intradermal tuberculin tests were not recorded, inasmuch as through this procedure we could have determined the presence or absence of tuberculosis. When one thinks of Addison's disease, the pathologic picture of caseation and calcification of the adrenal glands comes to mind. It is important to remember that all cases of this disease are not tuberculous, and it is evident from this fact that we must search for the etiologic factor in the absence of other signs of tuberculous infection.

Another interesting feature of the case is the absence of any anemia. In fact the red corpuscles are increased in number. The reason for this condition of the blood is not clear. No mention of the type of

leucocytes present in this case has been made. While a differential count is not necessary, it is desirable for this reason, namely, the frequency of an associated status thymolymphaticus in Addison's disease. Roentgen examination of the chest and of the kidney regions might have shown pulmonary tuberculosis, a large thymus and calcified adrenals. I wish to emphasize this last point. During the past year, I have been looking for thymus enlargement in all ductless gland dystrophies and have found it in several cases. Of still greater interest is the finding of shadows above the kidneys showing evidence of calcification of the adrenal glands. This was beautifully demonstrated in a case of hypoadrenia which I saw some weeks ago.

If we can have reports of cases such as the above, we will soon discover what we have to forget and what we have to learn about the endocrinopathies.

Dr. Henry R. Harrower, Los Angeles: This case report contains several points which demonstrate the truth of the statement that "there cannot be a disorder of one of the glands of internal secretion without some associated disturbance of one or more of the others." The patient shows a number of evidences of disorder of others of the endocrine glands than the adrenals. For instance, the dry skin and reduced perspiration would remind one of thyroid insufficiency, the absence of axillary hair and scant pubic hair coupled with the remark later that the sex impulses were diminished draws attention to a possible pituitary factor (though it is granted that it may accompany hypoadrenia as Doctor Tucker remarks) and it would be interesting to learn the findings of sellar radiography.

The greater our information on the subject of the internal secretions, the less frequently will we be able to make positive, named diagnoses. This may seem to be a contradiction, but it is none the less true. Take as an instance the condition under discussion—Addison's disease or organic adrenal disease with chrom-

affin insufficiency. It is impossible for so important a pair of organs to be the seat of destructive processes (not compensated by an hypertrophy or increased functional capacity of the remaining sound gland substance) without simultaneous functional disturbances in the gonads, thyroid or others of the glands of internal secretion. The typical toxic asthenia in these cases doubtless is of adrenal origin and, too, the adrenal part of the picture may be most prominent; but all the factors which go to make up the syndrome described by Addison are not purely adrenal, save indirectly. Herein lies the complexities of endocrinology.

From my own standpoint the diagnosis would not be exactly Addison's disease, but rather pluriglandular insufficiency or endocrine dystrophy with prominent adrenal manifestations; and the treatment would take this into consideration and include other organo-therapeutic extracts than the adrenal substance now being given. It has been my experience many times to see a case in consultation and to suggest that one or more organo-therapeutic preparations be given in addition to the one which may have been taken before I saw the patient, and more than occasionally decided additional benefit followed the change from mono- to pluri-glandular therapy.

Dr. Walter Timme, New York: The picture presented by Dr. Tucker is graphic and extremely interesting, but it lacks certain elements necessary to differentiate it from conditions allied to Addison's disease. The one important syndrome known as vagotonia seems to fit quite as well as Addison's disease to the case. Here we also have the slow pulse, low blood pressure, slow respiration, vasomotor mottling of the skin of the extremities, vomiting, alternate constipation and diarrhea, and pain in the abdomen that Dr. Tucker's case presents. One etiological factor that speaks in favor of this diagnosis is the fact of a previous invasion of parasites—a most prolific cause of vagotonia. The one symptom that apparently is

opposed to it is the bronzing of the skin. And yet the bronzing has left the mucous membranes free—a point of great significance and one upon which many authors insist before making the diagnosis of *Morbus Addisonii*. On the other hand we frequently see mottling of the skin alone in persons of uncleanly habits, such as farm hands are apt to be. Another point is the normal number of red cells in the blood—rarely found in Addison's disease.

As for the mental states accompanying this affection of the adrenal glands, they may be said to be of the retarded type. There is mental sluggishness and hebetude usually and rarely the compulsive character such as this boy shows in his attempts at flight. The patients usually show a desire to remain abed and at rest. And yet, it is almost imperative to view and examine such a case as this personally, before coming to a definite conclusion satisfactory to one's self. For, after all, diagnosis depends upon the correct interpretation of the signs and symptoms which one must elicit himself—each sign has for the individual evoking it a special significance. So that Dr. Tucker may be correct in his diagnosis and have a picture of his case quite different from the one that the writer gleans from the case report.

AN ENDOCRINE INTERPRETATION OF THE
DENTAL APPARATUS

By D. M. Kaplan, M. D., New York City

(Director of Laboratories, Neurological Institute, N. Y.)

THERE is not the least doubt that the glands producing internal secretions exert an influence upon the exterior of the individual. Although the uninitiated still may consider certain individual peculiarities as accidental, the endocrinologist knows which organ, or organs, were instrumental in the production of these seemingly accidental phenomena. To ascribe a certain bodily appearance to accident is a confession of ignorance which, however, is becoming less frequent the more one studies the mystic forces of the endocrines. The study of their functions can not be severed from the study of these glands, so much so, that one may justly call this specialty an investigation of the "compensatory dynamics of the endocrines in health and disease."

To understand the compensatory workings of the endocrines is to know "internal secretions"; and to be able to translate it into terms of physiology and pathology is to know how to handle your patient from an endocrine point of view. There are many external manifestations resulting from the work of the endocrines that have been carefully studied, many that are only superficially known, and still more to be discovered in the future. To the endocrinologist a pigmented mole is not an accident, nor the moustached female of twenty-five, nor the soft pulse at eighty, nor the high blood pressure at thirty, nor the enlarged non-infected tonsil. It is the why and wherefore of a peculiarity that is the constant question before the endocrinologist, and very often the answer

is radically opposed to orthodox allopathic thought. Therefore the uninitiated may be perplexed by the stand taken by the student of compensatory dynamics, who argues against the reduction of a high blood pressure in a certain patient, or the removal of the tonsils in another, and yet he may offer very sound reasons for both conclusions.

In his endeavor to arrive at the truth, the student of "compensatory dynamics" takes into consideration the fact that certain infections have an affinity or, as I have designated it, a "tropism" for certain glands with internal secretion. For instance, it is known to all that mumps is an infectious disease that often attacks the gonads. It has been noted that diphtheria and typhoid have a tendency to cripple the adrenals, so that mumps is known as a gonado-tropic infectious disease, while diphtheria is adreno-tropic.

There is also a definite tropism between endocrine disturbances and the dental apparatus. Ewan Waller, of Birmingham, England, has very definitely associated the teeth in children with the thyroid function. It seems that the glands with internal secretions play an important role not only in the structural, but also in the physio-chemical economy of the individual. A great many of the unclassified subjective disturbances formerly designated as neurasthenia, neurosis, or hysteria, and lately as vagotonia, can be more justly ascribed to an aberration or a disturbance in the compensatory dynamics of the endocrines. The thorough investigator of the constitution of an individual in health or disease takes into account the phenomena not only as pictured in our books on diagnosis, but also the time of day or night, the amelioration or intensification of symptoms in the evening, its involvement of the right or left side of the body, and he dif-

ferentiates where the same complaint appears in the juvenile, adult, or senile individual.

There are a great many points dismissed by the uninitiated as insignificant, which the endocrinologist employs to advantage in building up a picture of disturbed equilibrium in a patient. The peculiarities of the dental apparatus is one of them.

Thyrodontia. It is a fairly well-established fact that the calcium metabolism is governed chiefly by the thyroid apparatus, and secondarily, by the rest of the endocrines. The alkalinity of the saliva to a certain extent depends upon calcium salts. It is to be seen how a disturbed endocrine equilibrium could bring about dental decay by a disturbance in the calcium metabolism balance, particularly in children, who depend upon their thyroid and thymus more than the adult and senile. The calcium being deficient, the acids from food decomposition are not neutralized, and the dentine consequently suffers, this being one of the stages in the complete breaking down of the tooth. In children particularly, a well-balanced thyroid and sound teeth go together. If the thyroid is not performing its duties properly, the tooth to suffer first is the molar. The submaxillary saliva is said to be richer in calcium than the parotid, and in view of the fact that the molars lie behind the duct their supply of immunizing saliva is less than the front teeth, and hence, in case of calcium deficiency, they succumb first. This is manifestly apparent in the longer life of the lower front teeth as compared with the upper, the latter not having the constant salivary bath enjoyed by the lower teeth. This is very characteristically displayed by the woman with an exhausted thyroid, due to repeated pregnancies, who invariably loses her upper incisors. Of course in such

women the other endocrines enter into the mechanism conducive to the dental loss.

To start with, thyroidal teeth are distinguished by their slender frame, they are thinner, more transparent and graceful, and their color tends toward a bluish-gray-white. Children and married women with such teeth can be saved a great deal of dental trouble by the discreet and timely administration of thyroid extract. The frequency of the therapeutic display depends entirely upon the case and the acumen of the physician.

In the multipara the dental situation from an endocrine point of view is only partly thyroidal. The interplay and compensatory work of all of them are necessary to help her through this physiologic symbiosis, and if the woman is deficient in any of the endocrines she will display not only dental changes, but all kinds of other objective and subjective manifestations depending upon the glands or gland involved. The falling out of the upper incisors independent of decay, bears a distinct pituitary stamp, and one may say that the maxillary sockets become too large in some pregnant women, and that the root is not firmly implanted in such a jaw, at this episode of partial transient physiologic acromegaly. It is the duty of the discerning physician, as well as the dentist, to guard against irreparable loss, disfigurement and suffering of patients by a timely use of thyroid extract in cases of dental caries or late irruption, as well as in gestations that promise injury to the teeth.

Pituitodontia. Many individuals who are free from complaints that would compel them to seek a physician's advice, are the possessors of teeth characteristic of the acromegalic. The owners of such teeth need not develop acromegaly, nevertheless they

must be regarded as potentially pituitary. Chronic frontal headaches and the slightest limitation in the temporal visual fields, require very earnest attention and extremely judicious endocrine therapy, for at such a stage one might hold out some hope of deferring the advent of the full-fledged acromegalic picture. Increase in size of the acral parts is the chief objective sign of this disease, and the pituitary is the gland responsible for its appearance.

It must not be forgotten, however, that not only an increase, but also a very marked diminution in size, belong to the activity of the pituitary gland; so that giant and pigmy are endocrinologically related. The same applies to the teeth. The average pituitary dental arrangement shows large square teeth; more often than not the upper middle incisors are spaced (trema) and the rest of the teeth may share in their separation, stopping at the bicuspids. On the other hand, marked overcrowding is a feature which also belongs to the department of hypophyseal activity, so that one is frequently confronted with a situation requiring great care in endocrine interpretation. The gestating female has been referred to before, but it must be reiterated, that the falling out of the incisors, particularly the lateral ones, has a double meaning.* At present let us not forget that the middle upper incisors are pre-eminently the teeth closely associated with direct primary pituitary function. This does not signify that the individual has a pituitary abnormality incompatible with perfect health; it may show itself in anybody with accepted hypophyseal markings, such as being very tall or very short, having a very large head, particularly in

*This will be brought out in the paragraph on gonadodontia.

the frontal part, or manifesting a tendency to adiposity in the young or adult, with or without hypogenitalism. It may accompany the feminine type of man, who shows his abnormality in his teeth only, and his sexual anomaly in his psychanalysis.

Gonadodontia. Individuals with a gonadotropism may give in their history an attack of mumps during childhood. The close relationship between this contagious disease and the genital glands is established by the frequent involvement of the ovary or testis in a complicating inflammatory reaction. It is not necessary that the individual previously having had mumps should present ear marks of a definite gonad disease, he may yet show them in the future, or not at all. This depends entirely upon the compensatory work of the rest of the endocrines.

In all endocrine manifestations not only the some, but also the psyche is influenced.* Besides these psychic attributes most of them show definite somatic stigmata, of course not all of them, the exceptions here as elsewhere serving to establish the rule.

In the gonadotropic individual the dental apparatus carries a very striking ear mark of the tropism. If the middle upper incisors carry a message from the pituitary, the lateral upper incisors certainly do the same from the gonads. So that when the gonads are teratologically *ab ovo* definitely abnormal, one is sure to find some abnormality in the upper lateral incisors. The relationship, if any, is a crossed one, so that the right upper lateral incisor may point to the left testis or ovary, and vice versa.

It is also to be noted that the greater the devia-

*This is, perhaps, seen in the irritable thyreotrop; the gentle and kind giant or obese person—pituitotrop; the assertive, hairy adrenotrop; the juvenile or childish thymotrop and the bashful or secretive gonadotrop.

tions from normal, the more definite the markings in the dental department, so much so, that the lateral incisors, as the result of a marked gonad defect, may not have irrupted at all. Such a dental situation is rare indeed, so is also the clinical condition presented by the patient who has it. Here is a situation that the gynecologist could profit by, and the surgeon add another sign to the significance of right sided abdominal pain. Such a pain is usually ovarian,—when the left upper lateral incisor is faultily implanted, showing the mesial edge of the tooth anteriorly, and protruding in front of the middle incisor. The teeth presumed to be connected with the gonads (upper lateral incisors) carry the stamp of ovarian or testicular abnormality in their size, shape, or implantation.

The ovary should always be suspected where pelvic pain is manifested in a patient whose lateral incisors are abnormal. In the male, small stumpy laterals bespeak sexual impotence on a physical basis,—many gonorrhoeas, prostatic insufficiency, and chronic strictures. In such an individual one may obtain the history of mumps, and if he had a right-sided orchitis or epididymitis, more often than not his left upper lateral incisor will be found differing from the normal, taking his entire dental apparatus as a standard of comparison.

On rare occasions the compensatory work of the other endocrines is so well-adjusted that the dental anomaly is obliterated, and gives no clue to the existing gonadopathy. There are, however, other external signs from an endocrine point of view that would direct attention to the existing state of affairs. As the dental apparatus is the subject of this paper, the other signs will not be discussed.

There is a dangerous tendency among endocrinol-

ogists to designate with peremptory precision that this or that organ is involved, and is responsible for the endocrine picture. Very often the external manifestations are caused by another gland whose function it may be to bring about phenomena on the surface of the patient, such as, for instance, the adrenal system; and some students may be carried away by this easily demonstrable, superficial appearance, and be led to assign to the objective findings the place of first importance; whereas the adrenals have simply acted in response to a call from some other gland. The gonads always require adrenal help in performing their work, and when they do not come up to the physiologic requirement, be this in the form of under or over activity, the adrenals are then called upon for additional assistance, resulting, secondarily only, in manifestations appearing on the skin, mucous membranes, hair, etc. The primary, *ab ovo*, situation can be read from the teeth, and the gland responsible for the trouble more often than not, can be unerringly named and proper therapy suggested. It is remarkable how readily the patient responds when the proper drug is prescribed, but here, as elsewhere, the futility of attempting replacement therapy in some cases must be thoroughly gauged.

A young woman suffering from the torture resulting from a complete oophorectomy cannot be benefited much by ovarian extracts, be it the whole gland or the luteal portion. In such cases one must be able to read intelligently the symptomatology, and curb as much as possible the pituitary compensation, for in such cases this is the gland that may be causing much of the subjective discomfort. If the pituitary, however, is not capable of compensation, or is only partly able to assist, the adrenal and thyroid systems

are employed to overcome the deficiency. Depending upon the fitness of these glands one will have a predominating adrenal or thyroid symptomatology. Therapeutic success depends entirely upon our ability to recognize the vicarious execution of functions by glands with a different purpose.

Adrenodontia. It is to be conceded that the ability to perform better work requires better tools. In biology this is everywhere evident. From times immemorial the longer and sharper tooth was part of the outfit of the pithecanthropus, whose survival was assured. Such a specimen was perhaps also the hairiest of his tribe. As time advanced and the necessity for using the teeth in offensive and defensive existence became secondary to the special development of the thumb and hands, the chief fighting teeth, the canines, became shorter, and in some very peaceful members of our semi-simian ancestors, also less sharp. With the greater use of the hand came the perfection of that part of the brain that serves as the storehouse for memories. These memories became the heritage of the future man, and with the greater specialization of the hand, the teeth were gradually discarded as weapons of defense and offense. The emotions in a state of offensive rage still cause the display of teeth, although one does not use them.

Vasomotor force and the tone of muscles depends upon the proper work of the adrenals. Only when these glands work better than the others, is it possible to think of the enduring prizefighter. When the pituitary is equally well-adjusted, one has the heavy weight champion type. But the ability to scrap, whether curbed by education or environment, or not, is indelibly marked in the canines. As one of our ancestors would have learned by experience that his

short and blunt canine was no great weapon in a fight, and would have become the champion of peace instead of conflict, so also the present man prefers discretion to valor because of inadequate adrenal endowment or, as one may term it, lack of biologic equipment for strife. Whether man or woman, both show in a long sharp canine an atavistic remnant of a bellicose progenitor, and upon proper provocation justify the above contention.

Very often the large and sharp canine in a woman bespeaks the aggressive agitator, public speaker, or militant suffragette. Some of these women studied from the point of view of biologic balance possess other endocrine markings, showing that they are not women to the full extent that nature intended the average woman to be. The woman whose skin is rough, who finds pleasure in curbing wild horses, who cares not for the duties of home life, and who is an expert administrator (purposely using the masculine) must give up a certain amount of natural feminism in order to be able to enjoy and accomplish the above things. Very often with such traits goes a masculine hand, a moustached lip, a large pointed canine, and a deficient gonadont. The sexual psychopath could be detected by a study of his dental apparatus, and the endocrine therapist might supply the glandular extract that would give a more natural trend to the twisted psyche of its possessor.

The spinster who truly rejoices in her single blessedness does not do so from choice, but rather from her innate promptings. Being less of a woman than her well-balanced sister, she does not require the society of man, and frequently shows her genuine distaste for such company by an appropriate remark. In her pursuits she wants to dominate, and frequently

fills with credit a position requiring great virility. She abhors the evening gown, and wears clothes of a masculine type, low heels, no corsets, side pockets, collar and tie.

The male counterpart with short, stumpy and dull canines gives up some of his primordial male aggressiveness, and becomes the Jacob instead of the hairy Esau. The kitchen is his place. He can sing in high notes, never a basso, and has the greatest inward storms when the time comes for him to propose marriage to his heart's choice. Such a man stands a poor chance of being accepted by a girl well-balanced from an endocrine standpoint. It is the one who will not enlist to help defend his country, but will offer a thousand and one reasons why he should not fight, that war is a reversion to barbaric times, etc., etc. Such men are afraid that a gun might go off, and in business are equally nonprogressive. The eternal clerk, messenger boy, cook, and other nonprogressive occupations are theirs. Endurance, progressiveness, discovery, go hand in hand with an endocrine system that is perfect, and a canine tooth that fears not to face antagonism in any shape or form.

The adrenodont in its structure gives us a clue to the adrenal balance of the individual. There is another characteristic of the adrenal tooth, the color. The grinding surface of such teeth shows a marked reddish brown coloration, and although softer in texture than the thyroid or pituitary variety, they have a greater degree of endurance. Here again is a hint of the ability of adrenal secretion to protect. Old men or women will show short teeth still in a very good state of preservation and most conspicuously marked with this reddish brown pigment. Younger people with such teeth can be assured of

their lasting character, and it is astonishing to note how some of them remain intact regardless of the lack of care and the thick wall of tartar that surrounds them. Age or the ability to grow old goes hand in hand with proper adrenal work, of course with the assistance of the other endocrines, and so adrenal markings in the form of pigment insures not only the life of the tooth, but also its possessor. Individuals who become patients on account of improper adrenal work may show this peculiarity in their teeth also, the markings here indicating the gland affected as well as suggesting the proper therapeutic course to pursue.

Thymodontia. The tooth of the baby is bluish porcelain, thin at the grinding edge, and translucent in that part. The tooth in some children shows a tendency to scalloping at the grinding edge. This trait may outlast the baby and in rare occasions be found in the adult. The other infantile characteristics may go with it, such as a red cheek, an excellent digestion, and a tendency to diarrheas. The finding of such teeth in the adult points to the youth of the individual, regardless of years. In this persistence of juvenile characteristics one must always weigh the compensation offered by the other glands with internal secretion.

The purpose of this communication will have been accomplished if the physician and dentist will begin to see in the dental apparatus a greater purpose than the sole function of mastication. When fully studied upon lines suggested above, a volume of facts will be discovered that heretofore may have many times been entirely overlooked.*

*The work in this communication is gathered from the observations and studies pursued by Dr. Joseph Fraenkel and his followers, who are students of constitutional medicine, particularly as applied to therapeutics.

COMMENTS ON DR. KAPLAN'S PAPER

Dr. Isador H. Coriat, Boston: I have read Dr. Kaplan's paper with considerable interest as it opens up a new field of investigation in endocrinology. The recent appointment of a neurologist to the Forsyth Dental Infirmary, whose work will be particularly directed to the influence of the ductless glands on the growth of children, is in harmony with Dr. Kaplan's investigations.

We have noted at this institution that in children who show hypothyroidism or even slight signs of thyroidal insufficiency, without the necessity of going so far as cretinism, show certain disturbances in the nutrition of the teeth; but it will be necessary to have a large amount of data at hand before we can assert definitely that the relationship is always one of cause and effect. However, the fact that the teeth improve in their nutrition under the administration of thyroid gland, leads one to feel that he may be working in the right direction.

The abnormal spacing between the teeth has been a sign long known in acromegaly, and possibly in the future there may be pointed out other dental disorders which are the result of disturbances in hypophyseal activity. On the whole, while the relation of the ductless glands to the teeth is a stimulating subject, yet we must be very cautious in our endocrinological interpretations along these lines for some time to come.

Dr. E. G. Zabriskie, New York City: The manuscript of Dr. Kaplan's article on the Endocrine Interpretation of the Dental Apparatus has been read with care and interest. I believe that there is a great deal to be said in favor of his contentions; though his use of the term "tropism" is especially limited, as he bases it on the affinity which certain infections have to certain glands of internal secretion, and this is not warranted. His references to the instances of affections of the glands of internal secretion resulting from infectious disease as inflammation of the gonads ac-

companying mumps, and the tendency of diphtheria and typhoid to cripple the adrenals, are well known; but I believe it is wrong to designate these as "tropisms."

Then again the relationship between the lateral incisors and the gonads to my mind is not at all well established as yet. His contention about the contralateral pain in the region of the ovaries in individuals whose lateral incisors are either misplaced or badly affected, is not yet well enough established to be accepted unconditionally. Since my attention has been called to this I have noted its presence in several instances, but it is also true that in others I have seen the same thing where the canines were not affected.

The author's remarks about the dangerous tendency among endocrinologists to designate with peremptory precision the involvement of this organ or that, and its responsibility for the endocrine picture, is well taken. Perhaps it is only due to our present lack of more precise proofs of these statements but, as yet, we are too close to the threshold of the entire subject to accept them without further careful study.

THE RELATION OF THE NERVE SUPPLY OF THYROID GRAFTS TO THEIR ENDOCRINE ACTIVITY

By Dr. E. Kummer, Geneva, Switzerland

(From the Laboratory of Physiology of the University of Geneva.)

IT is generally believed that the thyroid secretion is subject to the influence of the nervous system, and Ascher has shown that the influx of secreto-motor influences is carried by the laryngeal branches of the pneumogastric nerve. Since this is so, should this not compromise or at least alter the endocrine function of a thyroid graft which is naturally separated from its nervous connections?

Experimental investigators have established the fact that a graft will supply the total endocrine function of the normal thyroid gland, irrespective of its location; but this opinion has found some contradiction amongst surgeons. Some of them, taking the logical but purely theoretical view, have stated that in order to give the maximum opportunity for a graft to take it must be made only in the cervical region in order to give the graft the opportunity of reestablishing its more or less normal nervous connections so that its secretory functions may not be compromised.

Modern research into the nervous mechanism of muscles, especially recent surgical procedures, has given a certain suggestion of reality to this question. If it is possible by nerve implantation to reestablish the contractility of a paralyzed muscle, should it not, perhaps, in the same manner, help the functional capacity of a graft of thyroid tissue? With this matter in view we have carried out some investigative work the results of which are related here.

The functional value of thyroid tissue may be established by three main tests of which only one in our opinion is of paramount value.

1. The chemical test or research into the chemical characteristics of the thyroid secretions.—A number of chemical bodies of more or less purity have been secured from the thyroid gland. Among these are certain lipoids, a lipolytic ferment, choline, and particularly the iodine-bearing protein substances including iodothyrene (Baumann), iodothyroglobulin (Oswald) and the alpha-iodine more recently isolated by Kendall.* The specific thyroid action appears to be identical, or at least very decidedly similar, to that of the iodized thyroglobulin, and in this substance the iodine content plays a preponderant role since the same thyroglobulin deprived of its iodine is likewise deprived of its specific action.

So far as the iodine content of thyroid extracts is concerned, this is a very variable factor. Generally speaking the quantity of iodine is in proportion to the amount of colloid substance. Goiters without colloid do not contain iodine. The colloid goiter is really a sort of iodine reservoir for the organism.

Following a hemistrulectomy, A. Kocher has found that the quantity of iodine accumulating in the remaining lobe was doubled. According to this same author, goiters in Basedow's disease show a notable reduction, or at least a large variability, in their iodine content. This last also depends upon the age, for absence of iodine in the fetus and the new born is progressively increased from one to thirty years, diminishing after 40 years. The iodine content depends also upon the species of animal. The herbivorous show a

*It so happens that a comprehensive resume of Kendall's work appears in this issue, page 153.

maximum, the carnivorous a minimum, and the omnivorous an average amount, of iodin.

From the above, despite their obvious interest, it is evident that the results of the chemical examination of thyroid tissue will not furnish information of a character which will enable us to prove conclusively the functional value of a thyroid gland, or a part of it.

2. Anatomical examination.—A thyroid graft to be successful, must secure a good vascularization with good conservation of the follicular apparatus and particularly of the normal epithelial cells, both as regards form and relation to one another, and retaining the colloid substance in the center of these follicles or in the perifollicular lymphatics. Such a graft thus presents manifest signs of functional activity; but in order to appreciate the degree and usefulness of its internal secretion really we have but one conclusive proof and this is the biological test.

3. The biological test, i. e., the study of the results of the removal of the graft.—The proof that normal internal secretory powers have been retained by a graft lies in its physiologic service to the organism. If an animal is thyroidectomized and successfully grafted and then dies in a state of thyroprivia following the extirpation of the graft, we are justified in assuming its endocrine value. We have found in our experiments that this biological test parallels the anatomical examination.

The dog, or better still the cat, offers the greatest facility for research of this character, for of animals convenient for laboratory study these are less likely to show aberrant thyroids and thus are more easily subjected to total thyroidectomy. On the other hand, the characteristic consequences of extirpation of the gland are not long in showing themselves. Because

of the very intimate connections present in the cat and the dog we really perform thyroparathyroidectomy and not simple thyroidectomy when we operate upon these animals and the tetany resulting from these operations lasts from six to eleven days. It is by judging the symptoms of tetany that we are able to determine the functional value of a thyro-parathyroid graft.

Dog No. 1. Adult.

July 3. Total extirpation of the thyroid and parathyroids. Immediate graft of both lobes into a pocket of the omentum.

July 5. Slight stiffness in the back legs.

July 6. Trembling and muscular tremor.

July 7. General convulsions.

July 8. Repeated convulsions.

July 9. Death, with nothing in particular autopsy. Examination of the epiploic graft showed a small nodule of firm consistence; slight fluctuation. When incised a mere indurated shell was seen, the center of which was soft greyish tissue microscopically showing a peripheral fibro-fatty structure, an inflammatory zone containing numerous leucocytes and the whole central part showing very indefinitely the original thyroid structure.

Dog No. 2. Young.

July 3. Thyroparathyroidectomy. No graft.

July 5. Prostration; no stiffness.

July 6. Slight tremor.

July 7. General muscular tremor.

July 8. Sudden spasmodic movements with subsultus.

No convulsions.

July 13. Death.

Dog No. 3. Young, with slight goiter.

July 20. Hemithyroparathyroidectomy (right). Immediate graft of one-third of the lobe removed, inserted into the structure of the goiter in contact with both vessels and nerves. Muscular suture to fix the graft in place.

July 28. Slight suppuration. Bichloride solution locally.

August-September. Perfect health.

Oct. 14. Hemithyroidectomy (left). Noticeable hypertrophy of left lobe, weight 14 gm.

Oct. 16. Death, cause unknown. No cramps or convulsions. Autopsy: Graft in right side presents normal thyroid tissue. A little hemorrhage into wound in left side. Microscopic examination showed the thyroid tissue to be normal with good vascularization and an abundance of colloid sub-

stance. No trace of nerve proliferation. Parathyroid tissue not found.

Dog No. 4. Young.

July 23. Hemithyroparathyroidectomy (left). Implantation of graft into thyroid notch under the superficial cervical aponeurosis.

Aug. 20. Suppuration in wound.

Oct. 23. Perfect health. Right lobe of thyroid (with parathyroids) removed. No evidence of hypertrophy. Implantation of graft (total) into great omentum (Cristiani's method).

Oct. 26. Dog found dead, not having presented any signs of tetany. Autopsy: Abscess at graft; cicatrice at site of first operation. Microscopically this latter showed no thyroid elements; in the second (omental) graft much leucocytic infiltration with some remaining thyroid tissue seemingly quite normal.

Dog. No. 5. Adult.

July 28. Left hemithyroparathyroidectomy. Immediate graft of whole piece into omentum.

Sept. 27. Perfect health. Right lobe removed, apparently normal.

Oct. 1. Slight exhaustion. No trembling.

Oct. 4. Tremor, no convulsions. Animal eating well, in good condition.

Oct. 14. Excision of graft. During ether anesthesia generalized trembling.

Oct. 22. Stiffness.

Oct. 23. Very violent perpetual trembling, stiffness of legs, back bent, trismus, cannot eat. Death. Autopsy: Scar in cervical region, no trace of thyroid tissue therein. Nothing abnormal in peritoneum save slight local suppuration. In omental graft much leucocytic infiltration, slight evidence of follicular tissue but great infiltration obscures appearance of thyroid structure.

Cat No. 1. Age about two years.

July 28. Right hemithyroparathyroidectomy with graft into neck in immediate contact with suitable vessels and nerves.

Oct. 21. First operation site all healed. Health good.

Oct. 23. Left side operation. Entire lobe (of normal appearance) then transplanted into great omentum.

Oct. 30. Abdominal suppuration (localized). Slight exhaustion. No stiffness.

Nov. 4. Persistent exhaustion. No cramps.

Nov. 30. Perfect health.

Dec. 2. Excision of cervical graft. Not certain that thyroid tissue is found; microscopically not definite.

Dec. 30. Dysphagia, no stiffness or cramps.

Jan. 22. Death with no signs of tetany. Autopsy: Nothing in particular. Cause of death supposed to be dysphagia. The omental graft was lost.

Cat No. 2. About one year old.

July 30. Right hemithyroparathyroidectomy. Whole piece engrafted into base of right ear.

Aug. 30. Healing. Perfect health.

Sept. 27. Left hemithyroparathyroidectomy.

Sept. 30. Stiffness of legs.

Oct. 1. Stiffness, trembling, dragging of back legs. Crisis of convulsions, tonic and clonic seizures, difficult respiration, eyes partly closed, consciousness lost. (?)

Oct. 3. Death. Autopsy: Nothing unusual. Microscopic study failed to discover trace of the graft.

Cat No. 3. One year old.

July 30. Right sided operation as before, with graft (total) into base of right ear.

Aug. 30. Healing, good health.

Oct. 22. Left lobe, etc., removed, grafting a portion of this into omentum.

Nov. 4. Healing with good health.

Dec. 2. Amputation of ear, with graft.

Jan. 27. Recovery, good health.

Jan. 28. Excision of other graft.

Feb. 1. Exhaustion; cannot eat.

Feb. 3. Trembling, muscular tremor (general), no convulsions.

Feb. 6. Death. Autopsy negative. Microscopic: (1) Ear. Thyroid follicles well preserved, no colloid material. Leucocyte infiltration. No parathyroid tissue noted. (2) Omentum. Very beautiful specimen of thyroid tissue with normal follicles, abundant colloid, rich blood supply and slight leucocyte infiltration. Parathyroid tissue uncertain.

Resume. We feel justified in answering the question set forth at the beginning of this article with the following remarks:

1. We have not observed any new formation of nerves in thyroid grafts.

2. The reestablishment of the function of the graft has not been any better when implanted in the neighborhood of the pneumogastric or its branches than when made in any other part of the body.

3. In spite of denervation the graft by itself alone

is able to satisfy the need of the organism (of the cat or dog) for the thyro-parathyroid internal secretions.

Conclusion. Whatever may be the importance of the role played by the autonomic nervous system as the secreto-motor nervous regulator of the thyroid body, the thyroparathyroid graft without any nervous connection is capable of furnishing the internal secretion which suffices to maintain health in both the dog and the cat. From a practical point of view attempts to enervate grafts are wanting in interest.

Judging from the well-known fact of the interchangeability of thyroid extracts of man and of certain animals, what we have found in the dog and the cat has every good reason to be true in man.

BOOK REVIEWS

THE SEX COMPLEX: A Study of the Relationships of the Internal Secretions to the Female Characteristics and Functions in Health and Disease. By W. Blair Bell, B.S., M.D. (Lond.), Gynecological Surgeon to the Royal Infirmary, Liverpool; Hunterian Professor, Royal College of Surgeons, England, etc. 1916. Pp. 233. New York, Wm. Wood & Co. \$4.00.

Gynecologists, of all physicians, are vitally interested in the study of the influence of the glands of internal secretion, for so many functional gynecological disorders are of endocrine origin. Many of us think that we are beginning to know something of what Blair Bell has aptly termed "The Sex Complex," and undoubtedly our knowledge is becoming more comprehensive and more useful. But the subject is indeed a "complex" and only its intensive study in the laboratory and the clinic will make possible much greater progress in the future.

For many years the investigations of the author of this book have been leaning towards endocrinology. To him the profession is everlastingly indebted for the introduction into therapeutics of the posterior pituitary principle.* He has also enlightened us very materially as to the role of calcium in the organism and has demonstrated the importance of the hormones in regulating the calcium balance in health and disease.

In this well-planned and well-written book Blair Bell has assembled the results of his years of study.

*The first paper on this subject was published by Blair Bell in 1909: Blair Bell (W.) "The pituitary body and the therapeutic value of the infundibular extract in shock, uterine atony and intestinal paresis," *British Medical Journal* (Lond.) 1909, ii, 1609.

He has made the "dry bones" of the experimental work become alive by his well-balanced philosophy. He has made the clinical side intensely practical by his evident wealth of actual clinical experience.

This is not "a difficult book to read," for there is not a barren page in it; and since the study of the endocrine glands in woman is such a fertile field for entry by practical physicians, we cannot but thank the author for having given the profession such a useful *vade mecum*.—H. R. H.

THE NEWER METHODS OF BLOOD AND URINE CHEMISTRY, by R. B. H. Gradwohl, M.D., and A. J. Blaivas of the Gradwohl Biological Laboratories, St. Louis. 1917. Pp. 240. St. Louis, C. V. Mosby Co. \$2.50.

This most recent addition to the list of laboratory text books is indeed welcome, for in the past two years clinical diagnostic procedure seems to have advanced further than in any similar period in the past.

The book is reviewed here not merely because the senior author is a charter member of the A. S. I. S., but because endocrinologists, of all students of medicine, are vitally concerned in the chemical relationship of the body in health and disease.

The early modifications of endocrine function without a doubt are responsible for blood and urine changes; some of these have yet to be worked out, while the recent advances in blood chemistry now make it possible for the diagnostician to be much more certain of his findings.

Naturally so important a book will be welcomed by our membership, and its perusal will serve them well.—H. R. H.

THE LITERATURE ON THE INTERNAL SECRETIONS

GENERAL SUBJECTS

Over-Activity of Vagus System and Anaphylaxis. Smith (J. H.) Jour. Nerv. & Mental Dis. (N. Y.) 1916, xlv, 26.

By vagotonia is meant the clinical appearance of chronic or recurrent symptoms recognized as manifestations of over-activity of the vagus system.

The two parts of the vegetative system, the sympathetic and vagus, exert a constant balance on one another. The normal excitant of the sympathetic is adrenalin; that of the vagal system is not known.

The fundamental fact in anaphylaxis is proteolysis. The vagus system and muscles supplied by it are chiefly influenced. Anaphylaxis manifests itself through vagus irritation.

Toxic influences, especially anaphylatoxins, may be considered as underlying the vagotonic state. Definite proof exists of the anaphylactic nature of certain cases presenting vagotonic manifestations, viz., parasitic infestations, food idiosyncrasies, asthma and hay fever.

In the interpretation of vagotonic symptoms without apparent cause, two toxic factors are among the possibilities—ductless gland disturbances and chronic bacterial infection.

Two types of thyrotoxicosis are mentioned, the division following the line of physiological antagonism between the vagus and sympathetic systems. In the vagotonic cases there is present a vago-irritant toxin; in these cases there is probably a preponderant influence of the thymus.

Increased sugar tolerance is a phenomenon connected with abnormal conditions of the ductless glands. This tolerance, seen in vagotonics generally, is suggestive of a causal relation of the ductless glands to the symptom-complex vagotonia.

In the treatment of vagotonic symptoms adrenalin gives good results in urticaria and sometimes in bronchial asthma.

W. B. T.

Histopathology of the Autonomic Nervous System in certain Somatic and Organic Nervous Diseases. Morse (M. A.) Jour. Nerv. and Mental Dis. (N. Y.) 1916, xlv, 1.

During the past year a routine study of selected portions of the autonomic system has been made in suitable autopsies

at the Boston State Hospital. Of the ductless glands the adrenals, pituitary, thyroid, reproductive organs, and islands of Langerhans were studied.

The material included representatives of the common organic nervous diseases, some common visceral diseases, and certain unusual conditions, as pellagra and katatonic hirntod.

Two cases of pellagra: Besides prominent chronic degenerative changes in the vertebral, semilunar and enteric sympathetic ganglia, the adrenals showed marked loss of lipoid, with areas of necrosis in the cortex, and collections of lymphocytes in the medulla. The thyroids showed an excess of connective tissue, with lymphocytic infiltrations in one case.

Two cases of paresis: In neither case did the ductless glands show anything of note. Autonomic ganglia show insignificant changes.

Two cases of cerebral syphilis: In one case an adenoma of the adrenal was observed. Autonomic ganglia showed mild lymphocytic infiltration.

Four senile cases: Two senile demented showed degenerative changes of the sympathetic system, associated with sclerosis of the anterior lobe of the pituitary. Two arteriosclerotics showed little changes in the ganglia besides an increase of connective tissue. In one of these cases the adrenal cortex contained an area of necrosis, multiple hemorrhagic foci and marked lymphocytic infiltrations. There was also a chronic thyroiditis.

One case of dementia precox: This patient died of pneumonia and the adrenals showed the loss of lipoid commonly found in death from acute infection. The ganglionic lesions varied at different levels.

Several other cases were reported. In no instance were the ganglia normal. However, the changes found in the ganglia did not appear to bear any relation to those of the endocrine system, most of which were minor in nature.

W. B. T.

Cerebral Associations of Raynaud's Disease. Norman (H. J.)
Jour. Mental Soc. (Lond.) 1916, lxii, 730.

After an historical retrospect, in which the author points out that a century before Raynaud described the symptom complex which bears his name, others had reported cases of it, yet it was reserved for Raynaud in 1862 in a thesis for the Doctorate of Medicine, to give the first real generalization of the condition and to marshal the facts in an orderly way. The author cites cases published by Raynaud in which the cerebral manifestations, associated largely with the crises of pain occurring in the disease, were hysterical in character and of major type. Other cases beginning hysterically progressed

into mental enfeeblement with slow cerebration and rapid mental fatigue. Three of his (Raynaud's) cases were attended with sudden loss of consciousness and left hemiplegia. Norman doubts the true hysterical character of these cases, believing them to be due to vasomotor disturbances in previously neurotic patients. He says that the hysterical phenomena in some cases shaded gradually into true epilepsy. Other attacks of epilepsy came on after exposure to cold weather and concomitantly with local asphyxiation.

Mania and melancholia are also noted in connection with Raynaud's disease; and in cases reported by Edgerley, Ritti and Esquirol the maniacal or depressive attacks were synchronous with the characteristic types of Raynaud's disease—local syncope and asphyxia. Norman has seen several cases of dementia precox in which Raynaud's disease became established. Three cases of the disease occurred in privates in the trenches, accompanied by mental enfeeblement with delusional trends.

Aphasia in connection with Raynaud's disease is rare. Raynaud thought it was part of an hysterical condition. In one case reported by Weiss the attack was a typical one in which the patient not only had difficulty in pronouncing familiar words, but she transposed words and syllables and used wrong ones. Her lips became pale and the retinal arteries narrowed to a striking degree. Voluntary movement was not affected, and the attack subsided in 15 minutes. It was followed by another in 4 weeks. Osler reports a similar case accompanied by paralysis of the right hand and foot. This passed off in less than a day. There were recurring attacks, involving the other side, with local syncope and asphyxia. Other authors (Stockman, Simpson) report similar cases.

Ocular symptoms were also frequently seen. The disturbance in vision occurred usually when the local acroasphyxia diminished. Ophthalmoscopic examination revealed narrowing of the arteries and pulsation of the veins when the discoloration of the extremities was at a minimum. In a case of Hutchinson, there was iridoplegia, with inequality of the pupils. Many Raynaud victims have headache, especially during the local syncope. Erythromelalgia has been often confused with Raynaud's disease. The consensus of opinion today is that the former is spinal in origin, probably syringomyelic in character.

As to the cause of the phenomenon in Raynaud's disease, the symmetry of the lesions must needs lead one to look to the central nervous system. Purves Stewart suggests profound molecular changes in the sympathetic system. Levi and Raynaud believe in an emotional factor.

(In spite of the instability of the vasomotor system in this disease, with spasticity of the vessel walls and lack of

maintained tone, together with the indubitable factor of emotional shock in the pathogenesis of the disorder, none of the authors mentioned by Norman, except the latter himself, ventures an opinion as to the basic factor being found in unstable adrenals—or at least in an imbalance in the endocrinous glands.)—W. T.

Achondroplasia in a Calf with Thymus in place of Thyroid.

Nickerson (W. S.) *Jour. Lancet (Minn.)* 1917, xxxvii, 7.

The "bull-dog calf" investigated was a dwarf with relatively big head, pug nose, prognathous jaw, short body and very short legs; weight 30½ pounds. Though a fairly common type of congenitally deformed monster it has been of uncertain position in our disease categories.

A comparison of the anatomic peculiarities of this dwarf with the list of fifteen essential characteristics of achondroplasia as recognized by investigators of that disease in man (Schirmer, *Centbl. f. d. Grenzgeb. d. Med. u. Chir.* 1907; Rankin & Mackey, *Brit. Med. Jour.* 1906; Fussell, *J. A. M. A.* 1909) reveals an agreement in twelve and a lack of agreement in those only (shape of hand and curves of spine) in which the human and bovine types are so unlike as to preclude comparison. The conclusion seems therefore justified that that form of monstrosity exemplified by the "bull-dog calf" is achondroplasia.

In an examination of the endocrine glands the facts of prime importance discovered were: the thymus was present and normal histologically; two large masses of tissue in the position of thyroid lobes were histologically typical thymus tissue and no thyroid tissue was found. In this case therefore achondroplasia is characterized by absence of thyroid and superabundance of thymus tissue.

A replacement of the parenchyma of one of the ductless glands arising in the embryo from the branchial clefts (thyroid) by that of another gland of the series (thymus) is a factor which, I believe, has not been reported hitherto in achondroplasia, and in view of what is known concerning the function of the thymus may well be a dominant etiologic factor in the production of the deformity.—W. S. N.

Cutaneous Conditions Associated with Diseases of the Glands of Internal Secretion and Vagotonia. Hazen (H. H.) *Interstate Med. Jour. (St. Louis)* 1916, xxiii, 824.

Hazen concisely and thoroughly reviews the recent literature pertaining to the relationship of cutaneous diseases and disturbances of the glands of internal secretion. He emphasizes the importance of differentiating the symptoms of vagotonia from those of true ductless gland disturbance, and observes that neurasthenics are usually sufferers from vagotonia.—L. F. W.

EXPERIMENTAL INVESTIGATION

ADRENIN; Effect on the Factors of Coagulation. Grabfield (G. P.) *Am. Jour. Physiol. (Balt.)* 1916, xlii, 46.

The intravenous administration of adrenin in minimal doses (0.143 cc. of a 1:100,000 solution per kilo) decreases coagulation time by increasing the amount of prothrombin in the circulating blood.—T. C. B.

THYMUS AND REPRODUCTIVE ORGANS; Direct and indirect Effect of X-rays in White Rats. Hewer (Evelyn E.) *Jour. Physiol. (Lond.)* 1916, 1, 438.

From results of experiments with X-rays the author sums up under three heads: effects of irradiation on A, the thymus; B, the male gonads; C, the female gonads.

A. Direct irradiation of the thymus does not appear to determine the appearance of Hassall's corpuscles, unless the gonads are simultaneously treated.

Irradiation of the thymus only causes slight degeneration of the male gonads, and delays sexual maturity. No alteration in the female.

Irradiation of both thymus and gonads causes degeneration of the male gonads, but weak doses cause an acceleration in young animals.

Irradiation of the whole animal when very young, and with a small dose hastens sexual development in the male.

B. The general result of other workers was confirmed, namely, that irradiation of the testes determines degeneration, the degree, broadly speaking, varying with the dose of X-rays.

C. Young ova are more resistant to X-rays than older follicles; the corpora lutea become abnormally vascular, and hypertrophy of the interstitial gland is constant, and persists.

Incidentally the effect of irradiation on the adrenals and pancreas are touched upon.—T. C. B.

THYMUS AND REPRODUCTIVE ORGANS; Structure of, in White Rats, together with Observations on the Breeding Capacity of these Animals. Hewer (Evelyn E.) *Jour. Physiol. (Lond.)* 1916, 1, 434.

After discussing the histology of the thymus and the gonads, the author points out that the feeding of thymus gland delays development of the testes in young males, and cause degeneration of the testes in adults; and that all rats are sterile, although ripe spermatozoa and ripe ova might be demonstrated histologically. There were no definite changes in the thymus itself.

The author refers to a previous paper in which it has

been demonstrated by feeding experiments that there is an interrelationship between the thymus and gonads.—T. C. B.

(SPLEEN) Le modificazioni anatomiche ed il contenuto in glicogene del fegato nei cani operati di recente di splenectomia. Verdozzi (C.) Arch. di Fisiol. (Florence) 1916, xiv, 81.

During the 5th to 7th days succeeding splenectomy in dogs the liver increases in weight and macroscopically and microscopically presents a picture of intense stasis of the portal circulation. During this period characteristic histological lesions are observed, attributable to the interruption of the venous circulation of the liver. These lesions are present in a minor degree from 10 to 15 days after splenectomy and are almost absent in those operated from 25 to 30 days previously.

From the 10th to 30th day after splenectomy an extraordinary accumulation of glycogen is observed in the liver cells. The author infers that the spleen intervenes actively in the amyolytic function of the liver, discharging a secretion having a stimulating action on the diastatic activity of the liver.

The augmentation in the weight of the liver during the first days succeeding splenectomy is attributable to the accumulation of venous blood consequent upon the stasis of the portal circulation. The later augmentation is attributable to the accumulation of glycogen. The karyogenetic figures observed in the hepatic cells several days after splenectomy are probably the expression of a proliferative reaction to the degenerative lesions consequent upon the stasis of the circulation.—T. B. R.

(SPLEEN) Determinations du contenu de cholestérine et de phosphore et de la résistance des globules rouges après l'extirpation de la rate. Donati (A.) Arch. Ital. de Biol. (Turin) 1916, lxiv, 239.

Splenectomy was performed on five dogs. In each case, as previously observed by Bottazzi, the resistance of the red blood corpuscles to haemolysis by hypotonic solutions was much greater after splenectomy than before the performance of the operation.

This increase in resistance was accompanied by an increase in the total phosphorus content of the red blood corpuscles. The inorganic and organic phosphorus were not separately determined. The cholesterol content of the red blood corpuscles undergoes no change.—T. B. R.

(PANCREAS Pancreatic Diabetes in the Dog. IV. The Influence of Pylorus Exclusion and of Gastrectomy upon the Effects of Pancreatotomy. Murlin (J. R.) and Sweet (J. E.) Jour. Biol. Chem. 1916, xxviii, 261.

The hypothesis is advanced that the hydrochloric acid produced in the stomach and left unneutralized in the duodenum after pancreatectomy is absorbed by the portal system and poisons the liver, causing the rapid onset of the resulting diabetes in well nourished animals.

Three dogs in good nutritive condition that had the pylorus ligated at the time of pancreatectomy excreted no sugar during the first 24 hours, owing to the absence of acid in the duodenum.

Five dogs with a previous gastrectomy, upon removal of the pancreas, developed little or no glycosuria; but one other dog when given artificial digestion and kept in good nutritive condition so that a considerable amount of glycogen was probably stored following gastrectomy and previous to pancreatectomy, developed a tolerably severe diabetes, exhibiting high blood sugar, and average G:N ratio of 1.7 and an increase of 36 per cent. in heat production. The respiratory quotient of this dog and of two others previously gastrectomized was but little lower than that of ordinary starvation. Dogs with pancreas removed after gastrectomy do not exhibit the usual profound toxemia of a simple pancreatectomy.

The results of this study taken in conjunction with the results of Rona showing the extreme sensitiveness of the mechanism which accomplishes the oxidation of glucose to the concentration of hydrogen ions, and the work of Murlin and Kramer demonstrating the beneficial effect of alkali administered to totally and partially depancreatized dogs on the oxidation of glucose, suggests that the internal function of the pancreas may be closely allied to its external function and that it preserves the proper concentration of hydrogen ions in the tissues for the combustion of glucose. It is suggested that the pancreatic hormone through which this latter function is discharged may prove to be a peculiarly adapted alkali produced by the islets of Langerhans.—T. B. R.

(THYROID) The Iodin Content of Food Materials. Bohn (R. M.) Jour. Biol. Chem. (Balt.) 1917, xxviii, 375.

Three methods for the determination of iodine in organic matter were compared, with the result that the method proposed by Kendall was found to be by far the most accurate.

Iodin determinations were made on many feeding materials, two natural waters and several rock salts. In the majority of samples no iodine could be detected; some showed a trace of iodine to be present.

It would appear that the presence of iodine in feeding materials of vegetable origin is accidental and serves no necessary nutritive function in the plant. Further, the iodine requirements of animals must of necessity be met by the traces that occur in plant materials, waters, etc.—T. B. R.

(PANCREAS) Preliminary Observations on the Influence of Sodium Carbonate, administered by Duodenal Tube, upon human Diabetes. Murlin (J. R.) & Craver (L. F.) *Jour. Biol. Chem. (Balt.)* 1916, xxviii, 289.

Description of the effects of treatment of five cases of human diabetes by duodenal administration of sodium bicarbonate and disodium carbonate. The latter salt is preferred. The results appear to confirm the observation by Murlin and Kramer on the effect of alkali in improving sugar utilization in depancreatized dogs. The administration of alkali in the cases investigated led to diminution in the output of sugar in the urine, a gain in weight primarily due to retention of water, and a reduction in the percentage of blood sugar independently of any factor of dilution. All of the patients felt an improvement, but this improvement was objective only in two out of the five cases.

The authors believe that their results are attributable to the facilitations of the oxidation of glucose by alkalies.

T. B. R.

(ADRENIN, PITUITRIN) Pharmacology of Uterus Masculinus. Waddell (J. A.) *Jour. Pharm. & Exper. Ther. (Balt.)* 1916, ix, 171.

This paper is a report of a part of a systematic investigation of the pharmacology of the generative organs of the male. It was found that the uterus masculinus of the rabbit exhibits spontaneous rhythmic contractions when suspended in warm oxygenated Tyrode's solution. Both adrenin and pituitary extract as well as several other drugs cause an increase in tone but a decrease in amplitude of contractions. The organ reacts pharmacologically essentially like the uterus of the female. The reactions indicate that it receives both sympathetic and parasympathetic innervation.—R. G. H.

(ADRENIN) Pharmacology of the Prostate. Waddell (J. A.) *Jour. Pharm. & Exper. Ther. (Balt.)* 1916, ix, 179.

Adrenin was found to increase the tonus of prostatic muscle of rats, guinea pigs, cats, hogs and rabbits. The reactions to other drugs indicate that the prostate has both sympathetic and parasympathetic innervation. The parasympathetic fibres have the more powerful control over the organ and are much more resistant to the injurious action of drugs than are the sympathetics.—R. G. H.

(ADRENIN) Role of Liver in Acute Polycythemia. Lamson (P. D.) *Jour. Pharm. & Exper. Ther. (Balt.)* 1916, ix, 129.

This paper reports a continuation of previous researches which include a study of the effects of adrenin injections on the red blood cell count. The marked increase in the cell

count which Lamson has shown follows injections of adrenin is due to the action of the drug upon the liver. In both dogs and cats a dose of 0.5 to 1.0 mgm. per kilogram body weight injected intravenously increases the red cells about two millions per cu. mm. The increase persists about half an hour. Removal of the stomach, intestines, spleen, etc., has no influence upon the reaction. The reaction does not occur when the blood circulates only through the thorax and head, when the hepatic artery is ligated or when the portal blood is shunted by an Eck fistula directly into the vena cava. Lamson's work suggests that the polycythemia following adrenin injections may be an adaptive reaction leading to greater circulatory efficiency. The doses used were, however, relatively large. They were something over a thousand times as great as the adrenin output per minute recently determined by Stewart in anesthetized dogs. That is, Lamson injected at a single dose about as much as the animal would secrete under the conditions of Stewart's experiments in a day. To what extent the quantitative criterion is actually applicable in such cases is as yet unknown but it should be borne in mind in evaluating results of the nature reported.

R. G. H.

MAMMARY Gland, Cyclic Changes in, Under Normal and Pathological Conditions. I. Changes in the Non-pregnant Guinea Pig. Loeb (L.) & Hesselberg (C.) Jour. Exper. Med. (N. Y.) 1917, xxv, 285.

This is a continuation of Loeb's extensive studies of the past ten years on the mechanism of the cyclic changes in the mammary gland, uterus and ovary. The observations reported in the present paper were made mostly on guinea pigs in which the existing period of the sexual cycle was definitely known. It was noted that in the mammary gland there occurs a cycle of changes which correspond with those of the uterus and ovary. The gland goes through a period of cell proliferation which is at its height during ovulating and heat. This primary proliferation does not occur when functional corpora lutea are present in the ovaries. After a period of quiescence on about the fifteenth day after ovulation proliferation again begins. In some cases in which the sexual period is prolonged proliferation occurs; in others, not. Two factors seem to favor proliferation in these cases: functional corpora lutea with deciduomata and imminence of heat. Extirpation of the ovaries prevents the primary mammary proliferation and probably also the secondary. In animals having "hypotypical" ovaries (usually without well-preserved corpora lutea) the mammary glands were inactive. Extirpation of the corpora lutea accelerates the primary proliferation and its associated ovulation and heat but seems to pre-

vent the secondary proliferation. The presence of well developed ovarian follicles is essential to the primary proliferation. After hysterectomy the corpora lutea were found well preserved and the mammary glands proliferating.—R. G. H.

(GONADS) Changes in the Pregnant Guinea Pig, the Effect of Lutein Injections, and the Correlation between the Cycle of the Uterus and Ovaries and the Cycle of the Mammary Gland. Loeb (L.) & Hesselberg (C.) *Jour. Exper. Med.* (N. Y.) 1917, xxv, 305.

During pregnancy mammary gland proliferation usually first begins about the 24th day. Pregnancy as well as living deciduomata and corpora lutea probably cause augmentation of the proliferation. With the initiation of active secretion mitosis in the mammary gland soon ceases. If abortion occurred during the first half of pregnancy no secretion was produced, but in two animals that aborted during the latter half secretion was noted. After castration early in pregnancy not causing abortion mammary proliferation was absent. Extirpation of the corpora lutea during pregnancy induces a new ovulation and attendant mammary proliferation. Bovine lutein extract in large doses did not produce mammary proliferation. The paper closes with a four page discussion of the significance of the foregoing results. It is not amenable to abstracting.—R. G. H.

ADRENALIN, Comparative Study of Certain Actions of, in the Cat and Rabbit. Githens (T. S.) *Jour. Exper. Med.* (N. Y.) 1917, xxv, 323.

Of technical interest. Compares the duration and extent of effects of adrenin on the pupil and blood pressure in cats and rabbits.—R. G. H.

THYMUS, Extirpation in Guinea Pig. Park (E. A.) *Jour. Exper. Med.* (N. Y.) 1917, xxv, 129.

Several investigators have reported results that indicate that the thymus has important relations with the sex glands, especially in the male. In a number of such studies the guinea pig has been used. The results have been somewhat conflicting. Park accordingly has subjected the problem to a careful renewed study. Previous work is criticised on the grounds of inadequate technique and failure to use proper controls. Careful study of serial sections through the neck region showed that the guinea pig has so much accessory thymus tissue as to render complete thymectomy impossible; earlier reports of thymectomies in this animal must be interpreted as partial only. In twelve cases Park performed thymectomies as complete as possible in young animals and kept them with controls of the same litter and sex under identical con-

ditions. (Two exceptions as to ideal controls.) No differences could be detected between the experimental animals and the controls either as to procreative activities, growth or conditions in the various endocrine glands. Thymectomy has been reported to cause rachitic changes. No such were caused in Park's series. These studies while they do not absolutely disprove the popular theory of an intimate relation between the thymus and testes do cast much doubt upon it. At the present stage of the endocrine literature such careful studies even though negative in outcome are especially valuable. It is to be hoped that many other insecurely founded statements in which the literature abounds may soon be subjected to equally rigorous investigation.—R. G. H.

PITUITARY, Experimental Studies on the Relation of, to Renal Function. Motzfeldt (K.) *Jour. Exper. Med.* (N. Y.) 1917, xxv, 153.

In view of the fact that pituitary extracts had been observed to check diuresis in cases of diabetes insipidus Motzfeldt has made an elaborate study of the relations of pituitary and other substances to kidney function. There is a somewhat extensive literature which indicates that pituitary extracts have a diuretic effect. The experiments on the subject have been made mostly, however, for short periods of time on narcotized animals. These limitations have been ignored in formulating the widely held theory that the pituitary has a normal stimulating effect upon the kidneys. Motzfeldt worked with unanesthetized animals,—mostly rabbits,—extending the observations over several hours. In most cases the animals were given water by stomach to cause diuresis. The pituitary extracts and other substances were administered usually subcutaneously, but occasionally by vein or by mouth. The urine was collected by catheter at half-hour intervals. Extracts of intermediate and posterior lobes of the pituitary were found to have a marked anti-diuretic effect; extracts of anterior lobe had a similar but much slighter effect. This effect was constant and independent of changes in blood pressure, intestinal absorption or vagus function. It was interfered with, however, by division of the sympathetic nerve supply to the kidney. Anti-diuretic effects were demonstrated also for *b*-imidazolethylamine, *p*-oxyphenylethylamine ("sympathomimetic" substances) the drug *secale cornutum*, small doses of nicotine, large doses of caffeine and extracts of adrenal cortex. No effect on the polyuria was caused by strychnine, morphine, adrenin, or by extracts of thyroid, thymus, pineal, pancreas or corpus luteum. In case of salt diuresis the anti-diuretics showed little effect. Motzfeldt suggests that the anti-diuretic effect is probably mediated through the sympathetic system acting upon the kid-

neys. He does not mention the other possibility that the changes may be produced in the tissues, decreasing the amount of "free water." These studies would seem to afford an excellent basis for the rational therapeutics of diabetes insipidus—R. G. H.

PINEAL Gland, Studies. Horrax (G.) Arch. Int. Med. (Chgo.) 1916, xvii, 607, 627.

From experimental observations on the pineal gland the author concludes that total experimental pinealectomy is possible in guinea pigs and rats. Male guinea pigs so treated show a hastened development of the sexual organs manifested by the relative increase in size and weight of both the testes and seminal vesicles compared with control animals. Histologically, the testes and seminal vesicles of these animals show a more advanced physiologic state than do the controls.

Clinical observations in three cases were noted, one of these was certified in full, the other two presented clinical pictures suggestive of pineal dysfunction. This first exhibited adiposity and macrogenitosomia, the others showed precocity of adolescence as well as overgrowth. The first case presented very marked precocious adolescence. In this case there were intracranial symptoms, and a diagnosis of tuberculous meningitis as well as xanthochromia of the spinal fluid. Autopsy revealed a struma of the pineal gland. He summarizes his article as follows:

"Extirpation of the pineal in young chickens and lower animals tends to hasten normal maturity. Tumors of the pineal gland in children occurring before the age of puberty usually give rise to a syndrome characterized by precocious adolescence. Feeding the gland substance to young animals is said to have the same effect as extirpation, but the observations are somewhat inconclusive. A report of three cases of supposed pineal tumor, one of which was certified by necropsy, is offered as a further contribution to the study of this gland."—W. B. T.

GOITER, Metabolism Study, with Effect of Thyroid and Thy-mus Treatment. Halverson (J. O.), Bergeim (O), and Hawk (P. B.) Arch. Int. Med. (Chgo.) 1916, xviii, 800.

This report is based on a study of the metabolism of nitrogen, phosphorus, sulphur, calcium and magnesium on a patient with exophthalmic goiter, with a slight hypothyroidism. The study was made in five periods of five days each, including periods of thyroid and thymus treatment.

Without treatment there was a pronounced loss of nitrogen, phosphorus and magnesium.

Thyroid medication stimulated metabolism, this stimulation continuing after treatment was stopped. Considerable

retention of all elements was brought about. Slightly better intestinal absorption of nitrogen followed this treatment, although the loss of nitrogen by the feces continued high.

The effect of thymus administration on the metabolism was not as marked as that of the thyroid but was distinct. While the gland was being administered all elements were depressed. When the administration ceased the retention was increased.

Thyroid causes diuresis. Thymus had the opposite effect. Following thyroid treatment there was a progressive decrease in urinary indican excretion.

The weight of the patient decreased on thyroid treatment. It increased following cessation of thyroid treatment and on thymus administration.—W. B. T.

(THYROID) Results of Recent Studies on the Ductless Glands. Cannon (W. B.) Jour. Amer. Med. Assn. (Chgo.) 1916, lxvii, 1483.

After reviewing briefly his work on the adrenal glands, especially in regard to the effect of the emotions on the glandular secretions, Cannon reports the result of electrical estimations of thyroid gland activity. With this method, he was able to show first, that the thyroid gland is subject to impulses from the cervical sympathetic; second, that the vagus nerve and pilocarpine (a stimulator of vagus endings) have no control; third, the influence of the sympathetic is not due to anemia.

Control by the sympathetic implies that adrenin may stimulate thyroid activity, and this was proven by intravenous injection of adrenin, and by stimulation of the adrenals via the autonomic system. By continuous stimulation (fusion with the phrenic) of the cervical sympathetic changes were produced which, in many respects resemble exophthalmic goiter. Hence exophthalmic goiter may be due primarily to over activity of that part of the nervous system disturbed in emotional excitement.

In conclusion, the author states that it is not unreasonable to suppose that the thyroid gland, as previously proven for the adrenal glands, has an emergency function, which would serve to increase the speed of metabolism and augment the efficiency of the adrenin secreted simultaneously.—F. C. P.

PINEAL Gland; Composition and Physiological Activity. Fenger (F.) Jour. Amer. Med. Assn. (Chgo.) 1916, lxvii, 1836.

Fenger collected 2344 pineal glands from full grown cattle, 1348 from adult sheep and 5062 from lambs and noted that the glands from cattle were long and fusiform and relatively small, that the sheep and lamb glands were short and plump.

He presents a table showing the average maximum and minimum weights of the various groups of glands with their loss of moisture and their petroleum-ether soluble substance. The glands from lambs contain less phosphorus than those from sheep, and these in turn less than the glands from cattle. No adrenin or iodine were found.

Pineal glands from both species show only slight contracting power on unstriated muscle, and only slight effect on the blood pressure, pulse rate, and excised heart.

In conclusion, Fenger states we cannot, with our present knowledge of physiological chemistry, accept or even consider the pineal body as an internal secretory organ of medicinal value.—F. C. P.

(ADRENIN, etc.) Endermic Reactions. Sollmann (T.) and Pilcher (J. D.) *Jour. Pharm. & Exper. Ther.* (Balto.) 1917, ix, 309.

This is an extensive research on the effects of various drugs applied to the scarified skin, amounting essentially to a study of experimental urticarias. In the research adrenin and pituitrin, among many other substances, were employed. Mulford's pituitary extract was found to produce within five minutes a marked blanching of the skin which extended somewhat beyond the scarified area and was surrounded by an area of slight reddening. There was no wheal nor any "goose-flesh" produced. The blanching persisted between $\frac{1}{2}$ and $1\frac{1}{2}$ hours. The effect of histamin which has been supposed by some to be the actual active substance in pituitary extract was quite different. It produced marked erythema and urticaria.

Adrenin produced marked blanching in the scarified skin of both human subjects investigated. This was true even with a solution of 1:100,000. With 1:1000 a very white area extending somewhat beyond the scratches was produced within one minute. This gradually faded away, disappearing in about $2\frac{1}{2}$ hours. In one of the subjects, but not the other, the blanched area presented a striking "goose-flesh" appearance. This was due to a stimulation of the *erectores pilorum* muscles rather than to anemia since it was not produced by pituitary extract. Adrenin applied even to the intact skin of one of the subjects produced a marked blanching. The observations as a whole indicate that neither local vasodilation nor vasoconstriction play any essential part in producing urticaria.—R. G. H.

CLINICAL STUDY

(PITUITARY) A Case Bearing on the Function of the Pituitary Body. Boyd (Wm.) Jour. Amer. Med. Assn. (Chgo.) 1917, lxviii, 111.

Boyd reviews briefly some of the theories relative to the function of the hypophysis, and reports a case of glioma of the interpeduncular space, involving the infundibulum of the pituitary body. Briefly the case exhibited the following points of interest: Boy, ten and a half years old, with the general symptoms of brain tumor, a slight enlargement of the sella (roentgenogram), very high sugar tolerance and absence of skeletal and sexual changes. Operation by Dr. Harvey Cushing, by transphenoidal route, death in a little more than three weeks. At autopsy, a glioma was found in the interpeduncular space, surrounding and constricting the infundibulum of the pituitary body. The author believes this case to furnish additional argument in favor of the theory that the secretion of the posterior lobe of the pituitary passes via the infundibular stalk into the third ventricle.—F. C. P.

HYPERTHYROIDISM and Its Relation to Certain Pelvic Disorders. Eastman (T. B.) Jour. Indiana St. Med. Assn. (F. Wayne) 1916, ix, 465.

Eastman calls attention to the close relationship between the thyroid gland and the genital tract in certain invertebrates, and reports two cases showing this relationship in the human race. In one case with a fibrocystic ovary associated with enlargement of the thyroid gland, removal of the ovary and tube resulted in relief from the hyperthyroidism. In the second case, one suffering with dysmenorrhea and menorrhagia, with a normal pelvis and all the typical findings of hyperthyroidism, removal of a part of the thyroid gland relieved her menstrual as well as thyroid symptoms. He concludes that there is a close interrelationship between the ovaries and thyroid. Thyroid secretion and ovarian secretion do not supplement each other, they neutralize each other.
F. C. P.

(THYROID) Hyperthyroidosis Associated with Gynecomastia. Freeman (J. K.) Therap. Gazette (Detroit) 1916, xl, 9.

The author reports a case of a man 37 years of age suffering with the typical symptoms of over activity of the thyroid gland, associated with an abnormal development of the mammae.—F. C. P.

(THYMUS) Myasthenia Gravis with Thymoma. Jones (W. A.) Jour. Amer. Med. Assn. (Chgo.) 1916, lxvii, 1354.

The author reports in detail a case of myasthenia gravis

in which at autopsy, following sudden death, a tumor about the size of a damson plum was found in the thymic region. Microscopically, the tumor consisted of fetal thymic tissue. He further calls attention to the unsatisfactory literature on this subject.—F. C. P.

THYROID Disease in Relation to Rhinology and Laryngology. Shurley (B. R.) Jour. Amer. Med. Assn. (Chgo.) 1916, lxxvii, 1726.

This author calls attention to the physiologic and pathologic relation of the tonsils to the thyroid gland, and states that his attention has been directed to this subject by the beneficial results of a series of tonsillectomies for the relief of recurrent tonsillitis and quinsy, attended by incipient typical and atypical exophthalmic goiter. In his experience, the laryngeal muscles often show some insufficiency, varying with the size of the goiter; hyperemia of the pharyngeal, bronchial and pulmonary mucosa is common in exophthalmic goiter; if the gland is hard, it may cause tracheal cough. He believes that more rhinologists and otologists should bear in mind the close relation between the thyroid gland and the organs in their special field.—F. C. P.

PINEAL Tumor with Invasion of Midbrain, Thalamus, Hypothalamus, and Pituitary Body. Warren (L. F.) and Tilney (F.) Jour. Nerv. & Mental Dis. (N. Y.) 1916, xlv, 74.

A boy of eighteen years was struck on the head with the buckle of a heavy strap in April, 1915, following which injury he developed symptoms of pain in the head, projectile vomiting and drowsiness. He later developed symptoms of thirst and had difficulty in seeing and hearing. History previous to injury negative. There was great emaciation and there were marked contractures over the entire body, so that the fingers, hands and knees were flexed. Definite catatonia was present. X-ray showed sella turcica eroded at base.

The contractures may be due to pineal gland disturbance or to pressure on the tracts and the peduncle.—W. B. T.

(PINEAL) Progressive Muscular Dystrophy as an Endocrine Disease. Timme (W.) Arch. Int. Med. (Chgo.) 1917, xix, 79.

The author reports a somewhat atypical form of progressive muscular dystrophy, resembling Erb's infantile type, of extremely benign and slow progress. In the cases examined it has occurred as hereditary now in the fourth generation. Fourteen individuals have been disabled thus far. Five out of seven living members of this group have been examined by Roentgen ray; of these five, four show changes in the pineal gland. The evidence presented by these cases, together with that in previous similar communications, makes

probable a close relationship between progressive muscular dystrophy and disease of the pineal gland.

In the author's cases the span of life seemed above the average, his findings differing from Gower's in this respect.

W. B. T.

PINEAL Body, Hyperplasia. Bell (H. H.) *Jour. Nerv. & Mental Dis.* (N. Y.) 1916, xliv, 481.

Few lesions of the pineal body have been observed. In man the epiphysis appears as a single evagination from the roof of the diencephalon. This outgrowth branches and becomes invested with a capsule from the choroid plexus. It develops rapidly until the sixth year when involutional changes begin which last until the fourteenth year, after which no further changes are observed. These involutional changes are characterized by proliferation of connective tissue, the formation of neurological plaques which may contain cysts, and the appearance of concretions.

The cells of the pineal body do not resemble those of the organs of internal secretion. The pineal cells in young individuals are similar in number and structure to those in pineal bodies of older individuals after involution is established.

Pineal cells appear to be modified neuroglia cells.

In association with the process of involution there may be tumor-like enlargement of the pineal body characterized by proliferation of the pineal cells. In association with hyperplasia of these cells there is no functional disturbance in other organs of the body.

Two autopsies are reported in which pineal bodies were found, measuring in one case 16 mm. long, 8 mm. wide and 5 mm. long vertically; in the other, 15 mm. long and 9 mm. in its other dimensions. The first gland described was more than three times, and the second more than six times, the size of the average normal pineal body. In Case I the enlargement was due to an increase in all of the pineal elements as well as cystic formations. In Case II besides a marked hyperplasia of all the pineal elements, cysts were also present but were microscopic in size.

The symptoms which have occurred with enlargement of the pineal are headache, vomiting, optic neuritis, mental apathy and drowsiness.—W. B. T.

(PITUITARY) Radiography of the Sella Turcica and Pituitary Body. Johnston (G. C.) *N. Y. State Jour. Med.* (N. Y.) 1916, xvi, 11.

The author describes in detail the technique in taking radiographs of this region, calling attention to the desirability of making a large number of observations so as correctly to diagnose the presence of pituitary disease from the radio-

gram alone. He claims that there are changes about the pituitary rather constantly present in cases of epilepsy not attended by evidence of optical changes or other evidences of pituitary struma.

He also considers radiograms important in the diagnosis of tumors of this region, of internal hydrocephalies and of "idiopathic" epilepsy.—M. B. G.

(PARATHYROID) Zwi Falle von Parathyreoideatumoren.

Schlagenhauser (—) Munch. med. Wchnschr. 1916, lxiii, 56.

Prof. Schlagenhauer demonstrated anatomical preparations from two cases of parathyroid tumors. The first case was that of a man of 43 years, who for the past five years had severe osteomalacic involvement of the ribs, pelvis, and bones of the extremities; also a softening of the vault and base of the skull, resembling an osteitis fibrosa. The left lower parathyroid gland was the size of a plum.

The second case was that of a woman of 62 years, who showed for the last fifteen years severe and typical osteomalacic changes. The right lower parathyroid was enlarged to the size of an almond.

In both cases the histological structure of the parathyroid showed no abnormality. He believes that the operative removal of the hyperplastic gland may improve the condition.

In discussion, Dr. Maresch reported his findings in 32 cases of osteomalacia: only three times did he find parathyroid tumors, ranging in size from an almond to a chestnut. In ten cases, the parathyroids were enlarged only relatively, and the rest of the cases (Paget's osteitis deformans and osteomalacia) showed no real tumors. These cannot always be found in severe osteomalacia. But as all other therapy is valueless in such cases, he believes that an operative removal would be advisable.

Dr. Julius Bauer remarked that not rarely does the symptom-complex of tetany appear associated with osteomalacia, which speaks for an insufficiency of the gland. Adenoma of the parathyroids is sometimes found in man without any signs of osteomalacia, as there are also cases of osteomalacia associated with functional disturbances of other ductless glands (ovary, thyroid, and possibly the hypophysis). He concludes that the pathogenetic relations of osteomalacia are extremely complicated.—L. N.

CORPUS LUTEUM, Life Cycle and Role in Menstrual Disorders. Novak (Emil) Jour. Amer. Med. Assn. (Chgo.) 1916, lxvii, 1285.

Novak's investigation embraces the clinical and histologic study of 137 cases from the Gynecological Department of Johns Hopkins Hospital. In 102 of these, both ovaries

had been removed, together with the uterus, so that it was possible to study the histologic picture of the endometrium side by side with the histologic variations in the removed ovaries. Only by thoroughly ransacking the latter by numerous sections could the possibility of overlooking important structures be avoided. The mere presence or absence of corpora lutea on the surface of the ovary means very little. The site of even large corpora lutea is apt to be marked by only a slight hemorrhagic discoloration on the surface. Only by cutting into the ovarian substance is the true nature of such an area revealed.

A careful study of the ovaries in this series enabled Novak to secure corpora lutea in practically all stages of development, and thus to trace the life history of the corpus luteum from beginning to end. In its earliest stages, just after rupture of the graafian follicle, it is usually a small, collapsed structure, with thin, moderately undulating walls, which are of grayish yellow hue instead of the brilliant yellow color of the later stages. For this reason the earliest stages are very inconspicuous, and are commonly overlooked. Indeed, their discovery, even with careful search, must be looked upon as in large measure accidental. With the exception of the questionable observation of Kreis in 1899, no example of such an early human corpus luteum had been described until the report of Meyer in 1911. Five such very early corpora lutea are described by Novak from his material. The clinical histories are given in full, together with the histological descriptions, illustrated by photomicrographs.

All five specimens are alike in the very important particular that in all of them the epithelial cells of the membrane granulosa are, to say the least, quite intact. This fact is of prime importance in the consideration of the origin of the lutein cells. One of the strongest arguments against the epithelial origin of these cells has been the alleged degeneration and disappearance of the membrana granulosa after the rupture of the graafian follicle. In all these five cases, however, it is well preserved, and in two of them it shows definite signs of a lutein-like transformation. Sobotta's studies indicate that, in the lower animals at least, it is from the epithelium of the granulosa that the lutein cells are derived. Novak believes that the study of his material demonstrates a similar origin in human beings. As to the time relation of these early corpora lutea to menstruation, this would indicate that ovulation occurred in the first half, or perhaps we may say the second quarter, of the intermenstrual period. Emphasis is laid, however, upon the great need of securing many more early corpora lutea, the study of which throws much more light on this problem than does that of the mature corpus luteum.

The second stage of development in the corpus, the stage of vascularization, is characterized especially by an invasion of the lutein layer by small bloodvessels from the theca interna. Some of the blood in the lutein zone is present in endothelium-lined bloodvessels, and some lies free between the cells, making its way to and into the cavity of the corpus. Even in this early stage, endothelial cells may be observed here and there pushing out into the lumen, forecasting the organization of the contents which takes place later. From a physiologic viewpoint, vascularization is important because, in addition to carrying nutriment to the lutein cells, it enables their secretion to be emptied directly into the blood stream. The further development of the corpus luteum is gradually traced to the stage of full maturity. Reference to the menstrual histories of the twenty-four cases in which mature corpora were found demonstrated that in all operation had been done at periods ranging from the eighteenth to the twenty-seventh days of the menstrual cycle, i. e., the period in which the endometrium exhibits premenstrual hypertrophy.

An interesting feature of many corpora lutea, especially near the age of maturity, is the remarkable development of the theca interna cells. They are often as well developed as the lutein cells, though of quite a different type. The contrast is very striking. The large size of these theca cells, their alveolar arrangement, the richness of their blood supply, all suggest a glandular structure and function. The name of "paralutein" cells was given to them by Pinto, who, however, credited them with no special function. With this view Novak does not agree, believing that these cells are probably concerned in the formation of one of the ovarian hormones.

After describing the retrogression of the corpus luteum, the author discusses the process of atresia folliculi. A distinction is drawn between the theca lutein cell so often found in the wall of the atretic follicle, especially during pregnancy, and the granulosa lutein cell which characterizes the corpus luteum. The so-called fibrocystic ovary to which so much pathologic importance has been ascribed, represents a marked exaggeration in the number and size of the atretic follicles. It is almost always associated with excessive menstruation. While not the cause of the latter, it, like the excessive menstruation, is to be looked upon as an evidence of ovarian hyperfunction. In other words, both the hyperfunction of the ovary and the excessive ripening of follicles which results in the fibrocystic disease, are the result of the pelvic hyperemia characterizing the inflammatory and neoplastic lesions in association with which such ovaries are commonly found.

Other subjects which are discussed are concerned with

the relation of menstruation and ovulation, as based on the study of patients before puberty, after the menopause, during lactation, during pregnancy, etc. Finally, an analysis of Novak's cases failed to reveal anything like a direct relation between the degree of lutein development in the ovary and the clinical intensity of the menstrual flow. Speaking generally, the corpus luteum from a case of excessive menstruation shows no greater development than that from a case of scanty menstruation. This does not, however, preclude the possibility of functional increase or decrease being the cause of increase or decrease in the menstrual reaction. Nor can we forget the all-important fact that even though the ovarian secretion is the immediate cause of menstruation, this function is also influenced by practically all the other endocrine glands of the body. The ovary is merely the portal through which the entire ductless gland change exerts its influence on the functions of the female generative organs.—E. N.

(THYROID) Exophthalmic Goiter. Mackenzie (Hector) *Lancet* (London) 1916, xcxi, 815.

During the four years 1911-1914 the number of deaths returned in England and Wales as resulting from exophthalmic goiter was 1,558 for females and 155 for males, a proportion of ten females to one male. The number of deaths increase in each five-year age-period up to 35-40. The author states that the disease is very rare in childhood, that he has yet to see a typical case under the age of twelve.

The disease shows a tendency to show itself in several members of the same family. In thirty-four private cases, other members of the family were afflicted besides the patient examined. In at least one-third of the cases the onset of the disease was preceded by some more or less severe mental shock, strain, worry or anxiety. As a rule, the symptoms of the disease develop gradually after the shock or strain, but in some cases the symptoms very quickly follow the mental disturbance.

The effect of profound emotional disturbances, such as sorrow, grief, anxiety and fear, is to produce exophthalmic goiter. The author considers fright to be a short attack of exophthalmic goiter.

From what is known of the causation of the disease, prevention is out of the question. Persons in whom there is a family history of the disease should steer clear of occupations involving more than the ordinary responsibility, worry or anxiety.

In the thirty-six post mortem examinations held on cases of exophthalmic goiter at St. Thomas' Hospital, the most constant feature next to the thyroid enlargement was the presence of a persistent or enlarged thymus gland. In three

of the fatal cases the duration of the disease was less than six months; in ten, less than one year; in twelve, less than two years; in eight, less than six years; and in six, over six years. In more than half of the cases it was less than eighteen months.

The blood picture of exophthalmic goiter is that of any disease of the endocrine system, namely, a white cell leucopenia with a relative lymphocytosis.

The hypodermic injection of the extract of the posterior lobe of the hypophysis slows the pulse in patients suffering from exophthalmic goiter. The instillation of adrenalin into the conjunctiva causes dilation of the pupil in goiter, and also diabetes. Exposure of the thyroid and thymus glands to the X-ray is the best means of treatment. It must be continued for a long time. The early cases are the ones most benefited by this treatment.

The author's experiences with the operative treatment of the disease have been unfavorable. If operated at all, local anesthesia should be used. Ligature of the thyroid arteries is not very effective. If possible, it is best to remove more than one lobe, otherwise it is probable that another operation will be necessary.—W. B. T.

(PANCREAS) Del diabete neurogeno. Silvestri (T.) *Rif. Medica* (Naples) 1916, xxxii, 281.

In an interesting study of the possible neurogenic origin of diabetes mellitus Silvestri reports the clinical course and autopsy findings in a case of diabetes in which there were no pathologic anatomic findings capable of explaining the diabetes. This author presumes that it was of nervous origin, as the neurasthenic man of 53 had a family history of much nervous and mental disease. The literature on the subject of diabetes developing after disastrous speculation or other nervous shock is reviewed, and authors cited for and against the assumption that diabetes can be brought on by nervous factors alone.

Four other cases in the practice of this writer also apparently confirm this beyond question. One patient was a neurasthenic man with inherited psychopathic taint whose urine was found to contain sugar after a period of much worry. The urine after a medical examination always contained sugar. In the course of a few years the neurasthenia subsided, and the urine became normal. At present there is no further trace of the neurogenous "diabetes" of eight years before, although no attempt at dietetic treatment had been made. Another patient was a woman with a family history of diabetes. After an attack of pneumonia she had mild glycosuria which yielded promptly to restriction of carbohydrates until her son developed typical diabetes which ran its course to a

fatal ending in three years. After this the mother's glycosuria became permanent, unmodified by dietetic measures. In the two other cases the glycosuria came on directly after a severe grief or fright.

These experiences testify that diabetes may occur for the first time or be roused or aggravated by nervous shocks, and Silvestri explains the probable mechanism by which this is brought about. He has been unable to trace it to any one gland or other organ, but the influence of a hereditary taint seems to be obvious.

OVARIAN Transplantation, with Report of Cases. Phillips (W. D.) *Texas State Jour. Med.* (Ft. Worth) 1916, xii, 213-16.

The author reviews the history of ovarian transplantation, and reports the results of twelve cases of autogenous ovarian transplantation which he has observed with Dr. C. Jeff Miller, since Dec., 1914. Phillips used grafts varying in thickness from one-sixteenth to one-eighth of an inch, and always sectioned the transplant from the healthiest portion of the ovary. One or more grafts were imbedded in each case. In seven cases the transplant was placed in the adipose tissue of the abdominal wall resting on the rectus sheath; in the remaining five cases it was embedded underneath the rectus muscle, resting on the peritoneum. No sutures were used to retain the grafts in place. In three cases the graft was alive and functioning two years after operation. Of the twelve cases, six are menstruating regularly, while the remaining six could not be reached by letter. The writer is convinced that the operation is without danger and its use will not only diminish the cases of precipitated menopause, but will also lessen the indications for second and even third laparotomies.

L. F. W.

(ADRENIN) Correlations between the Systolic Blood Pressure and Reflex Vasoconstriction (Anemic Dermography). Tracy (E. A.) *Boston Med. & Surg. Jour.* 1917, clxxvi, 15.

In a previous paper it was shown that anemic dermatography is caused by stimuli coming over the sympathetic fibers, together with adrenin in the blood stream. The present paper is based on a study of 125 cases in which the systolic blood pressure was noted and at the same time the time valuation of anemic dermatography was taken, on analysis of the data obtained two correlations were disclosed: (1) Low reflex vasoconstriction valuation was accompanied by or correlated with low blood pressure. (2) High blood pressure was correlated with high reflex vasoconstriction valuation.

These correlations are highly suggestive when we recall that German clinicians correlate hypertonicity with hyper-

plasia of the chromaffin tissue (which secretes adrenin), and that Addison's disease is associated with low blood pressure. The question at once arises, is there any relation between reflex vasoconstriction and the adrenin content in the blood? Experiment and reasoning lead the author to believe that the relation between them may be expressed briefly thus: reflex vasoconstriction—anemic dermatography—measures comparatively the adrenin content in the blood stream.—E. A. T.

PITUITARY Fossa, Accurate Radiography of, and of the Sphenoidal Sinuses. George (H. T.) Arch. Radiol. & Electrotherap. (Lond.) 1916, xxi, 169.

The author reminds us of the importance of accuracy in the Roentgenography of the pituitary fossa and for the purpose of bringing the saggital plane of the skull parallel with the plate, he places a ring of metal in the proximal ear and a smaller disc in the opposite ear and then centralizes them fluoroscopically.

This he considers an improvement over Finzi's method of using a coin for this purpose. Having obtained these parallel planes the author passes the central ray through the skull at a point 3 cm. in front of the external auditory meatus, and $2\frac{1}{2}$ cm. below the line connecting the external auditory meatus and the external canthus. This should give an accurate outline of the sella turcica.—G. E. P.

[Growth Anomalies in Women.] Schiötz (C). Norsk Magaz. f. laegevidensk. 1916, lxxvii, 909.

The author has studied the anthropological proportions in two cases of apparent infantilism. Contrary to the conditions in "true" infantilism there was an abnormal length of the extremities—more like the conditions in eunuchoidism.

Case I. Girl, 18 years old, 137 cm. high, weight 33 kg. No secondary sex characteristics. Arms and legs unusually long, as compared with the normal conditions. Bitemporal narrowing of the field of vision. High carbohydrate tolerance. The condition is chiefly due to insufficiency of the anterior lobe of the pituitary body and also of the ovaries.

Case II. Woman, 30 years old, 171 cm. high. Amenorrhea. Atropic uterus. Abnormal length of the extremities. No development of mammae. Very much like the castrate type. Primary insufficiency of the ovaries (?).—K. M.

[PITUITARY Tumors.] Schiötz (C.) Med. Revue. (Bergen) 1916, xxxiii, 91.

Case I. Man, 36 years old. Clinical diagnosis: tumor of the hypophysis and adipositas,—without other manifestations of dystrophia adiposo-genitalis. The autopsy revealed an adenoma of the pituitary body. Microscopic examination of

the other ductless glands showed: Colloidal struma of the thyroid, an unusual amount of fat in the parathyroids, and an augmentation of connective tissue in testes, with absence of Leydig's cells.

Case II. Man, 50 years old. The clinical manifestations, hemorrhagic pleurisy, hemiparesis and polyuria (3500 mils.) were considered due to metastases from a malignant new-growth. Roentgenogram showed destruction of the sella turcica. Autopsy: Carcinoma of the lung, pleurae, brain and the pituitary body. The anterior lobe was not involved, but there was a complete destruction of the pars intermedia and posterior lobe.—K. M.

Internal Secretions and Eye Diseases. Schirmer (O.) N. Y. State Jour. Med. (N. Y.) 1917, xvii, 1.

The author deals with the ocular manifestation of abnormal functioning of the glands of internal secretion.

He believes that all diseases of the eye due to hypophyseal or pineal gland trouble are the result not of the internal secretions of these glands but of direct pressure due to their enlargement.

He does not believe that the exophthalmos in Graves' disease can be explained by a continuous contraction of the non-striated muscular system in the orbit, but he assumes that at an early stage a swelling or even an hypertrophy of the fat tissue develops and keeps the eyeball protruded. This would account for the fact that in cases completely cured by surgical interference, all the Basedowian symptoms disappear whereas the exophthalmos frequently remains.

He calls attention to von Hippel's results in using the Aberhalden method for ascertaining the condition of the endocrine glands in eye diseases. Keratoconus is the one eye disease giving positive results by this method, using thymus and thyroid, frequently with both of them; sometimes the adrenals, the pancreas or the gonads give a positive reaction, indicating that in this disease the endocrine functions are disordered. The pathological changes must be slight as none of the well-known endocrine diseases have been observed in these cases.—M. B. G.

AKROMEGALIE, Beitrag zur Klinik und Therapie. Fürth (C.) Med. Klin. (Berl.) 1915, xi, 1347.

A case is reported which is of interest because ten years' observation showed certain peculiarities which may throw a light on the pathogenesis of acromegaly, its prognosis and the value of a therapeutic agency.

The patient, a woman forty years old at the time of first observation, had a typical appearance of acromegaly. Her father had a goiter and died at the age of 62, showing a rapid

disappearance of the goiter and a rapid physical and mental decline; family history otherwise negative. She was a healthy child menstruated at 14, married at 22, but never became pregnant. Toward the close of the second decade, the menses decreased in amount and frequency, and stopped entirely at 33. At this time the manifestations of acromegaly set in, the face becoming larger, especially the nose, chin, lips and tongue, and the teeth became separated. The hands and feet became more plump, and the skin of the chest and back grew short, stiff hairs. Light attacks of dizziness were the only subjective symptoms. For seven years the bodily measurements steadily increased so that finally the acromegaly was typical.

Then visual disturbances set in which were promptly improved by administration of iodides, and after one month of treatment the visual field became practically normal. Later the eyesight again became weaker.

The ophthalmological findings indicate that various disturbances of the visual field may be found in tumor of the hypophysis; secondly, that wide excursions of the visual disturbances may occur at short intervals; and thirdly, that therefore the prognosis of the visual disturbances, as well as the judgment of therapeutic results, must be given with caution.

In regard to therapeutics, the author cannot say much. Sodium iodide, at the time of the first visual disturbances, caused improvement and was continued. The patient felt so much improved, that she asked to have it continued. The dose had to be gradually increased, so that after three years she was taking 114 grams a month, and after five years 210 grams. The therapeutic effect of this dose was then lost, and the patient reacted only to such large doses as 8 and even 14 grams per day. For weekly periods she also took thyroïdin, which was well borne.

At the beginning of treatment, for about one year (on and off), five tablets of ovarian extract were given daily, and later for several years, three tablets of hypophyseal extract were given daily. These organic extracts, however, had absolutely no effect on the visual disturbances, whereas the iodide had a distinctly ameliorating, or at least a retarding, effect. After five years even this effect wore off, and despite the large dosage, vision gradually became poorer.

How is the patient's reaction to iodide to be explained? The radiogram proved the presence of a tumor of the hypophysis, also the destruction of the sella turcica, as well as the dorsum sellae and posterior clinoid processes, whereas the anterior clinoid processes and the anterior half of the pituitary fossa remained untouched. The influence of iodides on various neoplasms is well known, and perhaps the inhibit-

ing effect on tumors is not seen more often because of a too small dosage. In this case, enormous doses were tolerated, and this may have caused the regression of the tumor. However, the unusual tolerance in this case would speak for a specific effect.

According to the current views on acromegaly (Biedl, Pineles), the etiology is not only a disordered function of the hypophysis, but also that of the other ductless glands as well, and it would be nothing unusual for their iodine content to be disturbed. Palpation of the thyroid was negative. It is reasonable to believe that the power of absorbing large quantities of iodide was due to the diminution of the endogenous production of iodine, and that the otherwise toxic effects of this diminished iodine production were held in abeyance by the giving of sodium iodide.—L. N.

(PITUITARY) Ueber familiäre Akromegalie. Leva (J.)
Med. Klin. (Berl.) 1915, xi, 1266.

Leva maintains that in spite of animal experimentation and pathologico-anatomical investigations, the etiology and pathogenesis of this disease are still obscure. Acromegaly may appear at any age, although it has a predilection for the young. As exciting causes are given trauma, emotional disturbances, infections, pregnancy and plumbism; in addition, a hereditary family predisposition is claimed by some to play a definite part.

With special regard to the last mentioned cause, the author reports two cases. The patients were first cousins, one 28 years old, an assistant builder, the other 26 years old, a priest. They grew up in different surroundings and had no personal dealings with each other. Five years ago, both noticed that their fingers and toes gradually became thickened at their outer ends, and also progressively deepening folds appeared in the skin of the occipital region, and finally also the skin of the forehead and face. The skin condition has become more marked the past year, and there has developed a remarkable resemblance between the two patients never noticed before, which has resulted in their being mistaken one for the other.

The similarity of progress of the two cases and their family relationship prompted the author to investigate their family antecedents. Not only were the two patients the sons of two sisters, but a consanguinity was established, inasmuch as the grandfathers descended from a brother and sister of the same family as the mothers.

Previous studies of the causes of acromegaly rest upon anatomical and physiological studies. Pierre Marie claimed that this disease was caused by a neoplasm of the hypophysis. On the other hand, other authors assert that in many cases

of acromegaly no tumor was found, and again in other cases, hypophyseal tumors did not develop symptoms of acromegaly. This contradiction was only apparent: the neoplasms were often only microscopically visible, or they developed first in the vicinity of the hypophysis, escaping detection. Often the tumor was a simple adenoma or an hypertrophy of the hypophysis.

By means of extirpation experiments proof was brought by Biedl, Cushing, Aschner and others that the hypophysis may be divided into three parts according to their physiological importance: an anterior lobe, the pituitary gland, and the posterior lobe (neurohypophysis). The anterior lobe is the most important, and its extirpation leads to apituitarism and death. Partial extirpation of the anterior lobe results in obesity, polyuria, glycosuria, loss of hair, impotence, and atrophy of the testicles and ovaries.

Aschner proved that extirpation of the hypophysis in adult animals caused only minor changes of nutrition with a lowering of general resistance. Young animals showed greater changes, e. g., inhibited growth, loss of muscular power, obesity, separation of the epiphyses, colloid increase in the thyroid, and hypoplasia and atrophy of the genitals. The younger the animal, the greater was the disturbance.

It was demonstrated that functional disturbances of the hypophysis resulted in marked bodily changes, especially in growth and metabolism, and acromegaly was proved to result from hyperpituitarism.

Some authors claim hereditary neuropathic tendencies associated with consanguinity as an etiological factor of acromegaly; and de Cyon reports three cases in three sisters of one family. Schwoner reports a case of a woman of 50 years whose mother also had acromegaly, and was also 50 years old when it developed; the course of the disease in both mother and daughter was the same. In this case it was remarkable that all the members of this family, both on the mother's and father's side, grew to an extraordinary height.

Other observers noticed this fact and the question arose as to what relationship there was between acromegaly and gigantism. Klebs considered gigantism and acromegaly as the same disease. He believed the hypertrophied hypophysis is a constant accompaniment of gigantism. Gigantism could manifest itself as a simple increased physiological growth, or as a disease (acromegaly). He could not see an etiological relationship between hypophyseal hypertrophy and gigantism.

Virchow and Pierre Marie dissented from this view. Marie believed in a complete dissociation of gigantism and acromegaly. In his opinion, gigantism was a physiological process, whereas acromegaly was pathological.

To-day even this view is obsolete. Sternberg showed

that one-fifth of acromegalics are giants, and that a half of all giants are acromegalic. An intimate relation between gigantism and acromegaly cannot be proved; and although gigantism does not result from acromegaly, nevertheless, there is evidence that gigantism frequently accompanies acromegaly—it forms a predisposition to acromegaly. There is sufficient ground for the belief that certain constitutional causes can lead to the development of acromegaly.

Both of the author's cases show no signs of gigantism. Nevertheless in these cases, as in acromegalic giants, the etiology of this disease cannot be ascribed to a well defined change of the hypophysis. The similarity of the course and symptoms, and especially the results of the genealogical investigation bespeak for the fact that a constitutional substratum, plus the possibly cumulative effect of a neuropathic tendency, led to the development of acromegaly in the reported cases.—L. N.

(THYROID) Hyperthyreoidismus bei Kriegsteilnehmern, neurogenen Entstehung dieser Krankheit. Rothacker (A.)
Münch. med. Wchnschr. 1916, lxiii, 99.

Opinions as to the origin of Basedow's disease may be divided into two classes: the thyrogenous, as advanced by Moebius, and the neurogenous, as promulgated by Oswald.

The research on enzymes as conducted by the pupils of Abderhalden points to the former theory. They have concluded that Basedow's disease means not only a disordered function of the thyroid, but also that of the thymus and generative glands, inasmuch as goitrous serum strongly affects an exophthalmic goiter, and in relatively few cases even the normal or hypertrophied thyroid. At the same time there is a distinct atrophy of the thymus and generative glands. Lampe believes that hyperthyroidism involves the branchiogenic organs in their entirety. The author believes that it would be desirable to investigate the effect of goiterous serum on the nerve substance, and also to determine which organs would be affected by this serum in "nervous" or neuropathic individuals.

The majority of investigators to-day believe in the theory of Moebius. A close study of the histories of some cases of Basedow's disease will undoubtedly lead to the conclusion that this condition is of nervous origin. Oswald lays stress on the fact that all persons do not respond to a hyper-secreting thyroid with symptoms of Basedow's disease; a predisposition to this disease is necessary, and the genetic factor lies in the nervous system. It is in this manner that the thyroid secretion causes Basedow's disease in persons with an impaired nervous system. Mental strain or continuous excitement is an exciting cause. The primary cause is a

weakened nervous system (of no direct connection with the thyroid), and the struma is a secondary symptom resulting from the thyroid secretion. The thyroid receives its impulse from the nervous system of which it is physiologically a part and acts through a specific substance as an intensifier.

The author then gives histories of three patients in civil life, which show as the result of fatigue and overexertion, and mental excitement, not only a remarkable thyroid enlargement, but also typical Basedow's disease. The pathological manifestations receded immediately the disturbing elements were removed and the patients returned to their normal conditions.

Rothacker then cites three cases from military life, which showed an acutely developing Basedow's disease caused by the nerve concussion, the excitement of machine-gun fire and trench warfare. After a rest of several months all three cases made an uneventful recovery.

Many similar cases were seen by the author. These were often at first considered as "heart disease," but a close study of their histories reveals typical "acute Basedow's disease." These subjects are unfit for field service in modern warfare, as the exhausting long marches in water-soaked districts, the continuous fighting, and the forced marches by night and day caused overacting hearts, slight rises of blood pressure and "nervousness." Neither enlargement of the thyroid nor exophthalmos could be observed after exertions of short duration. It is noteworthy that many soldiers informed the author that at the time of greatest excitement in the field they had more frequent desire to urinate and daily polyuria as compared with peace times. Injury to the hypophysis may be excluded. Such conditions are known to happen in nervous states, but nothing definite is known of the cause.

The author cites these cases to support the theory that many cases of Basedow's disease are of nervous origin, and especially in these cases of soldiers, who develop these symptoms after great mental excitement, and return to normal as soon as the offending cause is removed. This proves, to the author at least, that these cases are of nervous and not of thyroid origin.

As a related subject, Rothacker recalled certain experiments of Abderhalden. He found that the serum from nervous or neuropathic patients, and also those with enlarged spleens of different origins (typhoid, cirrhosis of the liver, leucemia, etc.) almost always decreased the size of the normal spleen and lymph glands, and the thymus always. These patients showed no signs of Basedow's disease. He suggests that Abderhalden's experiments be used to investigate the origin of Basedow's disease.—L. N.

THERAPEUTIC EXPERIENCES

OVARIAN Extract, Therapeutic Application. Morley (W. H.) Jour. Mich. State Med. Soc. (Grand Rapids) 1916, xv, 372.

After describing briefly the anatomy and physiology of the ovary, Morley emphasizes the fact that the three divisions of the ovary, i. e., the follicular apparatus, the corpus luteum, and the interstitial gland, do not have their functions sharply defined, the one from the other. At times they all work in perfect harmony in carrying out the internal secretory power of the ovary. Exact histological studies have shown that menstruation and ovulation do not occur synchronously, as was formerly supposed, but that ovulation occurs in the interval, ten days before the menses are ushered in. Up to recent times, the ovary has failed to yield the active principle of its internal secretion. Morley states that practically no results have been obtained therapeutically except with the desiccated product. During the last year a water soluble powder was obtained from the corpus luteum. The most common indication for the use of ovarian extract is furnished by the troublesome symptoms of the menopause, such as flashes of heat or cold, insomnia, nervousness, etc. It is surprising what relief may be given by the use of desiccated corpus luteum, properly administered. One great advantage in this medication is that it does no harm if no relief is accomplished. As far as can be learned from the use of the soluble product, relief may be obtained in less time and with fewer doses, and it will be more permanent than with the dried gland. Perhaps the action of the gastric juice has some effect upon the efficiency of the product. At all events it is always better to use the active principle, where it can be obtained, than to trust to the action of the entire gland with its varying amount of inert substances. Morley also states that the use of either the desiccated product or of the soluble extract is often productive of good results in amenorrhea or in scanty menstruation. He believes that the failure to obtain good results in many cases in which the entire gland is given may be explained by the results of Seitz, who found that the corpora lutea of beef ovaries contain two antagonistic bodies which he called luteo-lipoid and lipamin. The former of these substances was found, when subcutaneously injected, to lessen the flow and shorten it. The second, lipamin, caused an increased growth of the internal and external genitalia in animals, while in women, by subcutaneous injection, it will cause the menses to appear in amenorrhea. In the young corpus luteum there is more lipamin, and the flow appears. Later

the luteo-lipoid has the upper hand, and the menses stop. This goes to show that until the active principles of the ovary are isolated beyond peradventure of a doubt, its therapeutic use will be more or less problematical.—E. N.

(GRAVES' DISEASE) Disease and Electrical Treatment.

Hernaman-Johnson (F.) *Lancet* (Lond.) 1916, ii, 920.

The X-ray is most efficient in the treatment of Graves' disease. The best results follow the application of the ray at frequent intervals, not less than three times a week in mild cases; in acute cases, daily. Hard rays, filtered through aluminum, should be used. Pain, anxiety, fatigue, constipation and dental trouble are given as possible causes of failure.

A portable apparatus may be carried into a private house if the patient is acutely ill; bedside applications of the ray in the early stages of acute exophthalmic goiter would save many lives.—W. B. T.

(PITUITARY) Ueber die Wirkung des Hypophysenextracts bei Thyreosen. Pal (J.) *Deut. med. Wchnschr.* (Berl.) 1915, xli, 1537.

The extract of the infundibular portion of the hypophysis (pituitrin, pituglandol, etc.) produces effects on hyperthyroidism or Basedow's disease of no mean therapeutic value. Prof. Pal's experiments were based on the use of pituitrin, to which he was led by the contradictory results of pituitrin and thyroid extract upon the arteries. It is still a moot question whether substances like pituitrin, pituglandol, or glanditrin circulate as such in the blood and have any effect.

The extract of the infundibular portion of the hypophysis was used in 16 cases of Basedow's disease and hyperthyroidism; different reactions were observed. At first 15 to 30 minims were given. Although remarkable results were obtained, subcutaneous injections were given instead. The author's interest was then attracted to the cases of cachexia with low blood pressure and signs of severe intoxication.

Of nine unoperated patients, seven gained in weight and improved subjectively and objectively, showing abatement of the restlessness, tremor, and sweating. The exophthalmos was improved very little or not at all. Tachycardia was only slightly improved, to return when treatment ceased. The most noteworthy effect was that the patients felt so much improved subjectively, that they requested that the resumption of the treatment whenever it was discontinued.

Three case histories of Basedow's disease are presented. Each was in such a reduced condition that an operation was inadvisable, and treatment with hypophyseal extract was tried. They improved but the thyroid became enlarged simul-

taneously, and later resections were done. In two cases the structure of the thyroid seemed to change with the decrease of the pulse frequency. The histological picture leads to the belief that the pituitrin injections inhibit the hypersecretion of the thyroid into the blood, and also that they do not prevent the escape of the secretion from the follicle, but even favor it, so that at the expense of the follicle the thyroid enlarges. This seems to be contrary to the findings in healthy animals.

In human beings with apparently normal thyroids, in whom pituitrin, pituglandol, glanduitrin or hypophysin were injected experimentally for cachexia or malnutrition of different origins (tuberculous, gastric or nervous disorders), no appreciable influence on the structure of the thyroid could be traced, although an occasional beneficial effect was seen on the nutrition. However, this may be due to the tonic influences of the pituitrin on the smooth muscle of the digestive tract. The influence on gastric secretion might also be considered, but nothing positive was noted.

It must also be mentioned that no effect was noticed on the normal or hypertrophied thyroid. The change is noticed only in those cases where the internal secretion is disturbed, especially in Basedow's disease during an exacerbation, and in hyperthyroidism. In the latter group, pituitrin gave most remarkable results, as was shown by a reported case of thyroid atrophy with symptoms of hyperthyroidism (intoxication). A few injections of pituitrin not only relieved the severer symptoms but, also, in a few days caused a visible increase of growth in the previously completely atrophied thyroid. It saved an almost hopeless life as if by magic. This teaches us that subcutaneous injections of pituitrin can arrest an atrophy of the thyroid associated with hypersecretion.

The rapid relief from thyreotoxic symptoms leads to the belief that the thyroid secretion is in some way inhibited or decreased by the pituitrin; at least it may be influenced in such a way that the secretion does not reach the circulation in the same amount as before. It must also be observed that the thyroid grew in size with the formation of nodules. We must conclude that there was an increased follicular secretion, and this explains the fact that the formation of colloid and the secretion of thyreotoxin has two opposite functions in the circulation. It should also be noted that the extract of the infundibular portion of the hypophysis has an inhibitory effect upon the irritated glandular epithelium of the thyroid.

The author claims that his experiments explain the beneficial effects of hypophyseal extract in Basedow's disease, and that it is due to an abatement or arrest of the symptoms of thyroid intoxication. A complete disappearance of the symp-

toms in pronounced cases of Basedow's disease was not observed. This form of treatment did not work as well in other cases, where, as in one case, 20 drops by mouth and one injection had no effect, and in another chronic case the improvement was relatively slight.

Another case of Basedow's disease following iodine therapy, was that of a man with arteriosclerosis. He improved under pituitrin, but the injections were discontinued after the appearance of arterial spasms, resulting in gangrene and ending in death from myocarditis. The author believes that the arterial disease was aggravated by the treatment, as in these conditions symptoms of hyperthyroidism usually supervene, and, therefore, he counsels caution in the use of pituitrin in these cases.

Occasionally increased blood pressure has resulted from the subcutaneous injections of pituitrin, but no ill effects were observed. The treatment of hyperthyroidism with pituitrin must be governed by the individual reaction, as effects have been observed from 0.2 to 0.3 gram of the dried hypophyseal extract in one case, which could be equalled in others only by very much larger doses.—L. N.

PITUITARY; Ueber Kachexia hypophysaren Ursprungs.

Simmonds (M.) Deut. med. Wchenschr. (Berl.) 1916, xlii, 190.

Simmonds reports a case, similar to the one he reported two years ago: A shoemaker, of negative past history, has steadily become weaker, thinner, and pale for the past two years. He constantly felt cold and finally had to discontinue his work. Despite careful and frequent examinations, no organic disease could be discovered. The blood count showed hemoglobin 60 per cent., erythrocytes numbered 3,500,000, and leucocytes 4,600. The differential count was lymphocytes 47 per cent., polynuclears 48 per cent., and eosinophiles 5 per cent. The temperature showed an occasional twenty-four hour rise. For months this was the only finding, and as the cachexia constantly increased, the diagnosis of a cryptic carcinoma was made. Only the eight days preceding death, caused by pneumonia, showed a continuous rise of temperature.

The autopsy findings were disappointing. Outside of the pneumonia and pericarditis, nothing abnormal was found in the chest and abdomen. The liver was enlarged, and the bone marrow and heart muscle were negative for pernicious anemia. The head, however, showed the seat of trouble. On removing the brain, there was noticed a tumor, the size of half a hazelnut, grayish white in color, corresponding to the hypophysis; separated from it by the sella turcica was an equally large second tumor, taking the place of the hypo-

physis. The sella turcica was much enlarged, smooth, and the optic nerves were displaced by the mass. Between the two masses (resembling an hour-glass) no recognizable remains of the hypophysis were seen. Microscopically the tumor proved to be an adenoma.

Although this was a benign tumor, nevertheless, by its encroaching size, it destroyed the hypophysis, and produced cachexia. The tumor did not cause acromegaly because of its basophilic character. The testicles and prostate, however, were distinctly atrophic, and the hair of the face and public region were very thin, but otherwise distinctly masculine characteristics were retained.

The second case cited by the author was that of a girl, 9 years old, with a history, autopsy and microscopical findings practically identical with the first case.

The remarkable fact of the three cases was the extremely severe chronic cachexia ending fatally, for which the most painstaking study showed no explanation. The only pathological finding of the three cases was a total destruction of the hypophysis, twice from a neoplasm, and once from an old embolus. Therefore it is assumed that the cachexia followed the destruction of the hypophysis, and the resulting absence of its secretion. This has not been previously noted, because there are so many complicating symptoms and diseases to this affection of the hypophysis, that the cachexia was either overlooked, or at least was not considered seriously enough, nor emphasized. The true relationship can only be seen in cases where there are no veiling circumstances. In fact, the cachexia appears only after total destruction of the hypophysis, and as long as only a part of it is left, the symptoms due to the loss of the secretion will not appear. The same rule holds as in the other organs of internal secretion.

If the author's premises are correct, that there is a cachexia due to the absence of the hypophyseal internal secretion, then follows the conclusion, that in all cases of cachexia of unknown origin, the administration of hypophyseal extract is indicated as a therapeutic trial.—L. N.

(PITUITARY) Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandlung mit Hypophysenextract. Hoppe-Seyler (G.) Münch. med. Wchnschr. 1915, lxii, 1633.

The author cites a case history with elaborate charts, showing the effect of pituitrin on the quantity of urine passed, the amount of fluids ingested, the specific gravity of the urine, and the percentage of its salts.

The picture is undoubtedly one of diabetes insipidus; other conditions with which this disease might be confounded

are ruled out. Polyuria from the excessive ingestion of fluids is differentiated by the specific gravity remaining low independently of the amount of food and drink taken. The oliguria resulting from atropine administration is demonstrated to be due to the fluid collecting in the body (shown by the weight of the patient on the chart). This proves that the polyuria is controlled by the vasomotor nervous system, and not by the disturbed kidney cells. Of course, rise of blood pressure and hypertrophy of the left side of the heart are absent.

The condition is analogous to polyurias observed in disturbances of the central nervous system, as irritation of the floor of the fourth ventricle. A tumor or chronic meningitis (cerebrospinal syphilis) was ruled out because of the negative Wassermann reactions of the blood and spinal fluid.

The following signs pointed to involvement of the hypophysis: Marked panniculus adiposus, loss of sexual power, loss of hair, and a remarkably prompt reaction to even such small doses of pituitrin as 0.25 gram resulting in a normal excretion of urine, sweat, and saliva, which were subnormal before the injections. It might be claimed that the resulting increased eliminative powers of the kidneys cannot be used as a diagnostic measure, as such an effect can also be observed in healthy persons, and even in certain chronic nephritics. In the latter cases, however, this phenomenon was not so marked. At any rate, there is never such a rapid rise of the specific gravity and salts as there was in this case. Besides, the general well-being, the saliva and sweat, and the appetite were so much improved by the very small dose of pituitrin, that an observer must admit that just that little pituitrin was missing to restore normal conditions. As the internal secretion was absent, and as it is elaborated by the hypophysis, the author believes that an insufficiency of that gland is the underlying cause, and that all signs point against the opinion that diabetes insipidus is due to an irritation of the gland, resulting in hyperfunction.

Nothing can be said as regards the nature of the hypophyseal changes. The X-ray shows the sella turcica plainly, with no modification in size or any other change. In regard to a chronic inflammation with increased connective tissue, nothing is noted, and signs of lues and tuberculosis are absent.

As to the therapy, it is well known that by limiting the ingestion of salt and fluids, we can decrease diuresis and the excretion of metabolic products. This was avoided in the treatment of this case. Pituitrin by mouth gave no results, nor did pituglandol, both internally and subcutaneously.

The author claims, therefore, that subcutaneous injections of pituitrin have a curative effect on diabetes insipidus, acting like thyroid extract in myxedema. He believes the

effect of pituitrin to be due to the compensation that is established by supplying the internal secretion which is wanting in this disease, and that diabetes insipidus should be considered as the result of an insufficient function of the hypophysis.

L. N.

(PITUITARY) Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandlung mit Hypophysenextract. (cont.) Hoppe-Seyler (G.) Münch. med. Wchnschr, 1916, lxiii, 47.

In the confirmation of his previous remarks on this subject (see item commencing on page 265 of this issue), the author mentions some of the references to the literature on this subject outlining the essentials of these reports:

As a result of pathological, anatomical, and experimental observations, Magnus and Schafer concluded that there was a hyperfunction of the hypophysis in this condition. Romer showed by animal experimentation, and by a clinical study of a case of diabetes insipidus resulting from a basal brain tumor with involvement of the hypophysis, that there was a hypofunction of the hypophysis in this disease. Von der Helden investigated the effect of hypophysis extract upon renal action in a number of cases including diabetes insipidus, and found decreased diuresis; nevertheless he (and Humber) does not believe that the action of pituitrin is responsible for hypofunction of the hypophysis. Farni also found decreased diuresis after giving pituitrin. Lately v. Konschegg and E. Schuster proved experimentally that the pituitrin injections caused first an increased then a lessened diuresis. They as well as Graul have noticed improvement in cases of diabetes insipidus, and therefore concluded that there was a hypofunction of the gland. F. Kleeblatt reports an interesting case of diabetes insipidus following a skull injury with loss of the polyuria, also the persistent thirst and excessive perspiration, after the administration of hypophysis extract. In this case the hypophysis was intact, the cause of the condition being an irritation of the floor of the fourth ventricle. This case demonstrates that the giving of hypophysis extract, with its results on the whole clinical picture, can be used as a means of differential diagnosis in disease of the hypophysis.

L. N.

(CORPUS LUTEUM) Menopause, Study of Vasomotor Disturbances. Culbertson (C.) Surg. Gyn. & Obs. (Chgo.) 1916, xxiii, 667.

Fundamentally this study resolves itself into a consideration of the interrelationships of the entire system of ductless glands. The author considers that the withdrawal of the secretion of one or more of these will result in discord, just

what happens at the climacteric due to the cessation of ovarian secretion.

The varied pictures presented by patients passing through this period are explainable by the predominance or subjection of different units of the complex endocrine system. Thus many present pictures resembling hyperthyroidism, a few may suggest myxedema, and others may suggest a tendency toward acromegaly, to dystrophia adiposo-genitalis, etc. The climacteric is monoglandular only in its etiology; in its manifestations it is distinctly pluriglandular. As the ovary decreases in activity the thyroid may maintain its usual action or may vary from insufficiency to excessive action.

Culbertson intimates that in some cases the endocrine glands other than those just mentioned may be affected, the adrenals, parathyroids or even pineal may enter into the situation; in short, the menopause may present as many different aspects as there may be single glands or combinations of them. An important factor is emphasized as being nearly always present, hypertension. It was present in all but four of Culbertson's cases. While the tension is elevated it is also unstable, being affected by relatively minor influences. It presents another peculiarity, the diastolic pressure is not so proportionately high as the systolic, and the pulse pressure is characteristically irregular but increased. This it is believed may be due to overactivity on the part of the adrenals and pituitary following cessation of ovarian activity. This being the case it is suggested that corpus luteum should neutralize the pressor substances and tend to decrease tension, and, in fact, this seems to be the case for excellent results have followed this treatment in the hands of the author in many cases. He prefers an extract made from the ovaries of pregnant animals. The effect on blood pressure is not merely a consistent reduction, but the systolic and diastolic pressures tend to assume a more nearly normal relation. Emphasis is laid on the need for frequent blood pressure readings in cases of this character.

(ADRENALIN) A Simple Procedure for Nasal Hemorrhage.

Lapat (W.) Jour. Am. Med. Assn. (Chgo.) 1916, lxxvii, 1159.

Lapat reports that spontaneous recurrent epistaxis is usually due to ulceration over capillaries or a vessel in the anterior nares, but at times it is difficult to locate the precise area from which the hemorrhage comes. This difficulty may be overcome by an application of adrenalin solution to the anterior portion of the septum. This blanches the whole mucosa except at the spots which give rise to the bleeding. These then stand out clearly against the pale surface as red, circular areas. The treatment is cauterization of these spots with ninety per cent. trichloroacetic acid.

(ADRENALIN) Certain Reactions following Intravenous Injection of Salvarsan, Symptoms and Treatment. Beeson (B. B.) *Med. Rev. of Reviews* (N. Y.) 1916, xxii, 881.

In the course of his consideration of the untoward incidents occasionally following Salvarsan or Neosalvarsan treatment, Beeson lends emphasis to the importance of the so-called "nitroid crises." The headache and diarrhea found in certain cases as well as serous apoplexy, indicated that there would seem to be a marked vascular dilation, and a vasoconstrictor remedy naturally would be thought of. According to Beeson adrenalin chloride solution (1:1000) is the best remedy for this condition and its effect is very satisfactory, at times even brilliant. The minimum dose should be one mil. representing one milligram of pure adrenalin. As much as four milligrams have been given in divided doses injected deeply into the gluteal muscle.

When given subcutaneously the effect is more transitory, while the intravenous route is reserved for more serious cases, as in apoplexy.

Beeson advises the injection of adrenalin ten minutes before the Salvarsan is given. The patient shortly becomes quite pale if the drug is exerting its effect and this "leuco-reaction," as it is called, is an index of the efficacy of the adrenalin in the case under treatment. The pulse is increased and there is a more or less generalized trembling, but these effects are of brief duration save perhaps of some local pain at the site of the injection.

Attention is called to the fact that flushing of the face during the injection of Salvarsan or Neosalvarsan should be an indication for stopping the procedure at once and the administration of one milligram of adrenalin.

In his conclusions Beeson heartily recommends adrenalin in all these cases. He states that it has been of real value, while the untoward effects following its use are almost nil and the benefits derived are often great.

MAMMARY Extract in the Treatment of Menorrhagia. Von Zelinski (W. F.) *Amer. Jour. Clin. Med.* (Chgo.) 1916, xxiii, 915.

Von Zelinski, of Chicago, calls attention to the therapeutic virtue which is apparently present in mammary extract, and reports favorable results following this method of treatment of preclimacteric uterine hemorrhage.

One of the cases outlined was an unmarried woman of 32 with a well defined case of dysovarism with no indication whatever of any organic change or neoplasm. The patient flowed two or three weeks at a time with intervals varying in length from two to three weeks. After approved methods of treatment had been tried and had failed—including curet-

tage and the use of styptics—mammary extract was given in five-grain doses three times a day for two periods of two weeks each. The hemorrhage was relieved “in a most satisfactory manner” and further experience confirms this author’s faith in this somewhat neglected phase of organotherapy. According to von Zelinski mammary extract “is one of our best remedies for the control of functional hemorrhage due to ovarian dysfunction.”

THROMBOPLASTIN, A Further Report on its Hemostatic Value. Hess (A. F.) Jour. Am. Med. Assn. (Chgo.) 1916, lxxvii, 1717.

Hess refers to his report given about a year from the New York City Department of Health, and a little later another report on the same subject from Cronin, both published in the Journal A. M. A., on the experimental work done with thromboplastin as a hemostatic. During the past year Hess has continued his clinical experiments at the Research Laboratory, Department of Health, New York City, along this line together with laboratory tests to determine more fully the various properties of thromboplastin.

Thromboplastin solution has been supplied to several of the maternity hospitals of New York City, where it has been employed locally in cases of melena neonatorum, in bleeding from the cord, skin, mouth, vagina, etc., and also as a dressing where there was undue hemorrhage following circumcision. Thromboplastin should be applied directly to the bleeding area; clots should first be removed. Hess reports the following results from his latest investigations: Tissue juice made from brain (thromboplastin solution) has proved itself of practical value in controlling hemorrhage wherever it can reach the site of bleeding. In cases of true hemophilia it may be regarded almost as a specific hemorrhage. It is to be recommended for local use in the bleeding of the new-born, in nasal hemorrhage, and in the parenchymatous bleeding associated with various operations, etc. Where local applications fail, it should be injected into the site of hemorrhage, as in bleeding from the gums following tooth extraction. This method can readily be resorted to, as thromboplastin solution loses but little of its potency as the result of dilution and cursory boiling.

(PITUITRIN) A Record of Personal Experience with Appendicitis. Ehrenfried (A.) Am. Jour. Surg. (N. Y.) 1916, xxx, 289.

In his personal report Ehrenfried tells of having recently acquired the habit of using pituitrin to forestall or relieve distention following abdominal operations, and he has given as many as six or more ampuls in twenty-four hours in severe

cases, always, it seemed to him, with benefit. He has not refrained, however, in cases of severe distention from using the time honored methods of stupes, drastic enemata and gastric lavage in the rare instances when they have been indicated. Moderate stimulation has been given when necessary, and morphine has been avoided.

(THYROID) Epilepsy. Drysdale (H. H.) *Ohio St. Med. Jour.* (Columbus) 1916, xii, 802.

In the course of a general discussion on the subject, Drysdale remarks that a considerable number of cases of epilepsy present symptoms of endocrine disorder. These stand out more or less prominently and it is quite probable that the internal secretions exercise some relationship to this disease.

Among the suggestions as to treatment, Drysdale includes the administration of thyroid extract and states that in some instances this "has true therapeutic worth."

CORPUS LUTEUM, Experience with Soluble Extract. Royston (G. D.) *Interstate Med. Jour.* (St. Louis) 1916, xxiii, 1119.

Royston observed the effect of soluble extract of corpus luteum in forty-seven patients, embracing the following conditions: Nausea and vomiting of pregnancy, sexual neurasthenia, sterility, amenorrhea, oligomenorrhea, dysmenorrhea, menorrhagia, metrorrhagia, premature and artificial menopause. The majority of patients showed marked improvement; the substance acts most favorably in menstrual disturbances, which are usually permanently relieved by a few weeks' treatment. The writer recommends that patients with severe symptoms receive one to two mls. intravenously every second day.—L. F. W.

(PARATHYROID) Research in Epilepsy. Knox (H. A.) *New York Med. Jour.* 1917, cv, 406.

The author mentions the pituitary, thyroid and adrenals as factors worth considering in connection with epilepsy, and reports, in passing, on 30 cases treated with dry parathyroid gland and calcium lactate. The initial dose was 2 grains of parathyroid 3 times a day. It was increased by two additional grains per dose each month. The calcium lactate was given in saturated solution and started with a daily dose of one fluid-drachm. Fairly good results were obtained.—J. D.

KEPHALIN to hasten Coagulation and Hemostasis after Surgical Operations. Cecil (H. L.) *Jour. Am. Med. Assn.* (Chgo.) 1917, lxviii, 628.

The use of the brain phosphatid, kephalin, as a local hemostatic in genito-urinary surgery is recommended by this

author who writes of the results following this method of treatment at the Johns Hopkins Hospital.

Sufficient kephalin is dissolved in an excess of ether, about a 5 per cent. solution being made, and this concentrated kephalin solution is poured over gauze strips 6 feet long and 6 inches wide. The packs are then folded, rolled, wrapped in two muslin covers and sterilized in the steam autoclave for 10 minutes.

Kephalin coated catheters are prepared as follows: A very concentrated solution of kephalin in ether is made and smeared on the terminal 3 inches of a large gum coudé catheter, the tip end eye of the catheter being left uncoated. This coating is best secured by allowing the solution of kephalin to drop on the catheter, which is being revolved at the same time. It is then sterilized in a glass tube by steam in an autoclave. A large amount of kephalin is thus brought into direct contact with the cut surface at the vesical orifice.

The hemostatic results were referred to as "striking," as there was practically no bleeding at all where the kephalin impregnated gauze was applied to the bleeding surface.

(ADRENALIN) L'insuffisance surrénale dans la paludisme.
Paisseau (M.) and Lemaire (G.) Presse Méd. (Paris) 1916, xxiv, 545.

The severe complications of malaria, such as coma, and the algid and choleric symptoms, are said to be of adrenal origin. Acute degeneration of the adrenals has been revealed at autopsy in such cases. This knowledge explains many of the clinical features of malaria, especially the changes in blood pressure, lumbar and abdominal pains, vomiting, diarrhea and the severe asthenia. According to these authors adrenalin should take its place next to quinine in the treatment of the severer malaras.—H. R. H.

[PITUITARY Therapy in Diabetes Insipidus.] Rosenfeld (J.)
Mediz. Klinik (Berl.) 1916, ix, 2521.

In a report of the January (1916) meeting of a Schleswig society Rosenfeld mentions the favorable effects of pituitary injections in diabetes insipidus. The polyuria was markedly diminished, especially when the sodium chloride intake was reduced, though with the use of salt the pituitary therapy made a great difference. Administration by mouth was just as effective as by injection. At the same meeting Frank stated that in his opinion diabetes insipidus was due to hypophyseal hyperfunction, despite the fact that in some cases good results follow pituitary therapy.—J. D.

ENDOCRINOLOGY:

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

JULY-SEPTEMBER, 1917

EDITORIAL ARTICLES

CLINICAL ENDOCRINOLOGY

THE important disease-pictures due to disturbances of the internal secretions were recognized by the clinicians as syndromes before their pathological anatomy and physiology were understood. Thus Graves' disease, myxedema, and Addison's disease, were all recognized and described as clinical entities by the clinician before they were known to be associated with disturbances of the internal secretions. Diabetes insipidus has long been known to the clinician, but only recently has it been recognized as a disturbance of the internal secretion of the hypophysis cerebri.

Some of these syndromes probably will be broken up into smaller groups. The syndromes known as Graves' disease may arise from several different lesions of the thyroid gland and possibly from lesions originating outside the gland. Pathological anatomy has already done much and will do more to clear up

the obscurities that exist. The anatomist and the histologist bring us information that may seem dry at the time, but one can never tell how soon it may have great clinical significance and importance. The experimental surgeon, the experimental pathologist, have already done a great deal in the study of these conditions and are still active. Later, the pharmacologist and the chemist began to come to our aid. They showed us how to separate specific substances from these endocrine organs. Now adrenalin and pituitrin are familiar to everyone. In the future we may expect much more from the chemist and the experimental pharmacologists. The chemical constitution of the active substances in the internal secretions will gradually be worked out. Then we shall learn how to synthesize these substances, so that the animal source will become unnecessary.

So, it is very desirable that all those who are interested in the internal secretions,—clinicians, surgeons, pathologists, anatomists, pharmacologists, chemists,—should be bound together in such a way as the “Association for the Study of the Internal Secretions” proposes.

Only by the careful gathering of the facts, and the arranging of these facts according to their similarities and sequences, shall we ever get at the general laws that underlie endocrinology, so that we shall be able to make accurate diagnoses, to prognosticate safely, and gain the power to control. For not only do we desire to be able to understand diseased conditions; we wish also successfully to treat people who are ill, and to prevent people from becoming ill.

REACTIONS OF THE THYROID GLAND TO
NOXIOUS AND DIETARY INFLUENCES

AS has long been recognized there is wide variability in the microscopic appearance of the thyroid even within supposedly physiologic limits. It reacts quickly to relatively slight variations of the body metabolism and consequently may show detectable histological changes even daily. Marine and Lenhardt ('09) distinguish as "physiologic" the following: (1) normal resting glands with low cuboidal epithelium; (2) hyperactive glands, with hyperemia, cells becoming hyperplastic and columnar, colloid disappearing; (3) colloidal glands (stage of recovery) in which conditions return to (1) with abundant colloid. In case, however, of over stimulation without adequate rest the colloid disappears and the cells die of exhaustion, becoming progressively degenerated and desquamated and showing various degrees of disintegration. In this case the nuclei are enlarged, often stain densely and vary in appearance. Similar desquamation and degeneration of the epithelium are said to occur in normal senile atrophy. At times the vesicles are small and irregular with projections into their cavities and the lining cells tall columnar. This, the hyperplastic stage, is normally associated with paucity of colloid.

This hyperplasia is commonly regarded as an expression of augmented activity but Marine and Lenhardt regard it as a compensatory reaction, giving an excess of physiologically inefficient secretion. That this interpretation is correct is indicated by the fact that puppies from mothers with hyperplastic glands, at birth have overgrown thyroids, a reaction due,

supposedly, to thyroid deficiency in the maternal blood stream. (Carlson '13.) A similar hypertrophy is observed in puppies from mothers from which a large part of the thyroid is removed. (Halsted, '96, Marine and Lenhardt, '09.)

By the administration of iodine the hyperplastic thyroid can readily be converted to the colloid type. (Marine and Lenhardt, '09, Bensley, '16.) On the other hand Bensley has found that when animals (opossums) captured in a wild state are brought under domestication the thyroids promptly change from the colloid to the hyperplastic condition. This result is supposedly due to change in diet—probably to increased ingestion of protein.

Effects of Diet. Watson ('09) has reported a somewhat extensive investigation of the variations in the thyroids of rats with particular attention to the effects of various diets. Four types of glands were described. In the first the vesicles are large, the colloid normal, and the cells are flattened and have darkly stained nuclei. In the second type the follicles are smaller, the cells cuboidal, with relatively little cytoplasm and with rounded nuclei. In the third type the follicles are small, the cells large with abundant cytoplasm, and the colloid has but slight affinity for stains, a condition which other observers have correlated with dilute consistency. In type four the cells are detached and distorted with pycnotic nuclei and cytoplasm variable in quantity and structure. In forty wild rats three fourths had glands of types I and II. Of these types Jackson ('16) regards I and II as probably due merely to deficient diet while the fourth corresponds to a degenerative type such as has

been recognized by a number of observers as fairly common. Marine regards this type as due merely to autolysis, a process which, on account of the simple architecture of the thyroid, produces changes that are easily recognized. This condition is likely to be seen in any gland in which fixation has been delayed. In a series of twelve rats Watson ('05) studied the effects of an exclusively meat diet. Ten animals showed marked changes in the thyroids such as congestion, degeneration of the follicles and eventually shrinking in the size of the follicles and of the whole gland. These changes were associated with retarded growth, dryness of the skin and falling off of the hair. In another series ('07) ten wild rats were killed as controls immediately after capture and ten were kept for several weeks on a diet of bread and milk. The controls had large colloid-filled vesicles with taller epithelium. As before mentioned, glands similar to both of these varieties may be produced by inadequate diet and the interpretation of the results is correspondingly difficult. In another series ('07) an oatmeal diet was employed for several weeks, at the conclusion of which the thyroids showed marked enlargement. In some cases the cells were swollen and detached.

Douglas ('15) has reported an extensive study of the effects of various diets upon the thyroids of pigeons, chicks, rats and rabbits. He noted glands similar to the various types described by Watson but stated that the histological appearances do not represent different stages of secretion comparable to those of secreting glands engaged in the process of digestion. Under similar conditions and in animals

fed on similar diets the appearances in the thyroid differ markedly. The variation seems to depend to some extent on the nutrition and is thus only in this way dependent on the diet.

Starvation produces a number of changes in the thyroid. On the basis of a review of the literature and extensive investigations of his own, Jackson ('16) states that the epithelium apparently undergoes at first a simple atrophy, which affects the cytoplasm more than the nucleus. The cells become reduced in height with relatively large nuclei. In advanced stages degenerative phenomena (found also to a limited extent in the normal gland) become increasingly evident. The vesicular cells usually are desquamated. The cytoplasm, typically vacuolated in the earlier stages, may become collapsed, deeply staining and more or less homogenous, or may disintegrate, forming an irregular granular mass. The nucleus becomes hyperchromatic, undergoing successive stages of hyperpyknosis, ending in extreme cases in karyorrhexis. Sometimes, however, it undergoes karyolytic changes.

Results very similar to these have been described in the thyroids of subjects that have suffered from severe burns (Valentine, '08.)

When animals are subjected to hemorrhage the thyroids, according to Wanner ('99) undergo characteristic changes. The epithelial cells become flattened, some of them enlarge and acquire a store of intracellular colloid and many of them disintegrate. These appearances were regarded as evidence of enhanced secretory activity but probably should be interpreted as degeneration changes.

The effects of various sorts of intoxication upon the thyroid glands have been studied extensively,—particularly by Roger and Garnier ('00), de Quervain ('04), and Martini ('13). In cases of acute infection, such as peritonitis or pneumonia, and acute poisoning, as by phosphorus and, possibly, alcohol, changes occur which are regarded by Martini and others as evidence of cell activity whereby the thyroid functions as an "antitoxic" organ. Among these changes are cell proliferation and excessive discharge of colloid. Others regard the changes merely as evidence of toxic thyroiditis,—as essentially degenerative in character. In cases of prolonged subjection to toxic influences in chronic diseases, such as tuberculosis, sclerotic changes in the thyroid have been described.

Despite a great deal of work the essential nature of the functional changes in the thyroid gland under both physiological and pathological conditions remains an open question. As soon as the criteria of secretory and degenerative phenomena are definitely established the whole problem should be exhaustively restudied. In view of the important influence of thyroid secretion upon bodily well being, a clean cut knowledge of all the factors which increase and decrease the functional activity of the gland is greatly to be desired.

THE EXTENT OF THE PRESENT-DAY ENDOCRINE LITERATURE

TO the average non-specialist the magnitude of the present-day literature on the glands of internal secretion is probably not suspected. Even most spe-

cialists, unless they have lately attempted to deal with the literature, would probably underestimate the number of articles recently published. Important contributions are appearing in several languages, scattered through hundreds of medical and scientific journals, books and "proceedings."

Until about 1890 relatively few articles of endocrine interest had been published. A great stimulus to the study of the glands of internal secretion was afforded by the epoch-making work of Brown-Sequard on testicular extracts. Following the publication of his conclusions, investigators everywhere began to study in this field.

In 1912 Biedl, in the second edition of his well-known book, published a systematic compilation of the literature on the internal secretions. He had utilized some 212 printed pages of references, including about 7000 articles, which dealt directly with the endocrine glands. The rapid growth of the literature at this time is evidenced by the fact that during the time that the book was going through the press some fifteen hundred additional articles appeared, necessitating the addition of 41 pages of bibliography. This brought the literature up to 1913. There were then some 8500 titles in Biedl's lists. There is no available record of the number of papers appearing during the period 1913-1916. Judging by the number of articles preceding and following this period, 4000 may be considered as a safe estimate. Despite the unsettled conditions and the handicaps to research throughout the civilized world, there have appeared since January 1, 1916, some 2000 contributions bearing on the endocrine glands. This brings the total

number of articles published up to approximately fifteen thousand, or an average of approximately six hundred articles per year since 1890. The average number recently appearing, however, is over one thousand per year. These vary all the way from the most superficial trash to the most abstruse contributions of the specialist.

A consideration of these facts brings the realization that a continuous, critical, systematic treatment of this voluminous literature is much to be desired. ENDOCRINOLOGY may drop, therefore, into a place already made for it and meet a need that has come to be realized by all who are interested in the various branches of biology and, especially, medical science.

A partial compilation of the nearly two thousand articles which have appeared in the past year and a half has been made in various places, but none approach completeness. "Chemical Abstracts," which is recognized as perhaps the most complete abstract journal in the world, has dealt with some 300 of the articles bearing on the chemistry of the endocrine glands. "Physiological Abstracts" during the same period has included some 500 of them which bear chiefly upon the physiology of the glands. A large number of the nearly two thousand articles have not as yet been abstracted.

Not only is this true, but in no one of the current publications can be found a complete bibliography of them. Of the American bibliographic periodicals, the "Index Medicus" is probably the most complete. Since the end of 1915 this journal has listed some 1100-1200 of the endocrine articles published. The

"Quarterly Cumulative Index" during the same time has listed about a thousand of them. Together these index journals miss the total number published by some 300. These publications besides being incomplete, contain only the reference to the various articles, which oftentimes are in a language unknown to most readers or are in journals inaccessible except to a favored few.

Many individuals during the past few years have voiced objections to the rapidly increasing number of specialized scientific publications. In the face of such figures as these referred to, however, and considering the increasing importance of the subject of endocrinology, it would seem unreasonable to object to a journal devoted to this subject.

The journals on specialized subjects which are now appearing, such as "Brain," "Archives des maladies du coeur, des vaisseaux et du sang," "Archives of Radiology and Electrotherapy," "Journal of Immunology," etc., although some have temporarily suspended publication, have proven a success and developed an inestimable value to those for whom they were originated. ENDOCRINOLOGY should at least do no less.

PRESENT-DAY ENDOCRINOLOGY FROM
THE STANDPOINT OF THE PEDIATRICIAN
NO specialist can be more interested in the newest
advances of endocrinology than the pediatrician.
Cretinism and myxedema with the associated thyroid
involvement; spasmophilia and the parathyroids;
marked inspiratory stridor and sudden deaths sug-
gestive of thymus involvement; collapse during the

course of an infectious disease, suggestive of adrenal insufficiency; all show how vital to the pediatrician is the study of the internal secretions. But when we turn with aroused interest to the vast literature that has accumulated during the past year, we are disappointed. Cases have been reported with typical symptoms suggestive of some endocrine anomaly, but have not been confirmed by post-mortem examination. Some authors have drawn extravagant conclusions from very few cases. In others, observations, to say the least, may be open to various interpretations; in others the gross methods of experimentation have invalidated the results and, finally, a certain hysteria has seized many writers who now attempt to attribute every pathological condition to some change of internal secretion. Were the whole literature of the past year boiled down and distilled, the residue would contain very few concrete, serviceable facts other than those already named.

We are still in a maze concerning almost every organ. Take the thymus for instance. Every study made has been disputed. Status thymo-lymphaticus is a condition by no means settled, for in the majority of cases data essential to the diagnosis are lacking, such as the weight of the thymus or evidences of status lymphaticus outside of the thymus, itself. The weight of the thymus is extremely variable. In a study of 50 still births, not the subject of status lymphaticus, Schridde found the difference in the weight of the gland at birth varied from five to twenty grams. How difficult then is it to draw conclusions from an X-ray picture for instance or from a study of only one case? Is the thymus a gland with

an internal secretion? We are led by Klose, Vogt, and Matti to believe that this gland secretes a substance essential to life or, if not absolutely essential to life, at any rate very important; for thymectomy produces grave changes with all the findings of rickets and additional extensive lesions in almost all organs. Other observers have denied these conclusions flatly and claim that all the changes found by the first observers were due to the poor hygiene in the kennels. So the battle still is waging.

In view of the conflicting opinions, the work of Hammar stands out strikingly. His carefulness and the saneness of his reasoning force his opinions upon us. His work is almost of mathematical accuracy. He has estimated the exact amount of parenchyma, minus fat and connective tissue, by means of serial sections and reconstructions; and in the same way he has determined the exact relation of medulla to cortex. The Hassall corpuscles, he counted. His first important contribution was to show that enlargement of the thymus in thymic death is by no means constant. In 13 out of 14 cases studied, only two were enlarged. Another very interesting paper is an analysis of the mechanical theory of thymic asthma. Up to recent times, it has been assumed that thymic death may be caused by the thymus becoming wedged between the upper part of the sternum and the vertebral column, exerting pressure upon the trachea. Hammar, in a very striking way, reminds us that the thickest portion of the thymus lies at the level of the base of the heart, considerably below the so-called critical point. Thus, any surgical maneuver of drawing the thymus upward could not possibly relieve the

condition but must actually intensify it. Again, the thymus is not forced upward into the neck with each inspiration but recedes into the thorax; so if it produces dyspnea by compression of the trachea anywhere above its thickest part, it would cause expiratory dyspnea rather than dyspnea during inspiration.

Thus Hammar proves that many of our notions about the thymus gland are false. His anatomical preparations, however, indicate that enlarged thymus may exert pressure upon the trachea close to the bifurcation, or on the bronchi, particularly in a newborn child, whose thymus is relatively much broader than at a later period. He does not commit himself however as to whether the thymus does actually compress the trachea at these points.

Hammar's studies indicate to us what we must demand in the future. What we seek is facts, not theories. Rather a few, definite, concrete truths than volumes of hypotheses. It is only by studies such as these that we can hope to make definite progress.

ORIGINAL COMMUNICATIONS

REPORT OF A CASE OF DYSTROPHIA ADIPOSO-GENITALIS

W. W. Roblee, M.D., Riverside, Calif.

THE case report herewith presented is of interest to the student of hypophyseal diseases for three reasons:

1st. As illustrating the fact that a patient may grow steadily worse symptomatically while under intensive treatment for the primary disease, in this instance syphilis, which is causing or has caused destruction or alteration of the parenchyma of a gland. This patient showed improvement in the clinical syndrome only after feeding of gland extract was resorted to.

2nd. The rather brilliant clinical results secured in this case should give encouragement to us in similar cases.

3rd. In this case, which was quite typical of the acquired Dystrophia Adiposo-genitalis of adults, the results achieved came by the use of anterior gland extract only.

These cases show adiposity, genital dystrophy, irritability, somnolence and usually a disturbance of carbohydrate metabolism as evidenced by a high sugar tolerance. The obesity and genital dystrophy are the presenting symptoms. These cases are not uncommon. In explaining these symptoms, Cushing has taught that the lack of bony development was

due to anterior lobe hypofunction; the adiposity, genital dystrophy and high sugar tolerance to a hypofunction of the posterior lobe. These conclusions must be modified in so far as the genital dystrophy is concerned and probably to some extent with reference to other symptoms. The work of both Goetsch and Robertson has shown conclusively that the development and proper conservation of the genital function cannot be secured without the active assistance of anterior lobe secretion. The fact that large doses of posterior lobe substance will cause emaciation and physical weakness gives reason for supposing that a hypofunction of this lobe will cause the opposite, viz., adiposity. Froelich, Cushing, Fischer and others have ascribed Froelich's Syndrome entirely to a disturbance of the posterior lobe. The operative and post mortem findings in these cases have been quoted as confirming this idea. The facts, however, seem to indicate that the new growth, either by pressure or infiltration, involves both lobes with a consequent uncertainty as to which is responsible for the clinical symptoms. If the feeding experiments of Goetsch and Robertson on rats and mice are to be accepted, they prove that both skeletal and muscular growth and genital development are dependent upon anterior lobe substances, whereas the feeding of posterior lobe extract has a retarding influence. Furthermore, when any considerable portion of the anterior lobe of a young dog is removed, if he withstands the operation he later develops a Froelich's Syndrome, whereas, the removal of the posterior lobe is not followed by any such effect. This is very conclusive evidence and my inclination is to ascribe the entire Syndrome to deficiency of this lobe and I feel

that the effects of glandular administration spoken of by Cushing are to be held as a contradiction which will have to be explained as we learn more of this subject or that there were enough epithelial investment cells in his posterior lobe material to give results.

E. L. S.—age 39; married; father died of cardiovascular hypertension; mother now seriously ill with same symptom complex. Denies venereal history. In 1911 I removed an epithelioma from the lower lip.

In spring, 1914, he developed a growth involving the tongue which was diagnosed in the Howard Kelly Clinic, at Baltimore, as syphilis. He received intensive treatment for several weeks, which included twelve injections of salvarsan and continued the use of K. I. more or less faithfully until he came under my observation again, November 10th, 1915. States that weight until two years ago was 190 to 200. Present weight 334; has been gaining in weight past three years; gained 36 pounds in past few months.

Symptoms: Dyspnoea, sleepiness, drops to sleep during a conversation but unable to lie down much at night on account of dyspnoea. A severe bronchitis is present. Irritable, though formerly of a very even disposition. Genital function failed during past six months and now absent. No erection for two months, penis smaller and retracted. During past year great craving for sweets—has eaten an average of half a pound of candy a day in addition to sugar and sweets at meals. During past year averaged urination every two hours at night and four hours in daytime. Quantity not large.

Urine— $\frac{1}{2}$ per cent. albumen by Esbach; otherwise normal. Temperature, 99.6; Pulse, 100, Nov. 28th.

No glycosuria after administration 300 grammes glucose.
Blood pressure—160 Systolic.

Nov. 10th, 1915. Wassermann, positive. Resumed K. I. sat. sol. to be increased to tolerance. Hg. protiodid to tolerance and 30 gr. anterior pituitary gland per day.

Nov. 28th reduced to 27 gr. per day.

Dec. 6, weight 321, not so sleepy in daytime, sleeps better at night.

Jan. 1, weight 317, not so sleepy in daytime, sleeps better at night.

Jan. 17, weight 311½, sleeps from ten to six, well; cough less; can sleep using only one pillow; no sleepiness during day; more energy; dose now 27 gr. per day; complains of slight nausea after last dose of three tablets at night, so advised one less.

Jan. 31, weight 305½, medicine now 40 gtts. K. I., T. I. D. and two ¼ gr. protiodid pills daily; 18 gr. pituitary gland per day divided into three doses.

Feb. 21, weight 303, reports feeling fine.

Mar. 7, weight 300, reports feeling fine.

Mar. 20, weight 300, some mental depression two days; advised to increase K. I. to 50 T. I. D.

Apr. 4, weight 295½, increased K. I. to 1 dr. T. I. D.

Apr. 17, weight 287, some sore throat; advised four 1-gr. pituitary tab. T. I. D.

May 2, weight 287.

May 26, weight 283, reports no dyspnoea, no sleepiness, genital function returned; very slight craving for sweets; reduced pituitrin to 2 tab. T. I. D.; stopped the mercury pills.

Oct. 6, weight 278½, reports everything better.

Apr. 15, 1917, weight 275, feels fine; sleeps well; genital function satisfactory. Attends to business affairs as usual. He is a big fat man but symptomatically well.

DISCUSSION OF THE REPORT OF DR. ROBLEE

Emil Goetsch, M. D., Baltimore: I think it is generally accepted now that the factors of growth and of sex development and function are largely dependent upon the activity of the pituitary body. The posterior lobe, that is including the pars intermedia, its epithelial investment, is concerned in its function with carbohydrate metabolism and with urinary output to a considerable extent. In other words, with pituitary deficiency there is apt to be polyuria, and

high sugar tolerance and with posterior lobe over-activity or after the administration of considerable amounts of posterior lobe the carbohydrate tolerance of the individual is considerably lowered. The urinary output is also reduced in amount. It is interesting to note the rapid loss of weight and the improvement generally and particularly in the genital function after the administration of anterior lobe extract of the pituitary gland. One must be careful in not attributing all the improvement to pituitary feeding for during the same time a very rigid antiluetic treatment was carried out. However, the improvement in the particular symptoms above mentioned is undoubtedly due to the gland therapy.

I am glad to see that the clinical application of our ideas gained from experimental work is being rewarded.

T. Brailsford Robertson, Ph.D., Sc.D., Berkeley:

I am especially glad of the opportunity which I have been offered of commenting upon this case because I think that investigations recently carried out in this laboratory by Dr. C. L. A. Schmidt have already placed in our hands the clue to the apparent contradiction to which the author alludes between the fact that the symptoms of Froelich's syndrome point largely to hypo-function of the posterior lobe of the pituitary body and the fact that these symptoms may be successfully combatted by anterior lobe therapy.

The active principle of the anterior lobe, Tethelin, does not exert any of the characteristic actions of posterior lobe extracts upon blood-pressure or upon the isolated uterus. Dr. Schmidt has found, however, that if Tethelin be subjected for a brief period to the action of strong alkaline, then the mixture of the products of decomposition which results has the characteristic effects upon blood-pressure and the isolated uterus which we recognize as those resulting from the administration of the posterior lobe extracts.

Anatomists have long suspected that the posterior

lobe derives its secretion from the decomposition of raw materials supplied by the anterior lobe. The microscopic structure and spatial arrangement of the glands invites such a supposition. The anterior lobe is provided with two methods of distributing its secretion. The one through the agency of an exceptionally rich blood-supply whereby the secretion of the anterior lobe finds its way directly into the general circulation. The other through the agency of intercellular clefts, whereby the secretion of the anterior lobe drains towards the posterior lobe. The posterior lobe being provided with but a scanty blood-supply the secretion which it elaborates from materials supplied by the anterior lobe reach the circulation slowly and in small quantities, while large amounts of the secretion accumulate in the tissues of the gland. Hence, weight for weight posterior lobe tissue is much more physiologically potent than anterior lobe tissue.

We see therefore that excision of or injury to the anterior lobe must be physiologically equivalent to excision of or injury to the posterior lobe as well, since its supplies of raw material are cut off or diminished at the source; and it will be sufficiently clear why anterior lobe therapy alone may in certain cases act remedially upon hypo-function of both lobes.

THE RELATION OF THE ADRENAL GLANDS TO THE CIRCULATION OF THE BLOOD

By R. G. Hoskins, Ph.D., Chicago

(From the Department of Physiology, Northwestern University
Medical School.)

IN spite of the publication of a considerable amount of evidence to the contrary the idea persists among various clinical writers that the discharge of adrenin into the blood stream plays a predominant role in the maintenance of the circulation. Some phases of the evidence were presented in articles by Professors Vincent and Stewart in the preceding number of *Endocrinology*. In the present communication it is proposed to present a few additional facts bearing on the problem and to discuss some recent work on the relation of adrenin to the distribution of the blood.

That the suprarenal glands are stimulated under certain "emergency" conditions to pour out their secretion in significant amounts has been asserted by several investigators of recent years. Cannon in studying the activities of the alimentary tract had noticed that an outburst of fear or anger resulted in a checking of peristalsis. This might well be due to an outflow of impulses through the sympathetic system, a phenomenon that is well known to occur under such circumstances. The investigator was struck, however, by the fact that the depression of peristalsis persisted for some time after all outward signs of emotion had subsided. Adrenin was known to inhibit peristalsis and the suprarenal glands were known to receive sympathetic fibers. It was suspected then that the prolonged depression of peristalsis might be due to an after-discharge of adrenin.

Testing this hypothesis, Cannon and de la Paz

(1) observed that in animals subjected to violent emotion blood collected from the suprarenal segment of the vena cava gave evidence of an augmented adrenin content. Similar results were obtained by Cannon and the writer (2) when anesthetized animals were subjected to vigorous sensory stimulation or asphyxia. In testing for the presence of adrenin segments of intestine were utilized.

More recently Stewart and Rogoff (3) have been unable for the most part to confirm these observations. They have utilized not only the intestinal segment but also the uterine segment and denervated eye tests. In such experiments the incidental trauma admittedly enters as a seriously disturbing factor. Cannon has recently noted, however, that if the denervated heart be used as a test object the trauma factor can be obviated. In a series of researches soon to be published in the *American Journal of Physiology* he has succeeded in confirming the earlier results. It would seem then to be fairly well established that under emergency conditions the glands play a part in regulating the circulation.

The question then arises: What part do the suprarenals play during periods of ordinary placid existence? A few years ago a satisfactory theory could have been constructed about as follows: An animal deprived of its adrenal glands dies. The blood pressure falls, indicating that the sympathetic system has failed in its function. Injections of adrenal extract cause a marked rise of blood pressure. Therefore, the function of the adrenals is to maintain the tonus of the sympathetic nervous system. This might be designated the "Tonus theory."

The first question that arises when one considers

the theory is this: Is there present in the blood as it leaves the heart enough adrenin to exert any appreciable influence on the nervous system? In the earlier literature occur various statements which indicate that the blood does contain considerable quantities. The concentration is given as, for example, one part in ten millions. But it is interesting to note that as the technique for adrenin determinations has improved the dilution of that substance in arterial blood has constantly approached infinity. The most sensitive of the practicable methods now known is to pass the blood to be tested through the capillary bed of a frog's legs and note the rate of outflow. Trendelenburg (4), a recognized master of this method, has found that the concentration in the blood from the carotid artery of rabbits is at most not more than one part in one or two billions,—a quantity quite without effect in the mammalian circulation, and in Trendelenburg's work the possibility was not wholly excluded that the trace of vasoconstrictor substance found was derived from traumatized blood platelets.

The fact that removal of the adrenal glands is for a relatively long period without effect on blood pressure and that the effect of smaller doses is vasodpression were brought out by Professor Vincent in his article previously mentioned.

In collaboration with McClure (5) the writer tested the tonus theory in another way. If adrenin be injected into a vein at a very small but gradually increasing rate, at first no effect at all is to be seen. Then various changes occur. One of the earliest is depression of intestinal peristalsis. If simultaneous tracings be taken of peristalsis and blood pressure it

is found that the gut is paralyzed before any rise of blood pressure occurs. This observation has been confirmed by Hartman (10). One need not comment upon the futility of an arrangement that could maintain blood pressure only at the expense of gastrointestinal paralysis. Attractive as the tonus theory was, in the light of all the evidence now available, it is no longer tenable.

But the fact remains: Adrenal extirpation is fatal and the final symptoms include a failure of functions that are under sympathetic control. Elliott (6) has offered the interesting suggestion that a minute quantity of adrenin is necessary, not to stimulate but to maintain the irritability of this system. That is, the terminal neurocellular substance of, say, the pressor fibers, in the absence of adrenin is no longer able to transmit impulses to the vascular musculature. This possibility was also investigated in our laboratory (7). It seemed to us that animals at the point of death such as Elliott worked upon are not capable of giving any very significant information. All sorts of secondary factors might have entered into the experiment. If sympathetic failure is a characteristic feature of the syndrome it should appear at an early stage. It was found that at a time when an animal deprived of its suprarenals was showing marked evidence of that fact,—when it could scarcely sustain its own weight,—its vasomotor system responded to stimulation perfectly well. Vasomotor failure, therefore, is a secondary feature. Both cardiac and muscular weakness precede it.

It would seem probable that if a trace of adrenin is essential to its functioning the reactions of the

vasomotor system should be improved if an animal previously deprived of its adrenals were to receive for a while a continuous infusion of very dilute adrenin. In carrying out such an experiment the surprising fact was noted that such infusions often seriously impede the reaction of the vasomotor system to stimulation. In some cases pronounced block was demonstrated (8). This observation which was confirmed many times both in normal animals and in those deprived of their adrenals would seem to dispose of the theory that circulating adrenin facilitates vasomotor functioning.

The possibility remains that minute quantities of adrenin are necessary for the metabolism of other tissues—for example, as Crile (9) supposes, the brain cells. If such were the case—if adrenin failure were the significant feature in suprarenal deficiency—it should be possible by continuous infusion of adrenin solution to preserve the life of an epinephrectomized animal. As a matter of fact no significant prolongation of life can thus be achieved. Laying all theories aside and facing this single fact one can scarcely escape the conclusion that adrenin deficiency plays no essential part in the Addison syndrome or its laboratory equivalent, experimental suprarenal deficiency. Adrenin discharge is apparently then merely a reserve source for use in emergencies.

But as such it is well worthy of detailed study. The fact that different components of the vasomotor system react differently to adrenin makes it necessary to study the effects of that substance throughout the body. This is in effect to determine the influence of adrenin on the distribution of the blood. Such studies, in fact, are needed in cases of various glands,

on account of their possible broad significance in endocrine biology. Theoretically, any hormone might exercise a profound influence upon body functions by shifting the circulation in favor of one organ at the expense of another. This possibility has received little attention at the hands of investigators.

In a series of studies made in our laboratory in the past two years the effects of adrenin in various organs of the body has been investigated. Similar studies have been made during the same period by Hartman of Toronto (10). Since the results of the two series are in general the same they will not be separately considered.

Effects in the Limb. Hartman has previously shown (11) that when the circulation was restricted to extra-splanchnic areas adrenin in dosages that normally would increase blood pressure had a hypotensive effect. This indicates that some extensive structure—presumably the musculature—had reacted by vasodilatation. The literature bearing upon the point indicated, however, that the limbs ordinarily contract under the influence of adrenin. This fact had been taken to show that vasoconstriction was caused in the skeletal muscle. Our investigations (12) showed that when massive doses are employed such vasoconstriction does occur but with all doses that can be regarded as in any way physiologic such is not the case (13). The limb was first placed in a plethysmograph and volume changes noted. It was found that adrenin in all doses generally causes contraction of the limbs and, hence, predominantly vasoconstriction. Occasionally, however, expansion occurs. Removing the skin from the leg converts the contrac-

tion to expansion. Also it was noted that adrenin in all but massive doses—both pressor and depressor—causes an increase in the venous outflow from muscle. It causes, therefore, a vasodilatation in the muscles. On the other hand the outflow from the cutaneous vessels was diminished, hence adrenin causes vasoconstriction in the skin. It is thought that the vasodilator effect of adrenin in skeletal muscle accounts, at least in part, for its beneficial effect in this tissue.

Effects in the Spleen: It was observed that adrenin in all effective dosages causes in the spleen brief dilatation followed by contraction. Occasionally the contraction is followed by a secondary dilatation after the administration of the adrenin is discontinued. The threshold for reactions in the spleen is lower than that of general blood pressure changes. Occasionally a quiescent spleen is stimulated by adrenin to rhythmic contractions. Adrenin causes a brief increase then a decrease in the rate of outflow from the open splenic veins (14).

Effects in the Kidney: According to our observations (15) adrenin in both pressor and depressor doses ordinarily causes contraction of the kidneys and a corresponding decrease in the venous outflow. One animal, however, showed renodilatation with smaller, and renocontraction with larger doses. The threshold for renal changes and blood pressure changes is about the same.

Various observations in the recorded studies suggest that adrenin causes diuresis when administered sufficiently slowly, by bringing about a dilatation of the renal blood vessels. This theory, our observations as a whole do not support. On the other hand,

they do not definitely exclude the possibility that in a normal unanesthetized animal such may be the case. The situation as regards adrenin diuresis may well be not unlike that as regards pituitrin diuresis. From the fact that pituitrin administered to anesthetized animals often gives a brief polyuria a theory has been deduced and widely held that this substance is a diuretic agent in the normal organism, whereas, as a matter of fact it is an efficient anti-diuretic (16). In view of the evidence (a) that adrenin in doses which cause renocontraction depress urine formation (b) that adrenin administered subcutaneously, and hence absorbed slowly, causes polyuria; and (c) that in anesthetized animals renodilatation has occasionally been noted following the administration of adrenin in high dilutions, or, as a secondary effect when larger quantities were used, the theory is not improbable that in normal animals adrenin in relatively small quantities causes a dilatation of the kidneys. Possibly the matter could be definitely determined by attaching metal guide strips to the poles of the kidneys and then after the animal had fully recovered from the operation, studying the volume changes with a fluoroscope when adrenin was administered in various doses without the use of an anesthetic.

Effects in the Intestine: There was no definite correlation between dosage and volume changes in the intestine but dilatation predominated, especially with larger doses. Often the dilatation was preceded by contraction. In some instances contraction alone occurred. The thresholds for volume changes in the gut and for blood pressure changes were about the same. In some cases enterocontraction coincided

with a rise of blood pressure but there was no constant relation between blood pressure and vascular changes in the intestine. The volume changes in the intestine usually persisted for some time after blood pressure returned to normal, indicating that there are compensatory reflex adjustments among the various organs so that a contraction or dilatation in one is followed quickly by a change of the opposite nature in another and the general blood pressure left practically normal.

Since the blood from the intestines is carried into the general blood stream through the liver, an organ which is itself sensitive to adrenin, the question arose: To what extent did hepatic changes play a part in the reaction of the gut? It was found that shunting the blood directly into the vena cava made no essential difference in the reaction, hence liver changes were a negligible feature. The outflow from a small cannulated gut vein was augmented by adrenin in all effective doses irrespective of changes of blood pressure or gut volume. In most cases the augmentation was preceded by a brief diminution (17).

From the foregoing observations it is obvious that adrenin in any general sense is neither a vasoconstricting nor a vasodilating agent. It is one or the other depending upon what vessels are involved. Also in some cases, as in the lungs, the effect depends upon the dosage, diametrically opposite results being obtained with change of quantity. Neither can one generalize to the effect that the splanchnic vessels are constricted while the peripheral vessels are dilated. In the peripheral circulation are included not only the skin but also other less extensive structures that

respond by constriction. The effect of adrenin in such a structure as a limb is a composite one, the limb as a whole either contracting or expanding depending upon whether vasodilatation in the muscle or vasoconstriction in the skin predominates. The fact that muscular tissues form the predominant mass in the trunk and limbs would seem to account for the fact that adrenin passed through the extra-splanchnic circulation causes a fall in arterial pressure.

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DISCUSSION OF PROF. HOSKINS' ARTICLE

Walter J. Meek, Department of Physiology, University of Wisconsin: Recent detailed studies of adrenalin have put the defenders of the tonus theory of adrenal action decidedly on their guard if indeed they have not been already vanquished. The fact that an animal may endure removal of the adrenals for some time before the vascular symptoms appear although we know adrenalin disappears quickly from the circulation, that neither injection nor infusion of the hormone will relieve the condition even though the vaso-motor reflexes are at the same time apparently perfectly retained, and the fact recently shown by Stewart and Rogoff that an animal may live with the adrenals denervated and no demonstrable secretion, all seem to leave no escape for those who would insist that either because of its direct stimulation or because of its sensitization of the sympathetics a small amount of adrenalin is constantly needed for the maintenanc of systemic blood pressure.

Certain other arguments against the tonus theory do not, however, seem so convincing. That the dilution of adrenalin, if there is any in arterial blood, must be as high as one to a billion need not disprove its pressor action for this amount though unbelievably small is still not so far below the limits in which

we can use definite biological tests. It may be remembered that Pysemsky and Kravkov have detected one part in 250 million in the perfusion of the rabbit's ear. The argument that adrenalin in small doses causes vasodilation does not seem very important, at least to us. Our experience, which now covers a very large number of injections, shows that exceptions must be taken to a literal interpretation of the statement that minimal doses of adrenalin are always depressor in action. That in the cat there is a small dose which will give a pure fall of blood pressure can easily be demonstrated. We have found however that in some of these animals if the dose is further reduced the fall in pressure may be replaced by a rise. In the dog it is almost impossible to find a dose that will give a pure fall in pressure. The so-called depressor dose here gives a rise and a fall as may be readily seen by referring to any of the published curves illustrating it, and if this dose be further decreased it is the fall in pressure, and not the rise, which disappears first. The rabbit apparently acts the same as the dog. Our experience then is that while a depressor dose may be found, or at least a dose showing depressor effects, the minimal effect in the majority of cases is a pressor one. It seems however really to matter little whether adrenalin in minimal quantities is pressor or depressor in view of the fact that different parts of the vascular system react differently to adrenalin and each has its own threshold. Hoskins and his co-workers have been adding valuable data by attacking the problem in the logical way, that is, to find out the effect of adrenalin on each organ separately. The effect of adrenalin on systemic blood pressure is only the algebraic summation of its influence on the different parts of the body.

Granted that the weight of the evidence is against the tonus theory, the energizing and integrating action of adrenalin in times of bodily stress and strain

seems to be its most likely physiological function. Although one may be tempted to question whether adrenalin as an integrator aids the organism in all the many ways pointed out by Cannon and his students, purely on the ground that no other physiological theory ever worked out so happily in all its details, yet enough has been verified to compel us to accept the theory in its broad outlines. It may be even somewhat in favor of the general conception to point out certain discrepancies that appear, as the details are investigated more and more closely. Hartman for example offers evidence that adrenalin causes a peripheral dilation in muscle and a central constriction in the splanchnic area. This mechanism fits nicely into the needs of the body during emotional excitement accompanied by muscular effort. Hoskins and Gunning have, however, reported that on plethysmographing the intestine the minimal effect of adrenalin is generally dilation or a transient constriction followed by vasodilation. Their results we can abundantly confirm from records taken in our own laboratory. This intestinal dilation is possibly passive, due to the relaxation of the circular coat of the intestine and a consequent relief of pressure on the arterioles. It must, however, oppose any increased circulation through skeletal muscle. It is of course quite possible that the advantage of inhibiting the smooth muscle of the intestine more than offsets the disadvantage of this moderate dilation.

From our present knowledge it might be concluded that the constant secretion of adrenalin is not necessary for life. This conclusion can not be secure, however, until we are able to explain why it is that every animal having the adrenals removed sooner or later dies with signs of muscular and circulatory collapse. With a few exceptions, recent workers have ignored the cortical part of the adrenals. It may be that here will be found the solution of the difficulties. Biedl has shown that it is the inter-renal or cortical

part that is necessary in the fish, and Crowe and Wislocki have presented evidence indicating that probably this is the part necessary for life in the dog. Voegtlin and Macht's isolation of a pressor substance from the adrenal cortex, a substance which certainly was not adrenalin but a cholesterin like body, is of particular interest in this connection. One is tempted to form an hypothesis that the adrenals are double organs, the cortex supplying a hormone necessary for life by virtue of its maintaining muscular and vascular tonus, and the medulla supplying a particularly active pressor substance, adrenalin, to be used in times of great emergency, which has remarkable powers of correlating and energizing various organs of the body.

THE VASOMOTOR EFFECTS OF ADRENIN WHEN ADMINISTERED WITHOUT ANESTHESIA

By E. L. Berry, Chicago

(From the Laboratory of Physiology of the Northwestern University
Medical School.)

ONE of the more important problems which now confront workers in the field of endocrinology is, what part is played by the adrenal glands in the normal and pathological activities of the body. An important feature in the solution of this major problem is the determination of the exact effects of adrenin on the various functional processes. These having been determined, the problem still remains as to whether the adrenals can and do secrete at a rate sufficient to produce the effects noted. In other words, the quantitative aspects of adrenin research are highly significant. This is particularly true because of the observations that the reaction to an injection of adrenin may vary diametrically depending upon the dose administered (Vincent (1), Tribe (2), etc.). We need definite information then as to whether adrenin is actually discharged into the blood; if so, under what condition and in what amounts and finally just what effects are produced by these amounts of adrenin.

Of the available data bearing upon these problems practically all have been derived from anesthetized animals. To what extent observations made upon etherized dogs are applicable to normal men, or even to normal dogs in many instances can not be accurately predicted. The burden of proof rests upon the investigator who wishes to generalize from such data. The whole problem of the pharmacology of adrenin

without the complications of anesthesia is therefore in need of further study. Certain aspects of this problem are now under investigation in our laboratory. A brief preliminary account of the results as regards the vasomotor reactions is herewith offered.

Technique. The work thus far has been done upon dogs and cats. The technique, in the case of the dogs, has been: first, to select animals of quiet temperament. After arranging them comfortably on the animal board 1 mil. of 1 per cent. morphine (1-6 gr.) was injected subcutaneously, then, using cocaine locally, the femoral vein and artery were exposed and canulas inserted. Usually the first dose of morphine was sufficient so that the animal remained quiet during the operation and subsequent manipulations. Occasionally, however, with large dogs the dose had to be repeated. Since morphine is an excitent to cats it was not used; otherwise the technique was the same as with dogs. The arterial canula was connected with a Harvard manometer, using 10 per cent. sodium citrate as an anti-coagulant. The changes in blood pressure were recorded upon a revolving drum. The venous canula was connected with a burette containing normal salt solution. Thus the amounts of solution injected each time were easily regulated. The intravenous injections were made into the tubing connecting the burette with the venous canula, then by opening a clamp they were flushed into the vein. Parke, Davis' "Adrenalin," diluted 1:200,000 was employed in the intravenous injections for all but the smallest doses, for which higher dilutions were used. The reactions to graduated decreasing doses were recorded until the threshold was reached. The ani-

mals were then anesthetized with ether and readings with the same dosages again taken.

Results. One of the most striking features of the research apparent at present is the marked depressor effect of ether anesthesia on the vasomotor reaction to adrenin. In various instances the threshold in the unanesthetized dogs was not reached until doses of 0.0078 to 0.0039 mils. of 1:100,000 were used. In two instances the administration of 0.5 mil. of 1:100,000 drove the mercury out of the manometer so that the connecting tube had to be clamped off.

As an example illustrating the difference in reaction before and after etherization the following specific case may be cited: Cat before etherization, on administration of 0.25 mil. 1:100,000 adrenin gave an increase in blood pressure of 90 mm. Hg., the effect lasting over a period of three minutes, and showing no depressor phase following the rise. After etherization 1 mil. of 1:100,000 solution gave a rise in pressure of only 48 mm. The effect lasted two and one-half minutes and was followed by a slight depressor reaction.

Almost without exception the duration of the effect of the adrenin is decreased from 10 to 30 per cent. by the ether. The type of the reaction is also changed. In only one or two instances have any depressor effects been noted following the injection of adrenin in the unanesthetized animals, whereas such are usually observed when ether is used. The return of the blood pressure to normal is much more gradual in most instances without anesthesia. The vagus action on the heart is frequently pronounced in the normal as compared with the etherized animals. In

some instances the heart was slowed from 130-140 to 60-70 beats per minute following the injection. The force of the beat, however, is often sufficient to cause a change in pressure of from 60 mm. Hg. to 80 mm. Hg. with each contraction. Both of these effects largely disappeared under ether. The fact that the vagus is especially susceptible to ether has been emphasized by Meek and Eyster. (3)

In the experiments so far made oral and subcutaneous injections even in large amounts have produced slight or no effects on blood pressure. One dose of 5 mils. of adrenin given intramuscularly in a cat was followed by a rise in blood pressure of 10 mm. Hg. in five minutes and at the end of twelve minutes it had increased to 28 mm. Hg. This rise in pressure was very gradual.

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COMMENT ON MR. BERRY'S ARTICLE

D. E. Jackson, St. Louis, Mo.: In a very striking manner Mr. Berry has emphasized in this paper the peculiarly uncertain influence which an anesthetic may exercise on the finer details of the pharmacological action of drugs. The depressing influence of ether is demonstrated here in a way in which, under ordinary circumstances, its action is either entirely ignored or at most not sufficiently emphasized. Presumably chloroform would have yielded more (and nitrous oxide less) marked differences in the vascular responses, while ethyl bromide and ethyl chloride

would have given intermediate results. The alkaloidal hypnotics, such as morphine, have been widely used for experimental procedures, especially as a preliminary to ether. It can easily be shown that morphine produces marked changes, both centrally and peripherally, in experimental animals, and the peculiarly involved and complicated influence which such hypnotic drugs may have on the action of other substances is by no means clear. Generally these hypnotic influences have not been considered of special importance.

From a pharmacological standpoint the question would arise at once as to how and where the ether acted in order to lower the animal's vascular responses to adrenalin. A depression of the brain and cord might indirectly tend to lower the general tone of the vascular system and thus reduce the vigor of the heart and of the muscular response of the arterioles, even though the stimulation of these was of peripheral origin. For not only will ether depress the tonic impulses which are normally constantly passing out from the central nervous system to the peripheral structures, skeletal muscles, etc., but the normal rate of oxidations is also lowered in the body by ether anesthesia. This effect on the tissue oxidations is of especial interest in the present instance. For it appears that adrenalin cannot exercise its full pharmacological activity on the sympathetic myoneuronal junctions unless there be a sufficient supply of available oxygen in the blood and tissues. This problem may, perhaps, be best approached in a spinal animal. In such a preparation, if one brings on a marked asphyxia by reducing the artificial respiration, or by injecting a drug like morphine which causes a profound broncho-constriction and thus indirectly an asphyxia, then the injection of even large doses of adrenalin will produce only a very small rise in blood pressure.

In this reaction the heart and arterioles are ap-

parently both directly concerned. The result is probably very largely due to a direct lack of available oxygen in the blood and tissues, for if the artificial respiration be mechanically increased (in either case) up to the normal, then almost immediately the normal responsiveness of the tissues is regained, and injection of the same sized dose of adrenalin as that which previously caused only a little rise in pressure will now produce a great increase in the vascular tension. But the exact inter-relations existing between the central and peripheral action of the anesthetic, the cause and results of the asphyxia, and the variability in responsiveness of the vascular and other systems to adrenalin injections is a matter of obscurity.

A further point of interest which may be developed from Mr. Berry's paper is this: How long will the depressing influence of ether on the vascular response to adrenalin persist after the animal has ceased to breathe the vapor of the anesthetic? Perhaps one might use a spinal animal to study this point also. In these preparations the actual extent of rise in blood pressure produced by a given injection of adrenalin is apparently pretty close to the result which would be obtained from the same sized dose of adrenalin in the etherized animal before its brain was destroyed. If in the spinal (or decerebrate) animal artificial respiration were carried on long enough, a fairly large percentage of the absorbed ether vapor might be excreted by the lungs and then the responsiveness of the vascular system to adrenalin might again be tried. It is only by such indirect processes as this that such problems as that now in hand can be satisfactorily investigated.

DIABETES INSIPIDUS. A METABOLIC
STUDY OF THE EFFECT OF PITUITARY
ADMINISTRATION

By John R. Williams, M. D., Rochester, N. Y.

Introduction: The following paper contains:

1. A brief resume of the literature in which most of the recent writers regard the disease as due to hypofunction of the hypophysis.
2. A clinical description of a case in a woman, age 58 years, in which the chief symptoms were thirst; polyuria; pain in head, back, and limbs; impaired eyesight; loss of weight.
3. Physical examination; leucodermic patches on arms and chest, dry skin, body otherwise normal. Patient nervous and irritable.
4. Previous illness negative; family history of cancer, diabetes, and insanity.
5. X-ray examination; sella turcica slightly enlarged, anterior clinoidal processes thin; posterior clinoidal processes thin and of mushroom type.
6. Eyes; concentric contraction of visual and color fields, and other changes suggesting a functional disturbance due to physiological factors.
7. Average amount of urine passed daily when no pituitrin was given (78 days), 6277 cc. Average amount passed daily when pituitrin was given (142 days), 3767 cc.
8. Diets low in carbohydrates, proteins, fats, and salt had little effect on diuresis.
9. Administration of anterior lobe pituitary body by mouth was ineffective in controlling diuresis.
10. Administration of posterior lobe by mouth was also without effect.

11. Removal of spinal fluid to lessen intracerebral pressure diminished diuresis for one day only.

12. The effect of pituitary administration is purely transitory. Its continued use over a period of 8 months has afforded no evidence of permanent improvement.

13. The blood sugar level on a diet rich in carbohydrates was inappreciably influenced by the administration of pituitrin.

14. There was a considerable increase in the cholesterolin and fat content of the blood which was uninfluenced by the treatment.

15. The study of the urine excretion by means of the Mosenthal two hour renal test showed that when pituitrin is not given the kidneys eliminate large and variable amounts of urine during the day and an even greater amount during the night period. The percentage of solids or specific gravity is fixed on a low plane and fluctuates very little. When pituitrin is administered, much less urine is excreted during the day periods but the night amount is quite as large as in the previous test. The percentage of concentration of solids in the urine is much greater and more variable. Without pituitrin, nitrogen elimination was quite variable during the day with a pronounced response to the noon meal although the percentage of concentration was fixed during all but two of the periods. The administration of pituitrin seemed to stimulate nitrogen excretion during the latter part of the day and during the night, more than half of it being eliminated during the night hours. Salt elimination is also on a higher plane after the administration of pituitrin.

When pituitrin is not given, salt elimination is on a low plane, there being quite a well-marked fixation of concentration. When pituitrin is administered, both the amount and the percentage of concentration vary considerably, showing that the kidneys have a greater amplitude of function. As in the case of water and nitrogen, more than half of the salt is eliminated during the night hours.

16. The blood creatinin was normal. The urea content of the blood was normal but the rate of excretion was apparently improved by the administration of pituitrin, as evidenced by the lower Ambard coefficient.

Resume of recent literature. Many writers have reviewed the literature relating to the hypophysis. In this paper no attempt will be made to do more than call attention to the views of recent students of the subject with reference to the relationship of the pituitary body to diabetes insipidus, in so far as therapeutics is concerned. In the first and second issues of this journal will be found abstracts of practically all the literature of value that has been published recently. From these reviews have been epitomized the following notes which have a bearing on the case studied in this paper.

Boyd reports a case of glioma constricting the infundibulum of the pituitary body which he believes supports the theory that the secretion of the posterior lobe of the pituitary body passes by the way of the infundibular stalk into the third ventricle. Hoppe-Seyler reports a case in which he brings out the following salient points: "Polyuria from excessive ingestion of fluid is differentiated by the specific grav-

ity remaining low, independent of the amount of food or drink taken. The polyuria is controlled by the vasomotor nervous system and not by the disturbed kidney cells. The prompt reaction of the body to small doses of pituitrin results in the normal excretion of urine, saliva, and sweat. In the case of the urine there is a rapid rise in the specific gravity and

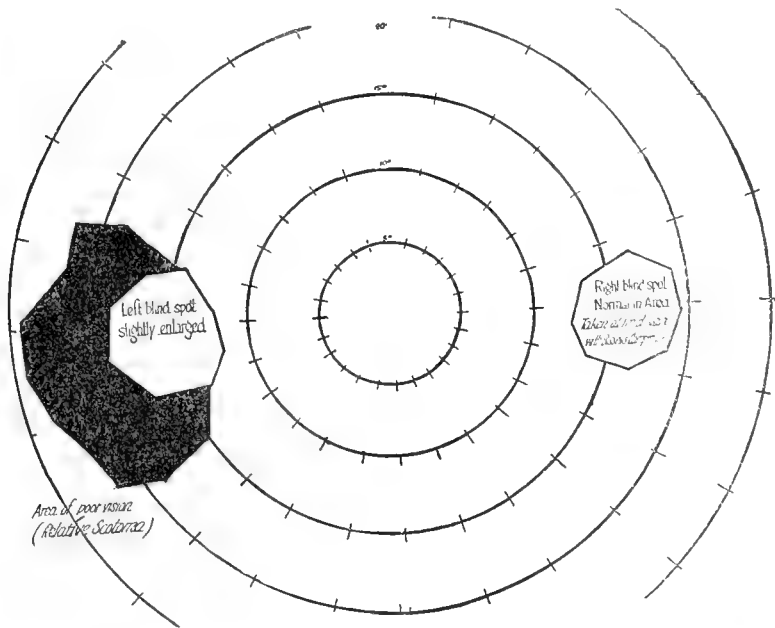


FIG. 1

Chart showing visual fields in the case reported (see page 321).

salts. Insufficiency of the pituitary gland is the cause. All signs rule against the opinion that the disease is due to irritation of the gland or hyperfunction." Hoppe-Seyler refers to work of Magnus and Schafer who conclude that there is a hyperfunction of the hypophysis. Romer showed by animal experimentation and clinical study that there is a hypofunction.

v. Konschegg, E. Schuster, and Graul, from clinical studies, conclude that there is hypofunction. Rosenfeld found oral administration of pituitrin as effective as injection.

Motzfeldt (Journal of Experimental Medicine, 1917, 25, 153) has shown that pituitrin does not influence the polyuria caused by the excessive ingestion of salt. He also shows that extracts of the pars intermedia and posterior lobe of the hypophysis, when given by mouth, subcutaneously, or intravenously, have an anti-diuretic effect on experimental animals. Extracts of the anterior lobe have a similar effect but to a lesser degree. The anti-diuretic action exerted by pituitary extracts on experimental animals is caused by stimulation of the sympathetic nervous system and the renal vasomotor system in this respect is of chief importance.

HISTORY OF AUTHOR'S CASE:

Patient is a widow, age 58 years, American born. Complains of excessive urination, thirst, pain in left side of head, tired feeling, pain in limbs, lower back, and distress in epigastrium; dryness of throat.

The illness began in the summer of 1911 with thirst and excessive urination and gradual loss of weight. Lips were dry and cracked, and healed with difficulty. Eyes ached much of the time. When the polyuria first began, the patient had peculiar spells as though she were sinking through the floor. These phenomena she ascribes to severe constipation from which she suffered at the time.

Urinary history. During the day, she urinates from 8 to 10 times, voiding from 4000 cc. to 6000 cc.; during the night, she urinates from 4 to 5 times, passing from 2000 cc. to 4000 cc.

Edema. Formerly, patient thinks eyes were puffy; there is no evidence of edema now. There is no cough or pallor.

Patient suffers daily from headache on left side and back of head; is dizzy nearly every day. Vision is gradually failing. No specks or light flashes before eyes. Complains of stiffness and lameness in limbs, but joints do not swell or become inflamed. Bowels are constipated; takes mild ca-

tharsis daily. Sleeps well except when disturbed by diuresis.

Weight. In 1896, 168 pounds; 1911, 150 pounds; 1916, 131 pounds; October 23, 1916, net weight, 118 pounds; April 9, 1917, net weight, 129 pounds.

Married 34 years. Pregnant twice; no abortions.

Previous illness. Measles, whooping cough, mumps, and scarlet fever as child; good recoveries. Pneumonia at 29 years, again at 32 years, with good recoveries. Had much trouble with teeth and all were removed except lower incisors which are in fair condition. Has been moderately nervous since illness began; is not hysterical and does not suffer from motor excitement. Is troubled somewhat with hemorrhoids.

Family history. Father died at 72 years of liver disease; had cancer on his nose. Mother died at 75 years of heart disease. One sister died of cancer; one paternal cousin died of diabetes mellitus, and two paternal uncles died of insanity. Patient has two living, healthy, adult children.

Physical examination. Patient is a middle aged woman, medium height, thin, pale, worried expression. Face, arms and chest blotched with large leucodermic patches. Skin is dry and elastic. Subcutaneous fat thin, muscles moderately developed. Hair, eyes, ears, nose, normal. Tonsils small, cryptic, no evident degeneration. Tongue slightly swollen and edematous. Thyroid normal; no evident thymus, lymph glands all normal, arteries, soft; no abnormal sclerosis. Blood pressure, systolic 115 mm., diastolic 70 mm. Veins normal. Lungs, normal resonance and breath sounds; no rales. Heart normal in size, rhythm regular, no bruit. Abdomen slightly pendulous, muscle wall flaccid. Aside from a slight tenderness on deep pressure in the region of the gall bladder, nothing abnormal is to be noted in the abdomen. Reflexes, pupillary and patellar both active. Romberg's sign negative. Coordination and tremor normal. Limbs, spine, and pelvis, normal. No evidence of edema.

Teeth, upper plate; lower molars removed; lower incisors normal except one which shows slight pyorrhea. Weight, 118 $\frac{1}{4}$ pounds.

Laboratory Examinations:

Blood. October 26, 1916: Red cells, 4,500,000; white cells, 7,600; Hb. 85 per cent.; Hb. index, 94.

Wassermann Test. October 31, 1916, negative.

Non-protein nitrogen in blood, 23 mg. per 100 cc.

A large number of urine examinations were made. The specific gravity was usually low, ranging from 1004 to 1013. Neither sugar nor albumen was found. Several microscopic examinations of the urine were negative.

Functional tests of the kidney were made October 30, 1916. Phthalein, 2 hours, 42 per cent.; November 5, 1916, Phthalein, 50 per cent.

Study of urinary excretion under various conditions. From October 23 to October 30 inclusive, patient voided from 5,500 cc. to 7,100 cc. daily, averaging approximately 6,500 cc. daily. On October 29th, 20 cc. spinal fluid were removed, after the suggestion of Dr. Dean Lewis. The fluid was normal in appearance and cell content. On October 30th the urine dropped to 3,600 cc. but on the two following days, it rose to over 5,000 cc. The effect of pituitrin hypodermatically was then tried. The results of this are shown in the following summary.

TABLE I
EFFECT OF PITUITRIN ADMINISTERED HYPODERMATICALLY
ON OUTPUT OF URINE

Date	Vol. Urine cc.	Sp. Gr.	Pituitrin		Diet		Calories	Remarks
			Sp. Gr.	hypo. cc.	Carb. g.	Prot. g.		
Nov. 2	2375	1007	1	50	40	48	790	No thirst
3	5850	1006	0	59	44	64	950	Severe thirst
4	1100	1011	2	53	44	72	1025	No thirst
5	1075	1013	1	73	62	68	1150	No thirst
6	3900	1005	1	74	63	78	1255	No thirst
7	1700	1010	1	74	63	78	1255	No thirst
8	2725	1009	1	74	63	78	1255	No thirst
9	2025	1010	1	61	50	107	1338	No thirst
13	3800	1008	1	125	67	106	1705	No thirst
14	2600	1008	2	109	51	91	1438	No thirst
15	1375	1011	1	116	70	116	1660	No thirst
22	3120		2	Diet approximately the same				No thirst
23	3100		2	Diet approximately the same				No thirst
24	4340		2	Diet approximately the same				No thirst
25	3840		2	Diet approximately the same				No thirst
26	3840		2	Diet approximately the same				No thirst
27	3360		1	Diet approximately the same				No thirst
28	4800		6	grains pituitary body (Armour) by mouth				Severe-thirst
29	6960		6	grains pituitary body (Armour) by mouth				Severe-thirst
30	6960		6	grains pituitary body (Armour) by mouth				Severe-thirst
Dec. 1	5520		6	grains pituitary body (Armour) by mouth				Severe-thirst
2	6960		6	grains pituitary body (Armour) by mouth				Severe-thirst
3	6960		6	grains pituitary body (Armour) by mouth				Severe-thirst
4	7000		6	grains pituitary body (Armour) by mouth				Severe-thirst
5	7720		6	grains pituitary body (Armour) by mouth				Severe-thirst
6	7300		1-10	grain pituitary body post. lobe by mouth				Severe thirst

TABLE I (continued)

	7	7000	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	8	7000	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	9	6800	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	10	7000	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	14	6400	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	19	5800	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	23	5900	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	24	2800	1 cc. pituitrin per hypo.	No thirst
	25	3000	1 cc. pituitrin per hypo.	No thirst
	26	2900	1 cc. pituitrin per hypo.	No thirst
	30	2800	1 cc. pituitrin per hypo.	No thirst
Jan.	1	1700	1 cc. pituitrin per hypo.	No thirst
	2	2850	1 cc. pituitrin per hypo.	No thirst
	3	4850	1 cc. pituitrin per hypo.	Patient has "cold"
	5	5450	1 cc. pituitrin per hypo.	Patient has "cold"
	5	5100	1 cc. pituitrin per hypo.	Patient has "cold"
	14	5700	1 cc. pituitrin per hypo.	Patient has "cold"
	29	3900	1 cc. pituitrin per hypo.	No thirst
	30	3800	1 cc. pituitrin per hypo.	No thirst
	31	6800	0	Severe thirst
Feb.	1	6300	0	Severe thirst
	2	6400	0	Severe thirst
	3	7800	0	Severe thirst
	6	5500	0	Severe thirst
	7	3300	1 cc. pituitrin per hypo.	No thirst
	8	3400	1 cc. pituitrin per hypo.	No thirst
	9	3100	1	No thirst
	10	2600	1	No thirst
	17	3100	1	No thirst
	18	5100	1	Ate candy freely
	19	4200	1	No thirst
	21	3500	1	No thirst
	27	6900	0	Severe thirst
	28	7100	0	Severe thirst
Mar.	1	7800	0	Severe thirst
	4	5450	0	Severe thirst
	5	7800	0	Severe thirst
	6	4000	1	No thirst
	8	3800	1	No thirst
	12	3200	1	No thirst
Apr.	10	3700	1	No thirst
	12	6000	0	Severe thirst
	14	7100	0	Severe thirst
	15	5200	1	No thirst
	16	2800	1	No thirst

Comment. It will be noticed that pituitrin administered hypodermatically appreciably lessened the urine output. One cubic centimeter was quite as effective clinically as were two

doses. Pituitrin by mouth had no antidiuretic action in this case.

TABLE II
TWO-HOUR RENAL TEST, APRIL 5, 1917

Diet: Carbohydrate 293 grams. Protein 85 grams. Fat 125 grams. Calories 2641. Salt approximately 5 grams. No pituitrin administered.

Hours	Fluid Intake	Urine cc.	Specific Gravity	Nitrogen		Salt	
				Grams	Per Cent.	Grams	Per Cent.
7-9 a.m.	300	250	1006	0.53	0.21	0.30	0.12
9-11 a.m.	540	100	1008	0.24	0.24	0.08	0.08
11-1 p.m.	720	300	1007	0.66	0.22	0.18	0.06
1-3 p.m.	810	550	1007	2.15	0.39	0.33	0.06
3-5 p.m.	0	500	1007	1.55	0.31	0.10	0.02
5-7 p.m.	900	350	1008	0.91	0.26	0.21	0.06
7-9 p.m.	60	200	1009	0.55	0.22	0.15	0.06
9 p.m.-7 a.m.	2040	3150	1007	4.73	0.15	1.88	0.06
Totals	5370	5400		11.32		3.23	

Summary. The excretion of urine is variable during the day, but there is considerable storage and elimination during the night. There is no evidence of fixation of elimination of water. The specific gravity is so constant as to suggest fixation of concentration of solids. The amounts of nitrogen eliminated during the daylight hours vary widely, suggesting an absence of fixation; there is considerable storage, however, for nearly half of the nitrogen is eliminated during the night. The percentage of concentration of nitrogen shows more tendency to fixation. The elimination of salt is on a low plane and, as in the case of the water and nitrogen, there is evidence of delay and elimination during the night. There is noticeable evidence of fixation of percentage of concentration and probably also of some salt retention. The response to the noon meal is fairly prompt in water, salt, and nitrogen.

TABLE III
TWO-HOUR RENAL TEST, APRIL 9, 1917

Diet: Carbohydrates, 300 grams. Protein, 85 grams. Fat, 119 grams. Calories, 2615. Salt, approximately 5 grams. 1 cc. pituitrin administered hypodermatically.

Hours	Fluid Intake	Urine cc.	Specific Gravity	Nitrogen		Salt	
				Grams	Per Cent.	Grams	Per Cent.
7-9 a.m.	0	450	1006	0.59	.13	.63	.14
9-11 a.m.	360	44	1025	0.43	.98	.38	.86
11-1 p.m.	90	64	1025	0.72	1.12	.60	.94
1-3 p.m.	510	42	1025	0.55	1.26	.24	.58
3-5 p.m.	90	100	1020	1.03	1.03	.54	.54
5-7 p.m.	0	175	1014	1.43	.82	.28	.16
7-9 p.m.	1230	300	1011	1.50	.50	.42	.14
9 p.m.-7 a.m.	0	3110	1007	6.61	.21	3.11	.10
Totals	2280	4325		12.86		6.24	

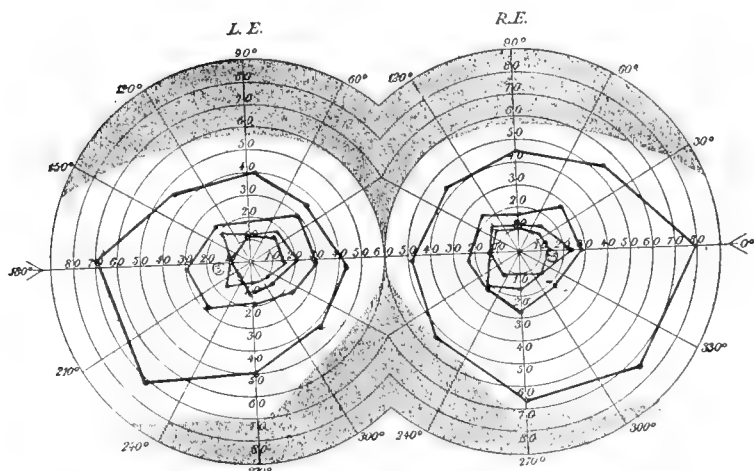


FIG. 2

Chart showing examination of visual and color fields, made February 9, 1917. The outer line is the boundary of the visual field. The next lines enclose the blue, red, and green color fields in the order named. Note the concentric contraction of both the visual and color fields.

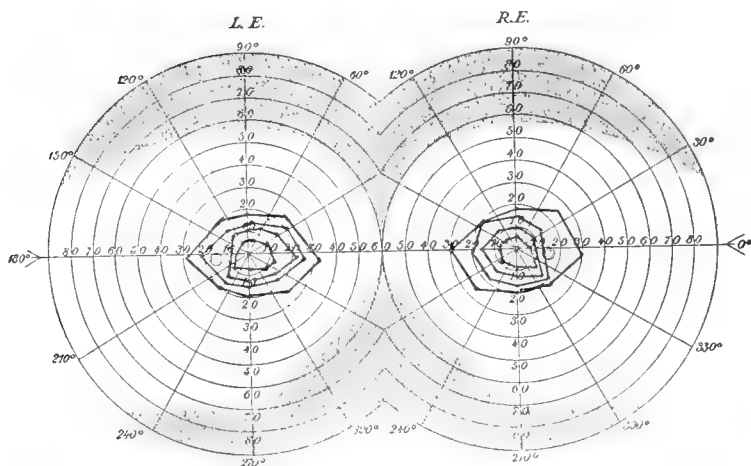


FIG. 3

Chart showing examination of visual and color fields, made July 17, 1917. Note the concentric contraction of both the visual and color fields which has occurred since the previous examination.

Summary. The elimination of water during the day is quite variable. It is on a much lower plane during the day than during the night when there is a noteworthy polyuria. There is little response to the noon meal. The specific gravity likewise fluctuates widely and is much higher than in the previous test. The elimination of nitrogen is normal as to quantity when compared with the protein intake; during the daylight hours, however, it is on quite a low plane, showing a moderate degree of fixation of amount and percentage, although there is considerable fluctuation in the daylight hours. As in the case of the water, more than half of the nitrogen is eliminated during the night. The response to the noon meal is much delayed. The elimination of salt is also on a low plane during the daylight hours, half of it being excreted during the night. There is little response to the noon meal. The percentage of concentration fluctuates considerably. It is noteworthy that the thirst of the patient varies in intensity during the day, the desire for fluid occurring chiefly at breakfast, dinner, and after supper, with none during the night.

Comment on the two-hour renal tests. It seems likely that the administration of the pituitrin assuages the thirst because during the first test when no pituitrin was given, the patient drank large quantities of water throughout the entire 24 hours, whereas during the second test, the effect of the pituitrin evidenced itself chiefly at meal hours and not at all during the night. Excretion of water, nitrogen, and salt apparently takes place continuously throughout the twenty-four hours, but apparently there is delay in excretion or storage of these materials so that night elimination is quite equal to that of the day. This is wholly unlike that of the normal kidney which eliminates quite promptly and efficiently the materials ingested during the day, so that the entire night urine may contain but little more water, nitrogen, and salt than any of the day two-hour periods. It is quite possible that the excessive thirst and the consequent ingestion of large quantities of fluid exhibited in this disease tend to exhaust the kidney rather than to produce a specific lesion. The absence of nitrogen retention in the blood, the normal nitrogen elimination in urine and nitrogen equilibrium in this severe case indicate that the disturbance is not one of faulty nitrogen metabolism or elimination. The same may be said of the salt although it would seem that salt and nitrogen excretion are stimulated by the pituitrin. The normal blood sugar and absence of glycosuria in diets containing large amounts of carbohydrate food, much of it in the form

of sugar, prove conclusively that there is no disturbance of carbohydrate metabolism and that the kidneys have the normal degree of resistance to the passage of sugar. The absence of albumen and renal elements is further evidence that the kidneys are not structurally diseased. It is possible that the improvement in renal output after the administration of pituitrin is partly explained by the rise in blood pressure which follows, although this is denied by some investigators.

TABLE IV
CHEMICAL STUDIES OF BLOOD AND URINE
With and without the administration of pituitrin hypodermatically.

Date	Vol. urine cc.	Blood					Diet					Pituitrin cc.
		Cholesterol mg.	Fat mg.	Non-prot. nitro. mg.	Pressure Syst.-diast.	Sugar	Carb.	Prot.	Fat	Fluid Intake	Calories	
Apr. 3	7100						297	85	122	4500	2670	0
4	6250	312	835	36	110-80	0.10	292	75	112	3180	2572	0
6	3000						300	85	125	2940	2670	1
7	2900						295	84	125	2160	2655	1
8	4075	312	906	36	140-75	0.08	300	85	119	2130	2615	1

TABLE V			Pit. cc.
June 27	Urea in blood	25.2 mg. per 100 cc.	0
June 28	Urea in blood	40.6 mg. per 100 cc.	Ambard Coeff. 0.16 0
June 29	Urea in blood	25.4 mg. per 100 cc.	Ambard Coeff. 0.11 1
June 29	Creatinin in blood	2.3 mg. per 100 cc.	

Comment. The samples of blood were taken before breakfast after the night's fast. Cholesterol and blood fat were determined by Bloor's method; the non-protein nitrogen by Folin's micro-kjeldahl method; the blood-sugar by the Lewis-Benedict method. Normal blood rarely contains more than 250 mg. cholesterol per 100 cc. This patient exhibits a well marked cholesterinemia, both before and after the administration of pituitrin. Normal blood of a fasting patient rarely contains more than 600 mg. fat per 100 cc. The blood fat in this case is increased. The non-protein nitrogen in the blood in this case is normal, both before and after the administration of pituitrin. There is no evidence of nitrogen retention. The blood pressure, both diastolic and systolic, are increased by the administration of the pituitrin. On the days when the patient had no pituitrin, twice as much water was drunk as when it was given. The fluid intake is a measure of the patient's thirst. The carbon-dioxide content of the

alveolar air was 41 mm. (barometric tension) before and 39 mm. after the administration of pituitrin. These figures are normal and show that acidosis is not a factor in the disease.

Examination of eyes by Dr. Elmer J. Bissell, February 12, 1917. "Patient has a moderate amount of hyperopia and astigmatia, and slight incipient cataracts which are not of the type found in diabetes mellitus. Retinal arteries slightly tortuous. Visual and color fields somewhat contracted. Surrounding the outer area of the blind spot in the left eye, there is a relative scotoma. These tests would indicate that there are some changes in the optic nerve fibres which are not yet discernible with the ophthalmoscope." Patient was re-examined June 17, 1917, and the following changes noted:

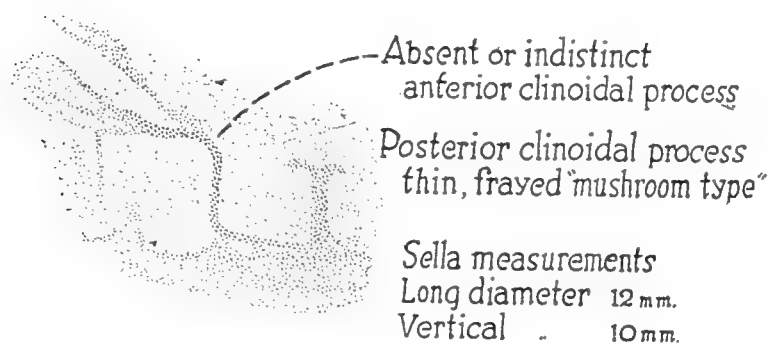


FIG. 4

Sella turcica. Drawing made from tracing of X-ray plate. Note the indistinct anterior clinoidal process and the thin dorsum sella and mushroom type of posterior clinoidal process. The measurements would indicate that the sella turcica is slightly larger than normal.

"No increase in the incipient cataracts. The retinal arteries are slightly attenuated and the temporal side at each optic disc is paler than normal. Visual fields for form and color are very much contracted concentrically. The relative scotoma which was present in the region of the blind spot of the left eye in February has disappeared. This is quite significant and may indicate that some physiologic condition is influencing the function of the retina without producing structural changes. The same condition may be the cause of the contracted visual and color fields."

Report of radiologist, Dr. M. W. Palmer. "The X-ray findings of the sellar region in this case, except in one or two important particulars, do not differ essentially from many other cases in which there is no history of diabetes insipidus. There are, however, certain markings which should not be

overlooked in future examinations of the sella turcica in this disease."

Stereoscopic plates were employed. Dimensions, long diameter of the opening, 11 mm., vertical diameter, 10 mm.

The anterior clinoidal processes are indistinct or absent. The posterior clinoidal processes are also thin. The dorsum sella is about 2 mm. thick; at the top it branches anteriorly and posteriorly into frayed edges to form the posterior clinoidal processes. This peculiar mushroom type is rarely seen except where the posterior lobe of the hypophysis is involved, therefore the absorption of the dorsum sella and posterior clinoidal processes should be considered in the interpretation of plates in this disease.

A CASE OF ADDISON'S DISEASE, DIAG-
NOSED AS SUCH AND VERIFIED BY
POST MORTEM

By Gustav Baar, M.D., F.A.C.P., Portland, Ore.

ON February 22nd, 1917, Mr. Charles Smitt, a Swede by birth, 45 years of age, steam-fitter by occupation, came to my office for examination; he was supposed to have stomach trouble. He complained of needle-like pains coming and going like lightning in the region of the right rib arch, feeling those pains mostly in the nighttime, though several times also in the daytime; he had no appetite the last four months and his bowels moved only on a cathartic and they were merely watery movements mixed with gas, without any pain; several times some blood was present. He had some protruding but not bleeding hemorrhoids. He complained also of flatulence relieved by bowel movement. The onset of his stomach trouble he thought was his "sea-sickness" he suffered from when coming down from Alaska to Seattle four months ago. He gradually got weaker and weaker and lost twenty-five pounds in weight. He noticed that his skin was getting brownish all last winter, could not sleep at night, was dyspnoic on exertion, felt needle-like pains in his limbs at times, admitted quite a bit of sore throat. About his habits he admitted moderate use of alcohol up to two years ago, when he discontinued its use entirely. For thirty years he chewed tobacco, swallowing the juice, but had to vomit it, so discontinued its use four months ago. He also admitted a hard chancre on the dorsal side of the sulcus coronarius about nine years ago; it stayed there hard for one

year; no secondaries or tertiaries. Eight months ago he contracted a soft chancre from a squaw, "cured" it with hydrogen peroxide, but it came back two or three times, the last time three weeks ago. This is the history of the case.

Physical Examination:

Color of Face: Pale, brownish, diffuse pigment spots on forehead, cheeks and temples.

Color of Lips: Rather pale, with three black pigment spots.

Gums: Pussy, easily bleeding. (The dentist, Dr. Kelty, pronounced this an "interstitial condition due to a faulty elimination of either the kidneys or liver, his gums having become eliminating organs for some of the waste products of metabolism.")

Pharynx: Kryptic follicular tonsils.

Tongue: Clean. Mucosa of both cheeks showed symmetric areas of black pigment, located corresponding to interspace of tooth rows of same color as pigment spots on lips.

Thyroid Gland: Not enlarged.

Lungs: Relative dullness on the posterior superior left apex of chest, distant respiration there; over left apex, posteriorly, inspiratory bronchitic rales; anteriorly on the right side of thorax between sixth and ninth ribs and between mamillary line and sternum edge, the skin appears elevated, round, fluctuating, very tender (seat of the needle pricking pain of which patient complains "in his stomach"). He noticed this swelling for one month.

Heart: Nothing abnormal; pulse easily repressible.

Abdomen: Nothing abnormal palpable.

Liver: Dullness, in front, starting on 5th rib in mamillary line and 6th (!) rib in axillary line: liver edge dull, very tender.

Kidneys: Not palpable.

Skin: Ashy color; on the neck many lentil-sized white scars from boils which patient had all his life (acne and furuncles).

Genitals: Head of left epididymis shows a pea-sized node, hard, tender; the prostate in the pole of the left lobe shows a bone-hard bean-sized tumor; in the sulcus coronarius of the dorsal penis a bean-sized white scar, seat of a former ulcer durum.

Hands and finger nails cyanotic and cold.

Glands: Bilateral nuchal glands palpable; also epitrochlear, very small axillary and inguinal.

Reflexes: Both patellar exaggerated; pupillary to light normal.

Fundi: Right papilla hyperemic, indistinct border line; left papilla normal.

Nose: Left middle turbinate covered with dry mucus.

Ear Drums: Left meatus clogged with cerumen; both drums normal appearing.

Coloscopy: Instrument introduced 25 cm. with patient in knee-chest position; end of instrument palpable on left ribarch; small hemorrhoidal nodules on sphincter ani; nothing else abnormal on linings.

Clinical Examination:

Ewald test (60 minutes, rice and raisins 12 hours previous): quantity, two ozs.; reaction, acid; color, yellow; odor, bread; layers, wash water contains $\frac{1}{4}$ oz. sediment of fine bread and mucus; no rice or raisins. Free Hydrochloric Acid: Congo red test: very positive. Gunzburg test: very positive. Total Free Hydrochloric Acid: 34. Total Acidity (Titration): 46. Achroodextrin: absent. Erythrodextrin: considerable. Amylum: mostly. Saccharomyces cerevisiae: moderate. Starch Bodies: sufficient Rhexis, mucus.

Blood Test Findings:

Wasserman Test: negative. Hemoglobin, 75 per cent. (Talquist); Polynuclear, 60 per cent.; Small Lymphocytes, 19 per cent.; Large Lymphocytes, 3 per cent.; Transition, 9 per cent.; Eosinophile, 1 per cent.; Basophiles, 1 per cent.; Myelocytes, 7. (!)

Feces Examination:

Color, light yellow; consistency, liquid; parasites, absent; muscle particles, moderate, rectangular, in some striation visible; connective tissue, absent; enthelminth-ovula, absent; protozoa, absent; fat-acid crystals, absent, on adding glacial acetic acid and heat a very few fat globuli; carbohydrates, a few, iodine positive, amyllum bodies, extra and intracellular; reaction, alkaline; benzidine test, negative; fermentation test, 25 per cent.; fermentation reaction, slightly acid.

The patient was put to bed and ran a temperature every day, in the morning 99 degrees and in the afternoon 101 $\frac{1}{2}$ degrees; the pain in right fluctuating abscess exacerbating in the nighttime; he complains also of pain in night in the upper right lumbar region. (!)

On March 6th the abscess was incised over the

right rib arch by Dr. Joseph Sternberg; the pus on guinea-pig inoculation proved to be tubercular; about one cupful was emptied and the cavity drained; the fever disappeared but patient feels very weak and drowsy most of the time; vomits frequently; visibly emaciated; hypodermics of adrenalin 10 drops a day and inunction treatments having no effect whatever upon the progress of the disease.

Exitus: March 20th, 1917.

Diagnosis: Basing my view of the case upon the peculiar color of the skin, the pigmentation on his lips and cheek linings, the extreme muscular weakness, the finding of apparent tubercular nodule in the prostatic lobe, as well as the apex of the left lung, and the tuberculous pus evacuated from the cold abscess over the right rib arch, I made the diagnosis of tuberculosis of the suprarenal glands, or, as the case is commonly called, "Addison's Disease."

Necropsy by—Drs. Menne and Benson.

Name—Mr. Charles Smitt; age, 45.

Physician's name—Dr. Gustav Baar.

Examined by—Dr. Baar.

Clinical Diagnosis—Tuberculosis of the Adrenal Glands, or Addison's disease.

Anatomic Diagnosis—Fibro-caseous tuberculosis of the suprarenal glands with cold abscess formation about the upper pole of the right kidney; tuberculous lymphadenitis of the glands about the abdominal aorta; tuberculous prostatitis; bilateral tuberculous epididymitis; localized acute conglomerate and miliary tuberculosis in the apex of the left lung; tuberculous abscess of the right costal cartilage; moderate bronzing of the skin; dry skin; general emaciation and anemia; serous atrophy of adipose tissue.

This is the emaciated body of a white man about 45 years of age. The head is covered with brownish black hair, streaked with gray. There is a mustache of similar color and similar hair is found on chest, axillae, abdomen and pubes. There is general emaciation; the eyes are sunken and rigor mortis is present. Body heat is still present.

On the right side at the level of the eighth rib, in the mid-clavicular line, is an incision 3 cm. long, showing ulceration and containing a slight amount of pus and hemorrhage.

In the usual midline incision, the subcutaneous fat is 2.5 cm. thick, is light yellow and is thickest at the navel. Beneath the ulcer at the eighth right costo-chondral junction a large amount of caseous pus is present. The musculature is bright red but small in amount. The great omentum hangs down over the front of the bowel and contains a small amount of yellowish brown fat. The small intestine is collapsed, the large intestine is distended with gas. The appendix is large, red, swollen with engorged blood vessels and is twisted on itself, being curved under and through the meso-appendix over the brim of the pelvis. Multiple retrocaecal fossae are present and there are many small pit-like depressions leading away from these fossae. The right inguinal canal is patent to the extent of two fingers breadth. The spleen is slightly enlarged. There are no adhesions about the gall-bladder, which is empty and extends to the liver margin. The mesocolon, peritoneum, and mesentery are adherent to the under lobe of the liver to the right of the gall bladder. The vessels are engorged and purplish. The lower edge of the liver falls 4 cm. short of the costal margin and is white, thin and fibrous.

The peritoneum is smooth, moist and glistening, and the cavity contains no excess of fluid. Anterior to the abdominal aorta and between it and the inferior vena cava are numerous lymph glands varying from 0.2 cm. to 3.5 cm. in their greatest dimensions. These become larger and more numerous towards the left renal vein, around which they form a cluster of adherent but distinct glands, which are grayish red and mottled with hemorrhages.

The lungs do not collapse but are hugely emphysematous, filling the chest cavity. They are grayish white and uniformly distended. The pleura are moist, smooth and glistening, and there is no increased amount of fluid here. The heart is free and the pericardium is smooth, moist, and glistening, and contains a small amount of blood-stained fluid. In the region of the thymus there is a small amount of thymic tissue, and a few scattered lymph glands, black with coal dust.

The mucous lining of the esophagus is unchanged. The entire intima of the aorta is smooth and glistening except in the isthmus, where there is a yellowish white indefinite scar 1 cm. in diameter. At the bifurcation of the trachea are small lymph glands, slightly hyperemic and containing coal dust but showing no foci of tuberculosis. There is frothy mucus in the trachea, the walls of which are red and the blood vessels engorged and show slight infection.

In the pulmonary artery there is free blood and a little clot. The left auricle is filled with a dark black clot. The mitral valve admits two fingers. In the right ventricle there is free and clotted blood—all clots being post mortem. The pulmonary leaflets are unchanged and there are no changes in the left auricle or mitral valve. The foramen ovale is closed and there is a narrow membranous Eustachian valve present.

In the apex of the upper lobe of the right lung there are scattered patches of conglomerate tubercles occupying a region 5 cm. in diameter. Lying along the common bile duct close to the cystic duct are three lymph glands which are soft and white and streaked with red. These are surrounded by scar tissue.

Addendum: In the globus major of the right testicle there is a discrete caseating tuberculous focus and more healed foci about it. In the prostate there are three or four tuberculous foci which are irregular in outline and definitely encapsulated but still caseating. Streaming up from the back of the prostate and growing progressively larger as the right kidney and renal veins are approached, is a chain of lymph glands alluded to elsewhere in this record; they seem to lead directly to a large fibrous mass covering the upper anterior two-thirds of the right kidney. This mass caps the kidney and includes the suprarenal gland. Upon incising this a cold abscess is found and the suprarenal gland is greatly enlarged and involved in a fibro-caseous tuberculous process which completely obliterates its normal markings and modifies its outline. From here glands similarly involved course across to the other suprarenal gland which is enlarged and occupied by a similar diseased process as that on the right side, thus the route of progression seems outlined by the anatomic changes.

The spleen is small and shrunken, the liver pale and atrophied. No generalized miliary tuberculosis can be found.

THE LITERATURE ON THE INTERNAL SECRETIONS

GENERAL SUBJECTS

A New Ductless Gland (*Glandula insularis cervicalis*). Pende (N.) *Mikroskop. Anatom. Arch.* (Bonn) 1914, lxxxvii, 193.

This gland is close to the thyro-parathyro-thymic system; is made of small epithelial islands (15-20), which surround the thymus and the thyroid lobes. Most of them are in the connective tissue of the superior lobes of the thymus, outside of the capsule.

In the newborn the glandular nodes are bigger and can be seen as many little clusters scattered around the perithymic and the peri-pa-tyroid tissue. They have no capsule, but can be easily distinguished from the surrounding tissue; so that under the microscope they look like cellular clusters neatly isolated. Inside there is no real connective stroma. The epithelial-like cells are rather large, with a well delimited protoplasm and a central vesicular nucleus. In some cells there are vacuoles, which increase with the age. The metaplastic granules of these cells are made up of lipoids (Ciaccio system) and according to the author they constitute the essential secretion of the gland. There are neither excretory ducts, nor follicles, nor colloidal spaces. The author calls this fourth gland *Glandula Insularis Cervicalis*.—G. V.

ENDOCRINE GLANDS, Effect of the Chloroform Narcosis on the. Scaglione (S.) *Virch. Arch.* 1915, ccxix.

Starting from the observations of Delbert, who believes the chloroform to act on the adrenals, the author, basing his opinion on a series of experiments, states that in case of death through chloroform narcosis there must be either lesion or insufficiency in the endocrine function.

During the first hours of narcosis he found the chromaffin reaction greatly reduced and no reaction at all under protracted narcosis.

In the other glands more lipoids and secretory granules were found in the beginning and a marked decrease under protracted narcosis. According to the author, these findings show that the endocrine glands rapidly secrete antitoxic substances.—G. V.

(THYROID) Etiology of Endemic Goiter. Stiles (C. H.) Detroit Med. Jour. 1916, xvi, 93.

A brief summary is given of the history of endemic goiter, also an account of goiter districts throughout the world. The article is of interest, chiefly, for the summary of the work of Marine and Lenhardt on thyroid carcinoma in trout. It was found by these authors that the degree, frequency and rapidity of development of thyroid hyperplasia in trout was in direct proportion to the degree of contamination of the water and that spontaneous recovery almost invariably occurred when the trout were removed from infected tanks. Mention is made, also, of the work of McCarrison, who produced goiter in himself and others by the administration of suspended matter gathered from the sides of tanks and wells containing goiter producing water.

Stiles speaks of the remarkable results following the administration of a vaccine made from an ameba obtained from the excreta of goiter patients.—F. B. L.

(THYROID) Over het voorkomen van struma (The occurrence of goiter). Kappenburg (B. D. G.) Nederlandsch Tijdschrift voor Geneeskunde, 1916, ii, 2079.

Kappenburg has found that of the 493 nurses in Utrecht, 56 (11 per cent.) had a struma. In other Dutch towns the number of struma patients is much less. He found also that though struma is very rare in children of six years and younger, in Utrecht many children under six years suffer from it. He found an enormous number in the little village Vreeswyk, where the people use the water of the river (the Lek). He also discovered a great number in places situated on another little river (the Linge) which gets its water from the Lek. He is quite aware that, though the theory of the water sounds very simple, it has never been proved. The author found also that nurses in lunatic asylums suffered much more from struma than other nurses.—J. K.

PARATHYROID Glands. Vermeulen. Nederlandsch Tijdschrift voor Geneeskunde, 1916, ii, 2520.

Vermeulen has examined the situation and the histological structure of the parathyroids in different domestic animals microscopically. He finds (according to Kohn) three types: 1. Glands composed of epithelium only, with very little blood and connective tissue (sheep, goat, and one of the glands of the horse). 2. Glands with much blood, much connective tissue and fat (cow, pig, the lateral gland of the

horse). 3. Glands composed of trabeculae of cells placed round a lumen (man, dog).

For practical purposes we can but utilize the glands of sheep and goat; horses may be used, too; however, it is difficult to find the glands in some cases. The ordinary source of parathyroid material is the pig, but this is, according to the author, not desirable as the situation of the glands is very inconstant.—J. K.

(ENDOCRINE ORGANS) Internal Secretory System in Ophthalmology with Special Reference to Goiter. Lamb (R. S.) *Ann. of Ophth.* (St. Louis) 1917, xxv, 244.

The author endeavors to state concisely the results of a vast amount of observation. He takes note first of the difficulty in attempting to identify most of the symptoms regarded as being due to the secretion, or lack of it, in connection with any one gland; though he emphasizes the necessity for making the attempt so to do. He calls attention to the very close association between the sympathetic proper and vagus or autonomic system and then endeavors to show the effect of stimulating the sympathetic in both mild and marked intensity—considering the probable etiology of Graves' disease—and then the effect of the stimulation on the vagatonic or autonomic system is considered and its possible effect as a causative factor in acute inflammatory glaucoma; the effect of internal secretory imbalance upon esophoria and exophoria; ciliary congestion and chorioretinitis; disturbance of visual acuity, ocular fixation and hemianopsia are also considered. The hope is that many reading the article may correlate their own observations and at as early a date as possible make contributions to the literature on this subject.—R. S. L.

(SEX, GONADS) The Theory of Sex as Stated in Terms of Results of Studies on Pigeons. Riddle (O.) *Science* (Lancaster, Pa.) 1917, N. S. xlv, 19.

In the concluding paragraphs of an article on the essential nature of sex differences the author states that: "Studies on the effects of castration, gonad-transplantation, and gonad-extract injection, constitute a large body of observations which deal with sexual phenomena associated with the internal secretions of the sex-glands. These internal secretions, let it be remembered, are themselves metabolites, which have the capacity to influence the metabolism of some, many, or of all the tissues with which they come in contact, or which they may reach indirectly.

"The results, as a whole, demonstrate that the extent of sexual modification in the experimental animal is, in general, in proportion to the immaturity of the treated animal. That is to say, the earlier the internal secretion of the gonad is supplied or withdrawn, the more profound is the sexual modification of the individual. The stag is a form that has long been known to show thus a considerable and beautiful series. The free-martin is now known (Lillie, 1916) to exemplify a much earlier point at which the foreign internal secretion begins to act; and here, true to the rule that has been established elsewhere in all this general line of work, the resulting modification is correspondingly strong and striking. When, by whatever means, we effect a change in the metabolism (which is the essential thing) at a still earlier stage—in the egg-stage, in our own and in some other experimental reversals of sex—then we obtain individuals whose sexual nature is quite thoroughly reversed; in many cases completely so, and in still other cases with varying degrees of completeness.

"Professor Whitman's main decisions concerning the nature of sex may here be briefly stated. These decisions were that the male proceeds from a 'stronger' germ, has greater 'developmental energy' and 'carries the processes of development farther' than does the female. I am confident that his results fully justify his conclusions; and that these are in the completest harmony with the later and fuller development of the sex-studies in the pigeons, and thus with the theory of sex which has been outlined in these pages.

"In conclusion, our present definite knowledge of the metabolic basis of sexual difference, and the methods of attack which this new knowledge brings with it, offer the surest guarantees that the problem of sex can now be studied—and, indeed, the basal facts of the problem must be studied—in the field of the elemental protoplasmic functions."—(Quoted.)

"INTERNAL SECRETION" The Nomenclature of. Bell (W. B.) *Lancet* (London) 1917, cxcii, 4871.

In a communication to the editor of the *Lancet*, the suggestion is made that the word "Hormone" be used indiscriminately for every internal secretion and that the hormone manufacturing organs, or the endocrine organs, be spoken of as the "Hormopoietic" organs and that the process be designated "Hormopoiesis."

The reasons for the use of these terms is that they are derived directly from the term "Hormone" and that their meaning is quite clear.—W. B. T.

A Contribution to Vegetative Neurology: Touching upon Heart Action, Status-Lymphaticus, and So-Called Vagotonia and Sympathicotonia. Tracy (E. A.) Boston M. & S. Jour., 1917, clxxvi, 538.

The skin of a normal individual, when stroked, gives the reaction of vaso-constriction, this appearing as a whitish streak (in Caucasians). The writer found some patients in which no reflex vaso-constriction appeared after stroking. These patients a few minutes after having had injected into them, therapeutically, a dose of adrenin, gave the reaction of vaso-constriction when again stroked. Stroking causes more stimuli to flow over the nerves concerned in the phenomenon, that is, it increases the tonus of the sympathetic fibres—if we regard the tonus of a nerve to be measured by the number of stimuli going over it. In the cases mentioned—those of patients without the reflex of vaso-constriction to stroking—we could increase the tonus of the nerves, that is, increase the stimuli flowing over them, as much as is possible by stroking, and yet no vaso-constriction resulted. In other words, increasing the tonus of the sympathetic nerve fibres—the nerves concerned in vaso-constriction—does not cause vaso-constriction. The same patients, shortly after having had an injection of adrenin, gave the reflex vaso-constriction on stroking. The only change in the conditions was the addition of adrenin to the blood stream. It must be granted, therefore, that reflex vaso-constriction is caused by an increase of the nerve stimuli plus adrenin in the blood stream. Heart action is brought into relation with the hormones in the blood stream—which are known to cause dilation and contraction of the peripheral blood vessels together with stimuli coming over the autonomic and sympathetic fibres. The heart, of similar musculature and with similar innervation, probably reacts to blood hormones in a similar manner as do the peripheral blood vessels. Stimuli coming over the autonomic (vagus) fibres together with hormone X in the blood stream cause diastole of the heart, and stimuli coming over the sympathetic fibres together with adrenin in blood stream cause systole. This view of heart action explains the occurrence of death in status thymo-lymphaticus, the cause being superabundance of hormone X in the blood stream and insufficiency of adrenin. The dilatation of the heart is provided for, but the insufficiency of chromaffin tissue causes lack of adrenin, without the stimulus of which the heart cannot contract, no more than, as we have seen, the blood vessels can.

Status-lymphaticus may be diagnosed by the absence of anemic dermatography, showing lack of adrenin in the blood stream.

Observation and experiment show that so-called vago-tonia and sympathicotonia are due to a hypercontent in the blood stream of the respective hormones, and not to a true hypertonus of the nerves involved.—E. A. T.

(The sum total of the available evidence makes the existence of "hormone X" extremely improbable. That adrenin in significant amounts occurs in the normal blood stream is also open to doubt. It is probable, therefore, that other explanations will be found for the phenomena discussed. The fact that artificially administered adrenin plus reflex vasomotor stimulation give greater effects than either alone is what would be expected as an example of "summation of stimuli."—Editor.)

(PARATHYROID) Physiology of the Parathyroid Gland.

Koch (W. B.) J. Lab. & Clin. Med. (St. Louis) 1916, i, 299.

The author in an excellent study of the subject shows that the behavior of a parathyroidectomized dog may coincide with either of two distinct groups of symptoms, or with a mixture of these two types, in which one may predominate.

(a) In one type, the dominant feature is over-excitability of the nervous system.

(b) In another, the dominant feature seems to be under-excitability.

In the former, tonic convulsions are characteristic and in the latter we observe a peculiar muscular flaccidity and a general depression of the nervous system. In either case, death occurs in from two to ten days.

The writer has varied from the usual studies in that he performs careful post-mortems on his subjects. In the dogs dying with typical tetany, the most striking changes were found in the blood, liver, kidney and brain. The ordinarily invisible intestinal vessels were so dilated as to be easily traced. The liver and spleen were markedly congested; the intestinal tract edematous and the bladder full of urine. The blood showed extensive ante-mortem clots. Section of the liver showed fragmented erythrocytes, normoblasts, erythroblasts and cell shadows. There were also many mononuclear cells with eosinophil granules. The kidney showed congestion and hemorrhagic areas in the cortex. Spleen contained much pigment. The brain showed the cells in the motor area with partial loss of Nissl substance and typical tetany nuclei.

The totality of all of these symptoms points to a hyperexcitability of the whole nervous system, including those neurons continued to the cord via the sympathetic.

Two of the 47 dogs exhibited what the writer calls a negative phase. They slept in a peculiar state of flaccidity with the limbs somewhat flexed. They moved very little and died in four days with no other symptoms. The writer thinks that these cases correspond to over-stimulation of the central nervous system comparable to shock.

As regards the relation of the parathyroids to tetany very few details are known. The one definite piece of work seems to be that of MacCallum who showed that the urine of these animals contained excessive calcium and that injection of calcium controlled the convulsions. Others have shown, however, that similar salts have an identical but not so marked an effect and that even the calcium action wears off in a few days. The writer observed that tetany could be controlled by aqueous salts and when this was no longer efficient the kidneys were no longer functioning. So he believes that all salts act as diuretics aiding in the excretion of a hypothetical toxin and that calcium is simply more efficient due to its depressing qualities. Accordingly, Koch advances the theory that tetany is simply an intoxication; that the toxin is subdued by diuresis, by neutralization and is not toxic in the presence of the parathyroid gland.

To confirm this supposition, he has attempted to isolate this body from the urine and has found two substances. One is methylcyanamide and the second trimethylmelanine. The injection of 27 milligrams produces tetany in rabbits.

Koch concludes: (1) somewhere in the body methylcyanamide is generated; (2) this substance has a physiologic effect in normal animals; (3) after parathyroid extirpation this substance accumulates to toxic quantities, and is responsible for the death of these animals.—J. R. G.

(ENDOCRINE GLANDS) A Review of the Advances in Our Knowledge of Internal Secretions During the Last Two Years. Park (E. A.) *Am. Jour. Dis. Child.* (Chgo.) 1916, xii, 477.

A very excellent review of the general subject of endocrinology and worth reading in detail.—J. R. G.

(ADRENALS) The Present Status of the Adrenal Problem. Hoskins (R. G.) *J. Lab. & Clin. Med.* (St. Louis) 1916, i, 512.

See *Endocrin.*, 1917, i, 292.

ADRENIN and Other Vasoconstrictory Substances in the Animal Organism. Baraden (D. W.) (Dissertation, Petrograd, 1916, 94 pp.)

The author shows that the serum and extracts of different organs, if perfused through the isolated ear of a rabbit, constrict the peripheral vessels, and this capacity, with the exception of the adrenal extract, is augmented by letting them stand, and especially by heating them; but this rise of the vasoconstrictor power by heating only occurs up to a certain temperature, after which there is a fall. Embden and v. Fürth showed that a mixture of serum and adrenalin gives a stronger effect than either does separately. Following this up, the author shows that the same result is obtained by a mixture of adrenalin and different organ-extracts. If the mixture of different extracts is used, only a slight vasoconstricting effect is produced, with the exception of the adrenals and liver, which are similar in their action. The same extracts and serum with isolated gills give a very strong constriction, whereas adrenalin by itself dilates their vessels. The action of the adrenal extract on them is very inconstant. It causes sometimes dilatation, sometimes constriction. Heating the extract diminishes its constricting power on the vessels of the ear, but apparently augments it with regard to the vessels of the gills. These properties of the adrenal extract show, according to the author, that in the blood and in the organs there are other vasoconstricting substances besides adrenin. In the adrenal extract the action of the adrenin and of these other substances is combined, and to that the variety of the action of this extract is due. The constricting action of the adrenal extract is diminished in phosphorus-poisoning. The action of serum and of the extract of other organs is, under these conditions, changed in a less degree.—(Physiol. Abstr.)

(ADRENALIN) Der Suprareninegehalt handelsüblicher Suprareninpräparate und die Art seiner Feststellung. Johannes-
sohn (F.) Biochem. Zeitsch. (Berlin) 1916, lxxvi, 377.

Folin's colorimetric method of estimating adrenalin proved very accurate when tested by the Lâwen-Trendelenburg transfusion method, but it was vitiated by the presence of alypin and novocaine. For the determination of the adrenalin content of commercial preparations a satisfactory colorimetric method was devised which was based on the Fränkel-Allers-Bayer reaction with iodic acid in presence of sulphanilic acid. Many fresh preparations yielded 70 to 80 per cent. of the stated content. The drug deteriorates less in

ampullae than in tabloid form, particularly if hydrochloric acid is present in the former.—(Physiol. Abstr.)

(THYROID) Relations between the Histological Structure of the Thyroid Gland and its Content in Iodine. Pellegrini (R.) Arch. sci. med. (Torino) 1916, xl, 92.

There is no definite relation between the amount of colloid and the amount of iodine per gr. dry substance in the human thyroid, the one often being high while the other is low. Six types of thyroid were recognized, a definite (within certain limits) content of iodine corresponding to each; many intermediate types also exist. The variations in the density of the colloid correspond to different degrees of functional activity, the more dense and recently secreted colloid being richer in iodine.—(Physiol. Abstr.)

(THYROID) Blood-Sugar Estimation in a Case of Infantile Myxedema. Nilsson (N. O.) Upsala Läk. Förhandlingar (Upsala) 1916, xii, 106.

A rise in the blood-sugar after the administration of sugar persisted for a long time, as it does in diabetes mellitus. The thyroid is believed to stimulate the chromaffine system. The reaction to adrenalin injection was therefore tested before and during thyroid treatment in this case. A dose of half a milligram of adrenalin before thyroid treatment raised the blood-sugar percentage from 0.09 to 0.17; the mononuclear leucocytes increased from 2210 to 7400. During thyroid treatment the response was in the same direction, but not so marked.—(Physiol. Abstr.)

EXPERIMENTAL INVESTIGATION

ADRENIN, Quantitative Studies on the Liberation of, from the Adrenals after Section of their Nerves, with Special Reference to the Question Whether Adrenin Is Indispensable to the Organism. Stewart (G. N.) and Rogoff (J. M.) *Proc. Soc. Exp. Biol. and Med. (N. Y.)* 1917, xiv, 145.

"1. We showed in a previous paper by the blood pressure and eye reactions that after section of the nerve supply of the adrenal no demonstrable liberation of epinephrin was present in cats as long as five weeks after nerve section.

"2. As it is easier to detect very small concentrations of epinephrin by the rabbit intestine and uterus segments, we have made a series of experiments (on 7 cats) in which these tests were used to supplement the eye reactions. In all the animals one adrenal was excised and the nerves of the other cut.

"In a cat tested two weeks after the operation, it was shown that the adrenal blood serum could not have contained 1:300,000,000, or the blood 1:400,000,000, of epinephrin; and that the rate of liberation of epinephrin could not have been at most 0.000001 mgm. per minute for one adrenal. In another cat three weeks after the operation the serum of the adrenal blood was proved to contain less than 1:400,000,000, and the blood less than 1:700,000,000 epinephrin. The output of epinephrin per minute could not have been as much as 0.0000009 mgm. per minute, for one adrenal. The segments used for the tests in these experiments were extremely sensitive, and the limits of adrenalin concentrations that could be detected with certainty were carefully determined. The eye reactions were negative. In these two cats the rate of liberation of epinephrin, if any liberation whatever was going on, must have been several hundred times less than the rate in normal animals under the same experimental conditions.

"It is scarcely necessary to point out that experiments yielding completely negative results indicating the absence of epinephrin with very sensitive test objects are much more important for the questions studied than experiments in which small amounts of epinephrin can still be detected. For it is impossible to be certain that when a little epinephrin is found some of the fibres concerned in the liberation may not have escaped section.

"3. Since these animals had completely recovered from the operation and behaved in every way like normal animals, it must be concluded that the liberation of epinephrin from

the adrenals is not indispensable for life or health, unless indeed the necessary quantity is, even in the adrenal vein blood, below the limits of detection by the methods used. It must be remembered that the epinephrin in the adrenal blood is diluted enormously (probably at least 100 times) in the right heart; so that in these cats the concentration in the arterial blood could not at most have reached 1:40 billions and 1:70 billions, respectively.

"If the liberation of epinephrin is abolished by division in the dorsal cord of the path concerned in it, as our experiments on 'Relation of the Spinal Cord to the Spontaneous Liberation of Epinephrin' indicate, this corroborates the conclusion that epinephrin is not indispensable. Numerous animals and men have long survived such lesions.

"4. These experiments indicate that the entire liberation of epinephrin from the adrenals is controlled by nerves.

"5. In a third cat (8 days after operation) the adrenal vein blood contained epinephrin but in concentration not exceeding 1:125,000,000. The output of epinephrin per minute was probably at most not more than one-hundredth of what might be expected in a normal animal.

"6. In a cat 15 weeks after the operation it was doubtful if any epinephrin was present in the adrenal vein blood. In two others 15 weeks after operation eye reactions and segment tests showed the presence of a small amount of epinephrin, the rate of liberation being a mere fraction of the normal. The possibility of regeneration of fibres after this interval must be considered. In the seventh cat (tested two weeks after the operation) the eye reactions were negative. The segment tests revealed a small concentration of epinephrin in the adrenal blood (less than 1:30,000,000) corresponding to a rate of liberation of epinephrin per minute of at most one tenth of the normal." (Original article quoted in full.)

(ADRENIN) Epinephrin and Ergotoxin, Action of, upon Single, Physiologically Isolated Cells. Spaeth (R. A.) and Barbour (H. G.) *Jour. Pharm. and Exp. Therap.* (Balt.) 1917, ix, 431.

This research was done upon the melanophores (pigment cells) of the common "killi fish," *Fundulus heteroclitus*. The melanophores of this fish as of all other vertebrates are controlled by the thoracico-lumbar autonomic (sympathetic) system. The melanophores are apparently modified smooth muscle cells. It was found that adrenin in all dilutions up to 1:50,000,000 caused complete contraction of the pigment cells. Ergotoxin has relatively slight effect upon the cells but causes a slight expansion. Melanophores exposed to the action of

ergotoxin, however, subsequently react to adrenin by expanding. This effect of ergotoxin is comparable to its influence upon the vascular smooth muscle; after a dose of the drug adrenin in quantities that previously had a pressor effect will cause a fall of pressure. The reactions to ergotoxin and adrenin confirm the belief that the melanophores are in reality modified smooth muscle cells.—R. G. H.

(ADRENIN) The Vascular Reactions in Experimental Acute Tartrate Nephritis. Karsner (H. T.) Jour. Pharm. and Exper. Therap. (Balt.) 1917, ix, 483.

In dogs subjected to experimental tartrate nephritis adrenin was observed to produce its ordinary effect, viz., renoprivation and depression of urine formation.—R. G. H.

ADRENIN, Relation of Spinal Cord to Spontaneous Liberation of. Stewart (G. N.) and Rogoff (J. M.) Proc. Soc. Exper. Biol. and Med. (N. Y.) 1917, xiv, 143.

In the experiments the pupil reaction was used as an index of the presence of adrenin, it having been sensitized by the previous removal of the superior cervical ganglion. The blood from the adrenal vein was collected in a pocket fashioned from the vena cava and liberated en masse in order to get the maximum adrenin reaction. The pupil test was supplemented in some instances by the rabbit intestine and uterus tests.

It was found that section of the spinal cord in the cervical region had no detectable influence on the adrenin output. (Several cases.) In one experiment section of the cervical cord had not checked adrenin discharge but cutting it between the fourth and fifth dorsal vertebrae checked the discharge. Stimulation of the cut cord caused a renewed discharge. In a similar experiment quantitative determinations were made. After section of the dorsal cord no discharge of adrenin could be detected; it was proven that if any discharge was occurring it was less than enough to give a concentration of 1:100,000,000 in the adrenal vein or at most not one one-hundredth the amount to be expected in a normal cat under the existing experimental conditions.

Cutting the nerves supplying the adrenal glands was shown to lessen greatly or completely to abolish adrenin discharge.

These observations would seem to establish the fact that adrenin discharge is under reflex control, the control being mediated by the spinal cord at a level below the cervical region.—R. G. H.

PINEAL GLAND, Function of, in Relation to Pigmentation.

McCord (C. P.) and Allen (F. P.) Jour. Exp. Zool. (Phila.) 1917, xxiii, 207

This paper records some very striking results obtained by feeding pineal substance or pineal extracts to tadpoles. The color of the animals depends largely upon a layer of sub-epidermal pigment cells (melanophores). When the melanophores are expanded the tadpoles are dark in color. When contraction of the melanophores occurs the color becomes much lighter and the organisms translucent. When fresh pineal gland substance was fed to ten-day tadpoles a marked retraction of the pigment cells took place so that at the end of thirty minutes the fed animals were noticeably lighter than the controls. Maximum translucency was attained in forty-five minutes and restoration to the original color occurred in three to six hours. Alcoholic and acetone extracts of pineal substance were also investigated. But little of the active substance was removed by alcohol while it was removed completely by acetone. Tadpoles placed in a 1:500 pineal emulsion (from acetone extract) were noticeably lighter in five minutes and the maximum effect was obtained in a half hour. In higher dilutions the effect was slower in developing and less complete in degree.

In commenting upon their results McCord and Allen mention the fact that the pineal gland has been evolved from a parietal eye which reached its highest form of development in certain of the lizards. In various animals the changes of color are regulated by the eyes. It is interesting to note that although the pineal has completely lost its ocular function it still retains an ability to produce a substance capable of controlling pigment cell changes. The technical methods of the investigators are worthy of high commendation. A large number of animals (12,000) was employed and the control animals were fed with indifferent tissues—brain or muscle. The research is valuable in affording a clean-cut proof of the presence of an active substance in pineal tissue—a fact which some investigators would not hitherto have been willing to concede.—R. G. H.

(DUCTLESS GLANDS) Changes in the Relative Weights of the Various Parts, Systems and Organs of Very Young Albino Rats Underfed for Various Periods. Stewart (C. A.) Anat. Rec. (Phila.) 1917, xi, 410.

Results: Increase in the weight of the adrenal glands, testes, ovaries, hypophysis, a decrease in the thymus and no change in the thyroid and pineal body.—E. R. H.

(GONADS) Early Castration of the Vertebrate Embryo. Reagan (F. P.) *Anat. Rec. (Phila.)* 1917, xi, 251.

An extirpation was made in young chick embryos of the small crescentic area of entoderm anterior to the body axis where the early germ-cells are found, and from which they were supposed by Swift to migrate via the blood vessels to the gonads. After the operation the embryos were allowed to develop but no germ-cells were developed in the gonads and hence Swift's view is upheld.—E. R. H.

(OVARY) The Ovarian Cycle in Mice. Smith (H. P.) *Anat. Rec. (Phila.)* 1917, xi, 407.

Ovulation in mice occurs spontaneously at intervals of 17.5 days. It occurs 18 days after parturition. The ovum of mice requires two days to traverse the greater part of the oviduct, and remains in the last loop one day.—E. R. H.

(THYROID) On Thyroidectomy in Amphibia. Hoskins (E. R.) and Morris (M.) *Anat. Rec. (Phila.)* 1917, xi, 363.

The thyroid anlage was successfully removed from young embryos of the frog and amblystoma before the functional stage. The operation seemed to delay growth and metamorphosis in the frogs, but there were no changes in the hypophysis. No change was seen during the three months of the observations in the amblystoma larvae except perhaps a slightly delayed growth. The experiment is to be repeated on a larger scale.—E. R. H.

(THYROID AND THYMUS) Studies on Internal Secretion IV. Treatment of Tadpoles with Thyroid and Thymus Extracts. Gudernatsch (J. F.) *Anat. Rec. (Phila.)* 1917, xi, 357.

Thyroid and thymus were each split chemically into seven products and tadpoles were treated with the substances obtained. The thyroid nucleo-proteins caused most rapid differentiation, and the precipitate from an alcoholic extract produced the greatest growth with the least differentiation. The other substances ranged between these two extremes in their action. Two of the seven thymus products delayed differentiation but the other five did not do so.—E. R. H.

THYROID, The Early Morphogenesis of, in *Squalus Acanthias*. Norris (E. H.) *Anat. Rec. (Phila.)* 1917, xi, 396.

The gland appears as a solid bud in the floor of the pharynx of embryos of 4 mm.. It becomes severed at 19 mm. and appears as a column, ovoid in section, and then forms into a diamond-shaped plate that is smooth at first, but is later

traversed by many ridges. Cavities that develop transform the plate into irregular smaller plates.—E. R. H.

(HYPOPHYSIS) The Development of, in Reptiles (Turtles, Lizards, Snakes and Alligators). Baumgartner (E. A.) *Jour. Morph. (Phila.)* xxviii, 209.

The epithelial anlage forms three parts of the hypophysis, namely, pars intermedia, pars tubularis and the anterior lobe. The first two are composed in the adult of columns of clear staining chromophilic cells, and the anterior lobe of columns or acini of clear staining chromophilic cells which may be either acidophilic or basophilic.—E. R. H.

HYPOPHYSIS, Effects of Inanition and Refeeding upon the Growth and Structure of, in the Albino Rat. Jackson (C. M.) *Anat. Rec. (Phila.)* 1917, xi, 368.

After birth the anterior lobe normally becomes relatively larger, the posterior lobe smaller and the intermediate part remains the same. In young rats held at maintenance, the anterior lobe loses relative volume. In an adult with chronic inanition, the anterior lobe was decreased, and in two adults with acute inanition, the anterior lobe appeared to be increased. After refeeding, the gland usually returns to normal. The loss in inanition and maintenance in the anterior lobe is confined to the parenchyma, and in this both the cytoplasm and nuclei suffer. Inanition decreases greatly the number of mitoses seen in the hypophysis, but they become more plentiful on refeeding. The nuclei in inanition become hyperchromatic and the cytoplasm may stain poorly. About four weeks' time is required for the hypophysis to return to normal on refeeding after inanition.—E. R. H.

GONADS. Further Data on the Relation between the Gonads and the Soma of Some Domestic Birds. Goodale (H. D.) *Anat. Rec. (Phila.)* 1917, xi, 512.

Data on ablation of testes and ovaries and on the transplantation of the ovary into castrated males has made it clear that different parts of the soma (body) react in different ways to the secretion of the gonads. The characters fall into 3 groups: 1. Those independent of either ovary or testes; size in females, voice, some phases of behavior, and mandible color in ducks. 2. Characters affected by the testes: comb and wattles, fat deposition, size in the male, some instincts and summer plumage in ducks. 3. Characters affected by the ovary: plumage, form and color and some phases of behavior. Castrated females are sexually neutral, but emascu-

lated (feminized) males (transplanted ovary) exhibit masculine sexual behavior. The entire series of gonadectomized individuals may be looked upon as a series of sex intergrades in which characters that are normally found in one sex may be experimentally transferred to the opposite sex while individuals composed of mixtures of such characters may be obtained.—E. R. H.

(HYPOPHYSIS, THYROID, GONADS, THYMUS) Extirpation of the Hypophysis and Thyroid Glands in *Rana Pipiens*.

Allen (B. M.) *Anat. Rec. (Phila.)* 1917, xi, 486.

Hypophysectomy caused failure in proper development of the dermal pigment, hind legs and amount of colloid in the thyroid, but no changes in the gonads and thymus. Thyroidectomy caused failure in metamorphosis although the tadpoles became very large. Feeding thyroid hastened metamorphosis in thyroid free larvae.—E. R. H.

(HYPOPHYSIS) The Effect of Hypophysectomy upon the Subsequent Growth and Development of the Frog. (*Rana Boylei*.) Smith (P. E.) *Anat. Rec. (Phila.)* 1917, xi, 57.

After hypophysectomy in young stages the thyroid, dermal pigment and hind legs failed to develop properly.
E. R. H.

HYPOPHYSIS of the Guinea Pig. Vanderburgh (C. M.) *Anat. Rec. (Phila.)* 1917, xii, 95.

A description of the gross and microscopic features of the hypophysis. In most respects it resembles that of other mammals. Cysts, some of which were lined with ciliated epithelium, were found in the pars intermedia and pars glandularis. These were interpreted as cut off portions of the cleft. The colloid in the cleft and cysts was granular and resembled mucus. Colloid was found in the pars nervosa and tuber cinereum, but it probably was secreted by the pars intermedia.—E. R. H.

(ADRENIN, PITUITRIN) Pharmacology of the Vagina. Waddell (J. A.) *Jour. Pharm. and Exp. Therap. (Balt.)* 1917, ix, 411.

Excised strips of vagina suspended in warm oxygenated Tyrode's solution were found to undergo spontaneous rhythmic contractions. The addition of adrenin stimulated the strips in case of rabbits, dogs, hogs and sheep while in case of rats, cats, guinea-pigs and cows depression occurred. In the former group, therefore, the sympathetic innervation is predominantly motor and in the latter group, predominantly

inhibitory. In case of the rabbit ergotoxin served to convert the stimulating effect of adrenin to inhibition. This animal, therefore, possesses both inhibitory and excitatory sympathetic fibres. (Probably true also of other animals.) In the various species studied the reactions to adrenin in the uterus and the vagina were similar.

Pituitary extract, as would be expected, stimulated the vaginal musculature.—R. G. H.

ADRENIN; Distribution between Corpuscles and Plasma.

Stewart (G. N.) and Rogoff (J. M.) Jour. Pharm. and Exp. Therap. (Balt.) 1917, ix, 393.

As nearly as could be determined by blood pressure, colorimetric or intestine and uterus methods of assaying, adrenin in blood occurs only in the plasma.—R. G. H.

HYPOPHYSIS, On the Relations between Neural and Intermediate Portions of. Atwell (W. J.) Anat. Rec. (Phila.) 1917, xi, 322.

Development of hypophysis in the rabbit. In early stages the neural and intermediate parts become fused in four regions where the basement membranes are lacking. Apparently this connection is lost later.—E. R. H.

HYPOPHYSIS, The Golgi Apparatus in the Cells of the Distal Glandular Portion of. Addison (W. H. F.) Anat. Rec. (Phila.) 1917, xi, 317.

The apparatus is found in both acidophilic and basophilic cells and persists throughout the changes in the hypophysis produced by castration, apparently functioning as a definite cell organ. In the large basophilic cells it appears near the nucleus as a round or oval condensed spot surrounded by a lighter ring.—E. R. H.

(THYROID) Influence of Thyroidectomy on Blood Sugar.

Janney (N. W.) and Isaacson (V. I.) Proc. Soc. Exp. Biol. and Med. 1917, xiv, 99.

Previous work in some cases has shown a decrease in blood sugar and in some an increase when the thyroids are removed. Injury to the parathyroids is probably one factor in the disparity. In Janney and Isaacson's dogs at least two parathyroids were left intact and the freedom of the animals from tetany showed that functional integrity had been maintained. After the thyroidectomy the blood sugar averaged about 25 per cent. lower than normal. Glucose feeding resulted in less elevation of the blood sugar level after than

before thyroidectomy. On the grounds that cretinism, myxedema, Addison's disease and experimental adrenal deficiency are all marked by hypoglycemia the authors offer this as a general sign of endocrine deficiency. They suggest that diabetes mellitus might possibly be benefited by removal of thyroid tissue—R. G. H.

(ADRENIN) Henle's Reaction of the Chromaffin Cells in the Adrenals, and the Microscopic Test for Adrenalin. Ogata (T.) and Ogata (A.) *Jour. Exp. Med. (Balt.)* 1917, xxv, 807.

The authors review at some length the literature on the so-called chromaffin reaction of adrenin producing cells. Whether the characteristic brown color which results from the application of chromium salts to the adrenin producing tissues is due to a specific reaction has been an open question. The problem was investigated using the fresh adrenals of various animals. Human adrenals were also used but were found not very suitable since the reaction was weaker than in the case of the adrenals of healthy animals. It was found that the chrome reaction as well as the silver and osmium reactions are merely reductions by adrenin. In their opinion the naming of the cells giving a positive reaction should not be based upon the reaction (i. e., chromaffin cells), but on the presence of adrenin itself. Biedl's terms, adrenal cell, adrenal organ, adrenal body, adrenal system, and also Bonna-mour's term, adrenalin-producing cells, are appropriate in this respect. They propose the names adrenalin cell, adrenalin tissue, adrenalin system, thereby indicating the presence of adrenalin.

The authors might well have gone one step further and eliminated the useless syllable in "adrenalin." One of the unfortunate features in the endocrine literature is its cumbersome terminology.—R. G. H.

THYROID, Effects of, upon Paramaecium. Shumway (W.) *Jour. Exp. Zool. (Phila.)* 1917, xxii, 529.

Earlier researches have established the fact that the division rate of pedigreed races of *Paramaecium* affords an index to their vitality. Determinations of the division rate can be utilized, therefore, in the investigation of various factors affecting metabolism. Shumway in the present paper reports an extension of earlier investigations of the effects of thyroid (and other endocrine gland substances) on these unicellular animals. Each experiment was carried out on a group derived from one known ancestor, the controls having identical heredity and environment with the experimental individ-

uials. The following substances were fed: desiccated thyroid, thymus, pituitary body, adrenals, pancreas and commercial iodothyryn and iodine. Among others the following results were obtained:

"Thyroid substance fed to *Paramaecium aurelia* or *caudatum*, either as emulsion of raw thyroids or as a suspension of the commercial powder, produces a constant and significant increase of 65 per cent. in the rate of division over that observed in the common laboratory medium—hay infusion. The thyroid is the only one of the internally secreting glands that produces this effect. Boiling the thyroid produces no change in the reaction. Iodothyryn and iodine fail to produce the thyroid effect. *Paramaecia* after prolonged thyroid treatment revert to the normal division rate when returned to the control medium. *Paramaecia* ingest and digest particles of the thyroid. It is suggested that the results of thyroid feeding here noted are due to the presence of a remarkably stable hormone in the thyroid which may be classified among the 'dissimilatory' hormones."

These results in conformity with those of various other recent researches indicate that thyroid substance is a highly potent general stimulant. It should be given a thorough systematic trial in practical therapeutics in cases where a general metabolic stimulant is needed, both alone and in connection with the various recognized "tonics."—R. G. H.

(ADRENIN.) The Mechanism of Cardiac Acceleration by Warmth and Adrenalin. Evans (C. L.) *Jour. Physiol.* (Lond.) 1917, li, 91.

Evans and Ogawa have shown that when a range of temperature of 7° was studied, the oxygen consumption by the beating heart varied directly as the pulse rate, or, in other words, the oxygen consumption per heart beat remained constant. Adrenalin in small amounts accelerates the heart, but there is no such constancy in gaseous metabolism as was observed in the case of temperature. More oxygen per beat was required when the heart was accelerated by adrenalin. The present paper is a continuation of these studies, and the conclusion is reached that the increased metabolism caused by adrenalin is apparently due to a direct and specific effect in increasing and accelerating the chemical changes associated with contraction.—T. C. B.

(PARATHYROIDS.) Does Parathyroidectomy in the Dog Affect the Blood Coagulation Time? Simpson (S.) and Rasmussen (A. T.) *Quart. Jour. Exp. Physiol.* (London) 1916, x, 145.

The problem was to ascertain if removal of the parathyroids (and incidentally the thyroid) would lead to any change in the coagulation of the blood, as might be expected if the ionic calcium content of the blood were affected by this operation. The graphic method of Cannon and Mendenhall was used to determine the coagulation time. The authors find that coagulation time in dog's blood varies considerably, not only in different individuals, but in the same individual from time to time. The removal of the thyroid and parathyroids does not appear to have any distinct effect on the coagulability of the blood, either before the onset of tetany or immediately succeeding it.—T. C. B.

(ADRENIN) The Epinephrin Content of the Blood in Conditions of Low Blood Pressure and Shock. Bedford (E. A.) *Am. Jour. Physiol. (Balt.)* 1917, xliii, 235.

The investigation was undertaken to determine the activity of the adrenals during shock produced by handling the intestine, by hemorrhage and by occlusion of the inferior vena cava. Strips of rabbit's intestine were used to indicate variations in the amount of epinephrin in the blood drawn from the vena cava close to the entrance of the adrenal vein.

The general conclusions to be drawn from the experiments are as follows: Increased quantities of epinephrin are thrown into the blood during conditions of low blood pressure and shock. This increase is due to a hyper-activity of the gland, and not simply to a release of epinephric material stored in the gland. The epinephric content of the blood increases only after a prolonged continuation of the conditions leading to shock. The quantity of epinephric material in the blood increases with prolongation of the period of low pressure and shock. The increased output of epinephrin into the blood may be a last effort of the organism to resist the forces that are tending toward a fatal degree of low blood pressure.—T. C. B.

ADRENIN, Effects of, on Distribution of Blood. II Volume Changes and Venous Discharge in the Spleen. Hoskins (R. G.) and Gunning (R. E. L.) *Am. Jour. Physiol. (Balt.)* 1917, xliii, 298.

A continuation of the studies begun in 1916, and abstracted in this Journal, Vol. I, p. 60.

The authors find that all effective dosages of adrenin cause a brief dilatation of the spleen, followed by contraction. This occurs whether the adrenin is injected instantaneously or by infusion. In no case was pure dilatation observed. The threshold for splenic contraction is lower than for changes in

arterial pressure. There is a brief increase of flow from the splenic vein, followed by a decrease.—T. C. B.

ADRENIN, Effects of, on Distribution of Blood. III Volume Changes and Venous Discharge in the Kidney. Hoskins (R. G.) and Gunning (R. E. L.) *Am. Jour. Physiol. (Balt.)* 1917, xliii, 304.

Adrenin in both pressor and depressor doses causes contraction of the kidney in dogs, and a corresponding decrease in the venous outflow. The results are the same whether the injections are instantaneous, or by the slower infusion. The threshold for renal changes and for blood pressure changes is about the same. The observations do not support, but also do not definitely disprove, the theory that in normal animals adrenin diuresis is due to renal dilatation.—T. C. B.

(ADRENIN) Further Observations on the Differential Action of Adrenalin. Hartman (F. A.) and McPhredran (Lois) *Am. Jour. Physiol. (Balt.)* 1917, xliii, 311.

In the experiments reported in the *Am. Jour. Physiol.*, 1915, xxxviii, 438, Hartman found that adrenalin acted differently on the splanchnic circulation and the peripheral circulation. The present work is an attempt to arrive at some conclusion as to the mechanism involved in the vascular adjustment caused by this differential action. The authors find that small doses of adrenalin cause constriction of the vessels of the intestine, the kidney, and generally of the spleen. The minimal dose necessary is of the same order of magnitude as that required to cause a fall of blood pressure, but not necessarily identical with it, nor is it the same for every organ in the same animal. Increase in the dose of adrenalin causes in all cases marked dilatation of the intestine, but the dose is materially less than that necessary to bring about a rise of blood pressure. This dilatation is under the control of the central nervous system. In all doses adrenalin usually has a constrictor effect upon the spleen.—T. C. B.

(OVARY.) Observations on the Influence of Isolated Ovaries on the Body Growth of the Albino Rat. Stotsenberg (J. M.) *Anat. Rec. (Phila.)* xii, 259.

In earlier papers it had been shown that removal of both ovaries from young rats caused an over-growth of the body, and that after removal of one ovary, the other hypertrophied and checked all tendency toward over-growth. In the present paper one or both uterine horns and one ovary were removed from young rats. The loss of the uterine horns had

no effect on the body weight nor did that of one ovary. Ovaries that were quite pathological and single ovaries (hypertrophied) alike inhibited over-growth. Hence the author concludes that the ovaries probably exercise their control of growth through some other member of the endocrine system.—E. R. H.

(OVARY.) Oestrus and Ovulation in Swine. Corner (G.) and Amsbaugh (A. E.) *Anat. Rec. (Phila.)* 1917, xii, 287.

In the pig ovulation occurs on the first or second day of oestrus, and is independent of coitus. The mature unfertilized ovum is 155 to 165 micra in diameter and contains much fat. Fertilization occurs in the uterine tube.—E. R. H.

HYPOPHYSIS, Effects of Inanition and Refeeding upon the Growth and Structure of, in the Albino Rat. Jackson (C. M.) *Amer. Jour. Anat. (Phila.)* 1917, xxi, 321.

Preliminary account abstracted elsewhere.—E. R. H.

(HYPOPHYSIS.) Effects of the Extirpation of the Anterior Lobe of the Hypophysis of *Rana Pipiens*. Allen (B. M.) *Biol. Bull. (Lancaster, Pa.)* 1917, xii, 293.

Preliminary account abstracted elsewhere.—E. R. H.

(ADRENIN) The Adrenalin Content of the Suprarenal Capsules in Bubonic Plague. Ragazzi (C.) *Arch. Farm. Sper.* 1916, xxi, 244.

The disappearance of adrenalin as a result of infection with bubonic plague is not due to a chemical reaction between adrenalin and a toxin, but is an index of histological insufficiency of the organ due to direct lesion of the cell and to bacterial destruction of the parenchyma.—(Chem. Abstr.)

(ADRENIN) Sugli effetti delle iniezioni sottocutanee ed endovenose di adrenalina nei cani. The Effects of Subcutaneous and Intravenous Injection of Adrenalin in Dogs. Cosentino (G. C.) *Arch. Farm. Sper.* 1916, xxi, 400.

Subcutaneous and intravenous injection of adrenin (1-4 mg.) does not invariably cause glucosuria, and never causes pentosuria. It diminishes diuresis, reduces nitrogenous metabolism and increases phosphorus metabolism. It produces no alteration in the kidneys, but causes severe disturbances in the gastro-intestinal organs.—(Chem. Abstr.)

(ADRENIN) The Time of Appearance of Adrenalin in the Suprarenal Capsules of the Fetus. Cevolotto (G.) *Atti. r. Ist Veneto (Venice)* 1916, lxxiii, 1159.

The suprarenal capsules of ox, sheep, pig, and human fetuses were extracted with five times their weight of Ring-er's solution. The presence of adrenin was tested biologically on the isolated mammalian heart, which is just as sensitive as the frog eye, or strips of arteries, uterus or intestine, the minimal quantity thus detected being 1:40,000,000. The results showed that adrenin is formed before the middle of pregnancy. The earliest time of appearance of the hormone was not determined.—(Chem. Abstr.)

(ADRENALS) Effect of Fasting on the Suprarenals. Pellegrini (R.) *Atti. r. Ist. Veneto (Venice)* 1916, lxxii, 781.

During fasting there is always a diminution of intracapsular chromaffin bodies which however do not correspond in intensity to the specific reaction with chrome salts. At the beginning of fasting this diminution is accompanied by some hyperfunctioning, in the later stages by a lessened functioning and regressive phenomena in the medulla. There is no definite parallelism between these changes on the one hand and the duration of fasting and loss of weight on the other. When fasting animals are treated with daily injections of adrenin (1.0 mg.) they have a lessened resistance, the medulla is congested and hemorrhagic, and the intensity of chromaffin reaction is augmented.—(Chem. Abstr.)

(PANCREAS) The Metabolism of d-Glucose in Surviving Organs. II. The Action of the Pancreas on d-Glucose Circulated in it. Artom (C.) *Atti accad. Lincei*, 1916, xv, 466.

In continuing the systematic study of d-glucose metabolism in the various organs Artom has made perfusion experiments with the pancreas of dogs owing to its double importance in the fate of carbohydrates in the body. No earlier perfusion experiments were found but a large amount of work has been done on the action of pancreas pulp or pancreas Buchner press-extracts on d-glucose. This work is reviewed; the discrepancies are such that Artom can form no clear conception of the role of pancreas toward d-glucose. It was thought that perfusion experiments with the pancreas, like those with intestine, would give some clear results. The results showed: (1) That in perfusing a pancreas of a dog with defibrinated blood containing d-glucose there is always a diminution of the reducing power of the blood that varies from case to case (max. about 50 per cent.). (2) The carbohydrate content of the pancreas is generally increased by circulating with blood but at most this only accounts for 55 per cent. of the d-glucose lost from the blood. (3) When

d-glucose is perfused through the pancreas of a dog in Tyrode's solution there is always a reduction in the reducing power of the solution that varies from case to case but is generally much less than that obtained with blood; it does not exceed 24 per cent. (4) The carbohydrate content of the pancreas increases in perfusions with Tyrode's solution but such increases are less than the corresponding loss of d-glucose from the solution; they amount to about 85 per cent. of this loss. Thus the pancreas, like the intestine, consumes more d-glucose when it is perfused in blood than in Tyrode's solution. The difference, however, is not great nor so constant. The pancreatic tissue is less resistant, less vital than intestinal tissue and it is harder to maintain its cellular elements in their full state of functional integrity under these conditions. It is safe to conclude in general that the isolated pancreas is capable of destroying d-glucose dissolved both in blood and in Tyrode's solution independently of the numerous other elements present.

(SPLEEN) The Metabolism of d-Glucose in Surviving Organs. III. The Action of the Spleen in d-Glucose Perfused Through It. Artom (C.) *Atti accad. Lincei*, 1916, xxv, 513.

The considerable volume of this organ, its function (still obscure in part), its richness in leucocytes which undoubtedly have an intense glycolytic activity and its relations to the glycogenic functions of the liver shown by the increase of hepatic glycogen after splenectomy (Verdozzi, *Chem. Abstr.* xi, 1455) were all considerations that made the artificial perfusion experiments such as the above of much interest. The few earlier experiments having a bearing on this subject are reviewed. The results of Levene and Meyer (*Chem. Abstr.* vii, 1204) showed no glucoytic action by themselves but gave a positive result when mixed with similar preparations from muscles, lungs, liver and pancreas. The methods used were the same as before. The results showed: (1) That in perfusing the spleen of a dog with blood containing d-glucose there is always a diminution in the reducing power of the blood, a diminution that varies from case to case and that may reach 25 per cent. (2) The carbohydrate content of the spleen generally increases in circulating with blood but not to the extent that corresponds to the d-glucose lost from the blood; it amounts to about 70 per cent. of the loss. (3) Perfusing d-glucose in Tyrode's solution through the spleen results in a diminution of the d-glucose content of the solution. (4) The carbohydrate content of the spleen also increases in the perfusion with Tyrode's solution, but it

is much less than the corresponding diminution of the reducing power of the liquid.—(Chem. Abstr.)

(THYMUS) The Partition of Phosphorus in Thymus Nucleic Acid. Hildegarde (C. G.) J. Biol. Chem. (Balt.) 1916, xxv, 189.

(PITUITARY) Tethelin as an Accelerator of Recovery of Weight Lost in Inanition, and in the Healing of Granulating Wounds. Robertson (T. B.) J. A. M. A. (Chgo.) 1916, lxvi, 1009.

See Endocrin., 1917, i, 24.

(GROWTH) II. Normal Growth of the White Mouse. Robertson (T. B.) J. Biol. Chem. (Balt.) 1916, xxiv, 363.

See Endocrin., 1917, i, 24.

(PITUITARY GROWTH) III. Influence of the Anterior Lobe of the Pituitary Gland on the Growth of the White Mouse. Robertson (T. B.) J. Biol. Chem. (Balt.) 1917, xxiv, 385.

See Endocrin., 1917, i, 24.

(PITUITARY GROWTH) IV. Influence of Tethelin, the Growth-controlling Principle of the Anterior Lobe of the Pituitary Gland, on the Growth of the White Mouse. Robertson (T. B.) J. Biol. Chem. (Balt.) 1916, xxiv, 397.

See Endocrin., 1917, i, 24.

(PITUITARY GROWTH) V. Isolation and Properties of Tethelin. Robertson (T. B.) J. Biol. Chem. (Balt.) 1916, xxiv, 409.

See Endocrin., 1917, i, 24.

(PANCREAS) Theory of Diabetes. VI. The Behavior of d1-Glyceric Aldehyde in the Normal and Diabetic Organism. Sansum (W. D.) and Woodyatt (R. T.) J. Biol. Chem. (Balt.) 1916, xxiv, 327.

(PANCREAS) Theory of Diabetes. VII. The Intravenous Tolerance Limit for d1-Glyceric Aldehyde, and the Improbability that it is a chief Intermediate in Glucose Katabolism. Sansum (W. D.) and Woodyatt (R. T.) J. Biol. Chem. (Balt.) 1916, xxiv, 343.

(THYROID).. Iodin Compounds of the Human Thyroid. Wilson (L. B.) and Kendall (E. C.) Am. J. Med. Sci. (Phila.) 1916, cli, 79.

See Endocrin., 1917, i, 153.

(TESTIS) On the Influence of Castration in the Horse. Vermeulen (H. A.) *Het paard* ('s Gravenhage) 1917, xiii, 3.

Contains nothing new and proves that the effects of castration in the horse are absolutely the same as in other animals.—J. K.

THYROID Insufficiency and Cholesterinemia. Martinez (B. D.) *Travaux du Laboratoire de Physiologie de la Faculte de Medicine de Buenos Aires*, 1914, No. 16, 245.

On ten dogs with complete thyro-parathyroidectomy, of which nine died in from four to thirteen days, the author observed that during the 24 hours after the operation there was a diminution of the blood cholesterin but there was a subsequent increase in the quantity with the onset and development of the symptoms of tetany. The cholesterin was measured by the Grigant colorimetric method.—B. A. H.

SPLEEN, The Relation of, to the Secretary Function of the Stomach. Madero (L.) *Travaux du Laboratoire de Physiologie de la Faculte de Medicine de Buenos Aires* 1914, No. 16, 179.

Studies on dogs with Pawlow gastric fistulas are reported, in which extracts of the spleen and lymph glands in subcutaneous injections produced both an increase in the quantity of the secretion and in the concentration of the digestive units. Extracts of leucocytes and red cells produced the same effects. Splenectomy produced a diminution both of the secretion and the ferments, but this progressively emaciated the experimental animals. The author infers that the lymphocytes and lymphoid organs play a part in the production of the gastric juice and its enzymes.—B. A. H.

(PANCREAS) The Enzymic Action of Blood toward Glucose. IV. Enzymic Properties of the Blood of a Depancreatized Dog before and after Circulation (with Glucose) in the Intestine of the same Animal. Lombroso (U.) *Atti accad. Lincei*, 1916, xv, 83.

Lombroso was especially interested in clearing up a contradiction in recent literature on this subject (Edelmann, *Chem. Abstr.* vi, 2104; Macleod, *Chem. Abstr.* vii, 3777). Edelmann maintains that the blood of the depancreatized dogs loses its glycolytic power, while Macleod maintains that it is not changed. Lombroso considers that Edelmann's experiments were not sufficiently prolonged and criticizes Macleod's

results because he failed to determine whether the glucose was condensed or destroyed. Verzar and Kraus (Chem. Abstr. vii, 3457) and Macleod and Smedley (Chem. Abstr. vii, 2597) conclude that the intestines of depancreatized dogs retain their power to utilize glucose in a Tyrode's solution. The technic was similar to that used before. The blood of a depancreatized dog shows a synthesizing power toward glucose nearly equal to that of normal blood. The glucolytic enzyme appears to be more or less diminished but not absent. It was observed that the greatest diminution in glucolytic power did not occur in the experiment in which the blood of a dog depancreatized for the longest time was used. The consumption of glucose dissolved in diabetic blood by the intestine of the same animal is much less in the same time interval than that observed with a normal intestine. The consumption of glucose in the intestine of the dog depancreatized for the longest time was least of all. The blood of depancreatized dogs circulated in the intestine of the same animal showed the presence of a very active glucolytic enzyme capable of destroying 10-15 per cent. of the glucose remaining in the blood after circulation in the first hour. The fact that the results vary from case to case is again emphasized. The general conclusions drawn are: (1) the blood of the depancreatized dog still possesses (although perhaps to a less extent) its glucolytic power and (2) that by circulating in the intestine of the same animal, this power is considerably increased.—(Chem. Abstr.)

THYROID Gland, Autotransplantation and Homotransplantation of, Using the Capsule as the Seat of Transplantation.

Hess (J. H.) and Strauss (A. A.) Arch. Int. Med. (Chicago) 1917, xix, 518.

The authors believe that the transplantation of homotransplants as well as of autotransplants of certain highly specialized organs into regions normally occupied by such tissues is often possible and certainly worthy of trial. Their work justifying this conclusion was carried out on dogs and guinea pigs, three autotransplants and thirty-one homotransplants composing the series. They found that there should be as little disturbance as possible of the blood supply in the region where the transplant was placed, and suture material as well as all other foreign bodies should not come in contact with the transplant.

It was noticed that a familial relationship, as well as the early age of the animals on which the operations were performed, were probably important factors in their results

The statement is made, "That the varying degrees to which a homotransplant takes depend on the reaction between the host and the tissue transplanted and so far we have found no means either in the blood or in the thyroid gland itself by which we could determine the factor which produces this different condition in the various animals."

The report is well illustrated with micro-photographs made from sections of the transplants at various lengths of time after transplantation occurred.—W. B. T.

HYPOPHYSIS. Experimental Studies in the Frog. Houssay (B. A.) *La Prensa Med.* (Argent.) 1916, June 10, page 8.

The results of hypophysectomy in over 300 frogs (*Leptodactylus Ocellatus*) were published in 1910. Their hypophysis consists of three parts (glandular, pars intermedia and neurohypophysis). In the glandular part there are two types of cells, chromophile cells and non-chromophile cells. The hypophysis is not necessary to the life of the frog, for it was found possible to keep them alive for a long time following total ablation, providing they were not killed by the trauma of the operation. Extirpation of the glandular portion rarely caused death. With previous grafts the survival period of the frogs after hypophysectomy was increased. The vagus nerve retained its reflex excitability in the hypophysectomized frogs. An extract of the hypophysis of the frog contains substances which slightly increase the arterial pressure and the energy of the heart, have a strong galactogogue action, increase the contractions in the esophagus of the toad, dilate the vessels of the kidney and produce diuresis.—B. A. H.

(ADRENAL) Nuovo contributo alla conoscenza del sistema cromaffine dei saurî Studi morfologici e eitologici sulla capsula surrenali con speciale riguardo al paragangli omonimi. Trinci (G.) *Arch. ital. Anat. e di Embriol.* (Firenze) 1916, xiv, 513.

A morphological and cytological study (embryological and comparative) of the suprarenal bodies in various species of amniotes. In different forms the relation of the cortex and medulla varies. The conditions vary from that in which the two parts are quite separate to that wherein the elements of the two are intermingled. One often finds in the cortex of saurians, groups of chromaffine cells. Chromaffine masses are often found in the walls of the veins adjacent to the suprarenals. The suprarenal (medulla) may be considered as an extraordinarily developed chromaffine body (paraganglion)

forming an integral part of a longitudinal series. The cortex of the suprarenal (interrenal body) in different species, varies in structure, and varies with age, sex, season and physical condition. Two types of chromaffine cells exist, one is large, granular, has cell and nuclear boundary ill defined, stains deeply with basic stains, and has an intense chromaffin reaction. The other is smaller, paler, and has distinct cellular and nuclear membranes. The first constitutes the paraganglion substance. The second is in direct contact with the interrenal parenchyma, or scattered among its cords. Also there are present cells which are intermediate between nervous and chromaffine tissue. There is no change of nervous tissue into chromaffine tissue, but both come from the same anlage. The yellow color of the cortex is due to droplets of lipid substance.—E. R. H.

(ADRENALS) The Nature of the Splanchnic Rise in Blood Pressure. Burton-Opitz (R.) and Edwards (D. R.) *Am. Jour. Physiol. (Balt.)* 1916, xli, 91.

When the splanchnic nerves are stimulated there is a two-stage rise in blood pressure. It was shown that when the fibres to all the splanchnic organs except the adrenals were sectioned the primary rise is practically abolished while the secondary rise persists.—R. G. H.

(PANCREAS) The Influence of Hypotensive Gland Extracts on Vasomotor Irritability. Beifeld (A. F.), Wheelon (H.) and Lovelette (C. R.) *Am. Jour. Physiol. (Balt.)* 1916, 1, 360.

The data herein recorded were obtained in a study of the endocrine function of the pancreas. It was found that pancreas extract as well as salivary gland extract given by vein caused an augmentation of the vasomotor reaction to nicotine. The action is probably not specific.—R. G. H.

(THYROID) The Control of Experimental Cretinism. Basinger (H. R.) *Arch. Int. Med. (Chgo.)* 1916, xvii, 260.

The experiments were made upon thyroidectomized rabbits with controls from the same litters as the experimental animals. The operation was performed at the age of two to three weeks.

Author's summary: Transfusion of normal blood serum into cretins has no effect on the condition of cretinism. Transfusion of thyroid-fed animal's blood serum into other cretins is effective in increasing the growth and in controlling the other symptoms of cretinism. The improvement is not as

marked, however, as with thyroid feeding. Standard thyroid preparations (containing 0.2 per cent. iodine in organic combination), when given in carefully controlled non-toxic doses, will increase the growth of cretin rabbits and prevent the development of, or counteract, the other symptoms of cretinism. But thyroid feeding fails to carry an absolute cretin to full normal development. Discontinuing the thyroid feeding leads to a return of some of the cretin symptoms. The thyroid metaprotein of Koch is somewhat more active than standard thyroid preparations, but also more toxic. Kendall's thyroid extract "B" has no effect on any of the symptoms of cretinism. It is non-toxic, at least in ordinary doses. Cretins are more susceptible than the normal animals to the toxic action of thyroid (thyroid feeding). Cretin rabbits, despite their retarded rate of growth, continue to grow for a considerably longer time (four to six weeks) than the controls of the same litter.

(THYROID) Further Observations on the Overactivity of the Cervical Sympathetic. Cannon (W. B.) and Fitz (R.) *Am. J. Phys.* (Balt.) xl, 126.

In animals in which the phrenic nerve was grafted into the cervical sympathetic, symptoms of hyperthyroidism arose; particularly the basal metabolism was markedly increased. These symptoms disappeared on removal of the thyroid gland of the operated side.—R. G. H.

(PANCREAS) On the Relation of Blood-Sugar to Glycosuria in Diabetes Mellitus. Epstein (A. A.) *Proc. Soc. Exper. Biol. and Med.* (N. Y.) 1916, xiii, 67.

This paper is based upon an extensive study of diabetics, human and experimental. It was found that, contrary to general belief, there is a definite mathematical relationship between the percentage of sugar in the blood and that in the urine. The relationship does not hold, however, in individuals with defective kidneys.—R. G. H.

(THYROID. ADRENALS) The Thyroid-Adrenal Apparatus and Its Function in the Heat Regulation of the Body. Cramer (W.) *Jour. Physiol.* (Lond.) 1916, 1, xxxviii.

The problem of heat regulation is one upon which physiologists have expended much study without reaching any very satisfactory conclusions. In these studies Cramer has brought the problem within the domain of endocrinology. He noted that exposure to cold and experimental hyper-pyrexia cause changes in the thyroid and adrenal glands and in the pyrexia studies disappearance of liver glycogen as well as constrict-

tion of the vessels of the ear were noted. It is inferred that thyroid discharge is caused which in turn stimulates the adrenals leading to glycogenolysis in the liver and a general rise in metabolism with increased heat production. With sufficient adrenin discharge vaso-constriction and diminished heat loss, according to the author, will accompany this. Whether, as a matter of fact, sufficient adrenin could circulate to produce a significant cutaneous vaso-constriction without violently interfering with other functions is doubtful. Also, the simultaneous vaso-dilatation in the underlying muscles would seem to oppose this as a heat conserving mechanism—R. G. H.

(THYROID) Carbohydrate Metabolism in Experimental Hyperthyroidism. Cramer (M.) and McCall (R.) *Proc. Physiol. Soc., Jour. Physiol. (Lond.)* 1916, 1, xxxvi.

The authors studied the effects of thyroid feeding upon the respiratory quotient in rats. This, they conclude, results in glycogen discharge from the liver and its oxidation with the food carbohydrate. Upon removal of the liver glycogen, carbohydrate is formed from protein and possibly from fat and this is also oxidized. Carbohydrate metabolism in hyperthyroidism indicates that the liver does not itself mobilize sufficient carbohydrate to cause glycosuria. The organism reacts to a discharge of carbohydrate into the blood by increased oxidation of the same. The "protein-sparing action of carbohydrate" is dependent upon the glycogenic function of the liver.—R. G. H.

DUCTLESS GLANDS, Studies of, by Electric Methods. Cannon (W. B.) *Proc. Nat. Acad. Sci. U. S. A.*, ii, 319.

See *Endocrin.*, 1917, i, 5, 58.

(DUCTLESS GLANDS) Some Results of Studies on Electrical Changes in Glands. Cannon (W. B.) and Cattell (McK.) *Am. Jour. Physiol. (Phila.)* 1916, xl, 143.

See *Endocrin.*, 1917, i, 55.

(ADRENAL) A Study of the Involutional Changes Which Occur in the Adrenal Cortex During Infancy. Lewis (R. W.) and Pappenheimer (A. M.) *Jour. Med. Research (Boston)* 1916, xxxiv, 81.

As shown by Thomas the adrenal cortex undergoes certain involutional changes during early infancy, resulting in a separation of an inner degenerated strip of cortex from an intact outer zone. The degenerated cells are resorbed,

leaving their connective tissue intact. There is no regeneration of these cells during the first three years of life. One hundred cases were examined. Syphilis may have a retarding effect upon the involution of the cortex and infection seems to be associated with an increase in the width of the intact cortex, but prematurity and inanition do not have any noticeable effect upon the process of involution.—E. R. H.

(TESTIS) Size and Length Relations of the Right and Left Testis of Pigeons in Health and Disease. Riddle (O.) *Anat. Rec.* (Phila.) 1916, xi, 87.

The paper contains tables giving the weight and length of the testis of pigeons. The right testis is usually larger than the left but the variability is great. The ratio seems to be different in disease and hybridization, but the significance of this difference is not explained—E. R. H.

(OVARY) Further Developments in the Ovariectomized Fowl. Goodale (H. D.) *Biol. Bull.* (Woods Hole) 1916, xxx, 286.

Brown Leghorn females after castration developed male characters at first, then changed back toward the female type and still later the plumage again changed to the male type. Examination showed that the ovary had not regenerated, but instead a new organ had developed. The organ is neither testis or ovary. It is necessary however for the assumption of male plumage by females. In structure it is composed of groups of small cells separated by connective tissue. Some of the specimens examined contained also tubules lined with simple square cells. The organ may be developed from the Wolffian body. A more complete description is promised.—E. R. H.

(THYMUS) The Differentiation of Cells as a Criterion for Cell Identification Considered in Relation to the Small Cortical Cells of the Thymus. Danchakoff (V.) *Jour. Exp. Med.* (N. Y.) 1916, xxiv, 87.

The author states that the balance of recent work supports the theory of the true lymphoid nature of the small thymus cells. These cells arise from wandering cells of mesenchymal origin that invade the epithelial anlage of the thymus. These small lymphoid hemocytoblasts increase in number by their own mytotic proliferation and also at the expense of the large lymphoid hemocytoblasts and finally differentiate into small lymphocytes. The anlage of the small lymphocyte is a stem cell polyvalent in nature, and capable of forming granular leucocytes as well as lympho-

cytes. Experimentally small lymphocytes can be changed into plasma cells and granular leucocytes. The author holds that all blood cells descend directly or indirectly from a polyvalent cell which is merely a cell of the loose mesenchyma. The article is excellently illustrated.—E. R. H.

(PINEAL) The Reactions of the Melanophores of Amblystoma Larvae—the Supposed Influence of the Pineal Organ.
Laurens (H.) Jour. Exp. Zool. (Phila.) 1916, xx, 237.

Among the numerous hypothetical functions attributed to the pineal body one advanced by Fuchs was that this organ has an inhibitory influence upon the movements of pigment in melanophores. Laurens was able to show that extirpation of the pineal body in amblystoma has no effect whatever upon these movements, they being controlled through the eyes. The significance of the pineal body has been so greatly overestimated that carefully performed experiments leading to negative results are especially valuable.—E. R. H.

(THYROID) Origin of the Chromophilic Colloid of the Thyroid Gland and Its Relation to Follicular Hemorrhages. (Origine de la Colloïde Chromophile de la Glande Thyroïde. Ses Relations avec l'Hémorrhagie Folliculaire.) Parhon (C. J.) and Enin (V.) C. R. Soc. de Biol. (Paris) 1916, lxxix, 502.

In certain thyroid glands coming from pathological cases one finds not infrequently follicles the contents of which deviate from the normal in the following respects: They are of a darker color; they give the impression of a substance more condensed than the normal colloid; and tinctorially they differ from the normal in that they take the hematoxylin in the hematoxylin and eosin stain and the fuchsin in the van Gieson stain, whereas normal colloid is stained with eosin and picric acid, respectively.

This chromophilic substance indicates an abnormal thyroid gland. It is neither a special secretion of the gland, nor a physical modification of the normal colloid. And, from the latter, it has been shown to differ, also, chemically.

In an earlier report the authors came to the conclusion that the chromophilic material arose in great part from desquamated and degenerated epithelium. However, on the basis of the present research, the writers believe they have definitely shown the source of the dark colloid.

In a case of general paralysis of the maniacal type six injections of neosalvarsan (0.15-0.60 gm.) were given at

weekly intervals. A few days following the sixth injection the patient succumbed. A study was made of the thyroid.

In sections stained with hematoxylin and eosin and with van Gieson were observed many follicles filled with the chromophilic colloid, and what was more striking, many also filled with blood. Between the two was found every transition. The writers were able to follow the transition step by step, from the red cell stage to that of the chromophilic colloid, both physically and tinctorially.

On the basis of this work, the authors have come to the conclusion that hemorrhages are the chief source of the chromophilic colloid, admitting, however, that leucocytes and desquamated epithelium may play a part. In support of the hemorrhage theory is the frequent presence of the unusual colloid in conditions in which convulsive seizures are common, namely, general paralysis and epilepsy.—A. F. B.

(ADRENALS) A Suprarenal Adenoma in the Mouse. Itami (S.) Proc. N. Y. Path. Soc., 1916, xvi, 45.

A description of the gross and microscopic appearance of an adenomatous tumor in a mouse. The tumor occupied the central region of the gland, was clearly defined and showed no tendency to invade the cortex. Itami thought the neoplasm originated from the medulla, although its cells did not give the chromaffin reaction.—J. P. S.

(THYROID) Further Observations on the Thyroid Gland. Edmunds (W.) Jour. Path. and Bact. (Cambridge, England) 1916, xxi, 23.

Edmunds reports the results of experiments on the effect of feeding milk and of administration of calcium lactate to thyroid- and parathyroid-ectomized dogs. In only six out of sixteen animals was the treatment successful. If this method is useful at all it generally succeeds in the first three months. After that the animal may live for months or even years on the milk with added calcium. From this it would appear that after a time some change occurs in the animal, and this would seem to be a compensating hypertrophy of the pituitary. It is necessary to give the calcium lactate in large amounts.—J. P. S.

CLINICAL STUDY

(ENDOCRINE GLANDS) **Abderhalden Reaction in Mental Diseases.** Cotton (H. A.) Corson-White (E. P.) and Sten-
venson (W. W.) Jour. Nerv. & Ment. Dis. (Lancaster, Pa.)
1917, xlv, 144.

This is a very interesting report, the object of which is to show the Abderhalden test can be of material assistance in psychiatry.

The technique of the test essentially followed that given by Abderhalden, with some improvements. The following substrates were used: Pituitary, thymus, thyroid, pancreas, adrenal and gonads (ovary and testicle), but no brain tissue was employed. The blood of the patients to be tested was always taken before breakfast and the test was made the same day within three hours after the blood was taken.

The most important findings were made in the groups of dementia precox and epilepsy. Other psychoses gave practically negative results; at least, the results did not warrant the drawing of any conclusion. The authors conclude from their findings that the results are practically negative except in dementia precox and epilepsy.

In dementia precox eighty-one per cent. of their fifty-eight cases tested gave a positive reaction to sex gland. Three cases out of fifty-five, two of these being of a catatonic type, gave a positive reaction to thyroid and sex. In connection with the Abderhalden test blood counts were made and wide deviations from the normal were noticed. There was usually a larger percentage of lymphocytes than polymorphonuclears present. In other psychoses the blood count was found approximately normal. The authors also mention the fact that seventy-five per cent of dementia precox cases die of tuberculosis, and the statement is made that possibly this large co-existence of tuberculosis and dementia precox justifies the hypothesis that the former stands in some etiological relation to the latter. Sixty-nine cases of epilepsy were examined. All were positive to the adrenal gland. The authors have treated these cases with pancreatin with considerable success.

The statement is made that the value of the report of these reactions is to lay the foundation for therapy based upon the facts deduced.

This report, though short, is of the utmost interest to all who are interested in psychiatry. The reviewer has personally observed the procedure in performing these tests and feels that every precaution has been taken against error in technique.—W. B. T.

SUPRARENAL Hemorrhage in Cerebrospinal Fever. Scott (S. G.) *Lancet* (London) 1917, cxcii, 4871.

Reporting the incidence of adrenal disorder accompanying meningitis and the autopsy findings as indicated in the title.—W. B. T.

(THYROID) Intrathyroid Injection of Boiling Water in Hyperthyroidism. Day (J. C.) *Ann. of Surg.* (Phila.) 1917, lxxv, 279.

The author has treated seventeen cases of hyperthyroidism by the injection of boiling water into the gland tissue. Following this procedure, nothing but good has resulted, even in those cases first treated before the technique had been fully developed. He reports a death following this procedure by another physician, which he believes is a very unusual experience due to the critical condition of the patient before operating.

The author believes that when existing conditions are such that the patient is a fairly safe surgical risk partial thyroidectomy is the procedure of choice. After this period has passed other methods should be utilized with the object of bringing the sufferer back to the point where surgery can be safely applied. It is in these cases that the injection of boiling water will be of the greatest value. Some of the patients were so relieved following this procedure that they later refused an operation.

The object of the injection is to destroy a portion of a gland. During its destruction, piece-meal by successive injections of hot water, other beneficial measures should be instituted, such as rest, quiet and diet.

It is thought best to exercise a little tact, not allowing the patient to understand that boiling water is to be injected in order that the nervous system may not be thrown into a condition of extreme fright and the thyroid stimulated.

The patient is given morphine previous to the operation and the operation is usually carried out under local anesthesia.

That no fumbling may occur while the hot water is being injected, several pieces of rubber tubing are slipped over the barrel of a ten cc. syringe, which is to be used in injecting the boiling water. Two pairs of gloves are used, cotton inside of rubber, that the operator may be able to work without fear of burning his hands.

The water must be injected boiling; otherwise it will not be hot enough to cook the tissue. The injection must be systematic and a note kept of the place of each injection in

order that the same region may not be reinjected. Sometimes the gland is exposed and the cooking carried out under the eye. As this is done, the injected portion of the gland is seen to whiten into a bloodless, pulp-like mass.—W. B. T.

"THYROID Stone." Pennell (V.) *Lancet* (London) 1917, i, 454.

A case report of a man forty-five years of age who sought advice for aphonia of three months' duration. A laryngoscopic examination revealed a complete paralysis of the left vocal cord.

A small, hard lump was felt on the left side of the neck in the position normally occupied by the left lobe of the thyroid. It moved on swallowing and did not appear to be firmly fixed to its attachments. It was tender on palpation.

The thyroid was exposed and a rock-like mass was removed from the upper pole of the left lobe. It was slightly larger than a walnut and was tightly wedged between the thyroid and esophagus, pressing on the recurrent nerve of the left side.

This mass was found to be a calcified adenoma. It occupied the site of the superior parathyroid gland and probably originated from that gland.—W. B. T.

THYMUS, Tumors of, in Myasthenia Gravis. Bell (E. T.) *Jour. Nerv. and Ment. Dis.* (Lancaster, Pa.) 1917, xlv, 130.

Starr, reviewing two hundred and fifty cases of myasthenia gravis, noted a pathologic condition of the thymus in twenty-eight of the cases that came to autopsy. Of fifty-six autopsies published since then, the thymus was found to be enlarged in seventeen and in ten others it contained a tumor.

The author reports a benign thymic tumor from a typical case of myasthenia gravis. This tumor was composed of thymic tissue fetal in type, i. e., a dense epithelial reticulum with lymphocytes. The usual thymic rests were found in the adipose tissue around the growth.

The thymic tumors occurring in myasthenia gravis seem to form a distinct group unlike any other thymic tumors. These may be classified as benign thymomata.

The statement is made that some abnormality of the thymus is found in nearly half of the cases of myasthenia gravis.—W. B. T.

(THYROID) Notes on Military Surgery. Ney (K. W.) *New Orleans Med. and Surg. Jour.* 1917, lxix, 546.

This author incorporates in a report on military surgery the fact that a large number of cases sent to the European base hospitals from the firing line come there with a diagnosis

of general fatigue and tachycardia. These patients are sent in by the hundreds, and in many instances absolute rest in bed and digitalis fail to cause abatement of the symptoms.

Such patients can stand no exertion, and even while at rest the heart action is very rapid.

Many of these people remain in the hospitals for months, during which time they develop a gradual enlargement of the thyroid gland. Quite a few of them are relieved only after the ligation of one or more of the thyroid vessels or after the removal of a lobe of the thyroid gland.

These cases, the author believes, indicate a derangement of the ductless glands due to the emotions.—W. B. T.

PITUITARY Tumor with General Edema in Two Cases of Nanism, one each of the Paltauf and Pituitary Types. Kraus (W. M.) *Jour. Nerv. and Ment. Dis.* (Lancaster, Pa.) 1917, xlv, 193.

The case histories of two patients are reported.

The first is that of a man aged forty-eight, admitted to the hospital complaining of swelling of the hands, feet and face, a similar attack having occurred previously several years ago. The man was small in stature and quite active. On admission his temperature was 103.6° but this dropped to normal in two days. There was a leukocytosis of 19,000, of which seventy per cent. were polymorphonuclears. He did not complain of pain anywhere. Blood pressure: Systolic, 88; Diastolic, 64. X-ray examination of the head showed a large sella turcica. His sight is poor, particularly on the left, with which eye practically nothing can be seen. He eats a great deal of candy, buying it by the pound when he has the money. There has never been any sugar in the urine. He always feels very sleepy. Hands are very large, skin thick and pigmented on the dorsal aspect. The arms were exceedingly long—the span was sixty inches. Evidence of disease of the central nervous system consisted of impaired visual acuity, double neuro-retinitis with atrophy, contraction of the color fields, poor hearing on the right and a curious unsteady gait; no Romberg and no real ataxia. Mentally, the patient acted like a well behaved, obedient child, doing what he was told, always agreeable and simple in his ways. He was very sneaky but in a harmless manner; for example, he would steal crackers from the kitchen when no one was looking.

The second case history was that of a vaudeville actor, age thirty-seven years. He was brought into the hospital in semi-conscious condition, with a history of having been perfectly normal the previous day, but on being awakened he was confused and could not dress himself. On physical ex-

amination the patient was found to be a small male forty inches tall, with dry yellowish skin, devoid of hair except that of the head and eyebrows. Genital organs quite small. The day following admission the patient had fourteen convulsions. White blood counts showed 18,000 cells; ninety per cent. of these were polymorphonuclears. During the next few days following the admission some edema of the extremities developed. He vomited continuously. The patient died fifteen days following admission. The autopsy revealed a degenerated posterior lobe of the hypophysis.

There is little doubt that both of these cases are instances of arrested development, starting very early in life. The first patient was no taller than a thirteen year old boy; his weight was normal for an adult. He was of the pituitary type. The second patient was of the Paltauf type, that is, an individual of normal size at birth, developing normally at first but in whom during early youth growth was arrested.—W. B. T.

(PITUITARY) A Case of Infundibular Tumor in a Child, causing Diabetes Insipidus with Tolerance of Alcohol. Newmark (L.) Arch. Int. Med. (Chicago) 1917, xix, 550.

The author presents a concise but full case history of a boy who died at fourteen years of age after suffering from diabetes insipidus for a period of five years. No signs of tumor were found until about two weeks before death and the author for this reason admonishes the profession against assuming the functional nature of diabetes insipidus even after some years have elapsed without definite tumor symptoms.

Not only was there an immoderate thirst for water, there being no limit to the amount of water craved, but he also desired strong drinks. He would drink home-made wine from the barrel by sucking it up through a tube. When possible he would persuade some person, under one pretext or another, to buy whiskey for him; but his favorite drink was beer, which he would drink one glassful after another in rapid succession. It is said that after a drinking bout shared by another little boy, who evidently received a very small proportion of the four and one-half quarts of beer, he reported at school and performed his tasks well, as usual. He was never seen in the slightest degree intoxicated.

On autopsy a tumor was found occupying the region of the infundibulum, extending forward through the lamina terminalis between the frontal lobes and backward into the third ventricle, destroying the neurohypophysis and nearly all of the pars intermedia, which accounted for the diabetes insipidus. Pineal atrophy was also noticed.—W. B. T.

THYMUS, The Reactivated. Hoxie (G. H.) Arch. Int. Med. (Chicago) 1917, xix, 564.

The author presents a short case history of what is usually called "persistent thymus." He believes that the thymic parenchyma persists throughout life and that this parenchyma may become reactivated and its secretion influence the hormopoietic system. The causes of such a reactivation are not known. He suggests as the best term to describe this case "Thymic Myasthenia."

The history is that of a farmer, age nineteen, who had been suffering for two years previously with shortness of breath. He showed great loss of weight and slept badly. The temperature was quite labile and was easily raised by emotional and physical excitement. The most important physical finding was increased submanubrial dullness. The roentgenogram of the chest showed an enlarged shadow in this area. The manubrium was resected and pieces of thymus removed. The pathologist reported that sections of this showed characteristic reactivation of the thymus gland.—W. B. T.

(PITUITARY) Contribution to the Symptom Complex Associated with Interpeduncular Tumors. Gosline (H. I.) Jour. Nerv. and Ment. Dis. (Lancaster, Pa.) 1917, xlv, 337.

An interesting case of pituitary tumor of considerable clinical and practical interest is reported. A man thirty years of age suffered from active symptoms of eight months' duration which were characterized by drowsiness of such persistence that he lost several positions. He died with signs of interpeduncular tumor.

On autopsy the tumor was found to be composed of undifferentiated anterior lobe cells such as are found in hibernating animals, and the suggestion is made that there may be some correlation between tumors of this sort and the possibility of human hibernation.

It is interesting to note that there was a high incidence of twins in the immediate family of the patient. His organs showed fetal lobulations and other variations from the normal.—W. B. T.

(PITUITARY) A Case of Dyspituitarism with Heart Block. Packard (M.) Jour. Nerv. and Ment. Dis. (Lancaster, Pa.) 1917, xlv, 362.

ADRENAL, Congenital, Intracranial. Meyer (A. W.) Anat. Rec. (Phila.) 1917, xii, 43.

The author found in a man an accessory adrenal body within the cranium lying upon the accessory nerve.—E. R. H.

OVARY, Human Graft of, in Exophthalmic Goiter. Celesia (F.) *La Prensa Med. Argentina*, 1914, i, 91.

The patient exhibited tachycardia and tremor. Her menses were irregular. After an ovarian homograft she felt better and the menses returned. The ovary was ultimately resorbed.
B. A. H.

(THYROID.) Exophthalmic Goiter, Surgical Treatment of. Chutro (P.) Meeting of the Argentine Medical Association, May 17, 1915.

Chutro advises the Porter treatment (injection of boiling water) and ligation of the thyroid vessels as the sole operation or as a preliminary treatment.—B. A. H.

HYPOPHYSIS, Tumor of, with Ocular Symptoms. Noceti (A.) and Houssay (B. A.) *Revista de la Sociedad de Oftalmologia de Buenos Aires*, 1914, No. 1.

The patient had neither dystrophia nor sexual hypofunction. He showed slight adiposity and bitemporal hemianopsia. The X-rays disclosed a tumor outside of the sella. He was operated upon by Hirsh (Vienna). His syndrome remained the same during one year, during which he complained of epistaxis and symptoms of cranial hypertension and then he became blind.—B. A. H.

DWARFISM, A Case of. Bordot (E.) and Ovidio (R.) *Assoc. Med. Argent. (Bs. Aires)* 1916, xxiv, 329.

I. L., six years old, is the son of Spanish parents, both healthy. Paternal history includes neither alcoholism nor syphilis. Mother gave a positive tuberculin skin reaction but has always felt well. Grandfather and mother were healthy.

The boy was born healthy, 5500 grams in weight and nursed until fourteen months old. His first tooth appeared at four months. He began to walk at nine months and to speak when one year old; he had complained of nothing but dyspepsia. Since his eighth month he has increased neither in weight nor height.

Present condition: weight, 8600 grams; temperature, 37 C; the sutures of the cranium solid; lungs and heart normal; pulse 100 per minute. The teeth are for the most part carious. Stools are normal; spleen and liver normal. Cryptorchidism is present. Boy is intelligent, speaks very well, is lively and joyful. All the measures of his extremities correspond to his stature, however the cranial belongs to a boy of 4 or 5 years.

The X-ray of the cranial base showed a sella not enlarged, and without deformities. The authors believe that the case is of tuberculous origin.—G. P. G.

(THYROID) The Basedow Syndrome at the Beginning of Puberty. Catalan (E.) *La Prensa Med. Argentina*, 1915, ii, 321.

All the symptoms of Basedow's disease (pulse 160, slight exophthalmos, thyroid tumor, tremor) appeared when the menstruation began. The subject was very nervous. These symptoms remained during three months and then she was able to resume her studies.—B. A. H.

PARATHYROIDS, Carcinoma of, with Metastasis Simulating an Aneurism of the Arch of the Aorta. Roffo (A. H.) and Landivar (A. F.) *La Prensa Med. Argentina*, 1914, ii, 177.

Describes a case of an Italian, 60 years old, who had two large tumors on the left side of the neck and on the superior part of the sternum. Histologic study proved them to be lobular carcinoma with cytologic characteristics of the chief cells of the parathyroids. In the early stage the tumors were benign but at the end they became malignant and the man died. An autopsy was made.

(Illustrated with photographs and micro-photographs.)
B. A. H.

ADRENALS in Normal and Pathologic Pregnancy. Gabastou (J. A.) *La Prensa Med. Argentina*, 1915, ii, 346, 358, 371, 382, 395, 408.

The constant presence of fat vacuoles in the medullary part of the adrenals was noted throughout pregnancy. The vaso-constrictor action of the serum was determined by the Laewen-Trendelenburg method. A positive test was obtained with the serum of twenty pregnant women; at parturition only one of six cases was positive and during the puerperium none. By the same method it was found that the adrenin was increased in the adrenals of pregnant bitches. The serum of eclamptics gave a negative reaction.—B. A. H.

(O'Connor and Stewart have shown that all sera contain vaso-constrictor substances other than adrenin, hence the evidence cited is not conclusive.—Editor.)

ADRENALS, Sarcoma of. Elizalde (P. T.) *Assoc. Med. Argent.* (Bs. Aires) 1916, xxiv, 309.

At autopsy there was found a sarcoma in the right adrenal and metastases in the left adrenal, pancreas and liver. The patient had been operated upon for obstruction of the cystic duct accompanied by enlargement of the liver and spleen.—G. P. G.

(THYROID) Goiter in a Girl Five Years Old. Iorge (I. U.) *Assoc. Med. Argent. (Bs. Aires)* 1916, xxv, 231.

Among 47,200 ill children from the Pediatric Clinic of the Clinical Hospital, only this case was found. The nodular part of the gland was removed. Thirteen days after the operation the patient was discharged. Histologic study showed the presence of two types of tissue. The neoplasm was an adenoma with the histologic features of exophthalmic goiter and the remainder of the tissue resembled the thyroid of an adult.—G. P. G.

(PINEAL) The Relation of Muscular Dystrophy to Disturbance in the Internal Glandular System. Timme (W.) *New York Neurological Society*, Dec., 1916.

The speaker reported a series of cases of progressive muscular dystrophy occurring in one family through three generations, with detailed examination of one of these cases and X-ray examination of the skull and other parts in five cases. These skiagraphs showed indubitable evidence of a diseased endocrine system, notably in the pineal gland. From his observations he concluded that the relationship between pineal gland disease and progressive muscular dystrophy was undoubtedly a very close one—E. M. A.

(AUTONOMIC NERVOUS SYSTEM) The Relation between Over-activity of the Vagus System and Anaphylaxis. Smith (J. H.) *Jour. Nerv. and Ment. Dis. (Lancaster, Pa.)* 1917, xiv, 26.

A clinical study of the vegetative nervous system and anaphylaxis, from which the author concludes that anaphylaxis manifests itself chiefly through vagus irritation, and further states that in the interpretation of vagotonic symptoms (sweating, increased salivary secretion, hyperacidity, nervousness, embarrassment of respiration, constipation, bradycardia, etc.) without apparent cause, two toxic factors are among the possibilities, ductless gland disturbances and chronic bacterial infection. In these two groups the most important are thyroid intoxication and tuberculosis.—E. M. A.

(THYROID) Quinine and Urea Injections in Hyperthyroidism. Watson (L. F.) *New York M. J.* 1916, ciii, 791.

See *Endocrin.*, 1917, i, 178.

(THYROID) Some Conditions Controlling Thyroid Activity. Cannon (W. B.) and Cattell (McK) *Boston M. & S. J.* 1916, clxxiv, 138.

See *Abstract, Endocrin.*, 1917, i, 55.

THYROID and Heart Disease. (Thyrogene hartstoornissen.)

Enthoven (T. H.) *Nederlandsch Tijdschrift voor Geneeskunde* (Amsterdam) 1917, lxi, 1461.

The author examined the hearts of 100 patients with goiter. Fifteen suffered from compression of the trachea. Five of these had perfectly normal hearts; ten others showed a rapid pulse (about 160). These ten patients were more than 24 years of age; the other five were younger. The youngest of all, however, a boy of 17 showed the most rapid pulse.

Forty-two patients without compression of the trachea showed a rapid pulse and sometimes heart failure. It is remarkable that the most serious heart failures were observed in cases in which the goiter was small.

Forty patients showed no heart symptoms. Three patients with goiter showed an enlargement of the heart without high blood pressure heart failure.

In cases in which heart symptoms are influenced by rest it will be necessary to examine the thyroid.—J. K.

(THYROID) Goiter, Cretinism and Chagas' Disease. Kraus (R.), Maggio (C.) and Rosenbusch (F.) *La Prensa Med.* (Argent.) 1915, Nos. 1 and 2.

Chagas has described in Brazil, a thyroid infested with *Trypanosoma Cruzi*, which is transmitted by *Eriatoma megalista*. The *vinchucas* of Argentine (*Eriatoma infestans*, Klug) contains the evolution forms of *Trypanosoma Cruzi* and infects mice, guinea-pigs, rabbits and dogs. The trypanosome appears in their blood, heart and other organs and in the parasitic cysts. No active case of Chagas' disease in man has so far been found in Argentine. The *vinchucas* infection has been found not alone in the provinces where goiter exists, but also in other and distinct places. The authors believe that the clinical difference which exists between Chagas' disease and goiter, infantilism and idiocy, associated with goiter and endemic cretinism such as is found in Europe, is not conclusive. The authors consider the etiologic relation of the trypanosome with endemic goiter. They do not deny the existence of the acute form of Chagas' disease.—B. A. H.

(THYROID) Clinical Aspects and Pathological Anatomy of the American Trypanosome. Chagas (C.) *La Prensa Med.* (Argent.) 1916, Nos. 13, 14, 15.

Three complete studies of Chagas' disease. The author attributes to the trypanosome the large number of cases of goiter which are observed in certain regions of Brazil.

(THYROID) Cretinism and Chagas' Disease. (Second communication.) Kraus (R.) and Rosenbusch (F.) *La Prensa Med. (Argent.)* 1916, No. 17.

The authors believe that the endemic goiter of the province of Salta is produced by the trypanosome. They found *Eriatoma infestans*, the transmitting insect, capable of producing trypanosomiasis in guinea pigs, not only in goiterous regions, but also in other distant places. They believe that Chagas' disease does not differ greatly from the classic cretinism.

In Salta they have found goiterous and cretin dogs. They believe that the goiter and cretinism of Argentine are identical with those of Europe.—B. A. H.

(OVARY) Pathogenesis of Uterine Fibromata. Piccardo (F. J.) *La Prensa Med. (Argent.)* August, 1916, 65.

The author attaches great importance in the development of fibromata to hyperfunction of the ovaries which he attempts to check by thyroid medication.

(INFANTILISM) A Case of, Associated with Stone in the Kidney. Tuechter (J. L.) *Lancet-Clinic (Cincinnati)* 1916, cxv, 483.

The author reports a case of infantilism associated with stone in the kidney. Of no particular endocrine interest.

J. R. G.

(THYMUS) Two Cases of Enlarged Thymus. Skaggs (C. S.) *Lancet-Clinic (Cincinnati)* 1916, cxv, 246.

The author reports two cases in which the symptoms point to thymus enlargement. He first reviews the literature and divides cases of enlarged thymus into three classes: (a) those showing thymic striae, (b) those with thymic asthma and (c) those with thymic death. The first child died suddenly with typical symptoms but he was unable to obtain post-mortem. The second child, after a history of considerable exposure, developed a wasting illness associated with attacks of coughing, resembling whooping-cough. The X-ray showed a shadow in the thymus region. No post-mortem was obtained.

The reviewer is not quite able to understand how this last case can be attributed definitely to enlarged thymus. From such a description, one would be justified in suspecting tuberculosis with pressure symptoms from enlarged bronchial glands.—J. R. G.

(HYPOPHYSIS) Teratoma in the Region of the Tuber Cinereum. Bosco (G. A.) *La Prensa Med. (Argent.)* 1915, No. 18, 249.

Observations together with autopsy and microphotographs. Illness of one year's duration with loss of attention and memory. Intense headaches, vomiting, diminishing vision in the right eye, incomplete right sided hemiplegia, papillary atrophy complete on the right and incomplete on the left side. The tumor was cystic, arising in the third ventricle and extending to the corpora quadrigemina. On microscopical examination, the structural part of the tumor was found to be made up of cords of cuboidal cells and the cystic cavities were filled with colloid.—B. A. H.

THYROID SECRETION, A Slight Insufficiency of, in Gynecology. Castano (C. A.) *La Prensa Med. (Argent.)* 1915, Nos. 5-6, 81 and 89.

A resumé of the results of thyroid medication in various gynecologic cases. The author advises such medication in cases of severe hemorrhage which are not due to lesions in the genital tract. Its administration was found efficacious in certain cases of dysmenorrhea and in a few cases of leucorrhœa; also in cases of repeated abortion which could not be proven to be due to another cause.—B. A. H.

(THYROID) Exophthalmic Goiter and Abnormal Growth. Busio (J.) *Sociedad Argent. de Pediatría.*, Aug. 31, 1915. *La Prensa Med. (Argent.)* 1915, 177.

Case: A girl, 13 years of age, without menstruation. For two years she suffered from pains in the joints with swellings of 10 centimeters at each attack. In the last attack there was evidence of goiter and of tachycardia. The mother is very nervous and an uncle had suddenly increased in growth at the age of 14. The patient has grown 50 centimeters in height since the beginning of her attacks.

In the discussion, Dr. Elizalde mentioned an analogous case of a girl 9 years old who did not have a goiter. Her mother did however have a goiter.—B. A. H.

HYPOPHYSIS, Clinical Considerations of Some Lesions of. Priana (P.) *La Prensa Med. (Argent.)* 1916, No. 35, 411.

Two cases of acromegaly and one case of adiposity with bitemporal hemianopsia are reported. One case of acromegaly was operated but at the end of a month, the patient developed symptoms of meningitis and died. At autopsy a large adeno-carcinoma of the hypophysis was found (100 gms.).

The case of adiposity with bitemporal hemianopsia was operated and died from accidental hemorrhage from the lateral sinus.—B. A. H.

A Case of Ateliosis. Webber (E. P.) and Stebbing (G. F.)
Brit. J. Child. Dis. (Lond.) 1916, xiii, 200.

The authors' report of the case of ateliosis in a boy 16 years of age. This name is given by Hastings Gilford to a kind of general and symmetrical dwarfism and infantilism, due to more or less complete bodily and mental arrest of growth and development. It is not confined to the head or limbs but involves the whole body; that is, a microsomia. The cases differ from each other according to the stage of growth and the time at which the arrested development occurs. These cases are of probably endocrine interest because they show (a) hypoplastic sexual glands, (b) very small thyroid and (c) the X-ray picture shows a very small pituitary fossa. The boy described was 109 centimeters in height and weighed 22 kilograms. The abdomen and head were large, conforming to infantile proportions; thyroid was not palpable; the sexual organs resembled those of a child of five and ossification seemed normal. The condition was first noticed at the age of four years. As regards therapy, thyroid extract had no effect.—J. R. G.

(PITUITARY) A Case of Dyspituitarism. Pou (R. E.) Lancet-Clinic (Cincinnati) 1916, cxv, 88.

A good clinical report.

(SPLEEN, ADRENALS) A Study of the Lipin Content of a Case of Gaucher's Disease in an Infant. Wahl (H. R.) and Richardson (M. L.) Arch. Int. Med. (Chgo.) 1916, xvii, 238.

While not of technical endocrine interest, the article is worthy of careful consideration; the authors' review of the literature shows a gradual increasing tendency of observers to ascribe the large pale cells to lipoid infiltration. In their case, the spleen, liver and lymph nodes presented the usual changes and in addition, the almost complete substitution of the medulla of both adrenals by clusters of large, pale, vacuolated cells.

Microchemical study showed not only this accumulation of lipoid in the large pale cells but revealed also that these bodies were not identical. These lipoids are not definitely proven to be cholesterolin and so it is safer to refer to them, as yet, by the more general term. Why in this case the

medulla of both adrenals was almost replaced by large cells is difficult to explain. Krylow believes that the adrenal cortex regulates lipoid metabolism. The authors conclude that in Gaucher's disease the liver and spleen show not only a marked increase in lipin, but also a serious alteration in the relation of lipins to each other. Fixed fats are greatly reduced while lipoids, such as cholesterin, are greatly increased.—J. R. G.

(DYSPIUITARISM) Two Cases of Dyspituitarism, Particularly of the Posterior Lobe. Niles (W. L.) *Med. Record* (New York) 1916, lxxxix, 6.

The author gives a good review of the literature, showing that most studies confirm Cushing's ideas, namely: that the two parts of the gland are antagonistic to each other, the anterior part influencing skeletal development; the posterior part being related to metabolism, chiefly, of carbohydrates. Functional hyperplasia of the anterior part gives gigantism if it exists before the completion of the epiphyseal union. Afterwards, it gives acromegaly. Insufficiency of the posterior part gives adiposity and an increased tolerance for carbohydrates. One case is of interest. A boy, aged 13 years, had a large appetite, particularly for carbohydrates; was always cold (the temperature ranging around 96 degrees), showed polyuria, fainted occasionally and was emotional. The examination showed feminine configuration of the body: broad hips and thighs, tapering extremities, small hands and feet, the skin was dry and coarse, there was no hair other than that on the scalp, the X-ray showed a very small sella turcica. The interesting feature in the case was the improvement under treatment. The food intake was reduced to 24 calories per kilogram and he was given grains 1-10 of a posterior lobe of pituitary t. i. d. by mouth. Temperature rose at once to 98 degrees but after two weeks began to sag. Upon doubling the dose, the temperature again rose to 98. Two months later, upon stopping the treatment, the temperature dropped one degree, becoming normal again, however, upon resuming the pituitary feeding. After four months, he was better in every way. He led in his class in school and everybody noticed his improvement.—J. R. G.

(HYPOPHYSIS) Les tumeurs de l'hypophyse (Pituitary Tumors). Hutinel (P.) *Rev. Gen. de Clin. et de Therap.* (Paris) 1916, xxx, 81.

The author describes a case of a girl of 13 years, with all symptoms of tumor of the hypophysis. Remarkable is the

fact that all of her symptoms disappeared following a decompression operation, except nystagmus and amaurosis. Two years later the reflexes were normal, there was no Koenig, no contracture, no hemiplegia; obesity disappeared and there were no increased signs of acromegaly. Such a report suggests that it might be advisable to try a palliative operation first before doing one more radical.—J. R. G.

(ADRENALS) Addison's Disease, with a Report of Two Cases. Goodwin (R. A.) *Providence Med. J.* 1916, xvii, 33.

The author reviews the literature of adrenal physiology and says that Addison's disease is now considered an affection of the entire chromaffin system. This is tissue having a special affinity for chrome salts. It is found along the vertebral column in the embryo and it becomes the medulla of the adrenal, the carotid gland in the arch of the aorta, the coccygeal gland and is found along the course of the sympathetic nerves. In Addison's disease, all of this tissue seems involved and particularly the medullary part of the adrenals. In both of his cases, autopsy showed tuberculous involvement of the adrenals, the first being caseous involvement, the second being part of a general miliary tuberculosis.—J. R. G.

(THYMUS) Enlarged Thymus in Infancy. Herrick (J. F.) *Surg. Gyn. & Obs. (Chgo.)* 1916, xxii, 333.

Herrick asks the very pertinent question, if it is true that many cases of dyspnea in children are due to thymic enlargement, how does one explain the fact that the trachea, which is cartilaginous, should suffer compression and the veins and arteries should not? Herrick suggests that possibly the respiratory symptoms are due to pressure upon other organs. He quotes a case in which autopsy showed an enlarged thymus pressing upon the right auricle and also on the veins about the base of the heart. He also describes five other cases showing X-ray plates with thymus shadows and symptoms suggestive of thymic enlargement. These were all helped by X-ray therapy.—J. R. G.

(PITUITARY) A Case of Probable Pituitary Tumor. Craig (C. B.) *Lancet-Clinic (Cincinnati)* 1916, cxv, 111.

The author describes a case of probable pituitary tumor. In addition to the usual symptoms, the sugar tolerance was increased to over 300 grams of levulose. Operation had not as yet been performed—J. R. G.

(PITUITARY) A Case of Hypophyseal Tumor. Davis (T. K.) *Lancet-Clinic (Cincinnati)* cxv, 567.

The case showed unusually large, heavy hands and feet with coarseness and heaviness of the face. There was a typical bi-temporal hemianopsia. This case showed a sugar tolerance of over 600 grams of glucose. The patient had not, as yet, been operated.—J. R. G.

PITUITARY INFANTILISM, Pathological Report on a Case.

Evans (J. J.) and Assinder, *Birmingham Med. Rev.* 1916, lxxx, 1.

The patient, aged 51, was first seen for failure in eyesight, headache and giddiness. Examination showed general appearance, contour and voice of a boy of 14. The height was 4 feet 7 inches; cerebation was slow and intelligence deficient. The thyroid was not palpable, breasts were prominent, the penis small and infantile and the testes soft. Optic atrophy and bi-temporal hemianopsia were marked. The X-ray showed extensive excavation of the sella turcica. The epiphyses of the long bones were unossified. No treatment had any marked effect. X-ray therapy seemed to aggravate the symptoms; thyroid therapy simply reduced his weight. Pituitary extract seemed to quiet him, increase the quantity of urine and raise the systolic blood pressure, but this was inconstant. Post-mortem revealed a tumor the size of a hen's egg in the pituitary fossa. The thyroid was in a condition resembling that of exophthalmic goiter. There was excessive subcutaneous fat and no sign of a thymus.—J. R. G.

ADRENAL Glands. Cobb (I. G.) *Med. Press. and Circ. (London)* 1916, cii, 186.

A good review of the literature. The author believes that the medullary secretion of the adrenals exerts an angio-tonic influence while that of the cortex is myo-tonic, i. e., it neutralizes the poisonous products of muscular activity. He describes the symptoms of adrenal insufficiency and suggests that all symptoms except pigmentation can be explained by vasomotor derangement and paralysis of the sympathetic nerves. He believes milder types give rise to symptoms usually called neurasthenia.—J. R. G.

(ENDOCRINE ORGANS) A Case of Progeria. Schippers. *Nederlandsch Tijdschrift voor Geneeskunde (Amst.)* 1916, ii, No. 26.

Description of the fourth case of progeria. The symptoms are: Tardy closure of the fontanelles, congenital absence of hair and mammary glands with atrophy and pigmentation of the skin, the subcutaneous connective tissue and fat have nearly disappeared. Theories explaining this

disease: Vasiot and Peronneau think of thymus and adrenal anomalies; Charcot thought of an abnormality of the kidney; others, of the thyroid gland. In the only case in which an autopsy was made (Gilford), there were found a sclerotic thymus and sclerotic adrenals and kidneys; there was atrophy of the digestive tract.—J. K.

(THYROID) On the Connection Between "Soldier's Heart" and Hyperthyroidism. Stoney (F. A.) *Lancet* (London) 1916, ii, 777.

Stoney emphasizes: first, the likelihood of confounding "mild" goiters following shell shock, with neurasthenia; second, the symptomatology of beginning exophthalmic goiter; third, the rapid disappearance of symptoms following the judicious use of the Roentgen ray.

The illness usually dates back to some severe shock, such as that produced by a bursting shell or by burial. These cases are frequently sent to the base hospitals with such a diagnosis as, "shell shock," "neurasthenia," "early phthisis," along with the parenthetical diagnosis of "soldier's heart." These hearts upon examination prove to be typical of early Basedow's disease and are characterized by a practically normal rate when lying down, an increase rate, 90-100 per minute, when standing or sitting, with a normal rate when the recumbent position is again assumed. Not infrequently the heart is somewhat dilated, the action tumultuous and irregular in force and rhythm. While murmurs are often present, the characteristic auscultatory sign is an abrupt short first sound lacking in tone.

These objective heart findings with such subjective signs as fainting, weakness, dyspnea, giddiness, precordial pain and palpitation subsequent to a severe shock are indicative of an early Graves' disease. The diagnosis, however, is easily and frequently strengthened by such findings as perspiration and a fine tremor, nervousness and the other well-known signs and symptoms.

Stoney considers X-ray therapy specific in early cases, enhanced greatly by the removal of oral and intestinal sepsis along with medical management. One Sabouraud dose through one or two millimeters of aluminum as a filter to each side of the thyroid for twenty minutes, is given weekly. The exophthalmos disappears after a few weeks, the gland softens and the heart becomes regular and slower and regains its original size. In support of these observations the histories of four cases are quoted.—F. B. L.

Adrenalectomy and Gastric Ulcer. Goodman (E. H.) *Prog. Med.* (Phila.) 1916, iv, 40.

Nothing new except that in five cases of gastro-duodenal ulcers pathologic changes in the adrenals were reported.
J. D.

**Zur Diagnose nervösen, insbesondere thyreogener Herzbeschwerden Heeresangehöriger mittels der Adrenalin-
augenprobe und der Lymphocyten—auszählung. Diagnosis
of thyrotoxicosis.** Curschman (H.) *Mediz. Klinik* (Berl.)
1916, No. 10, 253.

Curschman points out the importance of Löwi's symptom in the diagnosis of thyreotoxy. Löwi's symptom depends on the fact that in normal human subjects there is no enlargement of the pupils after adrenin, but in cases of involvement of pancreas or in cases of thyreotoxy there is a marked enlargement of pupils, persisting for several hours. Associated with this is an increase of the lymphocytes, the blood picture showing between 45 per cent. and 50 per cent. lymphocytes, about 50 per cent. leucocytes and 2 or 3 per cent. each eosinophiles and transitionals. He points to the presence of Löwi's sign as an important factor in the differential diagnosis between purely nervous cardiac disturbances and those due to thyreotoxic disturbances.

(The more recent researches have failed to support either the constancy or the significance of the Löwi reaction.—Ed.)

**Ueber den Einfluss eines Hormons des Corpus luteum auf die
Entwicklung maennlicher Geschlechtsmerkmale. (Influ-
ence of Corpus Luteum upon the Development of Male Sex
Characteristics.)** Hermann (E.) and Stein (M.) *Mediz.
Klinik* (Berl.) 1916, No. 15, 401.

In the case of rabbits, injections of corpus luteum into male animals resulted in diminution of the testicles, epididimis, prostate, and seminal vesicles. Other microscopical changes are mentioned.

(THYROID) The Relation of Mouth Infection to Goiter.
Reede (E. H.) *Washington* (D. C.) *Ann.*, 1916, xv, 230.

The work of Billings, Rosenow, and others upon the seeming relation of infected tonsils and teeth to goiter is reviewed briefly. Reede comments upon his personal observation of fifty cases, below the age of twelve, in which the thyroid enlargement was coincident with a chronic gingivitis. In addition, he cites, in support of this view, the case of a nineteen year old girl, who was relieved of the symp-

toms of Graves' disease, following the removal of two abscessed wisdom teeth, although the gland still remained large.

Another case twenty-two years old, with a recurring arthritis, developed a severe pyorrhea and also a goiter following the removal of tonsils. The patient, however soon regained her health after treatment of the pyorrhea and the removal of an abscessed incisor.—F. B. L.

(THYROID) An Analysis of Fifty Cases of Dysthyroidism.

Swan (J. M.) *International Clinics* (Phila.) 1916, 1, 777.

Swan, in rather an exhaustive study, analyzes in a statistical manner the relative frequency of signs and symptoms in fifty cases of dysthyroidea and lays particular stress on the failure of so many to recognize the early stages of goiter. Thirty-eight per cent. of his cases complained of the cardinal symptoms of the disease. If nervousness be excluded only sixteen per cent. came for relief of cardinal symptoms. Headache was present in five; tachycardia in thirty-three; exophthalmos in twenty-five; tremor in thirty-one; enlargement of the gland in forty-five; abdominal pain in nineteen; vomiting in twelve; restlessness in twenty-six. Of the eye signs, Dalrymple's was present in five cases; absent in twenty-two, no record in twenty-three. Moebius' sign was present in twelve, absent in twenty-eight, no record in ten. Nystagmus was present in twenty-six, absent in sixteen, no record in eight.—F. B. L.

(THYROID) Observations on Blood Pressure in Cases of Dysthyroidism. Swan (J. M.) *Interstate Med. Jour.* (St. Louis) 1916, xxiii, 186.

Swan prefaces his observations on fifty cases of dysthyroidea by stating the effect of that serum from exophthalmic goiter patients upon normal individuals. It has been found that such a serum, as well as alcoholic soluble and non-soluble residues from the struma of goiters, when injected intravenously produces a notable drop in blood pressure. In clinical observations, judging from his fifty cases, he concludes that the first effect of the intoxication is to produce a lowering of the systolic pressure with a corresponding increase in the pulse pressure. As the intoxication goes on, he finds the blood pressure rising until such a stage is reached that cardio-vascular and renal changes are produced. The cases then take on the aspect of chronic hypertension. The study of functional myocardial tests shows myocardial disturbances in all cases, whether there be clinical evidence or not. In one case, preceding hemithyroidectomy, there was a sharp fall of the systolic and pulse pressure. After operation

the systolic pressure rose to a high point, returning almost to normal following the administration of sodium nitrite.

F. B. L.

(INTERNAL SECRETIONS) Myopathy Related to the Disorders of the Internal Secretions. McCouch (G. P.) and Ludlum (S. D. W.) *Med. Record* (N. Y.) 1916, lxxxix, 1042.

The authors review the various myopathies, submitting the evidence which would go to show that these conditions are related to internal secretions:

Myotonia Congenita: This condition is found associated with tetany. The calcium balance is negative in those cases studied, which would suggest parathyroid involvement; lastly, the condition is found associated with impotence, testicular atrophy, loss of hair and cataract.

As regards myasthenia gravis, there is little evidence as to parathyroid involvement except that it is occasionally associated with tetany and sometimes shows a negative calcium balance. More frequently it is found with exophthalmic goiter. A further point suggestive of thyroid implication is the experimental evidence that thyroid extract depresses the voluntary muscles of the frog. Other observers have claimed that all of the symptoms of myasthenia gravis can be accounted for by low blood pressure, suggestive of adrenal involvement. Lastly the thymus has been investigated but statistics show that thymic enlargement occurs in only 28 per cent. of the post-mortems.

Muscular dystrophies lead one to suspect endocrine disturbance by the associated adiposity, and the high tolerance for sugar. The authors report a case of dystrophy in a woman aged 35 years. The symptoms had been present since 11. The patient had an infantile uterus, the X-ray showed a large sella turcica. The case combines adiposity, deficient development of both primary and secondary sexual characteristics, the small hands with tapering fingers and the enlarge sella turcica of Froehlich's disease, with the distribution of atrophy and sclera hypertrophy, proportional muscular weakness, diminution of tendon reflexes and diminished response to electrical stimuli.

In this case and several others Abderhalden tests were made. In all, there were four cases of dystrophy, one of progressive muscular atrophy, one of the perineal type of muscular atrophy and two of atrophy from syphilitic neuritis. In all but the last two cases, the reactions were positive to the adrenal and thyroid. The authors believe this further evidence of endocrine involvement.—J. R. G.

(ADRENIN) Anaphylactic Manifestations Following Cholera Revaccination. Adrenalin in the Treatment of Anaphylaxis. (Phénomènes Anaphylactiques consécutif aux Revaccination Anticholérique. L'Adrénaline dans la Traitement de l'Anaphylaxie.) Parhon (C. J.) and Bazgan (G.) C. r. Soc. de Biol. (Paris) 1917, lxxix, 506.

In view of the excellent results reported by a number of observers in their employment of adrenin injections in severe infections associated with adynamia (diphtheria, typhoid fever), the authors determined to ascertain the action of adrenalin in anaphylactic shock, in which there are present the two chief factors constituting the gravity of severe infectious diseases, namely, adynamia and low blood pressure.

The opportunity offered itself in the revaccination of three individuals against cholera. In each case a characteristic anaphylactic reaction occurred. In the first, while adrenin was being sought, ether and caffen were injected without benefit. The injection of 1 cc. adrenalin, 1:1000, brought about an amelioration of all symptoms within five minutes.

In the other two cases, adrenalin was used at once with a rapid disappearance of the symptoms.

In conclusion, the authors ask whether adrenalin may not be considered a suitable prophylactic measure in cases where anaphylactic phenomena might be expected.—A. F. B.

(ADRENALS) Toxic Lesions of the Adrenal Gland and Their Repair. Graham (G. S.) Jour. Med. Research (Boston) 1916, xxxiv, 241.

Graham produced necrotic lesions of the adrenal cortex in the guinea pig by the inhalation of chloroform, di-chloromethane and tetra-chloromethane. Similar but less constant and less extensive lesions followed the subcutaneous injection of phenol. Necrosis of the cortical parenchyma of the adrenal is common in infectious diseases both in the guinea pig and in man. During recovery from the intoxication or the infection the necrotic cortical cells are replaced by mitotic division of undamaged cells lying usually in the more peripheral levels of the cortex. Graham ventures the suggestion that the zona glomerulosa and particularly the outer levels of the zona fasciculata may constitute a growth center where cells are regenerated as needed. Mitoses occur in the chromaffin cells of the medulla, but much less frequently than in the cortex. It seems evident, therefore, that the adrenal cortex is very sensitive to poisons and its cells are readily injured or killed by them, but the cortical parenchyma also possesses a power of restoration when the cause of the lesion is

removed. Graham considers it possible that changes in the adrenal cortex may be partly concerned in the so-called "delayed chloroform poisoning."—J. P. S.

(PANCREAS) Zur Bewertung der numerischen Verhältnisse der Pankreasinseln beim Diabetes (The Islets of Langerhans in Diabetes). Heiberg (K. A.) *Centralbl. f. allg. Path. u. path. Anat.*, 1916, xxvii, 49.

Heiberg has made quantitative studies on the islands of Langerhans in the tail of the pancreas. Of 75 diabetics, 61 showed fewer than 50 islands per area of 50 square millimeters. Of 75 non-diabetics, 70 showed 76 or more islands per area of 50 square millimeters, while 17 showed more than 150. Heiberg thinks, therefore, that a quantitative study of the islands of Langerhans is as essential as a qualitative study in determining their relation to diabetes.—J. P. S.

(ADRENALS) Bilateral Infarction of the Suprarenal Bodies. Larkin (J. H.) *Proc. N. Y. Path. Soc.*, 1915, xv, 163.

Larkin reports a case of generalized peritonitis following rupture of duodenal ulcer. At autopsy, there was found thrombosis of both adrenal veins with complete infarction of both adrenals. The author was unable to find any report of a similar case in the literature.—J. P. S.

(THYROID) Paroxysmal Tachycardia Associated with Unilateral Exophthalmos in a Case of Basedow's Disease of Long Standing. (Acces de Tachycardie Paroxystique avec Exophthalmie Unilaterale chez une Ancienne Basedowienne.) Danielopolu (D.) *C. r. Soc. de Biol. (Paris)* 1916, lxxix, 103.

In the author's report is described a case of Basedow's disease of 15 years duration, the manifestations of which tend to confirm the view of certain observers (Vaquez, Douzelot) that hyperthyroidism is related causally to paroxysmal tachycardia.

The striking feature of the patient discussed was the appearance of a marked protuberance of the right eye at the onset of each paroxysmal attack and the recession of the exophthalmos at its conclusion. The left eye remained normal.

This apparent relationship of exophthalmos and paroxysmal attack points to an excitation of the sympathetic as the cause of the latter, a theory in accord with the work of Hering, Douzelot and Rothberger and Winterberg, who produced attacks of heterotopic tachycardia in the dog by stimulating the left stellate ganglion. The same observers have noted that while the right sympathetic innervates the sino-auricular

node (the normal pace-maker), the left sympathetic is in relation solely to the heterotopic cardiac centers. Excitation of the left nerve possesses the property only of giving rise to an heterotopic tachycardia, the right a homotopic.

The manifestations in the case presented demand, therefore, the assumption of an excitation of both sympathetics—the right causing the exophthalmos, the left the paroxysmal tachycardia.

However, as it is known that the simultaneous stimulation of both nerves causes a tachycardia of normal origin, the homotopic center possessing a greater automaticity than the heterotopic, another factor must be adduced in the case in question to explain the abnormal source of the tachycardia. This additional factor is assumed to lie in a diseased myocardium (probably in the His bundle), itself the result of the Basedow toxins, possibly via an intermediate action on the adrenal glands.

This theory accords with the views of Vaquez and Esmon, Keith and Mackenzie, who believe that a paroxysmal tachycardia cannot originate in an intact myocardium.—A. F. B.

(PITUITARY) An Unusual Case of Acromegaly. (Un cas exceptionnel d'acromégalie.) Marisnesco (G.) and Minea (J.) C. r. Soc. de Biol. (Paris) 1916, lxxi, 99.

The report concerns itself with a well-marked case of acromegaly, the unusual manifestation being an involvement of certain of the cranial nerves of the left side (I, II, V, VII, VIII). At autopsy was found a tumor of the base (the nature of which remained to be determined) arising apparently in the hypophysis and showing a tendency to grow along the trunks of the cranial nerves mentioned.—A. F. B.

THYROID Gland, The Failure of Extracts of, to Act upon Mucin in Vitro. (Absence d'action de la glande thyroïde sur la mucine "in vitro.") Parhon (C. J.) and Parhon (M.) C. r. Sos. de Biol. (Paris) 196, lxxix, 504.

This report concerns itself with the origin of the mucinous infiltrations in cases of deficient thyroid secretion. The point at issue is whether the state of thyroid insufficiency leads to myxedema by reason of an action upon the nervous system, or by exerting its effect directly upon the mucin itself. The particular object of the research was to repeat the work of Nerking, who found that thyroid extracts decomposed mucin in vitro.

The materials employed were mucin obtained by Hammarsten's method from the submaxillary glands of cattle, and thyroid extracts obtained also from cattle.

The writer goes in detail into the various steps of his test tube work. His results were consistently contradictory to those of Nerking, in that he found that thyroid extracts did not decompose mucin *in vitro*.—A. F. B.

(THYROID) Yets over de Classificatie van Kroppeswellen (Classification of Goiters). Lanz (O.) *Nederlandsch Tijdschrift voor Geneeskunde*, 1917, No. 8.

Lanz, who has been professor of surgery in Switzerland and Amsterdam, compares the forms of Dutch and Swiss goiter and suggests another classification, as he considers the classification of Mayo not practicable. Goiter in Holland is nearly always atoxic; in Switzerland this form is very rare. He suggests a classification as follows:

I. Non-toxic.

1. Diffusa parenchymatosa.
2. Diffusa colloidea.
3. Circumscripta: colloidea; cystica.

II. Toxic goiter.

1. Diffusa (s. vasculosa).
2. Diffusa (in Graves' disease).
3. Circumscripta.

J. K.

(KIDNEY) The Effect of Nephrectomy upon the Arterial Pressure and the Probable Role of the Kidneys in the Endocrine System (Effet sur la Pression Artérielle de la Nephrectomie et Rôle Probable des Reins dans le Système Endocrine). Backman (E. L.) *C. r. Soc. de Biol. (Paris)* 1916, lxxix, 406.

Nephrectomy causes a fall in arterial pressure followed by a slight—though sometimes great—(premortal) rise. The author explains this as due to the removal of a normal hypertensive secretion contained in the kidneys. Brown-Séquard believed in the existence of an internal secretion in the kidneys and Tigerstedt and Bergmann demonstrated hypertensive substances in the kidneys.

The writer calls attention also to the results of a number of observers who found that nephrectomy led to a hypofunction of the adrenal glands and a disappearance of the adrenin in the glands. Hence nephrectomy and epinephrectomy produce the same effects, namely, hypotension and a fall in temperature.—A. F. B.

(Neither observation affords valid evidence in support of a specific relationship. Many factors, including trauma, cause depletion of adrenin and also low blood pressure and temperature. The theory of an endocrine function for the kidney must be held dubious without more convincing evidence than has yet been offered.—Ed.)

THERAPEUTIC EXPERIENCES

(OVARY, ENDOCRINE GLANDS) A Physiological, Clinical and Therapeutic Study of the Functions of the Ovary. Gonolons (G. P.) Dissertation (Buenos Aires) 1917.

The author made a statistical study of menstruation in 1428 women from the "Corcuato de Alvear" Hospital. It was found that in Argentinean women the menses appeared commonly at an age of thirteen years and seven months; in Spanish and Italian women at the fifteenth year; in Uruguayans at the thirteenth, and in Paraguayans at the twelfth year. In the Argentine women the flow appeared regularly at 28-day intervals in 97.08 per cent. of the cases and in the Spanish and Italian women in 85.47 per cent. The flow was more abundant in the Argentine than in the Spanish and Italian women. It commonly persisted 3 to 4 days in the Spanish and Italian, and 3 to 9 days in the Argentine women but often a duration of 3 to 5 days was observed. As to dysmenorrhea, the menses were without pain in 55.86 per cent. of the Argentine, and 55.86 per cent. of the Spanish and Italian women. As regards etiology, menstrual disorders were most common in pulmonary tuberculosis, vaginitis (?), multiple arthritis and exophthalmic goiter.

The pulse rate was noted beginning one day before the onset of menstruation and arterial pressure (with Pachon's apparatus) beginning two days before. These decreased as menstruation progressed and increased after its completion. The respiratory rate followed a similar course.

The author believes, and the statement is borne out by statements of the patients, that the psychic phenomena and objective symptoms that precede menstruation are analogous to rutting in animals.

Experimental observations: One or both ovaries were removed from animals—rabbits, white rats and cavies—and numerous grating experiments were made, using one or both glands. In a few animals Steinach's experiments were repeated (grafting gonads into animals of the opposite sex to cause inversion of the sex characteristics). These gave negative results. Histological study of 146 preparations of the adrenals, pituitary glands, thyroids, parathyroids and ovaries from the various animals showed no noteworthy departures from the normal. The only positive conclusion from this series was that the ovaries are necessary to the normal development of the other sex organs.

Toxicologic studies: It was found that: emulsions (?) and centrifugalized solutions of corpus luteum from pregnant

young cows are much more toxic than those of ovaries. All the solutions were active and caused qualitatively similar symptoms. In some but not all animals immunity could be developed. In the comparative studies rabbits of similar age and weight were used.

Pharmacodynamic studies: The action of both luteal and ovarian extracts was observed on blood pressure, heart, stomach, intestine, bladder, uterus, kidney and mammary gland. It was concluded that: Both extracts are depressor but that the corpus luteum is more effective. Neither extract contains an active principle comparable to that of the adrenal or pituitary glands. Digestion of the organ substance in HCl, extraction with fat solvents and boiling 5 minutes failed to destroy or remove the depressor substance. The effective substance (1:1 solution) is not dializable. The liquor folliculi from ovarian cysts is not active. Vagotomy or atropinization do not prevent the depressor effect of the extracts. Adrenal and pituitary extracts counteract the effects of ovarian and corpus luteum preparations. The depressor effect is regarded as due to peripheral dilatation. In the rabbit a diminished excursion of the heart beat was caused. In the frog partial heart block was observed. The tonus and rhythmic contractions of the intestine, bladder, stomach and uterus were increased but the contractions of the esophagus of the toad (*Bufo marinus*) were depressed. The extracts caused dilatation of the kidneys and the lactating mammae. As regards glandular secretion the results were not conclusive.

Therapeutic observations: Ovarin administered to the fasting patient in doses of 0.10 cgm to 0.20 cgm. give better results than larger doses.

In 150 cases of scanty lactation excellent success has followed the use of desiccated corpus luteum from pregnant young cows. This is administered by mouth in doses of 0.05 cgm. daily for a period of one or two weeks.—G. P. G.

ADRENAL Cortex in Aspermia. Little (S. W.) Boston Med. and Surg. Jour. 1917, clxxvi, 355.

Little reports a case of aspermia previously examined by a competent genito-urinary specialist and found to be normal. By a process of exclusion it was decided that the cells from which spermatozoa develop were probably present but dormant. We know that some of the ductless glands have a great influence on the growth and development of the generative apparatus. These glands are especially the thyroid, the pituitary and the adrenal cortex. Furthermore in this case if the fault lay in any of the ductless glands, obviously it must be a case of hypo-function.

There were no symptoms of hypo-thyroidism, such as myxedema, even in slight degree. The pituitary was ruled out also for lack of symptoms such as polyuria, drowsiness, lack of ambition, obesity, low blood pressure and the like. On the other hand two facts pointed to a former hyper-action of the adrenal cortex—the body hairiness and large size of the external genitalia. Hyper-action of any organ implies eventual hypo-action of that organ. Accordingly we acted upon the theory that this patient for an indefinite time, probably from some time after puberty, had had a condition of cortical hypo-adrenalism.

He was given 4 grains of dried adrenal cortex daily, increasing to 6 grains daily. Treatment was begun on September 23rd. On November 25th a few perfectly formed spermatozoa were found in a condom specimen. The finding was confirmed by Dr. M. Y. Casey, pathologist to St. Mary's and the General Hospital.

LYMPH GLAND EXTRACT, Its Preparation and Therapeutic Action. Hadden (D.) Amer. Jour. Obst. (N. Y.) 1916, lxxiv, 989.

The author briefly reviews the manufacture of Leucocytic Extract and Lymph Gland Extract prepared by the Archibald-Moore method. He also discusses the therapeutic action of these agents. He cites his experience with Leucocytic Extract in acute infections. He uses it as a routine procedure in connection with his surgical work in all acute septic conditions, such as acute septic appendicitis, etc. Cases of streptococemia have proven very tractable with the use of Leucocytic Extract in conjunction with the magnesium sulphate solution advocated by Harrar.

Leucocytic Extract having proved so satisfactory, Hadden was attracted to the use of Lymph Gland Extract, which is also produced by an original digestive method by Archibald and Moore. Both these agents produce a leucocytosis in 2 cc. doses but not by reason of their protein content which amounts to less than 0.04 of one per cent.

The leucocytosis following Leucocytic Extract is due to the increase of the polymorphonuclear variety of leucocytes, while the leucocytosis produced by the Lymph Gland Extract is due largely to a greater increase of the number of lymphocytes.

Blood pictures made following the exhibition of Lymph Gland Extract in addition to the above mentioned phenomena show an enormous increase in blood platelets, which probably accounts for the fact that Lymph Gland Extract has a profound effect upon the coagulation time of blood.

The author and his co-workers are using extracts from lymph glands pre-operatively to control hemorrhage and in many pathological conditions such as hemophilia, pulmonary affairs, etc., where hemorrhage is a factor. The extract has been used by the author and some of his co-workers in a number of cases of inoperable sarcoma and carcinoma with splendid results.

There is no evidence of protein reaction or sensitization of patients even though five times the ordinary dosage is used.—G. M.

(HYPOPHYSIS) The Active Principles of Hypophyseal Extract. Houssay (B. A.) *La Prensa Med.* (Argent.) 1915, No. 5, 82.

A resumé of the present knowledge and the previous work of the author. After a preliminary study, Aldrich and the author in 1911 prepared from the pituitary gland an active crystalline substance. In 1913, Fuhner isolated four active substances which, together, he called hypophysin. Baudoin in the same year and, in 1914, Ancel and Bouin, published the methods of preparation. The author showed that the precipitate formed by the addition of subacetate of lead carries down the active principle which then may be recovered almost totally by manipulation at a low temperature and careful washing. Almost all the precipitate contains a larger or smaller quantity of the active substance. It is absorbed by charcoal. It is soluble in methyl alcohol but not in ethyl alcohol. The author believes from the plurality of the active substances that even the cartilaginous fish give a galactogogic extract, but this does not influence either the arterial pressure nor the smooth muscle of various organs. As it deteriorates the extract loses first its hypertensive action, then its potency as a heart stimulant. Next the action on the uterus and the intestine, and on respiration is lost. The last to disappear is the galactogogic action. The author in 1912 showed that the cerebro-spinal fluid gave reactions which slightly resembled those of extracts of the hypophysis but while the former lost its potency when treated with subacetate of lead, the latter did not. No galactagogue action from cerebro-spinal fluid could be detected. In the cerebro-spinal fluid, then, there is the same substance as in extracts of the hypophysis but in very small amounts. By the lead acetate method it is easy to detect hypophyseal secretions in the cerebro-spinal fluid. For biological assay of pituitary extracts the blood pressure and the uterus methods are advised and for the determination of minimal dosages, the galactagogue action.—Author's abstract.

(**ENDOCRINE GLANDS**) *Beitrag zur Organtherapie der Amenorrhoe. (Endocrine Therapy in Amenorrhoe.)* Köhler. Zentralbl. f. Gyn. (Leipsig) 1911, xxix, 667.

Köhler has an interesting article on the subject of amenorrhea and reports his results in its treatment with various animal extracts. He publishes protocols of about thirty cases. Assuming, as he does, that amenorrhea is due to hypofunction of the ovary, his first list or group was treated with "luteoglandol," an extract of the corpus luteum of beef ovaries. Of the eight cases so treated, five were improved and in three cases there was no effect. In a second group of cases, the amenorrhea was treated with "pituglandol." While the number of cases so treated was not given, the author claimed he obtained a good result in most instances. In a third group "enteroglandol," an extract of the small intestine, was used. Of twelve cases treated by this extract he got good results in eleven and no effect in one. In one patient treated with "luteoglandol," after seven injections, her menses reappeared. Six months later, she was injected with "enteroglandol" on account of not having menstruated for the previous three months. After ten injections, her menses reappeared. This patient entered the hospital a third time for treatment for amenorrhea and was given ten injections of "placentol" (placental extract) with no effect. After two injections of "luteoglandol," the menses reappeared. Some of the cases were treated with "ovoglandol," or extract of the whole ovary, with good effect. The number of injections varied from 3 to 18. They were given daily or at intervals from two to three days, usually intramuscularly, sometimes subcutaneously.

In view of his findings that reappearance of the menses can be produced by extracts of the whole ovary, of corpus luteum, of the hypophysis and of the upper part of the small intestine, Köhler had a synthetic preparation made, consisting of several of the amines, e. g., "uteramine," histamine, phenylethylamine and isoamylamine. This synthetic preparation caused some bad after effects and hence its value in the treatment of amenorrhea could not be determined. The author adds that in cases where pituitrin is indicated, to increase the pains of labor, he has used "luteoglandol," "enteroglandol," "splenoglandol," or extracts of testicle, mammary gland or thyroid with equally good effect. The details of this study, however, he leaves for a later report.—W. H. M.

(The history of endocrine research indicates that when a given effect is produced by a variety of tissue extracts it is non-specific.—Ed.)

Organextrakte als Wehenmittel. (Endocrine Therapy in the Parturient.) Köhler. Zentralbl. f. Gyn. (Leipzig) 1915, xxxix, 891.

The author injected parturient patients with extracts of thyroid, mamma, thymus, spleen, ovary, corpus luteum, testis, placenta and one made from the mucosa of the small intestine. The injection was usually made intramuscularly, but sometimes intravenously. The effect of all these different glandular extracts was about the same, except perhaps that the splenic, placental and testicular extracts produced a somewhat stronger and more lasting effect. Then follows the protocols of his cases, which may be summed up as follows: "Enteroglandol" was used in three cases, mammary gland extract in four cases, testicular in seven cases, "luteoglandol" (corpus luteum) in seven cases, "splenoglandol" in three cases, thyroid in one case, placental extract in two cases, thymus in three cases,—in all, thirty cases. In nineteen the patients were at the end of pregnancy; in seven the injection was given in inevitable abortion; and in four cases, it was attempted to produce abortion. The effect of the injection of these various extracts was produced usually about ten minutes after the injection. In only four cases was operative interference necessary. No bad after effects were noted and the puerperium in every instance was uneventful. The babies exhibited no injuries and only one had a slight asphyxia. Owing to the small number of observations with each extract, the author draws no conclusions and does not claim that these extracts are superior to pituitrin as an oxytocic but remarks that their cheapness makes them a deserving substitute.—W. H. M.

CORPUS LUTEUM, Experience with the Soluble Extract, with Report of Cases. Royston (G. D.) Interstate Med. Jour. 1916, xxiii, 1119.

Nausea and vomiting of pregnancy were greatly improved, although one case might have shown the same improvement under the treatment received without the addition of corpus luteum. Sexual anesthesia is a decided indication for the administration of corpus luteum. The effect in these cases justifies the assumption that this condition, so extremely common (33 1-3 per cent. of the women in Vienna, according to Oscar Frankl) will often respond to the long continued and persistent administration of corpus luteum. Sterility, in the presence of apparently normal female genitalia and living motile spermatozoa, is an indication, especially when the patient has periods of amenorrhea. Amenorrhœa and oligo-

menorrhoea are distinct indications for corpus luteum treatment although underlying constitutional disturbances, as obesity, tuberculosis, anemia, etc., should receive appropriate treatment. Dysmenorrhoea, having a hypersensitive nervous system as a basic factor in most cases, is improved through the effect of corpus luteum in reducing this hypersensitive state. Theoretically, membranous dysmenorrhoea should be an indication par excellence, because of its action in better sensitizing the endometrium. Metrorrhagia may be benefited. The most striking results were obtained in the treatment of menopause symptoms, best shown in cases of artificial (post-operative) menopause. All nervous symptoms show marked improvement, usually beginning after the third injection. A failure of improvement or relief indicates insufficient dosage. Patients with very marked symptoms can receive 1 to 2 c. cm. doses intravenously every other day without untoward effects, with quicker reaction to the substance. The effect upon patients thoroughly treated disappears two to six weeks after cessation of treatment. They can be continued on 1 c. cm. doses at longer intervals (as every seven to ten days; in some cases 1 c. cm. every two weeks). Patients who find it difficult to come twice per week for treatment can receive 2 c. cm. doses once per week, in which event the intravenous injection is recommended. The administration of corpus luteum may be intravenous, intramuscular or subcutaneous, the rapidity of effect seemingly being in the order named. The effects of the substances are of varying duration. Menstrual disturbances are apparently relieved, whereas artificial menopause patients seemingly require it indefinitely. (Short abstract previously published *Endocrin.*, 1917, 1, 271.)

THYROID Extract, The Treatment of Eclampsia with. Quant (C. A. J.) *Nederlandsch Haandschrift voor Verloskunde in Vrouwenriektes en voor Kindergeneeskunde* (Leiden) 1917, vi, 53.

A compilation of the literature on the treatment of eclampsia with thyroid extract. Contains nothing new.—J. K.

SEXUAL GLANDS and Their Internal Secretions. Cobb (I. G.) *Med. Press. and Circ.* (London) 1916, cii, 295.

A good review containing nothing essentially new. At puberty the internal secretions of the sexual glands sensitize nervous reflexes as proven by experiments upon frogs during the spawning season. During the period of sexual activity, the frogs developed additional nervous mechanisms. Clinically the sexual glands are related to the adrenals, the hypophysis and the chromaffin system. Removal of the sexual

glands leads to changes in the thyroid, thymus and pituitary. The author suggests the use of testicular extract in neurasthenia.—J. R. G.

ADRENALIN. Practical Therapeutic Referendum. Landis (H. R. M.) *Progressive Med.* (Phila.) 1916, iv, 369.

The author cites from the *N. Y. Medical Journal*, August 19, 1916, Meltzer's procedure in the treatment of acute poliomyelitis by means of intraspinal injections of adrenalin. Two c.c. of 1:1000 solution are injected every 4 to 6 hours after withdrawing a "large" (?) quantity of spinal fluid previous to the first injection. Injections are to be continued for 4 or 5 days after all paralysis has disappeared. (Personal observations have convinced me that above treatment is absolutely without benefit to the patient.)—J. D.

PARATHYROID Gland in Paralysis Agitans. Landis (H. R. M.) *Progressive Med.* (Phila.) 1916, iv, 422.

Nothing original.—J. D.

PITUITARY Gland. Practical Therapeutic Referendum. Landis (H. R. M.) *Progr. Med.* (Phila.) 1916, iv, 428.

Nothing original.—J. D.

PANCREAS, Advances in Our Knowledge of the. Cobb (I. G.) *Med. Press and Circ.* (London) 1916, cii, 211.

A good discussion of the modern idea that the islets of Langerhans secrete a substance which, circulating in the blood stream, prevents an undue amount of glucose from circulating in the blood. Perhaps this secretion inhibits the formation of glucose and glycogen in the liver. The pancreas is influenced by the thyroid and parathyroids. The thyroid seems antagonistic; the parathyroids seem to enhance pancreatic activity. After pancreatectomy, no carbohydrate is found in the liver. The pancreas may be related to the adrenals, as injection of adrenin induces glycosuria. Against this argument, is the fact that glycosuria also results in a depancreatized animal. In favor of it is the observation that adrenin glycosuria can be overcome by the administration of pancreatic extract.—J. R. G.

(Later researches do not support this conception.—Ed.)

HORMONES, Therapeutic Application of. Cobb (I. G.) *Med. Press and Circ.* (London) 1916, cii, 488.

The author reviews the different therapeutic applications of hormones, showing how extracts of endocrine glands play

an important role in our therapeutics. Pituitrin as used in labor, adrenin in cases of low blood pressure, spermin in neurasthenia, and thyroid in myxedema and cretinism, and also in some cases of enuresis. As regards the latter, he quotes the interesting idea of Hertoghe that enuresis is due to thyroid deficiency. His explanation is that the thyroid gland influences the nutrition of the skin, and in a like way the mucous membrane of the bladder is affected, and in cases of thyroid deficiency, desquamation of the epithelium leaves the bladder wall more sensitive to the irritation of the urine.

—J. R. G.

(The matter should be subjected to a conclusive experimental investigation.—Ed.)

ORGANOTHERAPY of Menorrhagia. Pulvermacher (P.) *Med. Klin. (Berl.)* 1916, No. 7, 182.

Pulvermacher injected principally: Glanduitrin and Hypophysin, in a few cases Luteo-glandol, a watery extract of the entire ovaries of cows or of the corpus luteum. He outlines in detail the treatment of cases presenting various complicating factors and reports excellent results.

(ADRENIN) The Action of Adrenalin in a Case of Incomplete Auricular-Ventricular Dissociation. (Action de l'Adrénaline dans la Dissociation Auriculo-Ventriculaire Incomplete.) Danielopolu (D.) and Danulescu. *C. r. Soc. de Biol. (Paris)* 1916, lxxix, 105.

The authors found in a case of 2:1 heart block that the injection of adrenalin Takamine (0.0015) caused the dissociation almost entirely to disappear in four minutes. In addition the rhythm of both auricles was considerably accelerated by the adrenalin and different types of extrasystoles appeared.

"All these phenomena are the result of the exciting action of adrenalin upon the sympathetic nervous system. The researches of Rothberg and Winterberger have shown that the normal center of cardiac contraction is innervated by fibers from the right sympathetic nerve, while the left sympathetic is related only to the bundle of His and to the centers of heterotopic contractions. The auricular acceleration in our case is to be explained on the basis of excitation of the right sympathetic, while the ventricular acceleration and the disappearance of the dissociation are the results of stimulation of the left nerve. As for the extrasystoles, they can be explained only by the hyperexcitability of the heterotopic centers due to the action of the left sympathetic nerve."—A. F. B.

(ADRENALIN, PITUITRIN) Hemorrhage of the Newborn, with the Report of a Case. Shaw (H. L.) Jour. S. Carolina Med. Assn., 1917, xiii, 408.

In an infant with profuse intestinal hemorrhages, adrenalin (by mouth) was of no value, while pituitrin (hypodermatically), given at first in doses of one minim every four hours, and later of two minims every eight hours, gradually caused the diminution and finally the cessation of the bleeding.—A. F. B.

(PARATHYROID) Treatment of Tetania Parathyropriva with Parathyroid Substance from the Horse. Stenvers (H. W.) *Nederlandsch Tijdschrift voor Geneeskunde* (Amsterdam) 1917, i, No. 2.

A patient with exophthalmic goiter undergoes thyroidectomy. Immediately, on the operating table, he suffers from a severe, very painful attack of tetany.

The patient is treated with fresh parathyroid glands of the horse, which were identified microscopically and given mixed with the food. The result was controlled by the electrical reaction of the muscles, the concentration of creatinine in the urine and the general appearance of the patient. During six weeks the administration of parathyroid went on. Then three parathyroid glands (of patient with exophthalmic goiter) were implanted. The effect has been splendid and the patient has been restored to perfect health.—J. K.

(THYROID) Über die Wirkung der Schilddrüse auf den Blutkreislauf. Oswald (A.) *Pflüger's Archiv*. 1916, clxiv, 506.

Iodo-thyroglobulin increases the responsiveness of vagus terminations, depressor nerve, and sympathetic to faradic stimulation. It increases the hemodynamic power of adrenalin, and is regarded as a most important stimulant to various body processes. Its activity is proportional to its iodine content. Baumann's iodothyryn has similar but weaker activities. Other iodine compounds of protein and protein products (iodo-casein, iodo-tyrosin, etc.) have no effect. Iodo-thyroglobulin obtained from the thyroid in cases of Basedow's disease acts like that obtained from the normal organ. All the symptoms of hyper- and hypothyroidism are explicable on the hypothesis that iodo-thyroglobulin is the effective agent concerned.—(Physiol. Abstr.)

ADRENALIN, Action of, on the Leucocyte Blood-Picture in Man. Castrén (H.) *Finska Läkaresällskapets Handlingar* (Helsingfors) 1916, lviii, 1605.

Half an hour after the injection of 0.001 gm. of adrenalin

in man, there is a marked increase in the lymphocytes, and a less pronounced increase in the polynuclear leucocytes. A somewhat similar result follows on muscular exercise. It is due to a driving out of the colorless cells from blood-forming organs. In one case with an enlarged spleen, that organ was reduced in size by the adrenalin.—(Physiol. Abstr.)

(LYMPH EXTRACT) Sull'azione biologica dell'estratto di gangli linfatici e sulla funzione ormonica degle stessa. Marfori (P.) Arch. di fisiol. (Firenze) 1916, xiv, 285.

Observations on the effects of a sterilized extract of lymphatic glands. These organs yield a substance, soluble in hot and in cold saline solutions, which is thermostable, for which the name "lymphogangline" is suggested. Lymphogangline is physiologically antagonistic to adrenalin. It diminishes cardiac tone and frequency, even under atropine. It dilates systemic arterioles, but constricts the coronaries. Moreover, it constricts the pupil, and inhibits adrenalin glycosuria. Lymph, from the thoracic duct, and from the pancreas of Aselli, produces effects similar to those of the lymphogangline. Both in modus operandi and in effect lymphogangline is regarded as a complete antagonist to adrenalin.—(Physiol. Abstr.)

(LYMPH EXTRACT) Azione antagonistica fra l' estratto di gangli linfatici e l'adrenalina sugli organi a fibre muscolari lisce. Chistoni (A.) Arch. di fisiol. (Firenze) 1916, xiv, 307.

Extension of Marfori's work to excised organs.

Lymphogangline antagonizes adrenalin on esophagus, intestine, uterus, and arteries, in Ringer's solution, in vitro. It appears, both from Marfori's and from Chistoni's account, that lymphogangline is very similar in its effect to B-iminazolylethylamine.—(Physiol. Abstr.)

ENDOCRINOLOGY:

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

OCTOBER-DECEMBER, 1917

EDITORIAL ARTICLES

THE PATHOGENESIS OF THE NEUROSES

THE pathogenesis of disease is quite as important as its pathological anatomy. The study of the changes wrought by disease was of course the foundation of modern medicine and Virchow cannot be too greatly honored for the part he played. The study of the ultimate causes of disease, especially of the bacteria, was of like value and Pasteur and Koch stand with Virchow in the establishment of a scientific medicine. There remains, however, much to be done of a nature as fundamental as that of either group. Thus far we have been halted by our inability to resolve the problem of the connection between material substratum and vital phenomena. And probably the enthusiasm attendant upon the study of the internal secretions is to some extent due to its apparent promise to shed light upon this obscure problem.

Eppinger and Hess called our attention forcefully to the effect of vagus overbalance. Freud has made

us realize that the psyche influences markedly the lower or somatic functions. Pottenger has shown that even the skeletal muscles are influenced by reflexes from visceral lesions. That is, the researches of the past five years have tended to show us the complexity of the interrelation of tissue and nerve. We have, in other words, some more definite illustrations of the well-known principle that usage affects form.

The next step was the work of Cannon when he showed that nerve tone was dependent upon the secretion of the endocrine glands. In other words, that conditions apparently purely nervous in origin were in reality the result of chemical or, if you please, material forces. He showed, however, that such a relationship was reciprocal; and that purely sensory stimuli could stimulate glandular secretion, that is, chemical action.

This demonstrates how complete is the cycle and how difficult it is in a given case to ascertain whether the original cause was psychical or material. In no disease is this more evident than in Graves' disease. Here a succession of nervous shocks may excite the adrenals until the thyroid is put into action, and the threshold of its action permanently lowered—with the attendant phenomena of hyperthyroidism. But again the stimulation of the vagus may come from so material a source as a uterine myoma, or other pelvic irritation—as Hertzler pointed out. But the outcome is the same; the thyroid becomes stimulated until its threshold is permanently lowered.

The importance of these considerations—the importance of realizing that we are dealing with a closed cycle—is evident when we consider the therapy of such condition. For it is obvious that all

cases need not be attacked at the same point or in the same manner. It is evident that by quieting the nervous system we can reduce the force impinging on the endocrine organs. But we may also reduce the disturbance by destroying the glands. Or again we may say that first of all we must remove the original irritant or stimulus, and then quiet the nervous system, or even remove glandular material in order to reduce the quantity of the secretions.

Similar reasoning leads us to hope that in the realm of psychiatry we may secure better definitions and more rounded out conceptions. Thus we may find that Abderhalden is right in believing that dementia precox is the result of a dysfunction of the sex glands—and that the disease may be attacked along lines similar to those in use with Graves' disease.

The conception of chorea as the result of intracranial localization of the streptococcus will at once clarify our vision and materially aid our therapy in that puzzling syndrome.

We might add other illustrations. But these are enough, we think, to enforce our plea for more definiteness in our attack upon this problem, and more clarity in our discussion of the neuroses.

It is evident that the internal secretions form an important link in the chain of events leading up to the obvious phenomena of diseases such as those we have named. And as such they afford us an important point of attack both in our understanding of the processes involved in pathogenesis and in our therapeutic attacks. But they form only one link in the chain. We must not forget their relation to material substrata on the one side, and to nervous stimulation on the other.

THE INTERRELATIONSHIP OF THE THYROID AND THE ADRENALS

DURING the past decade, the subject of pluriglandular syndromy has attracted considerable attention from investigators and clinicians. The thyroid-adrenal interrelation has probably served as the most attractive for study. Together with the recorded observations on this interrelation, have come various dubious conclusions and a considerable amount of theorizing.

Asher and Flack, (1) following up the observation of v. Cyon, (2) that the depressor nerve is more irritable to adrenin immediately after the stimulation of the thyroid nerves (laryngeal) than before, offered the first experimental suggestion of a functional relation between the adrenals and the thyroids. It was also observed that the blood pressure reaction to adrenin was increased after such stimulation. Cannon and Cattell (3) have recently concluded, that the cervical sympathetics, and not the laryngeal, are the secretory nerves of the thyroid glands. Asher and Flack (1) state, however, that they obtained the same results from the injection of thyroid gland extracts as from the stimulation of the laryngeal nerves, hence it is probable that their stimulation included some sympathetic fibers. They found, further, that after extirpation of the thyroid glands, stimulation of the laryngeal nerves no longer caused an augmented reaction to adrenin. They state that the increased rise in blood pressure is not observed unless the depressor nerves are cut. This, the authors think, is a regulatory mechanism by which oppositely directed actions are suspended unless the necessity arises for one or the other to preponderate. They

interpret their results as demonstrating a close relationship between the thyroids and the adrenals.

The phenomena reported by Asher and Flack have recently been subjected to renewed investigation by Levy. (4) It was observed that in cats, after stimulation of the cervical sympathetic nerves, adrenin raises the blood pressure—at times as much as 200 to 300 per cent more than before. Levy further observed that intravenous injections of E. C. Kendall's crystalline substance from the thyroid, in thyroidectomized cats, also produces an augmented adrenin reaction.

Goetsch (5) has recently made the observation that in cases of Basedow's disease, the intradermal reaction to minute doses of adrenin is exaggerated. He also observed that subcutaneous injections of adrenin in these cases greatly increases the symptoms. These reactions, he states, vary directly with the intensity of the symptoms or, as most authors believe, with the amount of thyroidemia. These observations then substantiate the experimental evidence that thyroid secretion serves to sensitize those tissues amenable to the action of adrenin.

A supposition that the thyroid secretion acts as a stimulus to adrenal activity has a number of observations to support it. Ott and Scott (6) have reported that intravenous injections of thyroid extracts increase the adrenin in the blood of experimental animals, but they obtained the same results with extracts of other organs. Hoskins, (7) just prior to this, showed that the administration of thyroid substance to new-born guinea pigs produced hypertrophy of the adrenals. Pregnant adult pigs, similarly fed, however, gave birth to young in which the

average weight of the adrenals was below normal. These apparently paradoxical observations were explained by the suggestion that the blood of the mother, overladen with the adrenal hormones, had inhibited the growth of the fetal adrenals.

Herring (8) later showed that the administration of raw ox thyroid in large doses, to cats, increases the amount of adrenin in the adrenals. There was also found evidence that the weight of the adrenals was increased. Herring (9) later showed that the administration of small doses of thyroid gland to white rats, produces hypertrophy of the cortex and medulla of the glands, with increase of the adrenin content. The hypertrophy of the cortex was found to be somewhat greater than that of the medulla. Accessory suprarenal tissues were also found to undergo enlargement. Herring's work, if confirmed, leaves but little doubt that the thyroid does stimulate the adrenals. Experimental evidence, then, would seem to point to the fact that the thyroid glands act as an activator to the adrenal glands.

There is but little evidence contrary to this. Biedl (10) observed that there was a slight hypertrophy of the cortical part of the adrenals in thyroidless, dwarfed dogs. Pick and Pineles (11) found an enlargement of the adrenals in two goats from which the thyroids had been removed at the age of 6-10 weeks. One of them had been treated with iodothyrim. This evidence, however, is not convincing since no controls were kept and nothing is known regarding the size of the glands before the experiments were begun. Carlson (12) maintains, however, that in young rabbits, after complete thyroidectomy, he invariably observed a marked hypertrophy of the

suprarenals. A satisfactory explanation of the paradox has not been offered.

That the adrenals have a functional reaction on the thyroid glands also has supporting evidence. Osokin (13) observed that repeated injections of adrenin produces marked histological changes in the cells of the thyroid, which he interprets as evidence that adrenin normally stimulates the thyroid to secretion. Cannon and Cattell (3) have shown that injections of small doses of adrenin produce an action current in the thyroid and hence secretory activity in the gland. Stimulation of the splanchnics, leading to adrenal discharge, produces the same results. Levy (4) observed that the injection of adrenin sensitized the vasomotor system to the action of succeeding injections of adrenin. He brings forth evidence to show that this sensitization is due to thyroid discharge produced by the first injection of adrenin. Contrary to these observations, Wiener (14) has reported that injections of adrenin led to storage of thyroglobulin in the gland. The weight of evidence as a whole, however, would seem to indicate that the adrenal secretion stimulates the thyroid gland to secretory activity.

That the thyroid and the adrenal glands each play a role in carbohydrate metabolism, is a well-established fact, which may indicate an interrelation between the two organs. Eppinger, Falta and Rudinger (15) from their work on the relationship between the thyroid and pancreas, arrived at the conclusion, that the thyroid and the chromaffine system, together with, as Falta (16) reported later, the infundibular portion of the hypophysis cerebri, constitute a group of vascular glands which accelerate the

processes of carbohydrate metabolism. The balance they state, is maintained by the antagonistic activity of those other vascular glands, which, like the pancreas and parathyroids, exercise a retarding influence upon the consumption of sugar. They stated that an adrenin injection which, in normal animals, provokes extreme glycosuria together with an increased metabolism of protein in the fasting animal, does not produce glycosuria in thyroidectomized animals, even when sugar is given at the same time. This was confirmed by Grey and de Sautelle (17) with dogs, and by Pick and Pineles (11) with young goats. Underhill and Hilditch (18), however, deny the occurrence of the phenomena in case of dogs. Since there is reason to believe that the thyroid secretion sensitizes the sympathetic system to the action of adrenin and that hyperthyroidism intensifies adrenin glycosuria and hypothyroidism abolishes the phenomena, there remains the possible indication that these glands exert their activity on sugar metabolism via the sympathetic nerves. Schaefer (19) states that the thyroid produces a mobilization of sugar in the body and that thyroid feeding tends to diminish the assimilation limit of sugar. This he states may be due to an increase in the secretion of adrenin or to a direct inhibitory effect on the internal secretion of the pancreas. From the work of Eppinger, Falta and Rudinger, one might conclude that a thyroid-adrenal interrelation plays a large part in the phenomena.

Frankel (20), Broking and Trendelenburg (21), Krause (22) and others, employing different methods, found an increase of adrenin in the blood of patients suffering from exophthalmic goiter, but the

more recent, careful work of Stewart (23) and others has entirely failed to corroborate this finding.

The weight of existing experimental and clinical evidence, then, supports the theories that the thyroid-adrenal interrelation is one of mutual stimulation; that the thyroid secretion sensitizes sympathetically innervated tissues to the action of adrenin, and that they both act on the sugar depots in the body, producing a liberation of carbohydrates.

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METHODS OF INVESTIGATING ENDOCRINE FUNCTIONS

TWO general types of investigation have been widely utilized in the study of the functions of the endocrine organs—augmenting or decreasing in various ways the function in question. In some instances a sequence of the two methods has yielded significant data.

Several different methods of increasing the hormone content of the blood have been employed, such as administration of extracts or organ substance by mouth or in various other ways, grafting into the body viable endocrine tissue or increasing the output from the individual glands as by massage or stimulation of their secretory nerves. Such studies can often be advantageously supplemented by study of human beings or animals in which spontaneous overactivity of the glands occurs.

Functional deficiencies can be created by gland extirpations, by injecting substances to cause bland infarcts in the glands or by ligating the blood vessels supplying the organs in question. Clinical observations of patients with spontaneous or surgical gland deficiencies are also of great value. Indeed, some of our most valuable data has been obtained in this way.

Gland Extracts, Intravenous Injections: Experiments with gland extracts are complicated by the fact that in addition to specific hormones, various more or less potent non-specific substances may be present. When given by mouth these substances are relatively unimportant but when the extracts are introduced by vein they often play a predominant role in the reactions. Cholin, which is a powerful vasodepressant, may be present to some extent in tissue extracts but

it plays a less important part than was formerly supposed. Nucleo-proteins as such have also come to be recognized as unimportant in such extracts. Possibly the well marked reactions that have been reported by certain investigators as due to specific hormones in tissue extracts have been due largely to split-protein toxic products. Largely through the work of Vaughn we have come to recognize that the most harmless protein substances at one stage of their disintegrations give rise to highly toxic bodies. The work of Jobling and Bronfenbrenner has brought out clearly the importance of the tryptic enzymes of the blood itself in forming such toxins. Unless one is on his guard in making gland extracts, these toxins can readily be formed and completely mask any specific reactions obtainable. Anaphylactic shock which apparently is merely a special phase of protein intoxication may enter in as a disturbing factor when the same animal is used in a series of injection experiments. There is ground for believing that even putrefactive products have in the past figured as specific hormones. From the foregoing it follows that the utmost caution must be observed in drawing conclusions from intravenous injection experiments.

The fact that some at least of the hormones will withstand boiling without serious loss of potency affords a means of eliminating the disturbing factors that reside in the protein content of gland extracts. If boiled in weakly acid solution the extract is both sterilized and freed from protein. If the filtrate from such an extract is hermetically sealed or evaporated to dryness it may retain its potency for long periods.

Administration by mouth: This method of introducing gland substances has been of great use clinic-

ally in the thyroid treatment of myxedema and cretinism. Various other examples of oral administration of gland substances are well known. In experimental work the method has been most useful, in the study of the hormone factors in growth. Gudernatsch's well-known experiments on the influence of thyroid substance on tadpoles form a case in point. In such work the possible importance of non-specific substances in the material fed should always be kept in mind. The presence of nucleo-proteins for example may be a determining factor in results. If the experimental animals were not receiving otherwise an adequate supply of protein the administration as gland substance of relatively small quantities of this important food element might cause considerable effect. The researches of Funk, Mendel, McCullom and others show that mere traces of certain as yet unknown food substances may exercise a very profound influence upon growth. These "vitamines" as Funk calls them must always be excluded as the determining factor in results. In all feeding experiments the control animals should be supplied with some indifferent tissue substance equivalent to the gland material administered to the experimental animals or else both should receive a maintenance ration so complete that the addition of the experimental gland substance can play no significant part merely as food.

Another possible source of error in growth experiments resides, according to Robertson, (1) not in the substance fed but in a failure to recognize certain essential features in the process of growth itself. "There is," according to this investigator, "a widespread and mistaken tendency to regard growth as a single process and to infer that if a given substance

or condition accelerates the growth of one particular tissue at any given time, the same substance or condition will also accelerate the growth of other tissues or of the same tissue at a different physiological age. Growth on the contrary is a multiplex phenomenon and factors which favor the growth of one particular type of tissue or the growth of the whole animal at one particular age may actually exert the reverse action upon another tissue or at another stage in the growth of the animal concerned." These facts have an obviously important bearing both upon selecting controls and interpreting any results secured.

Administration by Rectum: The effects of the digestive enzymes upon the endocrine gland substances is largely unknown. In case of the thyroid the fact that ingestion of desiccated gland substance is able to ward off the ill effects of deficient secretion shows that we are dealing with a stable body. In the case of adrenin on the other hand oral administration is largely or quite ineffective. It has been stated that in the case of most of the glands better results are secured by rectal than by oral administration. This possibility should be thoroughly investigated both on account of its clinical bearing and its importance in experimental work.

Parenteral injections: In some instances when fairly rapid but not instantaneous results are desired the gland extracts can be introduced into the intramuscular or subcutaneous tissue spaces. Absorption takes place both into the lymphatics and the blood capillaries. The same is true of extracts introduced into the peritoneal cavity. In this case the absorptive capacity of the omentum is probably of considerable importance. Parenteral injections have certain

advantages: the extracts are spared the possible deleterious action of the digestive enzymes of the alimentary tract; there is less danger to the experimental animal, as from thrombosis, and less disturbance of body functions than when intravenous injections are employed. In case of intramuscular injections the promptness of reaction is little less than when the extracts are given by vein. In case of adrenin the fact that it dilates the blood vessels of skeletal muscle probably accounts to a considerable extent for the rapidity of absorption.

Intrapulmonary injections: That the intrapulmonary route is not without advantages for the administration of adrenin has recently been reported by Auer and Gates. (2) The capillary circulation in the lungs is relatively profuse and the drug is separated from the blood stream only by the thin alveolar and capillary membranes. Absorption is correspondingly prompt. The method would seem to be particularly well adapted to getting adrenin to a failing heart. At the same time the chief danger in the use of adrenin in such cases would probably be avoided, i. e., the danger of inducing fibrillation of the ventricle. When adrenin is introduced directly into the heart it is likely to be carried in too great concentration to the coronary vessels thus causing an over stimulation and the result mentioned. The suitability of intrapulmonary injection as a method of administering other than suprarenal extracts remains yet to be determined. Except possibly for pituitary hormones it would seem not to be desirable.

Intravenous injections: In the case of glands that have a potent internal secretion the most instructive results are usually obtained from intravenous injec-

tions. The hormone is at once distributed throughout the body and the maximal effects are seen before it is destroyed or excreted. Most of our significant data bearing upon suprarenal physiology have been derived from this type of experiment. The method is beset with many pitfalls, however, and a rigidly critical attitude should be maintained in drawing conclusions—an attitude which is conspicuous in much of the literature by its absence. The mere introduction of saline solution into a vein is sufficient to produce as great changes of blood pressure as those that have sometimes been ascribed to a hypothetical hormone in a tissue extract. It should always be borne in mind that an organ extract is composed of many things besides any hormone that may be present. Vasodepressor substances are always found and according to Schaefer, those from different organs show specific variations in their effects upon blood pressure.

Even though a specific substance is shown to be present in a given gland extract the conclusion by no means necessarily follows that it is a hormone that is normally discharged from the corresponding gland. It might be some substance normally accumulated to be destroyed by the gland. It might be some abnormal substance formed during the process of extraction. Particularly is caution demanded in drawing conclusions if other than saline solutions are used in the preparation of the extract. Such a solution is the only menstruum the body has at its disposal and any "hormone" that requires strong reagents for its "liberation" is probably non-existent in the normal gland. More than one elaborate report in the literature if judged thus would be without significance.

Many if not all unboiled tissue extracts contain substances that are likely to induce intravenous coagulation. Kephalin is in this regard particularly important. If massive clotting should occur, death would at once ensue and the only possible erroneous conclusion to be drawn would be that the substance was "toxic." Localized clots, however, may be carried to or formed in the nervous system or elsewhere and produce striking effects that upon superficial consideration might seem to be a result of specific hormones. The inconstancy of such results are, however, sufficient to rule out specificity.

In the investigations of the physiology of the endocrine glands by injection experiments due regard should be paid to the quantitative aspects of the research. When at a single injection as much material is employed as a normal animal could be expected to secrete in several hours no conclusion can be drawn as to the physiological aspects of the hormone in question. At best such a research can afford data of pharmacological value. As a case in point the greatest amount of adrenin that can be obtained from the suprarenals by stimulation of the splanchnic nerve is but one two hundredth of the quantity necessary to produce glycosuria (Osgood). (3) Yet the glycosuric effect of adrenin injections has been made the basis of much discussion as to the physiology of the suprarenal glands. A theory of carbohydrate metabolism prominent a few years since had no more secure foundation than this. The chief difficulty in applying the quantitative criterion in such cases is the marked paucity of reliable data as to how rapidly a normal endocrine gland can secrete. In case of the suprarenals only have we as yet any information.

Neither by direct massage of these glands nor by stimulation of their secretory nerves can more than a moderate rise of blood pressure be evoked. While neither of these methods is exactly equivalent to a physiologic stimulation the fact remains that there is no reason to suppose that the maximal output from the glands is more than a small fraction of the quantities of adrenin injected in many so-called physiological investigations. In view of the fact that reactions to adrenin are known in some cases at least to be exactly reversed with change in quantity the point is of obvious importance.

Direct Application to Tissues: In many cases instructive results are obtained by application of endocrine extracts directly to the living tissues. The clinical use of adrenalin to blanch the nasal mucosa is a well-known procedure that illustrates this method. The adrenalin spray for the relief of asthma is another example. In following this method the tissues are frequently removed from the body and the extracts either applied to the surface or introduced through an isolated artery. Mammalian tissues employed for this type of experiment are kept in warm oxygenated Tyrode's solution or similar fluid; in favorable cases they will survive for hours. Ott and Scott have published many investigations of this nature. In such experiments also the quantity factor should receive due regard. A short segment of gut for example is but a small portion of the total body tissue and would be exposed to a correspondingly small fraction of any given amount of circulating hormones. In individual experiments the dosage should be correspondingly restricted. Just how much allowance should be made for this decreased irritability of the test tissues when

they are removed from the body is as yet unknown.

Organ Grafting: In some instances organ grafting has been used to augment the quantity of circulating hormones. In the early development of the thyroid treatment of myxedema this procedure was successfully employed. There are numerous technical difficulties, however, which limit the use of the method in practical experimentation. The only way in which grafting can be accomplished with anything like constant success is by the employment of the individual's own tissues (autografting) and that method is of obviously restricted utility. The more closely related are the host and the donor of the tissue the more likely is the graft to "take." Transference from one species to another (heterografting) is practically never successful. At best the tissue is soon absorbed and the net result is equivalent to that of a parenteral injection. Grafts ordinarily do not survive unless there already exists a physiological deficiency (Halstead). (4) In most cases the graft acts as a foreign body and stimulates the defensive processes of the host which thereupon destroys it. To secure adequate nutrition to keep the graft alive until it can become vascularized is difficult. Two methods are often employed for this purpose: the tissue is cut into thin slices and these are inserted into some highly vascular tissue such as the spleen. The sex glands seem to be the most easily grafted. Wheelon and Shipley (5) have recently submitted graphic evidence of the functional integrity of testicular transplants. As a method of producing the equivalent of a functional overactivity of any endocrine organ, grafting has as yet not been successful. Possibly in

the future some method of augmenting the tolerance of the host for transplanted tissue will be evolved and lead to valuable results. Up to the present time, organ grafting as an experimental method has been of value chiefly as a check on extirpation experiments.

Nerve Stimulation: In some respects stimulation of the secretory fibers to a given gland is the most satisfactory method of augmenting the amount of the corresponding hormone. The secretion thereby secured is supposedly normal in quality and not greatly outside physiologic limits in quantity. For this among other reasons a definite knowledge of the secretory innervation of all the endocrine organs is needed. In case only of the suprarenal and the thyroid glands is satisfactory information available. Artificial stimulation of the secretory nerves ordinarily involves a considerable degree of trauma as well as anesthesia, both of which detract from the adequacy of the method to reproduce physiologic conditions. To meet this difficulty Cannon has recently employed the method of nerve grafting, using the phrenic as a constantly active source of impulses. The method is technically difficult and was abandoned by Langley years ago after a brief trial as not feasible. Cannon and Fitz (6) have succeeded in several cases, however, in getting results apparently due to functional overactivity of the thyroid gland, when the phrenic nerve was grafted onto the cut end of the cervical sympathetic. These included marked symptoms of hyperthyroidism, particularly augmented basal metabolism. These symptoms subsided when the lobe on the grafted side was removed. The method is theoretically an ideal one to produce pure physiologic augmentation of gland functions under

controlled conditions. The most striking advantage is that there is no question as to what is the primary cause of any effects produced, a question which always arises in a baffling way when cases of spontaneous overactivity of different endocrine glands are studied. It is greatly to be hoped that the technical difficulties may be overcome and the method fulfill the promise it offers of unravelling some of the most puzzling problems in endocrine biology.

Maternal administration: Several years ago a method was proposed to create an excess of hormones in the circulation of developing fetuses by supplying the mother with the corresponding gland, either by feeding or injections. The method offers two theoretical advantages: the experimental animal is treated at the most plastic stage of its existence when maximal effects would be produced and the brunt of the experimental procedure is taken by the mother, which supposedly would be less likely than the young organism to suffer from incidental derangements due to the gland administration. The chief apparent defect of the method is the difficulty of interpreting any results secured. There are present all the possibilities of interaction among the endocrine organs not only of the fetus itself but also of the mother. The actual practical utility of the method has not been adequately determined.

Clinical studies of excessive hormone secretion: Some of the most significant data which bear upon endocrine biology have been obtained in the study of patients suffering from spontaneous overactivity of endocrine structures. The functions of the pituitary organ for instance were completely unknown up to the time Marie discovered the relation of that organ

to acromegaly. Practically all that we know as to the function of the suprarenal cortex is that subjects having enlarged glands are likely to show anomalies of the sex function. Many of our ideas as to thyroid physiology have been derived from a study of Graves' disease—a condition regarded by many as due to simple hyperthyroidism. The chief difficulty in this type of study is to determine what is primary and what are secondary factors. An organ hypertrophy that is taken as a sign of primary overactivity usually can be interpreted equally well as merely an incidental reaction to the same conditions that produce the accompanying symptomatology. The obviously necessary check on this type of study is to produce experimentally the symptoms of the patient by augmenting his supply of the hormone in question. In no case, however, has this as yet been done in a manner entirely satisfactory. Even in case of the thyroid, which seems to be the organ most amenable to this type of investigation, Carlson was unable by the administration of gland substance to produce the clinical picture of exophthalmic goiter either in animals or normal human subjects. Nothing like an experimental acromegaly from pituitary administration has ever been reported.

Endocrine Deficiencies: Several methods of creating endocrine gland deficiencies are known. Some of these are surgical extirpation, producing bland infarcts in the glands, ligating all or part of the blood vessels supplying the structures, injecting boiling water or injurious chemicals into the tissue substance and injection of specific cytolytic sera.

Extirpations: The most common method of cre-

ating a functional deficiency is the obvious one of removing all or part of the gland in question. With the development of modern surgical technique this method has acquired the utmost importance. The earlier investigators, however, had little confidence in results derived from extirpation experiments. Schiff's early observations for instance on the effects of thyroid extirpation were commonly ascribed to suppuration or to injury of important nerves. The method is particularly adapted to investigation of the problem as to what glands are essential to life. But even in this case concordant results have not in all instances been secured. For example Cushing maintains that complete removal of the pituitary gland is inevitably fatal while Aschner, another skilled scientist, is equally sure that animals may survive the operation. One maintains that death following extirpation of the gland is due to incidental trauma; the other that survival when it occurs is to be ascribed to bits of gland left behind in the operation. A serious complicating factor in many cases is the existence of bits of aberrant tissue lying at some distance from the main gland. Accessory thyroids may be found anywhere along the trachea. Outlying suprarenal tissue may be found anywhere along the aorta or even as far away as the epididymis. Parathyroids may occur in various parts of the neck as well as in the thymus. The possible existence of these aberrant structures in any given animal introduces an unavoidable element of uncertainty in many extirpation experiments. Nor will a careful autopsy in all cases determine whether the object of the experiment has been attained. Unless complete serial sections of

all possible tissue that might contain accessory glands are studied they may easily escape detection. Such study is obviously in many cases out of the question.

Infarction: Bland infarcts can be produced by injecting fine suspensions of inert insoluble material into the arteries leading to different glands. Tobacco seeds or lycopodium spores are most commonly employed. This process involves comparatively little trauma and can be regulated to produce various grades of deficiency. It is a method, however, somewhat difficult to control. So far it has not led to any striking results.

Vessel Ligation: Ligating the blood vessels of a given organ in order to decrease its functioning is employed both in clinical and experimental practice. It is a well-known method of treating exophthalmic goiter in patients who are in too precarious a condition to undergo thyroidectomy. For experimental work the method is in most cases unreliable. Small vessels may be left untied and quickly enlarge or capillaries from the surrounding tissue may soon grow into the anemic area and vascularize it so that parts of the gland can hypertrophy and continue to function. In case of suprarenal glands, the loss of which is rapidly fatal, ligation of the blood vessels seems to be essentially equivalent to extirpation.

Interstitial injury: Of the various methods of destroying the tissues by application of injurious materials the injection of hot water is probably the best. The method is relatively safe, no harm being done if the fluid penetrates a blood vessel, whereas in case of chloroform, chromic acid or other escharotics they

are likely to escape into the circulation and produce serious or fatal results. An obvious disadvantage of the injection method is the difficulty of control.

Specific cytotoxicity: After the discovery of the possibility of producing an increase in the cytolytic power of the blood a hope was entertained that the method would prove valuable in endocrine research. It has been reported that if an animal is given a series of injections of spermatozoa its serum acquires the power of destroying such cells without greatly affecting other kinds. Efforts were made to induce a similar cytolytic power for hormone producing cells as, for instance, those of the thyroid gland. Such a serum might then be injected into an experimental animal and cause the disintegration of its thyroid tissue *in situ*. The method has not as yet been successfully utilized. The cytolytic sera produced have not been sufficiently specific in action but have destroyed various tissues in addition to those desired.

Clinical studies: Many of the most significant data regarding hormone deficiencies have been derived from careful study of patients suffering from endocrine gland defects. Addison's discovery that deficiency of the suprarenal glands results in muscular and circulatory weakness remains as probably the most significant information yet offered bearing on the physiology of these glands. A similar statement may be made in regard to the discovery of the relation of the thyroid glands to myxedema and cretinism.

In such cases of frank primary deficiency of some one endocrine organ the problem is relatively simple. But as it presents itself clinically the problem is very

frequently complicated by the possibility of interaction among the various glands. A given cause may act simultaneously on several members of a related congeries of organs producing a hypertrophy due to over function in all. But a hypertrophy of one of a related pair may also be due to a vicarious assumption of the function of the other. This is a common interpretation of the pituitary hypertrophy which follows thyroidectomy. When one organ normally exercises a check on another hypertrophy of the second may result from a depression of the activity of the first. If, on the other hand, one organ normally stimulates the other as, possibly, the thyroid does the heart, hypertrophy in the second may be due to overactivity in the first. In view of these different possibilities, to ascribe to any observed phenomenon its actual cause is frequently difficult or impossible.

Moreover primary and secondary causes may be inextricably mingled. In the latter case various obscure "pluriglandular syndromes" may arise. The indefiniteness of the phenomena observable in such cases has led to much speculation and premature theorizing which have to a considerable extent cast discredit upon the recorded data themselves. Such cases should be given the most careful study followed whenever possible by painstaking autopsies. To elucidate this type of disease the conventional "post-mortem" is practically useless. Particular attention should of course be given to the various endocrine glands. The tissues should be fixed as soon as possible after death and subjected to a careful study, using the specific stains with particular attention to mitochondria and other evidences of secretory phe-

nomena. Difficult as is this type of study it offers promise of solving some of the most baffling problems now confronting the endocrinologist.

From the foregoing discussion it appears that research in the field of endocrine biology is beset with pitfalls at every step. In much of the literature of the past the difficulties have been unappreciated or ignored. In a field in which a rigidly critical attitude is indispensable careless credulity has been much in evidence. This is possibly an explanation of the fact that despite an immense amount of patient labor few facts of fundamental importance are unquestionably established. None of the experimental methods applicable to this field of investigation is free from defects. The development of our knowledge has been correspondingly delayed. It is only by the use of all available procedures, checking one against another, that we may hope ultimately to acquire an understanding of the significance of hormone factors, either physiologic or pathologic, in the animal economy.

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ORIGINAL COMMUNICATIONS

ON THE CONTROL OF DIABETES INSIPI- DUS BY MEANS OF HYPOPHYSEAL EX- TRACT IN A MULTIGLANDULAR ENDO- CRINOPATHY (THYREO-HYPOPHYSEO- GENITAL SYNDROME).

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ALL the recent evidence indicates that diabetes insipidus is due to underfunction of the pars intermedia of the hypophysis cerebri rather than to hyperpituitarism as was formerly thought. One of the most brilliant instances of the beneficial effects of a substitution-therapy that we have is the control of the polyuria (and polydipsia) with increase of the concentration of the urine in diabetes insipidus now possible by means of subcutaneous injections of the posterior lobe (and pars intermedia) of the hypophysis cerebri. A number of cases are now on record in which the patients were kept comfortable and excreting a urine of normal amount and of normal specific gravity by injecting 'Pituitrin' or 'Pituitary Liquid'* Until a much larger body of material has been made available for study and for critical judgment, it would seem desirable, for the present, that all syndromes and especially all endocrinopathies associated with diabetes insipidus be reported, especially if a pituitrin-therapy is applied. We must not be too sure that all cases of diabetes insipidus will re-

*For an example of a case thus treated and references to the bibliography, see the paper by Barker (L. F.) and Mosenthal (H. O.) *Trans. Ass. Amer. Physicians*, Phila. for 1917.

spond as favorably to injections of hypophyseal extracts as have those thus far studied, though should it prove to be true that all cases will respond favorably, a great therapeutic advance will have been made. The case we desire to report illustrates well the effects of pituitrin-therapy in diabetes insipidus in a patient suffering from a multiglandular syndrome.

The patient, Miss M. F., a teacher, aged 33 years, was referred to Dr. Barker for study and treatment by Dr. Kenneth Bradford, of Staunton, Va. She was kept under observation in a nursing-home from July 26th to Aug. 3rd, 1917.

Complaint:—Nervousness; thumping heart; weakness.

Past History:—Well, except for the usual diseases of childhood, until 12. At that age, she fell a distance of about eight feet. There seemed to be no serious injury, and no symptoms resulted from this, though when the menses appeared three years later, the periods were prolonged and painful, conditions that were attributed to the fall. During the next few years the patient had three uterine curettements, a uterine suspension, the ovaries were "replaced" and a double inguinal herniotomy was done. At 28 one tonsil was removed, and at 32 a nasal spur, the latter operation being done for hay fever, which the patient asserts she suffers from during nine months of each year. For four years past the patient had been treated for a mild psychosis, with delusions, and attacks in which she has vague, "far-away feelings", suggestive of an "unreality-complex." She tired easily and could not fix her attention. She has had a tendency to lose weight, has a capricious appetite, complains of palpitation, constipation, and depression at times when she thinks her blood pressure is high. Menstruation is said still to be painful and prolonged unless drugs are used (chiefly calcium and ergot). The patient has had frequent headaches, as well as pain in the back and legs much of the time. She states that her eyes are "weak", and that she has noticed some impairment in hearing for a long time.

Family History:—The patient lives at home, with her father, mother and sister, all of whom are sickly. The sister has suffered from hyperthyroidism.

Present Illness:—For three years the patient has passed from 8-10 quarts of urine per day and has taken large amounts of fluid. The urine has been of very low specific

gravity, but there have never been any casts or other indications of renal disease. The blood pressure has been about 120-140, systolic, and 70, diastolic. The patient says she has passed very large stools at times.

Physical Examination:—Aside from the fact that the patient is fifteen pounds under calculated ideal weight, has a slight gingivitis, a much scarred abdomen, very movable kidneys and hyperactive reflexes, the physical examination was practically negative except for certain changes referable to the glands of internal secretion. These signs, together with points of similar interest taken from the history, may be conveniently grouped in relation to the several endocrine glands, disturbances of which may be regarded as their cause. It is of course recognized that several of these points admit of more than one endocrinopathic explanation, but the following analysis of the symptoms and signs certainly points to an involvement of at least several of the endocrine glands.

Symptoms and Signs Possibly Pointing to the Hypophysis cerebri:—

1. Polyuria and polydipsia, with urine of low specific gravity.

2. Menstrual disturbances: Flow uniformly scanty until past seven years; since then uniformly profuse, often with slight bleeding throughout the entire month over a period of some months; considerable pain in the lower pelvis and in the back at menstrual periods.

3. Acra all prominent; eyebrows very wide apart; slight maxillary prognathism; nails blunt, with no lunulae.

4. Hair on the head very abundant; about normal in the axillae; abundant over the symphysis pubis and reaching in the linea alba nearly to the umbilicus (*Typus masculinus*); considerable fine hair on legs, especially below the knees.

Symptoms and Signs Possibly Pointing to the Thyroid Gland:—

1. Right lobe of thyroid somewhat enlarged.

2. Slight tachycardia (84-90); palpitation.

3. Fine tremor of fingers.

4. Emaciation (15 lbs. underweight).

5. Slight von Graefe and Moebius signs; eyes prominent.

6. Constipation.

7. Fine skin; gracile fingers.

Many of these points may be taken as indications of some overactivity of the thyroid gland, and yet the patient, even in hot weather, felt somewhat chilly, a condition that, like constipation, is often associated with hypothyroidism.

Symptoms and Signs Possibly Pointing to the Interrenal System:

1. Distribution of hirsuties as given above (Hypertrichosis; Typus masculinus).

2. Marked hypertrophy of breasts and of labia minora.

Symptoms and Signs Possibly Pointing to Chromaffine System:—

No definite signs of disturbance of the chromaffine system are present. There is no abnormal pigmentation. The blood pressure is normal, systolic 130, diastolic 70.

Symptoms and Signs Possibly Pointing to the Pancreas: There is a history of passing very large stools at times.

Certain Physical Measurements:—

Distance from symphysis pubis to floor, 84 cm.

Distance from umbilicus to floor, 96 cm.

Distance from top of shoulder to floor (right side) 134 cm.

Distance from top of shoulder to floor (left side) 136 cm.

Distance from top of head to floor, 162½ cm.

Distance from tip of middle finger to floor, when standing (right), 65 cm.

Distance from tip of middle finger to floor, when standing (left), 66½ cm.

Distance from middle finger tip of the right hand to that of left hand with arms outstretched, 154 cm.

Weight: 108½ lbs.

Laboratory Examinations.

The patient was under observation for eight days and the following laboratory studies were made:—

Blood:—R. B. C. 4,704,000; W. B. C. 6,600; Hb. 80%.

Differential Count:—P. M. N.73.2%

P. M. E.8

P. M. B.4

S. M.21.6

L. M.

Tr. 4.0

100.0%

R. B. C. and platelets normal. No abnormal cells.

Blood Wasserman: Negative.

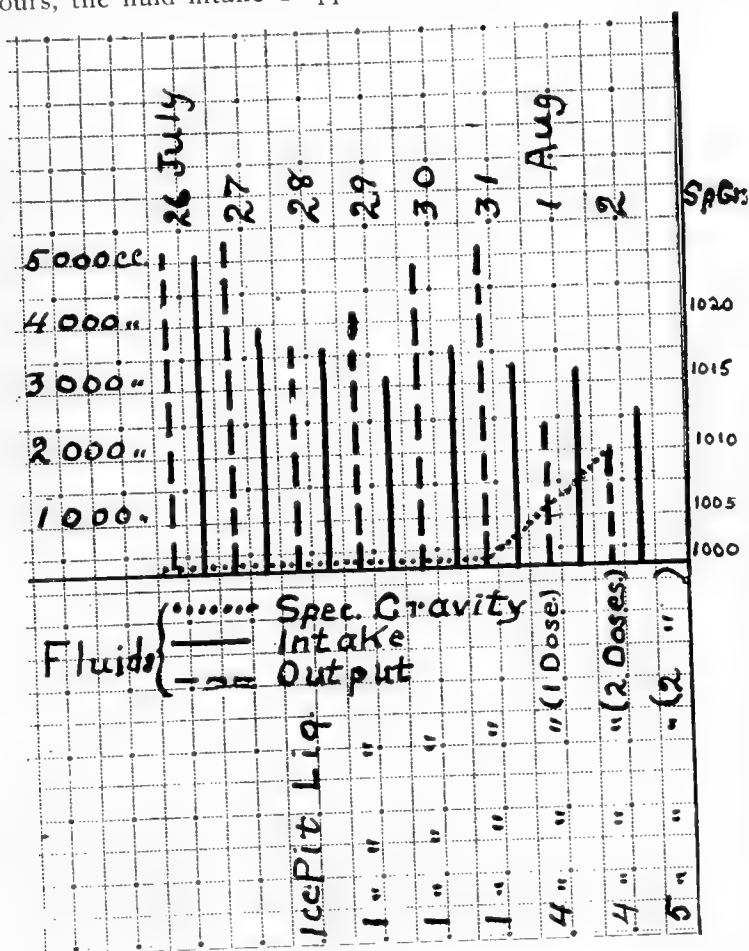
Stool: Negative.

Urine:—The accompanying chart shows the fluid intake and output, and how it was influenced by the administration of pituitary liquid.

Daily examinations of the urine showed a trace of albumin on one or two occasions, but never any casts or blood cells.

For the first two days, the output was about 4700 c. c., parallel with the intake the first day, and exceeding it by nearly 1000 c. c. on the second day. On the third day, therapy

was begun (with unrestricted diet and fluid intake), in the form of 1 c. c. of Armour's pituitary liquid subcutaneously at 9 A. M. daily for four days. On the first day of treatment, intake and output fell to about 3200 c. c. The specific gravity of the urine remained as it had been, at 1002. On the second, third and fourth days of treatment the output gradually returned to its original high figure (4700), the intake, however, being from one to nearly two litres less than the output, and the specific gravity remained at 1002. On the fifth day of treatment a single dose of 4 c. c. of pituitary liquid was given subcutaneously at 9 A. M., and during the next twenty-four hours, the fluid intake dropped from 3100 c. c. to 2700 c. c.,



while the output of urine dropped from 4700 c. c. to 1800 c. c., the specific gravity rising to 1006. On the next day, the same dose was repeated but split, 2 c. c. being given at 9 A. M. and 2 c. c. given at 9 P. M. The fluid intake again dropped, to 2100 c. c.; the output went to 1400 c. c., and the specific gravity rose to 1010. (See chart.) The patient was menstruating at the time and had considerable increase in pain in the pelvis and back for about an hour after each dose. Her general psychic state improved to some extent while under observation, but she was compelled to go home before the studies could be made more complete. It is probable that her thirst and urine can be controlled with smaller doses than those given, provided two doses be given in the 24 hours. Barker and Mosenthal found in their case that 1 c. c. injected twice a day satisfactorily controlled fluid intake, urinary output, and the specific gravity of the urine in a woman who, untreated, passed from 8-11 litres of urine every 24 hours.

Conclusions:

The patient's symptoms point to a diabetes insipidus in association with disturbance of the internal secretion of the hypophysis, the thyroid, the interrenal system, and the gonads. The diabetes insipidus in this case can be controlled by subcutaneous injections of extract of the posterior lobe (and pars intermedia) of the hypophysis.

INTERSEXUALITY AND THE ENDOCRINE
ASPECT OF SEX

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ANSWERING the invitation of the editor for a review of the work on sex-intergrades from the viewpoint of endocrinology, we propose to consider in a sweeping form the aspect of the sex-theory as it appears to the author, both in conclusion of his own work and from an open-minded consideration of all the work done upon the different aspects of the problem. In doing so, we think it will become clear wherein the endocrine aspect of the problem enters, and what are its possibilities and limitations.* The more recent work upon the sex-problem started from very different viewpoints and used very different methods, the methods of cytology, genetics, teratology, physiology, serology, endocrinology, etc. The result is a vast amount of information which, if viewed critically and without prejudice in favor of any method of working or thinking, allows us, we are convinced, to assign to every single phase of that research a place within a general conception of sex.

I

The basic problem of sex is the question why a differentiation into two sexes occurs generally in living nature. But this question can not concern us here. We take the fact of the existence of the two sexes for granted. Then the first problem which confronts us is to find what causes normally the distribution of the offspring among two different—often extremely dif-

*A detailed analysis of the problem following the same line of thought as presented here will be given in a book which is ready for publication.

ferent—types of individuals, males and females. This is the problem of the mechanism of the distribution of sex, a problem which is today as completely solved as it is possible within biology. We know that this mechanism is furnished by the existence of two types of gametes in one sex, namely in the male sex, of flies, grasshoppers, mammals, man, and in the female sex of moths and birds, whereas the opposite sex forms only one type of gametes. We know by hybridization experiments that this corresponds closely to the gametic mechanism, which produces the two parental types in equal numbers, when a homozygous form aa , forming only gametes a , is mated to a heterozygous form aA , forming gametes both A and a , the result of the mating being again $\frac{1}{2}aa$ and $\frac{1}{2}aA$. We know further by the cytological work of the past fifteen years that the sex-chromosomes (or X-chromosomes) are visible cell elements which correspond exactly in their behavior to the necessities of a sex-differentiator by being present in one sex, the homogametic (XX), in every sex-cell, in the other, the heterogametic sex (XY), in only half of the gametes. We know every phase of the history of these sex-chromosomes and their behavior throughout the life cycle of the two sexes, every single fact pointing to the idea that they really are or carry the sex-differentiators. We may even state, without running the risk of exaggeration, that the theory which regards the distribution of the XX - and XY -combinations to about equal numbers of fertilized eggs as the visible mechanism of sex-distribution, is today so far proven, that the demonstration stands on the level of an experimental proof in physics or chemistry. The main points which justify this conclusion are: 1. The in-

numerable morphological studies, which in every case that proved favorable to study, found the facts about the sex-chromosomes in accordance with the theory.

2. The cytological study of cases of abnormal sex-distribution, as in Aphids, Nematodes, Hymenoptera, Rotifers, where the behavior of the sex-chromosome fits completely the expectation, although very different ways lead to the result.
3. The cytological study of forms like the moth, which had been proven by experimental breeding to be heterogametic in the female sex, whereas all the forms in which the chromosome mechanism had been studied exhibited male heterogametia. As expected those forms were proved to form two kinds of eggs in regard to the X-chromosomes.
4. The facts about the relation of parthenogenesis to sex, of twinning and polyembryony and about sex-mosaics (gynandromorphism) which are all perfectly clear under the aspects of the sex-chromosome theory, but unaccountable otherwise.
5. The study of sex-linked inheritance, which showed that those characters which go in heredity with the sex distribution—both in male and female heterozygosis—follow exactly the distribution of the sex-chromosomes in which they must, therefore, be located.
6. The admirable studies on non-disjunction, which prove that in cases of (visible) abnormal distribution of the sex-chromosomes, all the characters which are known to be sex-linked, show special types of inheritance, which coincide exactly with that abnormal distribution, thus showing beyond a shadow of a doubt their location within the sex-chromosome.

We consider, therefore, in agreement with practically all biologists, whose personal experience in both genetics and cytology give special weight to

their opinion, that the mechanism of sex-distribution is known. Every further construction within the theory of sex has to be built upon this basis.

II

The knowledge of the mechanism which distributes in the right way those things which are responsible for the ultimate differentiation of male and female sex might be compared with information about the system of tracks and switches within a railroad station, which direct the trains into their different directions. But this knowledge does not furnish any information about the material, the destiny, the loads, or the moving power of the trains. So the next problem in regard to sex is to find out what is moved by the distributing mechanism and how it brings about the differentiation of one or the other sex. The problem of the mechanism of sex-distribution is followed by the problem of the physiology of sex-differentiation. The answer which is usually given as a solution of this problem is, that the sex-chromosomes carry a Mendelian factor, a sex-differentiator. But this solution is not satisfactory, first, because of being only formal and symbolic and referring the question to another unknown quantity; second, because, when worked out in detail, it leads into difficulties, which long since have convinced many cytologists and geneticists that not only the quality of the sex-factor but the quantity of the X-chromosome-substance must be the decisive fact; third, because we can not get around the fact that both sexes contain the anlagen of either sex, which can make their visible appearance irrespective of the gametic or zygotic constitution of the individual under certain experimental

conditions. We believe that these difficulties have been overcome now and the way towards a physiological understanding of sex-differentiation been cleared by the work on inter-sexuality.*

III

In order to make clear the relation of the facts of intersexuality to the mechanism of sex-distribution on one side and to the hormonal aspect of sex-differentiation on the other, one point has to be called first to the attention. We know that, in the animal kingdom at least, two types are found in regard to the differentiation of sex-characters (probably also in other processes of growth and differentiation). The one type present in insects, excludes the participation of endocrine activities of the sex-glands in the process of sex-differentiation. Castration or transplantation and transfusion experiments with gonads, blood, body extracts are without influence upon the differentiation of sex-characters. The decision is irrevocably reached at the moment of fertilization. (1) In the other group, however, including birds and mammals, the differentiation of the sex-characters is linked with the endocrine activities of the sex-glands, exactly as growth and metabolism are linked with other endocrine organs, as is proved by the well-known results of castration and transplantation. It is clear that it will be easier to derive the basic conceptions from the simpler case of insects. (2)

Our experiments, performed with races of the gipsy-moth, have enabled us to get under perfect ex-

*We have proposed the use of the terms *intersexe*, *intersexual*, *intersexuality* instead of *sex-intergrades* because the former terms can be used in all scientific languages, whereas the latter must be translated, e. g., *Sexuelle Zwischenstufen*" in German.

perimental control the production of intersexuality. (3) By building up definite combinations of races by means of cross breeding, we are able to produce without failure and in the expected numerical relations every single intergrade leading from a normal female to a male or vice versa, the end points, of course, being the complete transformation of a (genetically) would-be female into a male and a would-be male into a female. Without going into details, we might point to some steps in the analysis of the phenomenon, which justify the conclusions in regard to the problems of this essay. The normal mechanism of sex-distribution in this moth is that of female heterogametia, fertilization resulting in about equal numbers of male and female offspring. All of the races involved behave perfectly normally in this respect. But whereas certain crosses between different races are also normal, others invariably give an abnormal result: the cross A-female times B-male gives normal offspring, but B-male times A-female gives all males normal, all would-be females intersexual. In other crosses with other races the opposite happens,—all males are intersexual, all females normal. It could be shown then that the degree of resulting intersexuality is constant for a given combination; e. g. the female of race A will give all normal offspring with a male race M; but with the male N all would-be females will be slightly intersexual, exhibiting certain male characters; with the male O, all would-be females will be intersexual midway between the two sexes; with the male of race P, all would-be females will be high grade intersexuals, almost transformed into males; and with the male race Q, only males will be produced, although half of them are genetically

females. If we breed now another race B as female to all these males a similar series will be produced, but it might reach with the male O the point of complete transformation of all would-be females into males.

These facts and their further genetic analysis show that every individual is able to develop into one sex or the other or any stage between; further that every individual contains all the elements necessary for the development of either sex and its attributes; further that these elements or substances must have a certain quantitative relation to each other in order to secure to one of them the control of development; and that the introduction of quantities in a cross which do not fit the given quantity of the other partner set up the sex-differentiation in favor of the higher quantity. The analytical experiments proved then that the substances which control male differentiation follow the distribution of the sex-chromosomes and must therefore be considered to be carried by them. Whereas the substances controlling female differentiation are always transmitted maternally, that is, from mother to egg. From this it follows, that the mechanism of distribution of the sex-chromosomes results (in the case of female heterozygosis) in distributing to half of the fertilized eggs twice the quantity of the substance which causes male differentiation as to the other half, whereas the substance for female differentiation is constant in all cases. And as the tide of differentiation can be changed in favor of one sex and in a quantitatively increasing series, without any change in the mechanism of the chromosome-distribution it follows, that irrespective of this constitution the decision lies with the respective ab-

solute quantities of the two sex-substances; the greater quantity wins more or less completely.

But how can we conceive that the greater quantity acts in determining one sex or an intergrade between the two sexes? A careful analysis of the intersexual individuals has given the clue. In studying the different types of male or female intersexuality, we find that not every organ exhibits a definite type between the two sexes, say all of them half or one third between the characters of the sexes. The grade of intersexuality is, moreover, a statement applying to the condition of the animal as a whole. But the different organs are not alike. One organ is already say completely male, another still female, a third female at the base, male at the end. Now it could be proven that the organs or parts of organs which become first changed towards the opposite sex are the ones which are last in embryonic development and the ones which are transformed only in the last steps of intersexuality are the first differentiated embryologically. For example, the sex gland, which is differentiated very early, is transformed into a gland of the opposite sex only when all the somatic organs are already changed. And it is shown from the complete analysis of such facts, that in case of female intersexuality—the other way in male intersexuality—all organs develop female up to a certain turning point, when suddenly the development proceeds under the aspects of male differentiation. Therefore all organs differentiated when the turning point occurs are female, the ones which differentiate later are male, and the ones differentiated over the entire period start female and end male. Thus the degree of intersexuality is determined by the more or less early position

of the turning point in development. There we have a time coefficient coordinated with the quantitative differences in the amount of sex-differentiating substances, i. e., these are substances which increase the velocity of a reaction proportional to their quantity. It seems safe therefore to ascribe to them at present the character of enzymes.

The complete analysis of experimental zygotic intersexuality—zygotic because the result is determined at the moment of fertilization—has taught us then what the mechanism of sex-distribution by means of the sex-chromosomes means physiologically: the adjustment of the relative quantities of male and female enzymes, thus assuring to one the greater velocity of reaction. But there is now a limit to our analysis. We see no means of ascertaining what kind the reaction is which is brought about, or, in the language of chemistry, the velocity of which is influenced by the concentration of the enzymes. But the answer can be given, we believe, by the facts about hormonal intersexuality.

IV

It is well known to every student of biology and physiology that in the higher vertebrates, at least birds and mammals, the endocrine function of the sex-gland plays an important role in the development of secondary sex-characters. Early castration in mammals prevents the normal development of the visible characters, and results in the assumption even of the male secondary characters by female birds. Successful early transplantation of the heterologous gonad makes either sex assume to a more or less complete degree the characters of the other sex. (4) We might call this already the production of hormonal

intersexuality, which of course appears only in those organs which are physiologically able to change under the influence of hormones, irrespective of the genetic constitution in regard to sex. But the methods which have to be used exclude a complete experiment in intersexuality, where the entire body, including sex-glands, ducts, etc., must react. Fortunately nature has performed such an experiment for us, as F. R. Lillie's recent analysis of the case of the free-martin has revealed. (5) Among twin calves, cases of normal male and female are very rare. If both are not of the same sex, in most cases a normal male is combined with an abnormal "hermaphroditic" female, the freemartin. It is now proven that this freemartin is a typical case of hormonal intersexuality. Lillie could show that in this—and only in this—case an anastomosis between the blood vessels of the twins occurs, so that the same blood flows through both. In the male partner, the testis, with its interstitial tissue, develops first, when the ovary of the female has not yet reached the stage of endocrine function. So the female comes under the influence of the male hormones, the ovary stops differentiation and all the sex-characters develop further in the male direction. The result is the freemartin, a calf with very much female external sex-organs, almost male sexual ducts and a sex-gland containing sperm tubules but without spermatogenesis.

If we compare now this case of true hormonal intersexuality with the zygotic intersexuality of the moth, we see at once that the "turning point" from which sexual differentiation changed in the latter case corresponds exactly to the moment in the case of the freemartin, when the male hormones are

poured into the blood of the female. Comparing the facts carefully we feel justified therefore in giving the following answer to our former question: Of what kind is the reaction accelerated by the action of the sex-enzymes with a velocity proportional to their concentration? The reaction is the production of the specific hormones of sexual differentiation. In insects this occurs in every single cell of the body as an irreversible consequence of the combination in fertilization. In the higher vertebrates the reaction becomes more or less centralized within the interstitial tissue of the sex glands.

We have purposely dismissed with a few general words the work on castration and transplantation in birds and mammals in order not to interrupt our general line of argument. But we must now draw attention to the fact that some complication comes in here which is not at present completely understood. We mean the complexity of the action of the hormones of the sex-gland on one side and their relation to the genetic (chromosomal) constitution of the cells upon which they act. We have pointed out that the action of these hormones is required when the sex-characters are to differentiate normally. This fact is proved by the castration experiments in mammals, resulting in the failure of further sexual differentiation, and, furthermore, by the case of the freemartin. But there exists another activity of the hormones of the sex-gland, namely the inhibition of the sex-characters of the other sex. This is proved by the cock-feathering of old female birds and the fact that castration in female birds makes them assume the characters of the male sex. And this shows again that in these higher vertebrates sexual differentiation is possible without

specific hormonal action. The latter point is further proved by the fact that in birds typical bilateral gynandromorphs exist, that is, birds with female characters on one side and male characters on the other side of the body. We know from the study of gynandromorphs in insects that they are produced by an abnormality in the distribution of the chromosomes, resulting in the presence of the female set in one half of the body and the male set in the other half. In these gynandromorphous birds the hormones, whatever they are, must be present everywhere in the body; if they were the exclusively decisive factor, no gynandromorphs would occur. To make the case still more complex, gynandromorphic birds are known with an intricate pattern of male and female characters (7); and finally, others are known which, together with the rhythmical change of sexual plumage during one of the breeding seasons, exhibit in certain feathers a mosaic-like admixture of the characters of the other sex. And finally we have the case of the Sebright-Bantams, fowl where the roosters are normally hen-feathered. But when these roosters are castrated they develop normal cock-feathering! (8) No doubt this short account already shows the existence of an immense complexity, which cannot be regarded as easily to be disentangled. But we may state in what manner we think the facts may be brought together. We assume that in birds the genetic situation is the same as it is in insects. From the moment of fertilization, every cell contains the two enzymes of sexual differentiation which, in proportion to the quantity in which each is present, accelerate within every cell the production of the hormones

of sexual differentiation. But there is one principal physiological difference between the insects and birds: in the former the embryonal and larval development ends with one short period of sexual activity after which the animal dies; in the latter, however, a comparatively long period is necessary before the condition of sexual maturity, which then lasts for several years, is reached. If the conditions were alike in the two cases, then every bird would change its sex during its lifetime, that is, it would become intersexual when the amount of the hormones of the other sex within the cells reached a certain mark. This is, however, prevented by the additional phenomenon of the endocrine production of an inhibitory hormone for the characters of the other sex. This specific endocrine function is based on the presence of a sex-limited or, as we prefer to say, sex-controlled factor, as can be deduced from Morgan's Sebright-Bantam crosses. Thus we may account, at least in principle, for the cases in birds, although additional hypotheses will be necessary for special cases like the Sebright-Bantams or the rhythmical breeding-plumage of some birds.

In mammals, however, a further advance seems to have been made in the direction of centralization of the control of the process of differentiation. Here the production of the hormones of sexual differentiation seems to have been shifted from the individual cells to a special endocrine organ, the interstitial tissue of the sex-glands,—a fact most convincingly shown in the case of the freemartin. Castration alone, therefore, can not induce the development of the other sex-characters; that can be accomplished

only by the transplantation of heterologous gonads. And gynandromorphism seems to be impossible. Finally we repeat that these views can be regarded as provisional only and that much experimental work is still needed here.

V

Although no other cases of zygotic and hormonal intersexuality are known, where a complete genetic and embryological analysis was possible, the phenomenon will certainly be produced in many other cases. Collectors of insects have often described freaks, which probably are intersexual individuals (not to be confused, however, with gynandromorphs, which are a very different thing); and at least one instance is known where some of the steps produced in our experiments could be duplicated, as in Harrison's crosses of species of the moth *Biston*. Another instance is found in Daphnids, where Banta (9) found recently a strain throwing constantly intersexuals through many generations, although no experimental control was yet possible. Further the teratology of birds, mammals and man has furnished a considerable number of cases of so-called hermaphroditism and pseudohermaphroditism, many of which are probably cases of hormonal intersexuality, (10) judging from a comparison with the freemartin.*

*Some authors claim that the presence of perverse mating instincts is a type of intersexuality. Halban and others claim it for the case of man, Riddle for cross-bred pigeons, which are supposed to exhibit the perversion more regularly than normal pigeons do, as well as dogs, cows, etc. The possibility of such an explanation can not be denied; but the claim can only be regarded as justified when it is shown that perverted sex-instincts, though permitting also a normal mating, and combined with complete normality of primary and secondary sex-organs, are the starting point or end point of a graduated series of somatic intersexuality. No such evidence is yet available and the behavior of those instincts in intersexual moths—the only completely analyzed instance—is not in favor of such a view.

But there are other instances of abnormal sexuality known which we feel justified in considering as further types of intersexuality and which will throw further and important light on the problem. There is first the important case of the Gephyrean worm, *Bonellia*, as analyzed by Baltzer. (11) *Bonellia* is well known as the prototype of extreme sexual dimorphism: the female is an animal with a plum-like body to which a very long proboscis is attached, the male is a minute animal of the size of an infusorium, with a rudimentary organization, living within the uterus of the female. If a young larva attaches itself to the proboscis of an adult female and lives there "parasitically" for some time, it develops invariably into a male. Otherwise the larva stays in an indifferent state for some time and then becomes female in the majority of cases. If, however, the experimenter interrupts the "parasitic" stage at different times, individuals develop with different mixtures of male and female characters, that is, intersexual individuals. But there are a few more details which are important for the interpretation of the case. Among the larvae which develop into females, the ones which are late in development, form first sperm, before they become female. Further, a short stage in the parasitic condition accelerates development though it might be female. Then the combination of male and female organs in the intersexes is not orderless, but it seems that the stage of differentiation at the moment of the "turning point" (the interruption of parasitic life) determines the combination. Here we see at once a parallel to the other cases of intersexuality, which suggests the following interpretation: If we wanted to make a decisive experimentum crucis in

regard to the theory of the quantitatively regulated sex-enzymes, it would be, to find a method which accelerates or retards the velocity of growth and differentiation of the individual without influencing the velocity of reaction of the sex-enzyme. Such a method would enable us to force the processes of differentiation into the time when the male or female hormones are set free and therefore to make any individual as intersexual as we like. It seems that *Bonellia* performs this experiment, furnishing the acting substance by the secretion of the proboscis. The interpretation of the case would be, therefore: In the fertilized eggs of *Bonellia*, which probably are genetically alike, the relation between the velocity of reaction of the sex-enzymes and the velocity of embryonic differentiation is such that a very slow rate of differentiation is confronted with a system of sex-enzymes possessing a high concentration of the male and a low concentration of the female enzyme. In normal development, the time of differentiation of most organs lies beyond the point of the late production of female hormones and the animal is therefore female. The function of the secretion of the proboscis is an acceleration of the rate of differentiation, just as, for example, the hormones of the thyroid act upon the metamorphosis of the frog; differentiation then falls within the time of action of male hormones, the female hormones not yet being present at all. And an incomplete acceleration of the rate of differentiation produces intersexuality, i. e., differentiation first under male then under female hormonal conditions. We might therefore call this type intersexuality by activation. The secretion of the proboscis, activating the rate of differentiation, might be regarded as hor-

monic (although exocrinic) just as the similar action of the thyroidea. It need hardly be added that this hormonal function has nothing to do with the sex-hormones.

Another phenomenon should at least be mentioned in this connection,—the so-called protandric hermaphroditism of parasitic crustacea and certain molluscs. In the case of crustacea the simplest type—many others exist—is that the individual develops as a male and later, after having fulfilled as such his functions, begins a parasitic life and is transformed into a female. (12) Gould (13) has described a very similar case in the mollusc *Crepidula plana*, although no parasitism is here concerned. His experiments, however, show that the development of the male phase of an individual is induced by the presence of larger individuals of either sex. Even female individuals may develop male organs to a certain extent under such circumstances. A similarity is certainly exhibited here to the case of *Bonellia*, although the details are not so clear.

VI

There is another case of intersexuality which has to be regarded as a special case of zygotic intersexuality. This is the case of the frog, as analyzed by R. Hertwig and his students. (14) Here it is possible to produce by certain combinations of races (some races exhibit the same phenomenon in nature) animals which have first an ovary which is gradually changed into a testis during development. We refrain from reporting the complicated details of the important work, as there is no other endocrine aspect of this case of "transitory intersexuality" than the one common to all cases of zygotic intersexuality.

But another type of intersexuality can not be passed by, the intersexuality as consequence of parasitic castration, because it has been used as a starting point of attack against the hormonal interpretation of sex. (15) The male crab *Inachus*, if parasited by *Sacculina* assumes secondary sex-characters of a female and even eggs are formed within the testis. This is, of course, male intersexuality. But the parasited female does not change correspondingly. G. Smith, who analyzed this case, sees the cause of this change of the male towards femaleness in the influence of the parasite upon the fat-metabolism of the host, the metabolism assuming the female type. He doubts, therefore, an endocrine influence upon sex-differentiation and adheres to a theory of metabolic stimulation. The parasite as well as the presence of the ovary push the metabolism in the direction of fat-production, as can be demonstrated. Fat constitutes the nutritive material for the eggs and therefore the male sex-cells in the parasited animal grow into eggs.

The last conclusion can be disproved by some facts from our experiments in intersexuality. The normal female caterpillar stores vast amounts of fat, which are used in building up the eggs during pupal life. If now female intersexuality is of such a type that the turning point coincides about with the time of pupation the animal has the large abdomen of the female with all its nutritive material. But then male differentiation begins and no eggs develop in the ovary, which does not grow beyond the larval stage. The hatching intersexual female then possesses the large female abdomen filled with blood rich in fat which could nevertheless not induce the young eggs

to grow and fill out the abdomen; the presence of the male hormones after the turning point preventing it.

We further fail to see how the facts about parasitic castration could be used against the endocrine aspect of sex-differentiation. A different type of metabolism in regard to the sexes is well known for many classes of animals, even a different protein specificity, as shown by precipitin reactions. There is no reason for putting this difference upon another level than that of other sex-characters, but for the assumption that the hormones of sexual differentiation act upon the morphogenetic processes by the intermediary of a metabolic change. In view of the fact that all endocrine substances including those of the sex-glands, act in some way upon the general metabolism, such an assumption is certainly justified. And it would be in harmony with other physiological facts, e. g., the striking change of the type of metabolism in flies with the metamorphosis, according to Weinland (16) as compared with the influence of the thyroid on starting metamorphosis in frogs. (17) But this is a problem which concerns every phase of the physiology of development and the question of hormonal participation in the process.

We can hardly pass this metabolic aspect of our problem without referring shortly to views, which, in spite of some points of contact, seem to be in contradiction to the views which we derived from our work. We mean the work of Whitman and Riddle and Riddle on pigeons. (18) Riddle has revived the metabolic view of sex-determination which was held in pre-Mendelian, prechromosomal and prehormonic times. He assumes that the metabolic condition of the egg is responsible for the differentiation of sex.

The material on which he bases his views is genetic as well as physiological. The main genetic fact is, that from a family-cross of doves only males, and from a generic cross nearly all males are produced. But if reproductive overwork is forced upon these birds the early eggs produce mostly or only males, the later eggs mostly or only females. The chemical study of the eggs showed that their metabolic state or energy-content is correlated with the sex of the future animal in normal reproduction as well as in the above mentioned experimental conditions. Riddle seems therefore to believe that these metabolic conditions of the eggs are the basis of sex and controlling these conditions means the control of sex. In looking over all the facts regarding the mechanism and physiology of sex, we feel unable to agree with such a theory, although realizing the importance of the actual facts. One and the same egg of a Rotifer or a bee can develop into a male or female, the decision lying with parthenogenesis or fertilization; the same egg, however, can develop into a gynandromorph or mosaic of male and female parts of any mixture if fertilization is abnormal (the famous Eugster bees). (19) And nevertheless male and female bees are as different in regard to metabolism as any other animal on record (see Straus). (20) One and the same egg of the gipsy moth develops into a female, an intersex of any description, or a male, the result depending exclusively upon the genetic constitution of the fertilizing sperm, viz., the sex-chromosomes of the sperm, as can be proven with mathematical certainty. In every case of male heterozygosis the situation is the same and the metabolic differences of the sexes are the consequence of the combination in fer-

tilization, not the cause. We feel justified, therefore, in rejecting a theory of sex, which makes metabolic differences the cause instead of one of the effects of sex-differentiation. We think, moreover, that the importance of that work on doves lies in another direction.* It might belong to the same category of sex-problems as the overripeness experiments of Pflüger, Thury, Hertwig, etc., as the relation of the visible differences in egg-size of *Dinophilus* to sex, as the problem of male- and female-producers in Aphids and Hymenoptera; the problem of influencing the chromosomal mechanism of sex-distribution; a problem which is certainly of the greatest cytological, physiological and practical interest.

VII

We have tried to sketch the theory of sex as we see it, as the result of the different lines of research and our own work, and to assign to the endocrine aspects of the problem the right place within. We can hardly finish this very condensed review without pointing to the possibility of applying the same line of argument to the problem of heredity in general.* (26) There is no logical reason for separating the difference in regard to sex from the other specific differences in living nature. The characters which distinguish sex are of the same order as the characters which separate species, genera, families. They are size and shape, symmetry and subdivision, and all the results of differential growth; they are chemical qualities like pigmentation, and all the phases of metabolism; they are further the specificity of proteins. The

*See also Morgan's remarks in his paper quoted in Bib. 8.

†A detailed presentation of the following views will be published as soon as conditions permit..

mechanism of the distribution of the determinants of these characters in the process of heredity is in both cases the same, the distribution by means of the chromosomes. Then, just as the differentiation of sexual characters is influenced by endocrine action, important characters of general organization are influenced by the hormones of thyroid, hypophysis, etc., like growth, correlation of organs, metamorphosis, nervous functions, metabolism and instincts. We feel justified, therefore, in applying the same conceptions to all other processes of heredity which we were able to derive for the case of sex because all the differences occur within the offspring of the same parents. So we conceive of the mechanism and physiology of heredity thus: The fertilized egg furnishes in its protoplasm the chemical material and the physical substratum for the processes of growth and differentiation. The chromosomes furnish the determinants or factors for the specific direction of these processes, which make the offspring similar to the parents. These factors are enzymes, which are not only characteristic in regard to their quality, but which are handed over to the sex-cell in very exact quantities or concentrations. As the reactions accelerated by these enzymes take place with a velocity in proportion to their concentration, a very subtle mechanism is given for the production of definite reactions with a different velocity, thus assuring the always returning rhythm of differentiation. As only certain products of reaction will be influenced by the next working enzyme, localization is possible in addition to rhythm. And the reaction accelerated by the enzymes of heredity to a definite velocity, is the formation of hormones, directing growth, metabo-

lism and differentiation, similar in their action to the known hormones of the thyroid, hypophysis, etc. Thus the entire problem of heredity assumes at a certain point an endocrine aspect.

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BOOK REVIEWS

THE SECRETION OF THE URINE. By Arthur R. Cushny, M.A., M.D., LL.D., Professor of Pharmacology, University College, London. 1917. Pp. 241 with 36 illustrations. New York. Longmans, Green & Co., \$3.00 net.

In the words of Cushny, "no other organ of the body has suffered so much from poor work as the kidney and in no other region of Physiology does so much bad coin pass as legal tender." In the preparation of the book some 6000 pages had to be evaluated and the attempt to treat all of this literature in detail is frankly abandoned as impossible in a single monograph. Various papers therefore have been dismissed with scant consideration, whereas those which the author regards as more significant, have been treated at some length. Although the author writes to some extent as a partisan, the ascertained facts in regard to renal physiology are treated apart from his well known theory. The book begins with a study of the anatomy and histology of the kidney, then takes up the constituents of the urine, physical factors in secretion, and the work, gaseous metabolism and blood supply of the kidneys. This is followed by an interesting chapter on the theories of renal secretion. The chapter contains a considerable amount of material which is interesting from the standpoint of secretion in general. In the next section, the evidence bearing upon the functions of the tubules and glomeruli is treated at length. The relation between the blood and the formation of the urine is next taken up. The action of diuretics and other drugs is treated in a short chapter followed by a brief discussion of the subjects of glycosuria and albuminuria, nephritis and renal disorders.

From the standpoint of technical endocrine interest, it is unfortunate that lack of space prevented

any extensive consideration of the action of the hormones on renal function. Much of the work bearing on the relation of pituitary extracts to renal secretion is ignored, the author contenting himself with a brief review of Schaefer and Herring's work and the later paper of Houghton and Merrill. The situation is left with the statement that pituitrin is a diuretic, but whether the diuretic effects are exerted specifically on the renal cells or whether they are brought about by circulatory changes is left undecided. The inadequacy of the evidence offered for the diuretic functions of pituitrin is not brought out. Since Cushny's book went to press, Motzfeldt has shown that the existing evidence, in itself, is inconclusive and that as a matter of fact in normal animals, pituitrin is an anti-diuretic.

The effect of adrenin on the kidneys receives only seven lines which brings out the facts that this drug injected intravenously constricts the renal vessels and arrests the secretion of urine while in subcutaneous injections it increases the sugar of the blood and often causes glycosuria. Marshall and Davis' statement that extirpation of the suprarenal glands tends to impairment of kidney activity is also mentioned, the implication being that this is due to a lack of circulating adrenin. Whether or not adrenin in smaller doses or when slowly absorbed actually does cause constriction of the renal vessels has not been determined. It is possible, if not probable, that small doses intravenously or larger doses subcutaneously actually cause vascular dilatation in the kidney and hence diuresis. The supposition that suprarenal deficiency amounts essentially to adrenin deficiency is, in the light of present day knowledge, quite indefensible.

Despite the inadequacy of the monograph on these endocrine topics, it is one of great medical interest and value, embodying as it does, the well considered conclusions of a master in the field covered.—
R. G. H.

VAGOTONIA, H. Eppinger u. L. Hess. Die Vagotonie Eine Klinische Studie. Sammlung klinischer Abhandlungen über Pathologie und Therapie der Stoffwechsel—und Ernährungsstörungen. Herausgegeben von V. Noorden 9 and 10, Heft. Berlin, 1910, Hirschwald.

VAGOTONIA: A Clinical Study in Vegetative Neurology, by Dr. Hans Eppinger and Dr. Leo Hess. Authorized translation by Walter M. Kraus, A.M., M.D., and Smith Ely Jelliffe, M.D., Ph.D. Nervous and Mental Disease Monograph Series, No. 20. New York, The Nervous and Mental Disease Pub. Co., 1915.

Although the work of Eppinger and Hess appeared so long ago as the year 1910, the English translation is dated 1915. For this and for other reasons the present seems to be not an inopportune time for a discussion of the "Vagotonia" hypothesis.

It cannot be said that the views of Eppinger and Hess have received any general or widespread acceptance, but there are, in the current literature sporadic references to "automin", or "Hormone X", and some few clinical papers in which an attempt is made to explain obscure symptoms or pathological conditions on the basis of the Viennese hypothesis.

To a certain type of mind there is a strange fascination attached to a new long word, especially if it be not particularly cacophonous. The word "vagotonia" is not unpleasant in sound and bids fair to exercise the same kind of soothing effect on the ears of speculative clinicians as "that blessed word Mesopotamia" on the pious old lady in the story.

It will be necessary to state briefly the theory in question. This will be put out in the first instance in the form of an uncritical exposition, the Authors' own words (as they appear in the English translation), being used as far as possible. A discussion of the theory and its physiological foundation follows.

functioning of visceral organs is a well regulated interaction between the two contrarily acting forces.

After a brief account of the anatomy and physiology of the sympathetic and autonomic divisions of the vegetative nervous system, the Authors proceed to lay great stress upon the antagonistic actions of the two, particular reliance being placed upon pharmacodynamical investigations, and especially the pupillary reactions.

Eppinger and Hess restrict the term "autonomic" to the cranial, medullary, and sacral divisions, and employ it in contradistinction to the sympathetic. The word "autonomic" was first used by Langley to apply to all these divisions—the sympathetic and related systems of nerves.

According to Ehrmann, adrenin is continuously flowing from the adrenal bodies, and this exerts a continuous influence upon the sympathetic. "From this it must be concluded that the stimulating effect of the sympathetic upon its end organs is not an intermittent one, only produced when the affected organs become active, but is in reality continuous."

"It is probable that a similar state exists with reference to the autonomic system, and that a specific analogue to adrenalin, an 'automin' exists, even though it is not known at present. Substitutes for this are found in certain poisons, pilocarpin and physostigmin. These drugs act exclusively upon the autonomic system."

The Authors believe that "the entire vegetative nervous system is under the control of the glands of internal secretion. Even if the proof of the existence of a hormone for the autonomic system ('automin') is not as yet conclusive, yet there is no doubt that there is some substance which exerts a continuous stimulating action upon the autonomic nervous system. It is quite possible that in the central nervous system there exists some common centre which controls the antagonistic actions of these two systems. The normal progress of

Too much activity on the part of one, or too little on the part of the other, will result in either motor or secretory inhibition or stimulation, and may bring about a condition of disease."

The increased tonicity of the autonomic system in man—"vagotonia"—may be diagnosed by the reaction of the patient to pilocarpin. Those who react to 0.01 grm. hypodermically by sweating and salivation will show probably other vagotonic symptoms, such as hyperacidity, eosinophilia, bradycardia, mild arrhythmias, particularly respiratory or sluggish bowel action, approaching spastic constipation.

In order to realize the clinical picture of general vagotonia "there must exist a *vagotonic disposition*"⁽¹⁾ in the patient, that is, an abnormal irritability of all or only a few autonomic nerves which, under the influence of some adequate stimulus . . . may lead to the development of the symptom-complex vagotonia." The Authors give a full description of patients having this "vagotonic disposition." They are "nervous invalids." Among the symptoms are blotchy areas of redness on the skin, excessive perspiration, widening of the palpebral fissures, strabismus, sore throat, diminished respiration, cardiac excitement, etc. Under the head "pathologically increased vagotonia", we have sections devoted to bronchial asthma, vagotonic diseases of the stomach, nervous diseases of the intestines, and cardiac neuroses. Space will not permit any further details as to the pathological and clinical disturbances alleged to be due to "vagotonia."

The starting-point for the whole theory, the foundation of the entire superstructure, is the assumption that, since adrenin acts as a tonic continuous stimulus to the sympathetic system, there must be some substance which performs an analogous

1. The italics are mine.—S. V.

function for the cranial and sacral autonomic fibres. The work of Ehrmann quoted in support of the theory that adrenin serves normally to maintain the tonus of the sympathetic nervous system, was put forward as long ago as the year 1906, and since that time a great deal of work has been carried out upon the physiology of the adrenal bodies. With this work the Viennese Authors seem to be totally unacquainted. Some of it, it is true, has been published since the date of issue of the German version of "Vagotonia." None the less, the view expressed, and repeated in the translation of 1915, must be declared to be years out of date.

It is difficult to adduce any satisfactory evidence that the secretion of the chromophil tissue is of any service whatever in the normal state of the animal. The discharge of adrenin from the adrenal body is not indispensable for life or health, and there is indeed no reliable evidence that under normal conditions the circulating blood contains any adrenin at all. Space cannot be found here for an extended account of the recent investigations which justify the attitude just indicated, but the reader is referred to an article by the present writer in this Journal Vol. I. pp. 140-152, as well as to the comments thereupon by Professors G. N. Stewart and R. G. Hoskins, and an article by the Editor in the preceding issue of this journal.

If these observations are just, then it follows that the argument for the existence of "automin" by analogy with the function of adrenin, falls to the ground. But why should it be necessary to assume that "there is some substance which exerts a continuous stimulating action upon the autonomic nervous system"? Why not make the same assumption for the tonic influence of the spinal cord upon the skeletal nerves? Why not assume that the inhibitory and other influences of the cerebrum upon the lower centres is controlled by a special hormone? As pointed out by Hoskins (l. c.) much confusion has arisen from

the failure to bear in mind that the sympathetic system can of itself do anything that can be accomplished by adrenin. "The adrenals at most merely reinforce the effect of normal sympathetic impulses."

Now if this is the case in respect of adrenin and the sympathetic, what are we to say of "autonomin" and the rest of the autonomic system? Here we have not the excuse of having to find a function for a mysterious powerful drug occurring in the body. The "autonomin" is purely imaginary, and the functions assigned to it can in all probability be carried out perfectly well by the nerve fibres of the "extended vagus."

The work of Eppinger and Hess is called "A Clinical Study", though the amount of actual clinical evidence put forward is remarkably small. The present writer does not venture to deny that some of the pathological disturbances mentioned may be due to an exaggerated activity of certain of the autonomic fibres. It must be confessed, however, that the authors have not proved their case. The chief point of interest for us at present is to determine how far such disturbances are related to the glands of internal secretions and to increased or diminished hormone activity. The reader will have already foreseen what our attitude on this point is likely to be. In the opinion of the present writer the theory as a whole is highly speculative, is based upon a false analogy, and has little or no experimental or clinical evidence in its favour.

The arguments based upon the pharmacodynamics of certain poisons such as pilocarpin and physostigmin, are dangerous. The Authors believe that although nothing is known of their "autonomin", "substitutes for this are found in certain poisons which have been mentioned—pilocarpin and physostigmine. These drugs act exclusively upon the autonomic system." The use of the word "substitute" here is very baffling. It is to be supposed that the Authors mean no more than that there is an

analogy between the activity of their hypothetical hormone and that of certain drugs obtained from plants, and that something may be learned from the mode of action of substances which act selectively on the autonomic system. But readers will be tempted to imagine that the authors actually assume that because certain poisons produce a certain effect in the body, there must necessarily exist in the organism itself a substance having similar actions.

It will be impossible to enter into a detailed discussion of the ingenious attempts of Eppinger and Hess to explain a multitude of symptoms in terms of "vagotonia". We have already seen that individuals who react by sweating and salivation to 0.01 gm. of pilocarpin hydrochloride are stated to be probably vagotonic; and we can readily imagine that on careful search many of such patients will be found to show such symptoms as hyperacidity, respiratory arrhythmia or constipation.

Brief reference may be made at this point to some recent contributions to literature by authors who have given their allegiance to the vagotonic theory. Tracy ⁽¹⁾ for example, believes that the normal reaction of the skin to stroking is a brief vasodilation followed by a vasoconstriction. The vasodilation is caused by stimuli coming over the autonomic branch of the vegetative nervous system, acting on the hormone *x* in the blood-stream. The constriction is due to stimuli coming over the sympathetic and acting upon adrenin in the blood. It is stated that status lymphaticus may be diagnosed by the absence of anemic dermography, showing lack of adrenin in the blood-stream ⁽²⁾. Tracy is of opinion that the conditions known as vagotonia and

1. Tracy, E. A., (a) *Boston M. & S. Journ.*, 1916, clxxv. 197; (b) *ibid*, 1917, cixxvi, 538.

2. The subject is confused, because there appears to be another sort of "white line" produced by stroking. In this case the line is said to be a sign of adrenal insufficiency. (Sergent, *This Jour.* Vol. 1, No. 1, p. 18.)

sympathicotonia are due to a hyper-content in the blood-stream of the respective hormones. ⁽¹⁾

The essay of Eppinger and Hess is a glaring example of the one-sided study of the literature which is so common among German and Austrian writers. All the papers quoted are from German journals, and so far as I can determine, most of them are by writers of the Viennese School. Any impartial student of the literature of internal secretion and of the adrenal bodies in particular will hesitate to give the German workers any such prominent position.

An old story tells how once upon a time an international prize was offered for the best essay upon the camel. An Englishman took his gun and journeyed into a far country where camels abound. His essay was rejected. A Frenchman betook himself to the National Library and compiled an account of the animal. His essay was highly commended. A German shut himself in his study and "evolved a camel out of his inner consciousness"—and won the prize. The fable illustrates fairly well the parts played by the three nationalities in the investigations upon internal secretion. The English (and American) workers have made most of the positive discoveries. The French have written lucidly and elegantly upon the subject. ⁽²⁾ The Germans have speculated and theorized till an entanglement of unsupported hypotheses and elaborate imaginings has almost obscured the few fundamental facts at our disposal.

1. Other recent papers are:—Moltchanow and Lebedeff, "Vagotonus and Sympathicotonus in Scarlet Fever," Roussky Vrach, Petrog. 1916, xv. 457; Smith, I., "Over Activity of Vagus System and Anaphylaxis," J. Nerv. and Ment. Dis. (N. Y.) 1916, xlv, 26.

A very interesting paper has recently appeared on "The Autonomic System as an Integrator, with Special Reference to the Urogenital Organs," Jackson, Surg., Gyn. and Obstet., 1917, xxv, 346. This author justly criticises the pharmacological theories of Eppinger and Hess, but says nothing about "Hormone."

2. The present writer does not wish to underestimate the splendid work of certain of the French investigators. We cannot forget the parts played by Bernard, Brown-Sequard, and in later times, by Gley and his co-workers.

At any rate Eppinger and Hess have "evolved a hormone out of their inner consciousness". We are at present in complete ignorance and we are likely to remain in complete ignorance of any such substance. There is most probably nothing of the kind in existence and in any case we are not warranted in basing any theories, physiological or clinical, upon the evidences put forward.

—SWALE VINCENT.

ENDOCRINOLOGIA PATOLOGIA E CLINICA degli organi a secrezione interna. By Nicola Pende, Professor in Special Pathology in the University of Palermo, Italy. 1916, Pp. 1034 with 147 illustrations, 25 in colors. Milan. Dr. Francesco Vallardi. Lire 35.00. (Paper.)

This is the largest and most comprehensive book on endocrinology that has come to our attention, transcending in size the well recognized monograph of Biedl (while the two volumes of the second German edition of the latter cover 1226 pages, nearly 300 pages are devoted to a bibliography).

In going through Professor Pende's book it is very clear that he has given special study both in the laboratory and in current literature of all countries, and we regret very much that this book has not yet been translated from Italian and hope that an arrangement may eventually be made by which this may be done.

The book is divided into two principal parts, the first devoted to the physio-pathology of the endocrine glands (672 pages) and a second section (340 pages) devoted to clinical consideration.

As we look through this book with our limited knowledge of Italian, we can not refrain from remarking how much work has been done in this phase of medicine by our Italian confreres. In the index of authors alone no less than 650 names of Italian investigators are recorded, and it is not believed that

the work of these ardent students is as appreciated by the profession in this or other English speaking countries as it deserves to be.

To those members of the Association for the Study of the Internal Secretions who are conversant with the Italian language, this book will be of intelligent interest, and we again express the hope that provision eventually may be made for its translation into English or French, and congratulate the author upon his painstaking efforts.—H. R. H.

THE THYROID GLAND IN HEALTH AND DISEASE. By Robert McCarrison, M.D. (R.U.I.), D.Sc. (Belf.), F.R.C.P. (Lond.), Major, Indian Medical Service, Lauréat de l'Académie de Médecine, Paris, Member A. S. I. S., etc. 1917. Pp. 286. New York, Wm. Wood & Co. \$4.00.

Major McCarrison has made his name famous in medical literature by his ardent application to the problem of the etiology of endemic goiter and he seems to have made out a clear case in favor of the position that at least many goiters are due to bacterial or protozoal infections, and that a generous proportion of these infections are in the alimentary canal.

This new book is divided into three parts, the first (30 pages) dealing with the thyroid and parathyroid glands in health; the second (47 pages) with the factors which cause these glands to depart from health; and the third (162 pages) to the consideration of the morbid states resulting from this departure.

Without a doubt the treatment of goiter by the maintenance of a suitable intestinal antisepsis, as recognized by McCarrison and established by quite a series of clinical experiences in the author's work in the Indian Medical Service, is another important advance in the therapeutics of this disorder. The profession is beginning to realize that focal infections are the subtle causes of several endocrine disorders and

there is plenty of clinical literature establishing the importance of considering disorders of this nature from this standpoint. We believe that a good deal of this trend and investigation has come about as the result of Major McCarrison's numerous contributions to current medical literature, and since this book is the result of many years of experimental as well as clinical investigation, and combines the best in the author's previous papers and addresses, it is of double value to those fortunate enough to have it in their libraries.—H. R. H.

THE INTERNAL SECRETIONS IN PRACTICAL MEDICINE. By Henry R. Harrower, M.D., Fellow of the Royal Society of Medicine (London); Sometime Professor of Clinical Diagnosis, Loyola University, Chicago, Member American Medical Editors Association; Member A. S. I. S., etc. 1917. Pp. 254. Chicago, Chicago Medical Book Co. \$2.75.

This book contains a number of addresses and lectures given by the author before various medical organizations and is not, as its title might indicate, a complete survey of the clinical aspects of endocrinology. Among the twenty essays we note several which are of considerable practical interest:

"The Inconspicuous, Everyday Forms of Thyroid Insufficiency" properly directs attention to the frequency of disorders of this character in general practice and since these are so often overlooked its message is of extreme importance.

"The Adrenal Glands and their Significance in General Practice" brings up a subject emphasized previously by such men as Sajous, Sergent and Elliott and considers the matter purely from a clinical standpoint. We may not entirely agree with all the author's deductions. For instance, it is suggested (page 85) that some of the manifestations of malaria are of distinctly adrenal origin—"at one stage in the cycle

of experiences in malaria there is a decided adrenal excitation, due to the sudden periodical liberation of the plasmodia and, of course, their toxins. One encounters the dry mouth as often as salivation, both manifestations of sympathetic stimulation. The heart action is always rapid and sometimes irregular. Then, as an aftermath of the chill, we find the muscular relaxation, prostration, depression and asthenia, all of which are identical with the findings of severe adrenal insufficiency."

Other interesting chapters in which the practical flavor, and hence readability rather than scientific accuracy, is prominent are "The Relation of the Internal Secretions to Neurasthenia in Women," "The Defective Child from the Standpoint of the Internal Secretions," and "The Relation of the Endocrine Glands to Functional Disorders."

THE ORGANS OF INTERNAL SECRETION:
their Diseases and Therapeutic Application, A
Book for General Practitioners. By Ivo Geikie
Cobb, M.D., M.R.C.S., Late Assistant to the Out-
Patient Physician, Middlesex Hospital, London;
Member A. S. I. S., etc. 1917. Pp. 228. New York,
Wm. Wood & Co.

Dr. Cobb contributed a series of articles during 1916 to the *Medical Press and Circular*, and he has made these a basis of a very practical little book. The subject is largely considered from the standpoint of therapeutics and hence is more interesting reading to the general practitioner than to the laboratory investigator. As with many contributions to the literature of this subject one finds opportunities to differ with the author and until the endocrine literature is on a much more stable and permanent basis this can not but be the case. To the practical physician whose time is limited, Cobb's book will come as an easy means of getting in touch with the essence of this subject and properly may be called a brief, practical

and altogether readable compendium of clinical endocrinology.

THE ENDOCRINE ORGANS: An Introduction to the Study of Internal Secretion. By Sir Edward A. Schaefer, LL.D., D.Sc., M.D., F.R.S., Professor of Physiology in Edinburgh University; Member A. S. I. S., etc. 1916. Pp. 156. New York, Longmans, Green & Co., \$3.50 net.

Some years ago Sir Edward Schaefer delivered the Lane Lectures at Stanford University and as these were of such unusual importance they were published by the University and have lately been republished after having been carefully edited, brought up to date and embellished with numerous figures (there are 104). The author considers his subject from a purely physiological standpoint and his opinions are worthy of great respect for it will be remembered that the profession is indebted to Sir Edward for many advances in our knowledge of the glands of internal secretion. For instance, it was Sir Edward who first announced the fact that the pituitary body was an endocrine organ in 1894-5.

A peculiarity of this book is the author's frequent use of the term autacoid* which he originated and which as yet has not become generally accepted in medical literature.

Sir Edward's book is a carefully conceived and altogether praiseworthy contribution to the permanent literature on this broad subject and we can not but express regret that it contains only 150 pages.—
H. R. H.

*"A specific organic substance formed by the cells of one organ and passed from them into the circulating fluid to produce effects upon other organs similar to those produced by drugs. Such effects are either in the direction of excitation, in which case the endocrine substances producing them are excitatory autacoids and would come under the expression hormones, or in the direction of restraint or inhibition, in which case they are restraining or inhibiting autacoids and would be classed as chalones. The action of an autacoid may therefore be described as *hormonic* or *chaloneic*, according to the kind of effect it produces."

THE LITERATURE ON THE INTERNAL SECRETIONS

GENERAL SUBJECTS

AUTONOMIC SYSTEM, as an Integrator with Special Reference to the Urogenital Organs. Jackson (H. C.) Surg. Gyn. & Obs. (Chgo.) 1917, xxv, 346.

The autonomic nervous system plays a very important role in the combination of chemical and physical forces upon which rests the physiological state of dynamic equilibrium, so essential for the maintenance of life. It is intimately integrated with chemical correlation through hormones, each system tending to regulate the other. Although the autonomic impulses are in the main independent of volition, nevertheless the effector organs innervated by these fibers can be brought into reaction through reflexes whose centers exist in the central nervous system and whose afferent arcs may originate in the cortical areas. Certain pseudo reflexes (axone reflexes) are possible in this system in contradistinction to the cerebro-spinal outflow.

The autonomic system is divided according to the portion of the central nervous system from which the outflow of pre-ganglionic fibers takes place: (a) The cranio-bulbo autonomic tenth, and the eleventh cranial nerves. (b) The thoracolumbar autonomic covers the outflow between the second dorsal and third lumbar anterior roots. This is ordinarily called the sympathetic system. (c) The sacral autonomic is supplied by the second and third anterior sacral roots.

Considerable importance rests upon the close embryological development of the chromaffin and autonomic systems. Both are developed from the neural crest cells which eventually form the posterior root ganglia. In the lower forms (coelenterates) the former represents the latter as groups of chrome-staining cells placed similar to the sympathetic ganglia. As the autonomic outflow of fibers becomes more pronounced in the higher mammals, the chromaffin system assumes less and less prominence until at present in mammals it is restricted in the main to the medulla of the adrenal bodies. These cells represent post-ganglionic fibers of the sympathetic system. Most of the effector organs innervated by the autonomic outflow receive a dual supply from the thoracico-

lumbar division on the one hand, and the cranio-bulbo or the sacral portion on the other. The effect of the former is antagonistic to the latter.

The state of equilibrium determined by this extrinsic nervous control is dependent upon the ebb and flow of these two antagonistic sets of impulses. There is also distinct evidence of reciprocal innervation in the autonomic system similar to that shown by Sherrington to exist in the cerebro-spinal outflow. This mechanism is of exceeding advantage in the automatic filling and emptying of the small and large intestines, the biliary and urinary bladders. The uterus and ureters are also under autonomic control. The hormones and the autonomic system also possess reciprocal control over each other. Stimulation of the cervical sympathetic increases activity of the thyroid and pituitary glands.

Epinephrin exerts a sympathicomimetic effect through its action on the same peripheral mechanism as the thoracico-lumbar autonomic impulse. Pilocarpin reacts similarly upon the cranio-bulbo-sacral autonomic system, but more particularly upon the secretory fibers. This type of substance has been termed vagomymetic since the effects of the vagus as a part of this division of the autonomic are the most prominent and widespread. Acetyl choline was shown by Dale to simulate more closely the general effects of bulbo-sacral stimulation. Atropine removes the effects of vagomymetic substances or prohibits the onset of the effects. A similar paralyzant for the sympathetic system has not come to life, unless we consider ergotoxin as fulfilling the conditions.

Attempts have been made to clarify the pathology of the "vegetative" organs, by grouping together as a symptom-complex certain disturbances of the equilibrium in the autonomic system in its widest sense. Some of the symptoms of vagotonia, so called, may be ascribed to an increased activity of the organs or tissues supplied by the bulbo-sacral autonomic; or a similar set of conditions may arise following a decrease in the power of antagonistic impulses flowing over the sympathetics. Patients exhibiting such a syndrome are excessively reactive to pilocarpin. Other abnormal states occur as the result of augmented activity of the sympathetic or a decrease in the strength of the bulbo-sacral autonomic outflow. Such a condition is given the name of sympathicotonia. These patients are sensitive to adrenalin and become better after the administering of atropine. Certain methods are in vogue for the determination of vagotonia or sympathicotonia. Do these clinical pictures represent entities of abnormal functions? What is their value in diagnosis?—
Author's Summary.

PLACENTA, regarded as a Gland of Internal Secretion.

Frank (R. T.) Surg. & Obs. (Chgo.) 1917, xxv, 329.

The experimental work of the last decade proves that Halban was correct in ascribing to the placenta an action upon the uterus and breasts. Placental extracts (mainly the lipoid fraction) rapidly induce hyperplasia of the uterus and breast (gland tissue and nipples), in castrates or in non-castrated animals. The chemical substance which induces these changes is thermostable, very resistant to strong alkalies and acids, and completely soluble in 95 per cent alcohol. The substance appears identical in its physical, chemical and biological properties with a similar substance obtained from the corpus luteum. The substance can exert its influence in the absence of the thyroids, adrenals, pancreas, or in the absence of thyroid and adrenals combined. In view of the apparent identity of corpus luteum and placental substance the question arises whether placenta acts merely as a storage reservoir for corpus luteum secretion during the latter half of pregnancy, or whether the placenta elaborates a hormone of its own.—Author's Summary.

SEX GLANDS, Their Relation to Metabolism. Murlin (J. R.) and Bailey (H.) Surg. Gyn. & Obs. (Chgo.) 1917, xxv, 332.

Our results uphold the work of Loewy and Richter so far as the reduction of metabolism after castration is concerned. Removal of the ovaries of our dogs was followed by an increase in weight in both and a lowering of the metabolism in one of 12 to 17 per cent, and in the other of 6 to 14 per cent.

We feel that indirect action has a bearing on this reduction, and we do not believe that the indications point decisively to the loss of a specific stimulus from the ovary affecting the oxidative processes of the cells.

To throw more light on this complex subject, further experiments with animals are necessary.—Author's Summary.

(PARATHYROID, THYROID) Surgical Anatomy of the Thyroid with Special Reference to the Parathyroid Glands. Pool (E. H.) and Falk (H. C.) Ann. Surg. 1916, lxiii, 71.

The variations in the position of the parathyroids in relation to the thyroid are considered. From a study of twenty-five cases the authors conclude that it is advantageous in thyroidectomy to leave in situ the posterior parts of both lateral lobes of the thyroid, thus permitting the recurrent laryngeal nerves and the parathyroids to remain intact in most instances. Complete bilateral extirpation, leaving only the isthmus, should never be considered. The posterior part of one lobe must always be left.—F. A. H.

(UTERUS) Les produits endocrins de l'utérus humain dans les diverses phases de son développement et dans certaines conditions morbides spéciales. (Endocrine Products of the Human Uterus in the Different Phases of its Development and in Certain Special Morbid Conditions.) Fornero (A.) Arch. Ital. de Biol. (Pisa) 1917, lxx, 324.

The author describes the appearance of certain lipid cells in the uterus at different stages of sexual development and at different phases of menstruation. Reasons are given for considering these lipid cells as an endocrine tissue.

F. A. H.

(THYROID) Sur le contenu en iode de la glande thyroïde dans les divers âges de la vie et sur les rapports entre le quantitatif d'iode et l'aspect histologique de la glande. (Iodine Content of the Thyroid Gland at Different Ages and the Relations between the Amount of Iodine and the Histological Appearance of the Gland.) Pellegrini (R.) Arch. Ital. de Biol. (Pisa) 1916, lxx, 109.

Iodine was found in the thyroid of three out of thirteen fetuses or newly born children. Among children ranging from eleven days to two years of age, the thyroids of fifteen out of twenty-three contained iodine. The presence of iodine seemed to be independent of the state of nutrition.

From a study of the thyroids taken from one hundred and one adults the author finds the average weight of dry gland to be 3.78 grams. The average amount of iodine was 0.004 grams for the entire gland. The total maximum value of iodine was attained in individuals 45 to 55 years of age (0.007 gram). It decreased rapidly during the next ten years to 0.003 gram.

The variations in iodine content of the thyroid in different morbid conditions are discussed.

Thyroid glands of different histological types are described and their relative iodine content mentioned.—F. A. H.

(PITUITARY, ADRENIN) Does the Pituitary Gland contain Epinephrin or a Compound similar to it? Watanabe (W. K.) and Crawford (A. C.) J. Pharm. and Exper. Ther. (Balt.) 1916, viii, 1.

Certain similarities in the physiological action of extracts of the pituitary gland and of epinephrin have long been known. Watanabe and Crawford point out that there are probably several active compounds in the pituitary gland, one of which has an action much like that of epinephrin. The main argument in favor of this view is that after intravenous injection of ergotoxin into decapitated cats, they produced vasomotor reversal with extracts of pituitary gland, like that

from epinephrin. The color reactions which they obtained from pituitary extracts and which resembled qualitatively those from epinephrin were mostly made with extracts of the pituitary gland made by the method which Weidlein used in extracting epinephrin from the suprarenal glands. These might be due to decomposition products of some amino-acids and not necessarily pre-existing in the glands, but Watanabe and Crawford do not enter into the discussion as to whether the physiological reaction of the pituitary gland extracts, which resemble epinephrin, and the color reactions are due to the same or different compounds. This is to be discussed later. They argue it is the same.

Watanabe and Crawford find that the action of extracts of the pituitary gland can be explained by assuming the presence of a compound resembling epinephrin modified by the presence of a depressor compound.—Author's Abstract.

ENDOCRINE ORGANS, The Eye and. Zentmayer (W.) (Phila.) Jour. A. M. A. (Chgo.) 1917, lxiv, 1.

The author is to be congratulated upon having considered the subject broadly—taking into consideration the relative lack of familiarity of the subject among his listeners. He has summarized the present day information regarding the effect of the secretions of the different glands on the general system with special reference to the effects on the eye. As is to be expected, of course, the thyroid and pituitary are more exhaustively treated because of the greater availability of the literature concerning these glands.

The article is so comprehensive as to bear reading and re-reading by those especially who are sufficiently interested to want to apply themselves to observations along similar lines.

One point about which, of course, little has been written is the administration of endocrine substance in the treatment of ocular conditions. The author's proof of his having gone deeply into the subject leads one to hope that he will build on that foundation which he presents, chiefly historic and theoretic, a superstructure of practical organotherapy and give us his findings therefrom in a subsequent article.—R. S. L.

(PITUITARY) On the Relationship between the Hypophysis and Lethargy of Hibernating Animals, with Special Consideration of the Genesis of Lethargy. Salmon (A.) Lo Sperimentale (Florence) 1916, lxx, 345.

The article is an extensive, critical review of the relationship of the hypophysis to sleep, its possible relationship to hibernation and a general discussion of the latter condition. No new data are presented and its value consists in the extensive way in which previous work is reviewed.

The author discusses his theory of sleep based upon the relationship between the disturbance of sleep and changes in the hypophysis; the relation of hypersomnia and insomnia with hypopituitarism and hyperpituitarism. He believes that sleep has its seat in the cortical cells and is associated with the elaboration of a reserve substance for the organic repair of the nerve cells after the intoxication of the waking hours. The action of the hypophysis is due to its antitoxic and trophic property as regards the nerve centers, and consists in protecting the cortical cells from the toxic products of metabolism and caring for their nutrition.

He discusses at length the theory of Cushing and Goetsch on the relationship between the hypophysis and the lethargy of hibernating animals. He finally discards the theory on the following grounds: In hypophyseal disease the torpor never becomes nearly so great as is observed in hibernation; the hibernating animal awakens immediately in response to definite stimuli as changes in temperature; no pathological changes are noted in the nerve cells of hibernating animals as occur in hypophyseal disease; loss of hypophyseal function can not explain the marked hypothermia noted in hibernating animals. However, he believes that pluriglandular insufficiency plays a noteworthy part in the mechanism of lethargy. It should be emphasized that no new data are presented, and that his conclusions against the theory of Cushing and Goetsch are based wholly upon the dissimilarity between hypophyseal disease and hibernation.

He discusses the theories of hibernation in detail and presents his own theory based upon the function of the hibernating glands. Lethargy is the sign of a severe fall of the internal temperature, particularly that of the brain, as a result of which there is a distinct slowing of organic metabolism. The hibernating gland is the only organ which is very active during hibernation. It maintains the negative life of the animal and inhibits the function of all the other organs. In this respect it is a true endocrine gland, and while it is active it inhibits the activity of all other glands of internal secretion.

F. C. M.

(PARATHYROIDS) Tetania Parathyreopriva; its Nature, Cause and Relation to Idiopathic Tetany. Paton (D. N.) and collaborators. *Quar. Jour. Exper. Physiol.* (Lond.) 1917, x, 203-377.

Part I. Introduction. General methods and symptoms. Paton (D. N.) and Findlay (L.).

Idiopathic tetany and the various theories regarding its etiology are considered.

The previous work upon experimental tetany is dealt with in the three periods:

- (a) Before the recognition of the possible significance of the parathyroid;
- (b) While the distinction between the thyroids and parathyroids was still doubtful;
- (c) After the direct implication of the parathyroids in the production of the symptoms had been established.

The evidence that the condition is a true tetania parathyreopriva is considered to be conclusive.

The method of removing the parathyroids is discussed, and the authors infer that it is impossible to get rid of the internal parathyroids with certainty by any operation but complete thyroparathyroidectomy. The existence of supplementary parathyroid tissue in about 50 per cent of cats and in probably about 5 per cent of dogs is shown to explain the absence of symptoms in some cases of thyroparathyroidectomy.

The symptoms of tetania parathyreopriva are summarized and some of the factors modifying the character and onset of the symptoms are briefly considered.

Part II. The parts of the central nervous system involved.

Paton (D. N.), Findlay (L.) and Watson (A.).

The authors conclude that the nervous symptoms are due to the condition of the central nervous system.

In the production of the spasticity, tremors and jerkings the cerebral arc is not directly involved. The increased violence of these symptoms after decerebration is due to unopposed action of cerebellar and spinal arcs.

The tremors and jerkings develop independently of the cerebellar arc, but the integrity of this arc is essential for the production of the sustained spastic tone.

The integrity of the spinal arc is not essential for the development of the tremors and jerkings, since they persist after section of the dorsal roots of the spinal nerves. The efferent neurones are the structures primarily implicated.

In advanced cases of tetania parathyreopriva disturbances of equilibrium seem to indicate a secondary involvement of the cerebellum.

In such advanced cases the onset of epileptiform convulsions probably indicate the secondary involvement of the motor part of the cortex cerebri.

Part III. The changes in the peripheral nerves and in the muscles. Paton (D. N.), Findlay (L.) and Watson (A.).

Any marked decrease in the amount of parathyroid tissue is followed by a very marked increase in the electrical excitability of the peripheral motor nerves. The same is found in all cases of idiopathic tetany.

As a rule no alteration of the normal sequence of the various responses results.

Mechanical excitability, so characteristic of idiopathic tetany, does not appear to be such a prominent feature of tetania parathyreopriva.

The increased electrical excitability of the peripheral nerve is independent of changes in the central nervous system. It occurs after section of the nerve and persists until degeneration sets in; whether the nerve be cut before, with or after the removal of the parathyroids.

The electrical excitability of muscle to direct stimulation is increased after parathyroidectomy, although not generally to the same extent as that of the nerve.

This is chiefly due to an increased electrical excitability of the neural structures in the muscle, since it is generally abolished by a dose of curare sufficient to block nervous impulses and the increased excitability of the muscles decreases as the nerve degenerates after section. In some cases there is evidence of increased excitability of a post-neural substance.

The nerve-ending is the part of the neural element which is acted upon, since in cross-circulation experiments the result of stimulation of the sciatic nerve bathed in the animal's own blood varies with the changes produced in the peripheral nerve supplied with foreign blood.

In tetania parathyreopriva the increased electrical excitability of the peripheral motor neurone is not proportional to the intensity of the symptoms due to the conditions of the central nervous system and after a definite fit it may be markedly reduced. In idiopathic tetany the relation is somewhat closer, but is not directly proportionate.

Hence increased electrical excitability can not be regarded as a measure of the severity of the condition.

Part IV. The etiology of the condition and its relationship to guanidin and methyl-guanidin intoxication. Paton (D. N.) and Findlay (L.).

The authors conclude that there is no direct interrelationship between the parathyroids and the thyroids.

There is no evidence that the parathyroids exercise a direct controlling influence on the central nervous system.

The symptoms of tetania parathyreopriva are not primarily due to decrease in any constituent of the body, e. g. calcium ions.

The symptoms are not due to an increase in ammonia or xanthin or iminazolyethylamin in the blood.

The symptoms are identical with those produced by the administration of salts of guanidin and methyl-guanidin.

Part V. Guanidin and methyl-guanidin in the blood and urine in tetania parathyreopriva and in the urine in idiopathic tetany. Burns (D.) and Sharpe (J. E.).

The analytical results are summarized as follows:

Guanidin (and the methyl-guanidins expressed as guanidin) in mg. per 1000cc.

A. Blood. Dogs—Normal (average of 5), 1.0. Parathyroidectomy (average of 8), 8.7.

B. Urine. Dogs—0.25 (average of 6). 1.1 (average of 6). Children—Average of 5 (8 analyses). Idiopathic tetany (average of 3 cases; 13 analyses). Active tetany, 0.58. Latent tetany, 0.38. Recovering from tetany, 0.12.

The authors infer that there is a marked increase in the amount of guanidin and methyl-guanidin in the blood of dogs after parathyroidectomy and in the urine of children suffering from idiopathic tetany.

Part VI. The action of the blood-serum of animals in tetania parathyreopriva on the skeletal muscles of the frog. Wishart (G. M.).

In certain cases the serum of parathyroidectomized dogs acts upon the muscles of the frog in the same way as do dilute solutions of guanidin and methyl-guanidin. But the variations in the susceptibility of the muscles of different frogs renders this biological test unreliable.

Part VII. A comparison of the influence on the protein metabolism of parathyroidectomy and the administration of guanidin. Burns (D. A.).

After the administration of guanidin hydrochloride to dogs the excretion of nitrogen was increased immediately and out of all proportion to the dose. The ratio of urea nitrogen to total nitrogen was decreased. The proportion of the total urinary nitrogen excreted in the form of ammonia showed a slight decrease in feeding animals and generally a slight increase in fasting animals.

The excretion of creatin was only slightly if at all increased, but the percentage of unidentified nitrogen rose markedly immediately after the injection of guanidin.

From the close similarity of these effects to those resulting from parathyroidectomy in dogs, the author concludes that the two states are probably identical.

Part VIII. The functions of the parathyroids and the relationship of tetania parathyreopriva to idiopathic tetany. Paton (D. N.) and Findlay (D.).

Summarizing the results of their investigations, the authors conclude:

A. The parathyroids regulate the metabolism of guanidin in the body. By doing so they probably exercise a controlling influence on the tone of the muscles.

B. Tetania parathyreopriva and idiopathic tetany are identical as regards their character and metabolism, and, although the histological evidence is not conclusive, in all probability the parathyroids are implicated in the latter as in the former.—T. B. R.

The Preparation and Standardization of Ovarian and Placental Extracts. Morley (W. H.) Surg., Gyn. and Obs. 1917, xxx, 324.

Morley gives due emphasis in his article to the need for more uniform methods in the preparation of ovarian and placental extracts. Tangible laboratory and clinical data are still moreover lacking in extent. A review of the more important articles on the above subject reveals the circumstances that it is only within the last ten years that an attempt has been made to isolate the active principle of the ovary and placenta, especially the former. Iscovenso (1908) obtained "lipoids" from the red blood corpuscles, hypophysis, kidney, adrenals, ovaries, the testicles and the corpora lutea, and discovered they exerted a certain action on the female genitalia. The "homo-stimulating" lipoids, he found, had an action on the same organ from which they were derived, the "hetero-stimulating" lipoids exercising an action on different organs—this division he discovered later being purely arbitrary. Hermann (1915) believes he has succeeded in separating the "active substance" of the corpus luteum and of the placenta as a specific chemical substance, having identical physiological properties. Hermann possibly obtained his so-called active substance in a purer state. After engaging in special research work along this line during the last two years, Morley expresses the opinion that up to the present time no ideal method of preparation has been formulated, and until that is accomplished, standardization of the product will not be attempted. Considering the newness of the subject, the article concludes with quite an extensive bibliography.—Author's Abstract.

(THYMUS) *Sull 'anatomia patologica e normale del timo nei lattanti.* Vassiototschkin Charkowski. La Pediatra, 1917, xxv, 433.

The thymus from birth to the twelfth month increases in weight from 7 to 12 gm. In some cases of general atrophy the thymus is larger as if to compensate for the loss. The gland is heavier in males. Degeneration is brought about by insufficient alimentation. Hereditary syphilis causes atrophy of

the thymus. Diseases of the respiratory tract, if not tubercular, do not interfere with the development of the thymus; but there is usually hyperplasia in gastro-enteric diseases, while tuberculosis and diphtheria both cause degeneration.—G. V.

(INTERNAL SECRETIONS) Lipodystrophia Progressiva:

Weber (F. P.), Brit. J. Chil. Dis. 1917, xiv, 81.

The author makes an exhaustive study of the literature on this rare condition and concludes as follows:

1. That lipodystrophia progressiva is not always progressive, certainly not in regard to the extent of the area affected.

2. That it usually commences in childhood at 6 or 8 years of age.

3. That in some cases, the fat atrophy in the upper parts was preceded by increase of fat in the buttocks or legs; this increase of fat was, therefore, apparently the first sign of the commencement of the disease or syndrome in question.

4. That this disease or syndrome is not confined, as at first it was supposed, to the female sex. Genuine examples have been recently recorded in males, and it is probable that some of the cases, especially in males, which were formerly labeled "bilateral facial atrophy" were likewise genuine, though less extensive examples of lipodystrophia progressiva. Perhaps it will be found that, in males, the fat atrophy is more often limited to the face and neck, than in females.

5. That the etiology is unknown, but is probably connected with a disorder of the internal secretions.

6. That the fat atrophy, however disfiguring it may be, and though it may give rise to annoying suspicions of tuberculosis, etc., does not signify any danger to life, and is not usually accompanied by loss of strength or general health.—M. B. G.

EXPERIMENTAL INVESTIGATION

(SPLEEN) *Beitrage zur Physiologie der Drusen. 24 Mitteilung. Fortgesetzte Beitrage zur Lehre von der Funktion der Milz. Das Zusammenwirken von Leber und Milz.* Asher (L.) and Ebnother (G.) *Biochem. Zeitschr. (Berlin)* 1916, lxxii, 416.

Spleen-extract by itself has practically no hemolytic action. Liver-extract by itself has a definite hemolytic action of varying magnitude. A mixture of the two extracts has a much more intense hemolytic action than liver-extract by itself. The activating substance in spleen-extract is destroyed by heat. Spleen-extract in physiological salt solution has a slight power of decomposing hemoglobin. Liver-extract has a somewhat greater power of decomposing hemoglobin. A mixture of the two destroys hemoglobin more rapidly than either alone. This substance in spleen-extract is heat resistant and is not a lipid. A new function of the spleen is thus demonstrated, namely, that of supplying substances which activate the functions of the liver.—T. B. R.

(TESTIS) *The Effects of Testicular Transplants upon Vasomotor Irritability.* Wheelon (H.) and Shipley (J. L.) *Am. Jour. Physiol. (Balt.)* 1916, xxxix, 394-99.

The article deals with the relationship between the sympathetic nervous system and the internal secretions of the testis. Vasomotor reaction to intravenous injections of nicotin was taken as the criterion of the activity of the sympathetic system. Nicotin was used because of its selective action upon the sympathetic ganglia and the vasomotor centers proper.

Responses of the vascular system to nicotin gave evidence that one of the effects of castration is to depress the activity of the sympathetic system. From six to eight weeks after castration pressure responses to nicotin averaged 50 per cent. lower than reactions to the same dosage before removal of the gonads. Readings made from 10 to 22 days after the reception of a testicular transplant demonstrated a rise of 55 per cent in the activity of the vasomotor mechanism, or a return to 77 per cent of the normal. The transplants were found to remain active for at least 22 days. Castration and subsequent transplantation of testicular tissues caused but slight change in blood pressure. The series of dogs gained 5 per cent in weight during the period after castration.

The findings point to the conclusion that a direct relationship exists between the sympathetic nervous system and the primary reproductive organs. Castration results in a depres-

sion of the sympathetic mechanism, while the re-establishment of the lost parts partially reinstates normal activity.

Normal dogs which gave a feeble nicotin reaction subsequently proved unusually susceptible to infection.—Authors' Abstract.

(PANCREAS) The Absorption of Fat in Partially and in Completely Depancreatized Dogs. McClure (C. W.), Vincent (B.) and Pratt (J. H.) Jour. Exp. Med. (N. Y.) 1917, xxv, 381.

Recently McClure, Vincent and Pratt of the Harvard Medical School have made investigations concerning the possible control of fat absorption from the intestines in dogs by means of an internal secretion of the pancreas. In 1856 Claude Bernard presented detailed evidence to show that the external secretion of the pancreas is of great importance in the process of digestion and in the absorption of fat from the intestines. His findings were not accepted by the physiologists of that time. Since then most of the investigators of the subject have been unable to confirm Bernard's results. In 1905 Lombroso working with dogs found that a large percentage of fat was absorbed after all direct communication between the pancreas and duodenum was supposed to have been removed. This was also true if the pancreas was extirpated except for a small portion which discharged its juice through a permanent fistula in the abdominal wall. When complete depancreatization had been effected there was either slight or no absorption of fat. He concluded that the absorption is governed by an internal secretion of the pancreas. Fleckseder and Jansen confirmed these findings. McClure, Vincent and Pratt found (1) that the absorption of fat was always markedly disturbed by the exclusion of pancreatic secretion from the intestines; (2) that after the complete removal of all pancreatic tissue from an animal, the absorption of considerable amounts of fat can still take place, and (3) that dogs with a subcutaneous transplant secreting and discharging juice externally absorbed no more fat than dogs in which the pancreatic remnant was undergoing rapid atrophy and sclerosis. Hence, the condition of the pancreatic tissue remaining in the body does not influence the amount of fat absorbed by the intestine. From these findings the authors conclude that there is no evidence that fat absorption from the intestines is governed by an internal secretion of the pancreas.—Authors' Abstract.

(THYROID) Quelques resultats de la methode de cultures de tissues. V La glande thyroide. (Some Results from the Tissue Culture Method. V The Thyroid Gland.) Champy (C.) Arch. d. Zool. Exp. et Gen. (Paris) 1915, lv, 61.

In tissue cultures of adult thyroid of rabbits and dogs the colloid is rapidly absorbed, the cytoplasm of the epithelium becomes quite granular. After about 24 hours the cells of the vesicles multiply and the lumen is obliterated and the vesicles are transformed into nodules. The epithelial cytoplasmic granules are large and resemble colloid. After 48 hours the tissue resembles parathyroid rather than thyroid in appearance. The epithelium in the center of the culture may be completely destroyed through asphyxiation, but at the periphery normal mitosis may be seen. The epithelium proliferates rapidly, and after about four days it is difficult to distinguish the different elements of the culture. The epithelial cells tend to inhibit the growth of connective tissue in the cultures. At the periphery of the culture vesicles may form.—E. R. H.

ADRENALIN and Pituitrin, On Antagonism and Synergism of. Vershinin (N. V.) Publications of Imperial University (Tomsk) 1916, lxiv.

Experiments were made on the isolated frog heart (Williams' method). The drugs were either perfused through it, or the heart was placed into the solutions. Adrenalin and pituitrin are physiological antagonists with regard to their action upon the heart. The functional state of the cardiac nervous system is of great importance (experiments under atropine and chloral-hydrate). It follows that the above mentioned drugs do not act on each other physically or chemically, but there is a pure physiological process, adrenalin acting on the sympathetic fibers, pituitrin on the peripheral inhibitory system of the heart.—Physiol. Abstr.

(PITUITARY) The Appearance of the Pressor Substance in the Fetal Hypophysis. Lewis (D.) Jour. Exp. Med. (N. Y.) 1916, xxiii, 677-681.

Extracts of the entire gland were used in this work as separation of the anterior and posterior lobes is impossible at the age when the pressor reaction is first obtained.

Extracts of the hypophysis of fetal pigs measuring from 275 to 285 mm. (crown-coccyx measurement) gave a decided pressor effect. Intravenous injection of 0.05 gm. of dried hypophyses from fetal pigs measuring 175 mm. extracted in 5 cc. of normal salt solution gave a decided pressor effect, such as is usually obtained by the intravenous injection of extracts made from adult glands. Intravenous injections of saline extracts of hypophyses from fetal pigs measuring 125 mm. gave different results. In some cases a slight pressor effect following a primary fall was observed, while in other instances no change in the tracing was noted.

From these studies it seems probable that the active principle of the pars intermedia, using the pressor substance as an index, begins to appear in fetal pigs measuring 125 mm. or slightly more. As far as can be estimated a fetal pig measuring 125 mm. is about nine and one-half or ten weeks old from conception. During the period represented by the differences between 125 and 175 mm. the secretion of the pars intermedia becomes as active as that of the adult gland.

In the glands of the ages above mentioned there are no traces of the hyaline bodies described by Herring, but the pars intermedia is physiologically active.—Author's Abstract.

(ADRENIN) Note on Vagus Stimulation of the Adrenalised Heart. Kuroda (M.) and Kuno (Y.) Jour. Physiol. (Lond.) 1915, 1, 154.

The experiments reported indicate that the inexcitability of the cardiac vagus after injection of adrenin is due to its direct action rather than to an increase in intracardiac pressure.

Small amounts of adrenin were ineffective, larger amounts (0.07 to 0.1 mg.) abolished vagus response. In the "heart-lung preparation" the vagus did not recover from adrenin while such effects were only temporary in the intact animal. Moreover in the latter the amount of adrenin necessary to abolish the action of the cardiac vagus was less than that required to double the blood pressure.—F. A. H.

(ADRENIN) Evidence that the Active Principle of the Retroperitoneal Chromophil Tissue has the Same Physiological Action as the Active Principle of the Suprarenal Gland. Fulk (M. E.) and Macleod (J. J. R.) Am. Journ. Physiol. (Balt.) 1916, xl, 21.

Inhibition of intestinal contraction and augmentation of contraction in the virgin uterus were taken as evidence of the presence of adrenin. Acid extracts of the retroperitoneal chromophil tissue of man, dog, cat, rabbit, guinea pig, white rat, calf, sheep and pig gave positive evidence of adrenin. Extracts of the sympathetic ganglia and of the epididymis of the dog gave negative results.—F. A. H.

(THYROID, PITUITARY) Morphogenetic Changes in the Pancreas Produced by Thyroid and Pituitary Feeding. Kojima (M.) Jour. Physiol. (Lond.) 1916, 1, xlv.

The addition of thyroid or boiled thyroid extract to the food of rats causes increased growth of the pancreas. In a few days the cells multiply and become smaller, the zymogen diminishing. After two or three weeks the multiplication ceases, zymogen accumulates and the cells increase in size.

Feeding of posterior lobe of pituitary body (anterior lobe has no effect) causes vacuolization of the cells, accompanied by edema of the whole organ excepting the islets of Langerhans. There is an accumulation of granules in the cells of the latter. Edema is also produced in the liver and testicle.

F. A. H.

(ADRENAL) The Liberation of Epinephrin from the Adrenal Glands by Stimulation of the Splanchnic Nerves and by Massage. Stewart (G. N.), Rogoff (J. M.) and Gibson (F. S.) *Jour. Pharm. and Exp. Ther.* (Balt.) 1916, viii, 205.

The authors employed cats and dogs, one eye of which had been denervated by removal of a superior cervical ganglion several days before. It was found that stimulation of the splanchnic nerves causes dilatation of the pupil of the denervated eye provided the blood is allowed to flow from the adrenals to the eye. Slowing of the circulation increases the time between the beginning of the stimulation and the response. A belated response occurs even with the carotids clamped provided a longer or stronger stimulus is used. The latent period of the eye response obtained by injection of adrenin into the renal vein or the femoral vein was about equal to that after the stimulation of the splanchnic nerve, showing that the latent period for the liberation of adrenin from the adrenal is short (a fraction of a second). Latent periods are given under various conditions. The amount of response increases up to a certain point with the duration of the stimulation.

Massage of the adrenals produces an eye response even after splanchnic stimulation ceases to be effective. Massage reaction is soon exhausted.

Previous fright or administration of morphine to cats did not render exhaustion of the adrenals, by splanchnic stimulation, easier.

An interesting fact was the great number of successful eye responses obtained from a single gland of a cat weighing 1.5 kg. In one case fifty responses which, according to the amount of adrenin necessary to evoke similar responses, would require a total of 0.4 mg. Judging from the amount of adrenin found in adrenals by assay (Elliott, *Jour. Physiol.* 1912, xlv, 374) it seems improbable that all could have come from the initial store.—F. A. H.

(TESTES) Histological Changes in Testes following Vasectomy. Myers (B. D.) *Anat. Rec.* (Phila.) 1916, x, 228.

In albino rats ninety days after vasectomy degenerative changes in the seminiferous tubules was observed, but the interstitial cells, which are believed to produce an internal secretion, were not affected by the operation. After 120 days

the seminiferous tubules were almost completely disintegrated, but the interstitial cells still remained intact. The author concludes that vasectomy brings about sterilization without disturbing the secondary sex characters or the psychic life.—E. R. H.

The Effect of Adult Chicken Organ Grafts on the Chick Embryo. Murphy (J. B.) *Jour. Exp. Med.* (N. Y.) 1916, xxiv, 1.

Bits of spleen, liver, kidney and bone marrow of adult chickens, when grafted on to the membranes of growing chick embryos, caused certain changes in various organs of the embryo. The membranes contained small nodules of developing leucocytes. The spleen was enlarged and hemorrhagic or congested, and in the stage of developing blood cells was advanced. The skin and subcutaneous tissues also contained developing blood cells. Similar nodules occurred within the liver and kidneys.—E. R. H.

(CORPUS LUTEUM) Heredity and Internal Secretions in the Origin of Cancer in Mice. Loeb (L.) *Am. Jour. Physiol.* (Balt.) 1916, xl, 127.

In earlier investigations the author found that a combination of a mechanical stimulus and the influence of a substance secreted by the corpus luteum led to the production of rapidly growing tumor-like formations. These facts suggested the possible importance of corpus luteum for the spontaneous development of cancer in mice.

Castration of mice at six months of age or less diminished the cancer incidence from 60 or 70 per cent to 9.9 per cent. Non-breeding mice with functional ovaries developed cancer in a smaller percentage of cases and at a higher age than normal breeding mice. Castration eliminates the effect of the corpora lutea; non-breeding diminishes or modifies them.

F. A. H.

PANCREAS and ADRENALS, Relation Between. Kamo (K.) *Kyoto Igaku Zasshi*, iii, 1.

Pancreatectomized dogs were studied, using as controls dogs which had been subjected to operations of equal severity and involving the same loss of blood. Blood was taken from the suprarenal veins by the method of Ehrmann and O'Connor; and its adrenalin content was determined on the ear of a dog by Pissemski's method. "The blood in the suprarenal veins contained less adrenalin after pancreatectomy than before, thus indicating the absence of any restraining action the pancreas had been said to exert upon the suprarenals, but

rather indicating that the functional loss of one depresses the action of the other."—Chem. Abstr.

PROSTATE, The Lipoid Pigment in, with Special Reference to the Pigment of the Ejaculatory Duct and Prostatic Musculature. Ishihara (M.) Tokyo Igakkwai Zasshi, xxx, 1.

After puberty, under physiological conditions, pigment bodies are present in the glandular epithelium of the prostate, usually in the basal part of the cells near the nucleus. The number and size of the granules correspond to the age of the person. The granules are fine or coarse, irregular, angular masses, with a peculiar yellow or yellowish brown color; they are not doubly refractive, are gradually decolorized by bleaching solutions, are soluble with difficulty in fat solvents, are unchanged by acids and alkalies, are stained orange red by Sudan III and scarlet-red, purplish by Nile blue, and brownish black by osmic acid, and may also be stained by the method of Ciaccio, Smith-Dietrich and Fischler; they probably contain phosphatides, cerebrosides, soaps, pigment, modified by fatty acids, and cholesterol mixed with fat. Their appearance in the prostatic secretion is evidence of the destruction of granule-bearing epithelium and liberation of the granules, which are not an integral part of the secretion. The pigment granules in the epithelial cells of the ejaculatory duct consist of degeneration pigment, with the same significance as that of the seminal vesicles; the number and size of these granules correspond well with the age. Two kinds of pigment bodies occur in the physiologically pigmented smooth muscle fibers of the prostatic musculature; one class of pigment body is found as very fine, brown granules, giving a faint reaction for fat; the other class of pigment body is characterized by a distinct reaction for fat and a faint reaction for iron.—Chem. Abstr.

(ADRENIN) Researches on the Perfused Heart. Burridge (W.) Quart. Jour. Med. (Lond.) 1917, x, 157.

Adrenin has a two-fold action on the frog's heart; a primary depressing action resembling inhibition, and an augmenting or sympathomimetic action. Three factors are concerned in the depressing action of adrenin: (1) The concentration of the drug; (2) the concentration of calcium in the perfusing solution, and (3) the condition of the heart at the time of the experiment. The relations between adrenin and calcium are found to be four-fold and depend upon: the concentration of adrenin, the concentration of calcium, the state of the heart induced by the adrenin and the state of the heart induced by the calcium. Evidence is given that traces of

adrenin render balance between the constituents of an inorganic saline solution of secondary importance in regard to their suitability as media for the manifestation of cardiac activity. The behavior of a heart perfused with a well-balanced Ringer solution never approximates to the behavior of the blood-containing heart, and the change takes place immediately after one solution replaces the other. Unbalanced Ringer solutions, i. e., those containing too much calcium, too little calcium or a considerable amount of potassium, interfered with cardiac activity. Traces of adrenin rendered these unbalanced solutions capable of maintaining cardiac activity and of preserving in great measure the resemblances between the behavior of the heart perfused with them and of the heart containing blood. On the basis of these experiments it is suggested that the proportions between the inorganic constituents of the blood are such as to render it an unsuitable medium for the manifestation of cardiac activity except in the presence of adrenin. The origin of certain symptoms of Addison's disease is traced to such lack of balance. Numerous plates and references are given.—Chem. Abstr.

PARATHYROID GLAND, its Physiological and Pathological Importance from the Experimental Aspect. Voegtlin (C.) Surg. Gyn. & Obs. (Chgo.) 1917, xxv, 244.

The parathyroid gland has a definite physiological function which is still incompletely understood. The presence of a minimum of parathyroid tissue in the body is essential for life and the continuation of normal metabolism. Parathyroid insufficiency seems to be characterized by an increased irritability of the nervous system to the galvanic current, which may be due to the withdrawal of the calcium salts from the blood and tissues. Parathyroid insufficiency leads to an alkalosis which is converted into an acidosis as a result of active tetany. Definite metabolic changes take place in animals after complete parathyroidectomy. Pregnancy puts an extra strain on the functions of the parathyroid, as evidenced by tetany during this period in partially parathyroidectomized animals. Tetany has been observed during lactation in animals with parathyroid insufficiency. Interruption of lactation was followed by recovery. The offspring of partially parathyroidectomized animals exhibit a marked increase in nerve irritability. An intravenous injection of soluble calcium or strontium salts or hydrochloric acid almost instantly removes the symptoms of tetany. However, tetany may reappear after this treatment and the life of such animals can not be saved by the continuous administration of calcium. The administration of parathyroid extract seems to have a temporary cura-

tive effect on tetany animals. Iso-transplantation of parathyroids into animals with parathyroid insufficiency is usually successful. The spontaneous recovery from tetany in experimental animals is probably due to changes in their metabolism (acidosis) caused by the hyperactivity of the skeletal muscles during tetany. The experimental facts do not support the theory that eclampsia is due to hypo-parathyroidism. A condition which might justly be termed hyper-parathyroidism is unknown at the present time.—Author's Summary.

(LIVER) Effect of the Emotions on the Catalase Content of the Liver. Burge (W. E.) and Burge (E. L.) *Am. Jour. Physiol.* (Balt.) 1917, xlv, 75.

Burge has shown that when there is an increased oxidation the catalase content of muscle is increased, and vice versa. "The object of the present investigation was to determine the effect of stress and combat, where extreme muscular effort is put forth by the animal, on the catalase content of the different organs and tissues of the body with the hope of determining if catalase is formed in situ in the tissues or if it is formed by a particular organ and given off to the blood." In this paper special attention is given to the liver.

Ten young cats from one home, living under the same conditions were used. Five of these cats were placed in a wire cage and a dog with a particular dislike for cats allowed to bark and bite at them for one hour on two consecutive days. At the end of the frightening process on the second day, the cats were killed, and the vessels of the liver washed out with 0.9 per cent NaCl solution until they were free from blood. The livers were then removed, ground up and strained. The amount of oxygen liberated from hydrogen peroxide by one gram of this material, in ten minutes, reduced to standard atmospheric pressure, gave the catalase content of one gram of liver. The other five cats were used as controls.

It was found that the catalase increased by about 90 per cent in the livers of the "fighting" cats, as compared with the normal ones. "This catalase is given off to the blood and is carried to the tissues to be used presumably in producing increased oxidation."—T. C. B.

(This paper derives its endocrine interest from the supposition that emotional stress results in augmented activity of the adrenal and thyroid glands.—Ed.)

(ADRENIN) Effect of Adrenalin on Muscular Fatigue. Gruber (C. M.) *Am. Jour. Physiol.* (Balt.) 1917, xliii, 530.

Recently Hoskins, Gunning and Berry have shown that adrenin produces active vasodilatation in muscle, and they

think this is the cause of the betterment of muscular contraction which Gruber found to follow the administration of this substance. The present work has been carefully planned to show that adrenin has an action on muscle tissue apart from the improvement in its circulation.

"In the fatigued unaltered nerve-muscle adrenin may increase the height of muscular contraction by a two-fold action, by improvement in the blood supply (vasodilation) and by its chemical action upon some substances in the muscle."

Since adrenin does not better the circulation in a muscle in which the nerve is cut and stimulated, its action in improving the contraction must be due to its chemical action alone. This chemical action may be one or all of the three following processes which are accelerated by adrenin:

1. Conversion of glycogen into sugar.
2. Reconversion of lactic acid into sugar (transformation of fatigued products).
3. The oxidizing of lactic acid into carbon dioxide and water (destruction of fatigued products).

T. C. B.

(SALIVARY GLANDS) Contributions to the Physiology of the Stomach. XLI. The Alleged Influence of the Removal of the Salivary Glands on the Secretion of Gastric Juice.
Swanson (A. M.) *Am. Jour. Physiol. (Balt.)* 1917, xliii, 205.

The presence of a secretagogue in the salivary glands has been both affirmed and denied, and Swanson's problem was to decide the point if possible. Dogs with a Pavlov pouch were used. After recovery from the operation the gastric secretion was measured at hourly intervals for six to eight hours, beginning one hour before feeding a standard meal of lean meat, and the observations were continued for from seven to ten days. A curve of normal secretion was thus obtained for comparison, after which the salivary glands were removed and the observations repeated.

Swanson finds that neither the rate of secretion nor the quantity of the gastric juice is altered by removal of the salivary glands. The peptic concentration, as determined by Mett's tubes was also unaffected. There was a distinct rise in the acidity of the gastric juice, but this can be accounted for by the absence of alkaline saliva. The conclusion is that there is no hormone in the salivary glands stimulating the secretion of gastric juice.

In describing the condition of the dogs after operation, the author says (p. 209) that their mouths did not appear as dry as would be expected, and also that their sense of taste did not appear to be altered. Later, in his conclusions, he

accounts for a slight retardation in the maximum secretion rate after a meal by the "decreased psychic secretion owing to the dryness of the mouth and consequent impaired taste."—T. C. B.

ADRENIN. The Effects of, on the Distribution of the Blood.

IV. Effect of Massive Doses on the Outflow from Muscle.

Gunning (R. E. L.) *Am. Jour. Physiol. (Balt.)* 1917, xliii, 395.

Small doses of adrenin were used, and the amount gradually increased. When the dosage reaches 1 or 2 cc of a 1:1000 solution the pure dilatation changes to constriction as evidenced by a diminished venous outflow. After return to normal there is a tendency to "over recovery" shown by an increase in the rate of outflow. This "over recovery" is probably due to fatigue of the vascular musculature.

The threshold for vasoconstriction varies. Prolongation of the experiment tends to lower the threshold. Increase of concentration has the same effect. For example, 5 cc of a 1:5000 might produce local dilatation without blood pressure reaction, whereas 1 cc of a 1:1000 would cause vasoconstriction.—T. C. B.

(ADRENALS) The Vascularity of the Adrenal Bodies.

Burton-Opitz (R.) and Edwards (D. J.) *Am. Jour. Physiol. (Balt.)* 1917, xliii, 408.

Burton-Opitz's recording stromuhr was inserted into the suprarenal vein of large dogs, and it was found that a gland weighing 1.72 grams (average) receives 0.142 cc of blood per second or 8.5 cc per minute. At a pressure of 100 mm. Hg. 100 grams of gland receives 490 cc per minute. Compared with his figures for other organs, the suprarenals are exceeded in vascularity only by the thyroid.

The question of splanchnic stimulation is also discussed, and some doubt is expressed as to the existence of a dilator mechanism in the adrenals.—T. C. B.

SECRETIN, Influence of, on the Number of Erythrocytes in the Circulating Blood.

Downs (A. W.) and Eddy (N. B.) *Am. Jour. Physiol. (Balt.)* 1917, xliii, 415.

Beveridge and Williams claim to have observed an increase in the number of red corpuscles after the administration of secretin. Their proteomorphic theory of immunity depends upon the power of the red cells to hydrolyze proteins. If this be correct, any agent which increases the red cells is of therapeutic value. Such an agent, however, to be efficient, should not only produce, but also maintain, a largely increased

erythrocyte count. These ideas led the authors to try the effect of arbitrarily fixed doses of secretin when given intravenously, and also the effect of the same dose when given hypodermically.

They prepared secretin from dog's intestines, and rabbits were used for the experiments. The results of a long series of experiments show that it is possible to produce a considerable increase in the red corpuscle count per cubic millimeter by administering secretin. The effect appears quickly, but is transient. Repetition of the dose at short intervals may prolong the increase, but it promptly drops after the last dose. Daily doses over a period of five days have no lasting effect on the red count. The most efficient dose was found to be 1 cc per kilo of body weight.—T. C. B.

ADRENIN, Effects of, on the Distribution of the Blood.

V. Volume Changes and Venous Discharge in the Intestines.

Hoskins (R. G.) and Gunning (R. E. L.) *Am. Jour. Physiol.* (Balt.) 1917, xliii, 399.

Plethysmographic studies and determination of the outflow from the intestinal veins, under ether anesthesia, resulted most frequently in an augmentation of the gut volume, and of the discharge from the veins. The doses of adrenin injected varied from 0.25 to 8 cc of 1:100,000 solution. Often the dilatation phase was preceded by contraction, and in some instances contraction only occurred.

As the liver contracts under the influence of adrenin, it was necessary to determine to what extent the reactions of the intestines were due to back pressure from the liver. Several dogs were tested before and after the establishment of Eck fistulae. In all but one experiment there was no change in the reactions. In the one exception, shunting the portal blood directly into the vena cava converted an enterodilatation into an enterocontraction.—T. C. B.

(THYROID) The Effect of Thyroid on the Catalase Content of the Tissues. Burge (W. E.), Kennedy (J.) and Neill (A. J.) *Am. Jour. Physiol.* (Balt.) 1917, xliii, 433.

This investigation was undertaken to determine if thyroid feeding increases the catalase content of certain tissues, and thus accounts for increased oxidations in animals fed on thyroid, while in other tissues (muscles, fat) it causes a decrease which would account for the increased autolysis in these tissues.

After feeding cats on thyroid for at least five days, 25 cc of blood was collected and allowed to clot. The blood vessels were then washed free of blood with 0.9 per cent NaCl. The

various tissues were ground up in a hashing machine, and the catalase content determined by adding one gram to 45 cc hydrogen peroxide. The gas was collected over water in an inverted burette and reduced to standard atmospheric pressure. The blood was pressed through several thicknesses of cheese cloth and ground up in a mortar. Ten drops of this was added to 500 cc of hydrogen peroxide. In all cases the peroxide was diluted with an equal volume of distilled water.

The authors find that feeding thyroid increases the catalase of the blood and decreases it in the heart, and probably also in the fat and skeletal muscles. This will account for the increased oxidation in thyroid fed animals, and also for the increased autolysis of muscular tissues as indicated by loss of weight and strength.—T. C. B.

(THYROID) Effect of Thyroid Feeding upon Carbohydrate Metabolism. Kuriyama (S.) *Am. Jour. Physiol.* (Balt.) 1917, xliii, 481.

The glycogen content of the liver of white rats is distinctly decreased in three to five days of thyroid feeding. When thyroid feeding is discontinued the liver shows a normal glycogen content in two or three days. When dextrose is introduced parenterally in fasting rats the liver glycogen is increased in a few hours. This does not seem to be the case in thyroid-fed animals.

Experimental hyperthyroidism does not change the sugar content of the blood in either rats or rabbits.

Spontaneous glycosuria does not result from thyroid feeding in either rats or rabbits.

The tolerance of thyroid fed rabbits for dextrose, parenterally administered, does not differ from that of normal animals.

Nearly the same degree of hyperglycemia and glycosuria can be induced by adrenin injection in thyroid-fed as in control rabbits.

The adrenal gland of thyroid-fed rats contains approximately the same amount of adrenin as that of normal rats.—T. C. B.

PITUITARY, Experimental Operations on. Bell (W. B.) *Quart. Jour. Exp. Physiol.* (Lond.) 1917, xi, 78.

After a brief historical introduction there is a careful description of operative technique, fully illustrated. The experimental part deals with total and partial extirpation of the pituitary, clamping and separation of the stalk, and imitation tumors in the neighborhood of the pituitary.

Total extirpation of the pituitary is fatal, confirming the observations of Paulesco and of Cushing. Removal of very

large portions of the anterior lobe is also fatal. Removal of the pars posterior is without effect.

The most striking difference between Bell's results and those of Paulesco, Cushing and others is in the production of dystrophia adiposo-genitalis. In none of Bell's cases was partial removal of the pars anterior followed by this syndrome, although genital atrophy was usually found if there was a sufficient lapse of time after operation. Bell found, however, that dystrophia adiposo-genitalis occurred in two out of three cases where the stalk was clamped, or separated. In one case the increase in body weight amounted to 66 per cent in fifty-one days. Bell thinks the explanation of this fact lies in the view he has long held, that the pituitary is one organ, not two, and that the secretion can pass directly into the blood stream like other internal secretions, and not into the third ventricle, as held by Herring. Clamping of the stalk interferes with the blood supply to the organ, and causes atrophy of the cells of the pars anterior and intermedia.

Attention is called to the peculiar somnolent condition following operations which decrease the pituitary secretion. It was suggested by Gemelli that hibernation might be due to hypopituitarism, and the same shrunken, inactive cells are present in hibernation that are observed in experimental cases, and in dystrophia adiposo-genitalis in the human.

"Artificial tumors in the neighborhood of the sella turcica may produce irritation which is accompanied by glycosuria and emaciation; or by interfering with the blood supply may lead to degenerative changes in the cells of the pars anterior, and so give rise to the syndrome dystrophia adiposo-genitalis."—T. C. B.

Action of Gland Extracts and Drugs on the Uterus of the Rat. Itagaki (M.) Quart. Jour. Exp. Physiol. (Lond.) 1917, xi, 39.

For experimentation, the uterus of the rat offers certain advantages over that of larger animals. It is easily obtained. Being small, only a comparatively small quantity of the solution to be tested is required. The rhythmic spontaneous contractions in oxygenated Locke's solution at 37 deg. C is fairly regular. The results of the author's experiments may be briefly summarized: 1. Extract of posterior lobe of pituitary always produces an increase of tone. This corroborates the findings of Dale and others. 2. Solutions of adrenin inhibit rhythmic contractions, with or without diminution of tone. 3. Extract of thyroid occasionally produces increase of tone, but generally has no effect. 4. Extracts of orchitic substance, of uterus and of brain, have no appreciable effect.

As for the drugs, the action of nicotine is variable, the action of pilocarpine is inconstant; weak solutions of atropine cause increase, stronger solutions diminution, of tone. Barium chloride stimulates.—T. C. B.

THYROID, Feeding of, on Weight of the Suprarenals and on their Adrenalin Content. Herring (P. T.) *Quart. Jour. Exp. Physiol.* (Lond.) 1917, xi, 47.

The feeding of 0.2-0.5 gm. of fresh ox thyroid to white rats results in an increase in the size and weight of the suprarenals, and also an increase of the adrenin content of these glands, confirming the observations of Hoskins on new-born animals. The hypertrophy involves both the cortex and medulla of the gland, and the author thinks there is "reason to believe that when accessory suprarenals are present, they, too, undergo enlargement." Reckoned in mg. per 100 gms. body weight, the increase may amount to as much as 76-78 per cent.

As the amount of adrenin in the blood is likely to vary, a "better index of any change in the adrenalin content of the body is furnished by an estimation of the amount in the suprarenal capsules and chromaphil tissues." Folin's micro-chemical method was used, and an increase of about 50 per cent over normal animals was observed. When present, accessory suprarenals probably also show an increase in adrenin.

The author notes that when rats are fed with thyroid they sometimes die suddenly, and post mortem shows cardiac hypertrophy. Investigations along this line are being continued.—T. C. B.

(THYROID) Carbohydrate Metabolism in Relation to the Thyroid Gland. II. The Effect of Thyroid Feeding on the Gaseous Metabolism. Cramer (W.) and McCall (R.) *Quart. Jour. Exp. Physiol.* (Lond.) 1917, xi, 59.

According to Cramer and Krause, feeding with thyroid causes complete disappearance of glycogen from the liver, yet there is no glycosuria as would be expected. There are three possible explanations of this apparent paradox: 1. The suspension of the glycogenic function of the liver is compensated for by an increased deposit of glycogen in the muscles. 2. The thyroid hormone has a direct stimulating effect on the oxidation of carbohydrates. 3. The carbohydrates might be transformed into fats and deposited as such. The first possibility may be excluded, as there is no increase of muscle glycogen in thyroid-fed animals. The third possibility can be dismissed at once, since the fat rapidly disappears in animals fed on thyroid. As to the second possibility, that the thyroid directly stimulates the oxidation of carbohydrates, it may be excluded

on the ground that glycogen is "absent from the liver immediately after a meal rich in carbohydrates, whereas one would expect to find only a more rapid disappearance of glycogen from the liver of thyroid-fed animals and a replenishing after a meal, if the effects on the liver glycogen were merely a secondary one." Other facts confirm this conclusion. If the thyroid has a direct stimulating action on carbohydrates, one would expect to find a rise in the assimilation for sugar in Graves' disease, whereas there is a tendency to glycosuria in this condition. On the other hand, thyroid insufficiency ought to lower the sugar assimilation limit; but in myxedema there is the reverse tendency.

The authors think the condition in experimental hyperthyroidism cannot be explained by the orthodox conceptions of carbohydrate metabolism, and determined to approach the problem "without the bias of a theory." If, in experimental hyperthyroidism, the "carbohydrates are neither deposited, nor excreted as such, nor transformed into fats, we must arrive per exclusionem at the conclusion that they are oxidised." Their problem was to determine if this conclusion was justified. The observations were made on rats, and the gaseous metabolism was determined by the method of Haldane and Pembrey, with some modifications. The experiments were all carefully controlled.

From their observations Cramer and McCall conclude that the thyroid secretion produces an increased oxidation of carbohydrates. The action is not direct, but "follows its action in discharging glycogen from the liver." They distinguish an "early" stage (second or third day after feeding thyroid), and a "later" stage (third to sixth day). In the "early" stage the pre-existing carbohydrate of the food and of the deposits in the organism is oxidised. In the "later" stage there is, in addition, a formation of carbohydrates from protein and possibly also from fat, and a subsequent oxidation of carbohydrates thus formed." There is a marked rise in carbon dioxide excretion and oxygen absorption. Illustrative curves are reproduced.

"The action of the thyroid secretion on the glycogenic function of the liver lies thus at the root of the increased oxidation of proteins, carbohydrates and probably fats produced by thyroid feeding."—T. C. B.

CORPUS LUTEUM, Influence of Extracts upon Plain Muscle, Especially that of the Uterus. Itagaki (M.) *Quart. Jour. Exp. Physiol.* (Lond.) 1917, xi, 1.

In view of the conflicting evidence as to the action of extracts of corpus luteum on the contraction of the uterus, it

seemed "desirable to submit the subject to renewed investigation." The extracts in most cases were made from the corpus luteum of the cow, immediately upon receipt from the slaughter house; occasionally they were kept over night in an ice chest. The extracting medium was Locke's solution. The contractions were recorded by Schafer's modification of Magnus' method.

Using one of the cornua of the rat's uterus, the author finds that in the majority of cases "there is a marked increase of tone, having almost the appearance of tetanus." In rare cases the effect was just the opposite—diminution of tone, and even abolition of rhythmic movements. Strips of rabbit's uterus showed the same result, eight out of ten experiments giving stimulation, and two inhibition. Cats, dogs and guinea pigs, all gave increase of tone, with one exception in the case of cats, where there was inhibition. The effects were the same whether the uterus was pregnant or non-pregnant.

Itagaki thinks the difference in the action of extracts of corpus luteum on the uterus is due to the presence of two antagonistic substances. These substances can "sometimes" be separated by alcohol, the chalonic substance (inhibiting hormone) going into alcoholic solution. It is very small in amount, while the (stimulating) hormonal substance, soluble in water, but not in alcohol, ether or chloroform, is much larger in amount. The proof is not very convincing; extracts of the ash of corpus luteum cause inhibition in strong 5 per cent solution, due probably, as the author suggests, to the preponderance of potassium found in the ash of corpus luteum.

Corpus luteum extract generally produces relaxation of the intestine and bladder of the rat, but contraction of the whole intestinal tube of the rabbit and kitten; "although, when isolated strips of either the longitudinal or circular muscle of the intestine of these animals were taken they showed relaxation." No change in the frog's iris was observed. There was very little effect on blood pressure; if anything, there is a slight fall. There is no evidence that its action is through the nerve endings.—T. C. B.

(OVARIES) Action of Various Extracts obtained from the Cow's Ovaries upon the Muscular Tissue of the Uterus, Intestine and Blood Vessels. Itagaki (M.) *Quart. Jour. Exp. Physiol. (Lond.)* 1917, xi, 27.

In this paper the author describes the results of experiments with extracts of different parts of the ovary upon smooth muscle. Using an extract of part of the ovary about the hilum, he finds that out of forty experiments on the rat's

uterus "thirty-one showed diminution or inhibition of rhythmic movements, with or without relaxation of tone; five showed inhibition of rhythmic movements, followed after a time by a recurrence of contractions; in three no change was observed; in one there was increase of tone from the first."

"The uterus of other animals is affected differently, for in the rabbit, cat and guinea pig an extract of the hilum usually has the result of producing an increase of tone."

"Liquor folliculi produces an increase of tone of the uterine muscle in the rat, rabbit and cat, or at any rate an increase in height of the rhythmic contractions."

Extracts of the whole ovary produced diminution or complete inhibition of the rhythmic movements of the rat's uterus, but increase of tone or height of contractions in the rabbit, in four out of five cases.

"When applied to the whole thickness of the intestinal tube, all the extracts tested—hilum, liquor folliculi, whole ovary—determined an increase of tone, whereas a strip of the longitudinal coat of the rabbit's intestine is sent into relaxation by extracts of hilum."

Intravenous injection causes a fall of blood pressure in all cases.—T. C. B.

(CORPUS LUTEUM) The Cause of Hyperplasia and Secretion of the Mammary Gland. Athias (M.) C. R. Soc. de Biol. (Paris) 1916, lxxix, 557.

From the results published in a previous paper he concludes that the corpus luteum is not necessary for the development and secretion of the mammary gland. He suggests other structures that may be responsible for the development and secretion of the mammary gland.—F. A. H.

(SECRETIN) Action of Secretin on the Kidney. Piticarín (J.) C. R. Soc. de Biol. (Paris) 1916, lxxix, 871.

See abstract, *Endocrinology* i, 71.—F. A. H.

(THYROID) Effects of Thyroid Removal upon the Development of the Gonads in the Larvae of *Rana pipiens*. Allen (B. M.) *Science* (Lancaster, Pa.) 1907, n. s. xlvi, 216.

The thyroid anlagen were removed at their inception. It has been shown in a previous article that the thyroidless tadpoles failed to undergo metamorphosis, although the size attained became much greater than in normal tadpoles. The gonads of these thyroidless tadpoles develop normally, as far as sexual maturity in the male and at least as far as the period when the ova are visible to the naked eye in the female.

F. A. H.

(ADRENIN) Absorption of Adrenin after Intratracheal Injection. Auer (J.) and Gates (Frederick L.) *Jour Exp. Med. (Balt.)* 1916, xxiii, 757.

Experiments were performed on rabbits under ether. Adrenin solution in 0.1 per cent strength was injected into the respiratory passages, into the tracheal cannula, into a bronchus by means of a catheter, or directly into the lung tissue by passing a hypodermic needle through the chest wall. The dose varied from 0.15 to 0.03 cc. per kilo of body weight.

The absorption of adrenin caused a marked rise of blood pressure in a few seconds, which lasted from six to ten minutes. As a result of their experiments with adrenin the authors conclude that the intratracheal path would be useful in the administration of other substances.—F. A. H.

(CORPUS LUTEUM) Histological Study of Ovaries Grafted upon Castrated Pigs and Removed After the Establishment of Lacteal Secretions. Athias (M.) *C. R. Soc. de Biol. (Paris)* 1916, lxxix, 553.

Ovaries from both virgin and non-virgin guinea pigs were employed in making the grafts.

The author studied eight grafts, of which four were taken during the first three days of secretion of the mammary gland. False corpora lutea are found in these grafts, but in no instance did he find a true corpus luteum.—F. A. H.

(TESTIS) On the Occurrence of Spermine. Rosenheim (M. C.) *Jour. Physiol. (Lond.)* 1917, li, 4.

The author has isolated spermine from testis, pancreas, spleen, brain, cancerous lymphatic tissues, cod's roe, Liebig's meat extract. She was unable to isolate the substance from serum, blood or protein-free milk. Yeast was the most convenient source of preparation. Evidence supports the view that spermine is an aliphatic base.—F. A. H.

(PITUITARY) Pituitary Standardization. Hamilton (H. C.) and Rowe (L. W.) *Jour. Lab. Clin. Med. (St. Louis)* 1916, ii, 120.

The authors found the pressor test more dependable than the uterus test, because of the great variation in sensitiveness of different specimens of uterus. They believe that the pressor test is an indicator of the oxytocic value.

By injecting small amounts of pituitary extract and allowing not less than fifteen-minute intervals, often between twenty and thirty doses of 0.05 cc Pituitrin (Parke-Davis) have been injected intravenously into dogs without the depressant effect becoming increased.—F. A. H.

(ADRENIN) On the Pharmacology of the Ureter. I. Action of Epinephrin, Ergotoxin and of Nicotin. Macht (D. I.) *Jour. Pharm. and Exper. Ther. (Balt.)* 1916, viii, 155.

Longitudinal strips and rings of the ureters of pigs and oxen were employed. Adrenin increased the rate of ureteral contractions and the tonus of the ureter, large doses producing a tonic spasm. After previous administration of ergotoxin adrenin inhibits the ureteral contractions. Adrenin produced similar effects upon the human ureter.—F. A. H.

(ADRENIN) Effect of Epinephrin on the Medullary Centers. Brown (E. D.) *Jour. Pharm. and Exper. Ther. (Balt.)* 1916, viii, 195.

The medulla of dogs was perfused by a mixture of defibrinated blood and either Ringer-Langendorff solution or a 0.9 per cent solution of sodium chloride entering the carotid and vertebral arteries.

In a majority of cases where adrenin was introduced into the perfusion mixture there was slowing of the heart and a fall in blood pressure. Adrenin seemed to act directly upon the vagus center because the slowing of the heart was immediate and was not connected with a rise in blood pressure. Occasionally there was a lowering of the blood pressure without slowing of the heart.

Small doses of adrenin often increased both the depth and rate of the respiration, while large doses usually diminished the depth and rate or might even stop respiration.—F. A. H.

(THYROID) Therapeutic Applications of Human Thyroid Extract. Beebe (S. P.) *N. Y. Med. Jour. (N. Y.)* 1916, civ, 445.

Certain cases of hypothyroidism, in which the administration of animal thyroid preparations only partially controlled the symptoms, were almost completely relieved by human thyroid extracts.

A method for the preparation of human thyroid extracts is described.—F. A. H.

(PANCREAS) Influence of Pancreatic Extracts on the Production of Lactic Acid in Surviving Muscles. Winfield (G.) and Hopkins (F. G.) *Jour. Physiol. (Lond.)* 1915, 1, 5.

Pancreatic extract has an inhibitory action on the formation of lactic acid in surviving muscle. The responsible factor is heat stable.—F. A. H.

(PITUITARY) Studies on the Properties and Action of Tethelin. Schmidt (C. L. A.) *Jour. Lab. and Clin. Med.* 1917, ii, 711.

The properties and action of tethelin, the active principle of the anterior lobe of the pituitary body, have been studied. It was found that tethelin is nonantigenic and nontoxic; hence its use therapeutically is warranted. It cannot be used as the antigen in the Wassermann test, has no effect on the proteins of blood serum, does not cause a specific hyperleucocytosis, can be used as a medium for the growth of certain bacteria, is not split by trypsin or lipase, and does not stimulate contraction of the isolated cat or guinea pig uterus.—Author's Summary.

(PITUITARY) On the Possible Derivation of the Active Principle of the Posterior Lobe of the Pituitary Body from the Tethelin Produced by the Anterior Lobe. Schmidt (C. L. A.) and May (E. S.) Jour. Lab. and Clin. Med. (St. Louis) 1917, ii, 708.

The authors investigated the possibility of the production of the pharmacodynamic substance found in posterior lobe extracts from an inactive secretion of the anterior lobe. They found that treatment of tethelin with barium hydroxid gave rise to a substance having both the uterus-stimulating and the blood pressure raising property of posterior lobe extracts.

R. G. H.

(PITUITARY) Physiology of the Pituitary Gland, and the Actions of its Extracts. Cadwallar (J. C.) Lancet-Clinic (Cinc.) 1916, cxv, 33.

A brief review.—F. A. H.

(SEX) The Accessory Chromosome in the Frog Possessing Marked Hermaphroditic Tendencies. Swindle (W. W.) Biol. Bull. (Woods Hole) xxxiii, 70.

The number of chromosomes in the germ cells of the frog (*Rana pipiens*) is twenty-five in the male and twenty-six in the female. In the latter there appears at one stage a chromatin body that seems to be an accessory (sex-determining) chromosome. In an hermaphroditic frog there was an unequal distribution of chromatin to the daughter cells during the first maturation division. This may account for the presence of these individuals with hermaphroditic tendencies in this species of frog.—E. R. H.

(OVARY) The Experimental Production of Hypotypical Ovaries through Underfeeding. A Contribution to the Analysis of Sterility. Loeb (L.) Biol. Bull. (Woods Hole) xxxiii, 91.

In female guinea pigs which were underfed "hypotypical" (not properly developed) follicles were found in 69 per

cent of the cases examined (twenty-six animals) and the uterus was in the resting condition and smaller than normal. None of the follicles matured. In these typical follicles the granulosa cells degenerate early from lack of proper nourishment. The larger follicles are more readily affected than the smaller (younger) follicles.)—E. R. H.

(THYMUS) Experiments with Feeding Thymus Glands to Frog Larvae. Swindle (W. W.) Biol. Bull. (Woods Hole) xxxiii, 116.

The author fed fresh thymus and commercial powdered thymus to the larvae of *R. pipiens* and other species. One hundred and twenty-five larvae were fed fresh thymus and an equal number were fed liver. The thymus had no effect upon the growth nor upon metamorphosis of the animals as compared with liver-fed larvae. In other series, fed powdered thymus, there was no effect upon growth, but there was a slight retardation of metamorphosis, which, however, the author regards as too small to be important on account of the extent of normal variability. The gonads were not affected. The author concludes logically that thymus has no effect when fed to frog larvae. This is in keeping with the growing belief that the thymus is not concerned with general metabolism. It is possibly merely a hematopoietic organ such as it appears to be when examined microscopically, and not an endocrine structure at all.—E. R. H.

(PANCREAS) Studies in Experimental Diabetes after Pancreatectomy. Epstein (A. A.) and Baehr (G.) Jour. Biol. Chem. (Balt.) 1916, xxiv, 1.

The authors were able to produce excessive hyperglycemia in cats by totally extirpating the pancreas. The amount of blood sugar was estimated by a micro method of their own by which they were able to work with as small samples as 0.1 cc. to 0.2 cc. They noted that after pancreatectomy animals were very thirsty and drank large volumes of water. Investigation showed that this increased ingestion of fluid increased the blood volume as much as 50 per cent. Their percentages of blood sugar are corrected on the basis of the original volume. The volume increase of blood was determined by finding proportion between blood plasma and cells.

After removal of the pancreas blood sugar rose from .084 per cent to .431 per cent in twenty-six hours. It stayed constant until about the one hundredth hour, when it jumped to .603 per cent, from which time the increase was progressive; at 141 hours it was .838 per cent, and the emaciated animal became stuporous. This terminal rise occurred in three other cats. Simultaneous with progressive hyperglycemia was a

diminished glycosuria. After the eighty-fourth hour there was no sugar, and after the 108th no acetone in the urine. Albuminuria was progressive. It was thought that these conditions might have been the result of renal insufficiency, so that in six other cats—three nourished and three starved nine days—the pancreas and both kidneys were removed. Animals drank water copiously as before. In well-nourished cat blood volume increased as much as 58 per cent, while blood sugar rose from .085 per cent to 1.713 per cent, or more than twenty fold, while liver and muscle contained .42 per cent and .99 per cent glycogen respectively, as against .144 per cent and 1.7 per cent in control cat not operated upon. With the starved cats the blood volume increased as much as 65 per cent after forty-eight hours and blood sugar from .58 per cent to 1.980 per cent, or thirty-four times, while glycogen in liver and muscle was 0.0 and 0.06 respectively. Hyperglycemia developed earlier in nourished than starved cats.

The author believes that the hyperglycemia in experimental diabetes in cats mounts progressively in the terminal stages because of diminished permeability of the kidneys. This would furnish an explanation of the excessive rise in the blood sugar of diabetics prior to the development of coma. Experimental interference with glycosuria of depancreatized animals brings about a rapidly progressing hyperglycemia caused by a mobilization of carbohydrate from the liver and muscles. Detailed tables of experimental work accompany the original article.—J. R. M.

(PARATHYROID) Some Observations on the Tetany of Parathyroidectomized Dogs. Greenwald (I.) *Jour. Biol. Chem.* (Balt.) 1916, xxv, 223.

Greenwald has endeavored to determine the cause of the parathyroid tetany in dogs. In a previous paper he reported that there was a marked retention of phosphorus after parathyroidectomy, and that this retention was followed or accompanied, but never preceded by, a retention of sodium and potassium. Experimental work shows the impossibility of phosphorus retention as O-phosphate acting as the cause of tetany. Attempts were made to show a probability of inosinic acid as the cause of tetany. This is one of the simplest nucleic acids; upon hydrolysis it yields, beside phosphoric acid, a pentose, d-ribose and hypoxanthine. The latter produces convulsions in frogs. Intravenous injections of xanthine causes tetany in dogs similar to parathyroid tetany.

A solution of sodium inosinate prepared from the barium salt was injected intravenously into a dog from which the thyroids and parathyroids had been removed five hours previ-

ously. Results were negative. Determinations made after injection and after tetany appeared showed that amount of acid-soluble phosphorus in serum was less than in the first instance. The hypothesis that inosinic acid is the toxic agent in the tetany of parathyroidectomized dogs must be abandoned.—J. R. M.

(ADRENAL) The Effect of Certain Procedures upon the Course of Fatigue in Frog's Muscle. Crider (J. O.) and Robinson (W. W.) *Am. Jour. Physiol. (Balt.)* 1916, xli, 376.

This article is not primarily of endocrine interest. The author finds that the ligation of one leg of the frog and the excision of the gastrocnemius of that leg increases the working power of the other leg when the latter is excised after a wait of thirty minutes between the two excisions. He suggests that the ligation of one leg may bring about an increase in the working power of the other leg by reflexly causing an increase in blood pressure and thus improving the circulation of the non-ligated leg during the thirty minutes' wait. He suggests that this may also be due in part to secretion of adrenin following the operative proceedings. He gives five pages of tables showing his experimental work.—J. R. M.

(ADRENAL) Le rôle des surrénales dans l'hypertension artérielle consécutive aux embolies cérébrales. (The Part played by the Adrenals in Arterial Hypertension following Cerebral Embolism.) Roger (H.) *C. R. Soc. de Biol. (Paris)* 1917, lxxx, 427.

Cerebral embolism was produced in the rabbit by injection of lycopodium into the carotid artery. This is followed by an initial fall in blood pressure, then a marked rise in blood pressure which persists. If the adrenals have been removed the blood pressure soon returns to normal. The author concludes that the first rise in blood pressure is due to nervous excitation resulting from the embolism, while the permanent hypertension is due to the secondary action of the adrenals.—F. A. H.

(ADRENIN) Lé sécrétion surrénale d'adrénaline ne tient pas sous sa dépendance l'effet vaso-constricteur du sang asphyxique. (The Vasoconstrictor Effect of Asphyxiated Blood Does Not Depend upon the Secretion of Adrenalin from the Adrenals.) Gley (E.) and Quinquaud (Alf.) *C. R. Soc. de Biol. (Paris)* 1917, lxxx, 15.

The authors found that suppression of the adrenal secretion did not diminish the vasoconstrictor effect due to asphyxia.—F. A. H.

(THYROID) The Influence of Partial Thyroidectomy in Pigs.

Palmer (C. C.) *Am. Jour. Physiol.* (Balt.) 1917, xliii, 572.

Palmer reports the results of thyroidectomy on six young pigs from the same litter with the view of establishing the probability of inducing cretinism. The main thyroid was excised from three and three were controls.

He gives a very complete exposition of the anatomy of the thyroid in the pig, pointing out the position, size, etc., of the thyroids and parathyroids at varying ages, both before and after birth. After excising the main thyroid at the ages eight, twelve and fifteen days respectively no differences were noted between operated and control pigs until they were two months old. Then a much lowered resistance was apparent in those operated upon. This was made evident by susceptibility to parasitism, by slowness of injuries to heal and by skin lesions on the abdomens of two. These troubles continued till the autumn, when the pigs were about six months old, at which time, with the advent of cold weather, all became very much improved; the improvement was especially notable in the case of the operated pigs. These did not gain in weight as rapidly as the controls, but became more healthy looking. Body temperature taken at frequent intervals showed no variation from normal. At forty weeks (maturity) the average weight of the operated pigs was thirty pounds under controls. Sexually all males were active. Two sows (operated and check) were bred to an operated boar; both conceived; post mortem shortly before parturition time showed in the normal sow one fully formed fetus and in the operated sow one mummified fetus. When about ten months old three thyroidectomized and one check developed pneumonia and pleurisy and all died inside of two weeks. Post mortems showed extensive tissue changes in operated pigs which died from pneumonia, but only slight lung lesions in the check.

The author believes that extirpation of the main thyroid does not induce cretinism within a year. Growth is retarded and resistance is lowered, but otherwise the operated pigs are apparently normal. A post mortem examination shows marked hypertrophy of accessory thyroid tissue, but the accessory thyroid cannot completely compensate. In pigs the degree of hypothyroidism which occurs is insufficient markedly to change the physical appearance, but it lowers resistance to infection and impairs the function of reproduction.—J. R. M.

(THYROID) Recherches expérimentales sur l' "hyperthyreosis" et l' "athyreosis" et sur quelques actions de l'adrénaline.

(Experimental Researches on Hyperthyreosis and Athyreosis and Some Effects of Adrenalin.) Albertoni (P.) *Arch. Ital. de Biol.* (Pisa) 1916, lxx, 63.

The excitability of the cardiac vagus in the dog and rabbit was diminished after prolonged administration of large doses of thyroid, such as are necessary to produce hyperthyroidism.

The author describes the symptoms produced by prolonged thyroid feeding.

There was a large increase in the amount of water in the blood, liver and kidney, while that in the muscles decreased. The liver contained very little glycogen, but showed an increase in nitrogen. The brain had not changed in water or nitrogen content.

After extirpation of the thyroid in a dog, substances with hypotensive action accumulated in the blood.

The experiments of Sutherland Simpson on sheep were confirmed. No ill effects resulted from removal of the parathyroid and thyroid in the adult sheep or goat.

Albertoni produced hemorrhage in the brain of a dog by the injection of two doses of adrenalin 1:1000, one cubic centimeter in each dose. As a result, paraplegia developed.

F. A. H.

(PITUITARY) Concerning the Action of Various Pituitary Extracts upon the Isolated Intestinal Loop. Shamoff (V. N.) *Am. Jour. Physiol.* (Balt.) 1916, xxxix, 268.

From experiments described it is concluded "that certain posterior lobe preparations are capable of producing relaxation of the isolated intestinal loop and of inhibiting its rhythmic contractions, resembling in this respect the extracts of the adrenal medulla."

"In view of the foregoing observations, it may be stated that there exists in the posterior lobe of the pituitary body some substance which has an action on the isolated intestinal loop resembling the action of adrenalin, a substance moreover which may be other than that which raises blood pressure and causes diuresis. The substance is not constant in the extractives prepared in the usual ways, and may indeed be inconstant in the fresh glands from which these substances are prepared."

—T. C. B.

(PITUITARY) On the Secretory Discharge of the Pituitary Body Produced by Stimulation of the Superior Cervical Sympathetic Ganglion. Shamoff (V. N.) *Am. Jour. Physiol.* (Balt.) 1916, xxxix, 279.

A continuation of the work of Weed, Cushing and Jacobson, and deals with the effect on the urinary secretion, of stimulation of the cervical sympathetic ganglion.

As a rule, stimulation of the superior cervical ganglion results in a decided diuresis, resembling that which follows an intravenous injection of posterior lobe extract. The increased

flow of urine is independent of the elevation of blood pressure, for it often takes place at the moment of the lowest depressor phase. Glycosuria was also observed. All nervous influences to the kidney were excluded by section of the vago-sympathetics and section of the spinal cord at the fourth thoracic segment. The conclusion is that stimulation of the ganglion causes a secretion from the pituitary.—T. C. B.

(ADRENIN) The Relation of the Rate of the Spontaneous Liberation of Epinephrin to the Rate of Blood Flow through the Adrenals. Stewart (G. N.) and Rogoff (J. M.) *Am. Jour. Physiol. (Balt.)* 1917, xliv, 149.

In previous papers the authors have shown that in the cat the output from the adrenals is fairly constant over a wide range in the rate of blood flow, the concentration in the adrenal vein blood varying inversely as the flow. The present paper deals especially with the question whether with such quantitative methods as have been employed (rabbit's intestine and uterine segments) an exact inverse ratio between epinephrin concentration and adrenal blood flow can be made out.

The paper is largely taken up with protocols and their discussion, and the conclusion is reached that within the limits of error of the method used the concentration of epinephrin in blood from a "cava pocket" varies inversely as the blood flow through the glands, the rate of output of epinephrin being constant. The rule fails when the rate of blood flow falls below the value at which the concentration of epinephrin has reached the possible maximum.—T. C. B.

ADRENIN, Effects on Distribution of the Blood. VI. Venous Discharge from the Thyroid Glands. Gunning (R. E. L.) *Am. Jour. Physiol. (Balt.)* 1917, xliv, 215.

Adrenin in all doses causes vasoconstriction in the thyroid. There is a slight tendency to over recovery, due probably to vascular fatigue.

The apparent paradox that increased secretory activity is accompanied by vasoconstriction is explained by supposing that the gland stores its active substance, and discharges it periodically in response to emergencies. If this be the case, no anabolic activities are necessary at the time of discharge and hence there is no need for immediate functional hyperemia.—T. C. B.

ADRENIN, Action of, on the Blood. Menten (M. L.) *Am. Jour. Physiol. (Balt.)* 1917, xliv, 176.

Spectroscopic examination of the blood from the adrenal vein shows the absorption bands of oxyhemoglobin nearly as well marked as in blood from the carotid artery, indicating that adrenin causes increased formation of oxyhemoglobin. The

same is true when adrenin is added to venous blood drawn from other parts of the body. Attention is called to the fact that the increase in oxyhemoglobin is greater in blood drawn without anesthesia than in blood drawn under the influence of ether or chloroform, and that this should be taken as a factor in interpreting experiments on the action of adrenin *in vivo*.

The bright color of oxyhemoglobin is gradually replaced by a darker color of some other hemoglobin compound when adrenal blood is kept a few hours with a minimum of oxygen. This substance gives the spectrum of urobilin. Microscopically the erythrocytes are seen to be disintegrated. Here, too, ether has a retarding influence.

It has been shown that increase of OH ions is a factor in augmenting the formation of oxyhemoglobin, and Menten and Crile have reported that adding adrenin to serum or venous blood increases the OH concentration. Menten points out that this may explain in part at least the tonic influence of adrenin on the heart. Haldane's observation that the oxygen tension in the lung capillaries is greater than in the alveoli may also be explained by the fact that the affinity for oxygen is increased by adrenin. The observations of Cannon that in asphyxia and emotional disturbances where there is urgent need for oxygen there is an increase in the secretion of adrenin, also supports this view.—T. C. B.

(GONADS) On the Internal Secretion of the Sexual Glands.

Lipschütz (Alex.) *Jour. Physiol.* (Lond.), 1917, li, 283

Steinach has shown that the internal secretions from the gonads act in a sex-specific manner. The male gonads cause development of the male sex characters only, inhibiting the development of the female characters, and vice versa. The author had the opportunity of examining some of Steinach's animals, operated on a few years ago.

In addition to the signs of a "successful masculation" of a female guinea-pig, there is a growth of skin at the urethric tubercle resembling a male preputium, and when this is drawn back there are two excrescences that are evidently the corp. cav. clitoridis which have changed into corp. cav. penis. The developed organ gives the impression of a hypospadiac penis. Two spikes have developed, similar to the "horny spikes" in the normal male.

The average temperature of normal female guinea-pigs is higher than that of the male by nearly a degree. It is found that "feminized males" have a temperature approaching that of normal females.

Judging by the references this paper is based on reports published in the *Anz.d.Akad.d.Wiss. in Wien*, 1916 and 1917.—T. C. B.

(ADRENIN) The Mechanism for Vasodilatation from Adrenalin. Hartman (F. A.) and Fraser (L. McP.) *Am. Jour. Physiol.* (Balt.) 1917, xliv, 353.

In attempting to explain the action of adrenalin in dilating the intestine, the authors found that if the splanchnics were cut constriction replaced dilatation; this led to the study of the part played by the central nervous system in adrenalin vasodilatation.

Volume changes in the small intestine were studied after all connection with the nervous system were severed, the dilating dose of adrenalin having been previously determined. Three dogs and four cats were studied, and in every case but one dilatation was replaced by constriction when the splanchnics were cut, and the coeliac and superior mesenteric ganglia were removed.

Simultaneous plethysmographic records were made of the two hind limbs, one of which was denervated by cutting the femoral and sciatic nerves as high as possible. Small doses of adrenalin usually gave dilatation of the normal limb and constriction of the denervated limb. Large doses, such as those which usually produce a rise in blood pressure, caused constriction in both limbs.

Perfusion experiments were also tried. The circulation was cut off in the part to be studied (limb or intestinal loop), and oxygenated Ringer was perfused. Under these conditions injection of adrenalin into the general circulation resulted in dilatation of the intestine, and an increase in the volume of the hind limb, indicating vasodilatation.

The failures that occurred were in animals that were not normal. Disease, emaciation, intoxication with alcohol and anocain, asphyxia may cause inhibition of the vasodilator mechanism. It also seems that afferent impulses due to cooling or cutting the muscles of a limb, may impair or inhibit the adrenalin dilator reaction.—T. C. B.

CLINICAL STUDY

(THYROID) Early Diagnosis of a Case of Myxedeme Fruste.

Wechsler (I. S.) J. A. M. A. (Chgo.) 1916, lxvi, 1549.

Wechsler mentions briefly the incomplete form of myxedema described by Hertoghe and reports a case in a woman of twenty-one, who complained nine months after parturition of diffuse headaches, sense of tiredness, profuse menstruation, sparse hair in outer one-third of eyebrows, dry skin and falling hair. She was instructed to wean the child and to take one grain of thyroid extract t. i. d. Treatment was continued for two months, and four months later none of the symptoms mentioned were in evidence.—F. C. P.

(PANCREAS) Endocrinopathic Inheritance. Stein (I. F.) J. A. M. A. (Chgo.) 1916, lxvi, 1811.

A brief report, with heredity chart, of a diabetic family, in which one member of the first generation suffered with diabetes; in the second generation there were seven members of the family, and three had diabetes; one woman (normal) in this second generation married a man with a simple goiter; in the third generation all members (eleven) are reported as normal; one member of the fourth generation (twelve members) was moderately obese. Stein states that this family does not bear out the conclusions of Timme (J. A. M. A. 1916, lxvi, 1438) that the inheritance of endocrine defects follows Mendelian laws.—F. C. P.

(PITUITARY) A Case Bearing on the Function of the Pituitary Body. Boyd (W.) J. A. M. A. (Chgo.) 1917, lxviii, 111.

After briefly reviewing the anatomy and physiology of the pituitary gland and quoting points from Cushing and Goetsch bearing on his case, Boyd reports a case of glioma of the floor of the third ventricle involving the left optic nerve and the infundibular stalk.

A boy of ten and one-half years complained of headache and vomiting and an inability to see more than one-half of the clock. Eye examination revealed nothing. Seven months later the examination of the eyes showed right eye 20-70 vision; left eye only feeble light perception; exophthalmos; dilated, sluggishly reacting pupils; no visual field on the left side; right temporal hemianopsia with reversal of the color fields and hazy injected disks with dilated and tortuous retinal vessels. A roentgenogram showed slight enlargement of the sella, with thinning of the bony walls. Sugar tolerance was greatly increased. There was no thermal response to injections of anterior lobe of the hypophysis. Operation via the transsphenoidal

route revealed a soft translucent struma extruding from the floor of the sella. As much of the tumor was removed as seemed advisable. On November 21 the patient became semi-comatose and developed convulsions. Death occurred on the third day. At autopsy, the pituitary body appeared normal. In the interpeduncular space apparently growing from the floor of the third ventricle, surrounding the left second nerve and the infundibular stalk, there was a soft, grayish mass. Microscopically, the tumor proved to be a glioma.

The author believes this case to be additional proof that the secretions of the posterior lobe of the pituitary pass to the third ventricle via the infundibulum.—F. C. P.

(CAROTID BODY) A Case of Tumor of the Carotid Body.

Cahill (G. F.) and Taylor (R. M.) J. A. M. A. (Chgo.) (lxviii, 1898).

A Russian Jewess, age fifty-one, with a tumor on the right side of the neck. Tumor mass present eight years, but small until one year ago, when it began to grow slowly. It caused no symptoms. Tumor felt lobulated and was not movable. At operation a lobulated, reddish, roughly rounded mass, 4 cm. in diameter, was found very firmly attached to the deep structures of the neck. It was located between the external and internal carotids, extended down into the bifurcation and surrounded the internal jugular vein. The microscopical examination showed the characteristic picture of the carotid body.—F. C. P.

(THYROID) Tonsillar Endamebiasis and Thyroid Disturbances. Evans (J. S.), Middleton (W. S.) and Smith (A. J.) Am. Jour. Med. Sci. (Phila.) 1916, cli, 210.

Tonsillar lesions of an infective cryptic character were found in 22.8 per cent, and nasal together with tonsillar lesions existed in 90 per cent of 362 goiterous individuals examined from this standpoint. In typically diseased tonsils, out of thirty-four cases examined microscopically 97 per cent were found to harbor *endameba gingivalis* (Gros) in the tonsillar crypts. Of sixteen individuals of this group who after treatment by means of emetin hydrochloride were re-examined, thirteen, or 81 per cent, were shown no longer to have *endamebae* in the cryptal contents. In twenty-three individuals to whom emetin was administered a reduction in the bulk of the goiter was appreciable in eighteen individuals, and in seven dysthyroid cases included in this group of treated cases six were benefited in degrees varying from slight amelioration to apparent cure. Inability to demonstrate *endamebae* in the thyroid gland renders improbable any direct causal relation of the amebic infestation of the tonsils per se to the develop-

ment of thyroid disturbances. However, the improvement, morphologically and symptomatically, in the treated cases leaves little doubt, after ruling out a vasomotor influence from the emetin employed, as to an indirect relationship. A symbiosis of endamebae with appropriate bacteria, leading to the elaboration and absorption into the thyrioid of selective thyrotoxic poisons, is at least conceivable in explanation of such relation. In no sense do the writers care to be understood as advancing other locations of infections capable of producing thyrotoxic toxins, perhaps, too, toxic substances having similar influence but derived from metabolic or alimentary fault, or even entering the body from without, are all of possible influence; nor is the influence of sympathetic stimulation, however accomplished, to be overlooked.

The writers are unable to reach any satisfactory explanation of the known occurrence of belts of endemic goiter along certain well defined glacier drifts.

(It should be noted that Nowlin (*Jour. Parasit.* July, 1917) was unable to find amebae in the tonsils in one or more cases of seven pyorrhoea with amebiasis.)—G. H. H.

(THYROID) Studies of the Basal Metabolism in Disease and their Importance in Clinical Medicine. Means (J. H.) Bost. *Med. and Surg. Jour.*, 1916, clxxiv, 863.

The author concludes that basal metabolism can be readily studied in a hospital clinic with comparatively inexpensive apparatus. The normal basal metabolism is fairly constant, and hence wide variations from it in disease are of interest to the clinician. A marked rise occurs in hyperthyroidism and a marked fall in hypothyroidism. In regard to hyperthyroidism it seems probable that the basal metabolism furnishes: (a) The best index as to the severity of the disease, and hence is a quantitative means of following the course and of judging of the effectiveness of treatment, and (b) a valuable aid in differential diagnosis. Enormous grades of obesity are possible in the presence of a normal basal metabolism. When a reduction in the metabolism was found in obese subjects there was also clinical evidence of a defective internal secretion. A clearer conception of the food requirements in disease is furnished by the basal metabolism than by any other factor.—G. H. H.

(PITUITARY) Acromegaly with Extreme Degree of Exophthalmos. Weidler (W. B.) Bost. *Med. and Surg. Jour.*, 1916, clxxiv, 506.

Weidler presents the symptoms and findings in a progressive case wherein the X-ray shows enlargement of the base of the sella and of the posterior clinoid processes. He summarizes his findings thus:

1. Gradual onset and progress of the cephalic changes, but more especially of the brows, ears, nose and lower jaw, the protruding abdomen, sloping shoulders, trouble with the feet and hands.

2. Gradual decrease of sexual desire and sexual power, and loss of physical strength.

3. Exophthalmos and changes noted in the field of vision make one think that this is a case of acromegaly without any of the well-marked symptoms, which will undoubtedly be present in a later stage of this patient's disease.—G. H. H.

(OVARY) Progress in the Study of Ovarian Transplantation and Ovarian Secretion. Martin (F. H.) Surg. Gyn. & Obs. (Chgo.) 1917, xxv, 336.

The review of the literature for the past two years serves to confirm the conclusions arrived at two years ago, namely, that so far the only form of ovarian transplantation that is practicable is autotransplantation, and that this has a rather limited field of usefulness in the retardation and modification of the symptoms of the artificial menopause brought about by complete removal of the ovaries. In spite of the perhaps overenthusiastic conclusions of a few workers, neither homo- nor heterotransplantation has as yet justified its use in human surgery. The great problem yet remaining to be solved in ovarian transplantation is to find some means of overcoming the resistance of the body to homografts, for this is the only means of opening up a wide field of usefulness for the operation. The way to a solution of the problem lies through a closer study of the internal secretion, not only of the ovary itself, but of the other glands of internal secretion, all of which seem to be so closely interrelated that absolute separation of their functions seems impossible. Some hopeful work has been done in endeavoring to find substances which will inhibit the resistance of the host to the graft, but for the most part the work still remains to be done, and the surgeon in adopting ovarian grafting, instead of solving a problem, has rather opened up a greater one which awaits solution by the serologist and endocrinologist.—Author's Summary.

OVARY, Its Relation to the Uterus and Mammary Gland from the Experimental Aspect. Loeb (L.) Surg. Gyn. & Obs. (Chgo.) 1917, xxv, 300.

The ovary is a complex gland of which the most important constituents are follicles in various stages of growth and atresia, and corpora lutea. In addition, we find in some species interstitial gland and sometimes embryonic structures developing parthenogenetically from eggs. Cyclical changes occur both in the ovary and secondarily in the uterus and mammary

gland. The primary cyclical changes in the ovary are in sequence: follicle ripening, ovulation, corpus luteum formation. In some species ovulation is accompanied by degeneration of all but the smallest follicles.

An elaborate self-regulating mechanism controls ovulation. Normally the corpus luteum inhibits ovulation. During pregnancy the life of the corpus luteum is prolonged. Experimentally ovulation can be influenced at will, accelerated by excising all corpora lutea, or retarded by producing artificial deciduomata. The retarding action of the corpus luteum is chemical, not mechanical.

The corpus luteum has a sensitizing action upon the uterus. This action can be analyzed by experimental methods. If the uterus is incised or mechanically stimulated at the time during which the corpus luteum is elaborating this growth substance, maternal placenta (deciduoma) is formed. The mechanical stimuli, therefore, assume in this respect the function which the ovum exerts under normal conditions. The form of growth response of each species is characteristic. The localization of sensitization varies in different species, being limited to the uterus in rabbits and guinea pigs, but distributed more widely in the human female. No specificity exists in the sensitizing substance given off by the corpus luteum as far as different individuals of the same species are concerned. The life period of experimental deciduomata is short except in pregnancy, during which their persistence is prolonged. Corresponding to and dependent upon the cyclical ovarian changes, uterine cyclical changes occur. The cycle consists of heat, regression and interval. Heat probably is due to maturation of the follicles and dependent upon the absence of the corpora lutea; growth activity is the result of corpus luteum secretion; regression marks the cessation of corpus luteum secretion, which is followed in the interval by a condition of rest. Pregnancy causing a persistence of the corpus luteum is characterized by an accentuation but not a prolongation of the active phase, and an inhibition of the uterine cyclical changes throughout gestation.

While it is possible to produce experimentally during pregnancy a new ovarian cycle, through incision of the corpora lutea, such a new ovarian cycle is not followed by a new uterine cycle. During pregnancy a mechanism is at work preventing the uterine mucosa from responding to the stimuli given off by various ovarian structures. It follows that the corpus luteum subserves at least two functions, inhibiting ovulation and producing a substance which causes growth in the uterus.

The ovary shows other non-cyclical functions. It has a trophic influence on the genitals and either primarily or sec-

ondarily determines the development of the secondary sexual characters. The ovary likewise controls the development of the mammary gland. It exerts a trophic influence on this organ and determines its normal cycle. During heat and subsequent to ovulation proliferative changes occur; these cease while the corpus luteum develops and functionates. The incidence of breast cancer in mice is greatly reduced by castration.—Author's Summary.

ADRENALS, The Experimental and Clinical Evidence as to their Influence Exerted upon the Genital System. Vincent (S.) Surg. Gyn. & Obs. (Chgo.) 1917, xxv, 294.

What we call the adrenal body represents the anatomical association of two elements, each of which is derived from a separate and independent system. The adrenal proper, or "cortex," is part of the "cortical" or "interrenal" system. The medulla is simply an accumulation of chromaphil cells of the same nature histologically, chemically and pharmacodynamically, as similar masses of cells in other parts of the body. There is no clear evidence that these two systems are functionally related. The adrenal medulla (as well as the chromaphil tissue generally) is developed from the sympathetic nervous system. Its duty seems to be to facilitate the functions of this system in certain physiological emergencies. The adrenal cortex (as well as the "accessory cortical adrenals") is developed from the germ epithelium, and the evidence is now strongly in favor of the view that it has certain important functions in connection with the development and growth of the sex organs. There is a considerable amount of clinical evidence that tumors of the adrenal cortex are frequently associated with sex abnormalities. The clinical evidence also favors the view that when cortical tumors occur in the female an accentuation of male secondary sexual characteristics develops, and simultaneously a hypoplastic condition of the internal generative organs supervenes. Additional evidences as to a connection between adrenal cortex and the sexual organs is furnished by the enlargement of the cortex during breeding and pregnancy. Feeding young animals with adrenal gland substance seems to stimulate the growth of the testes. It is possible that a final solution of the problem will only be arrived at when the more general problem of the relationship between the ductless glands shall have been solved.—Author's Summary.

PANCREAS, Its Endocrine Function and Its Relation to the Sex Life of Women. Carlson (A. J.) Surg. & Gyn. Obs. (Chgo.) 1917, xxv, 283.

All evidence supports the view that some substance or hormone secreted by the islands of Langerhans into the blood is necessary for utilization of sugar by the tissues. This function is specific for the pancreas. Other endocrine organs may influence sugar metabolism in a superficial way by altering the sugar mobilization (adrenals, thyroid) or by increasing or decreasing the rate of oxidation in the body in general. The rest of the endocrine glands can not maintain the power of the tissues to oxidize sugar in the absence of the pancreas, and the hypo- or hyperactivity of other endocrine glands do not produce actual diabetes in the presence of normal pancreas. While the failure of the tissues to use sugar in the absence of the pancreas is the central and definite established fact, there are probably other primary defects involved in the development of acidosis, lipemia, increased metabolism, lowered resistance to infections, etc. All the evidence points to the view that true diabetes mellitus in man is primarily the result of pancreatic deficiency (islets). There is, at present, no organotherapy of diabetes, experimental or clinical.

There is, at present, no evidence of any specific relations of the endocrine functions of the pancreas to the gonads, male or female, or to menstruation, pregnancy and lactation. Absolute diabetes, induced after conception, leads to death of the fetus. Absolute diabetes probably renders conception impossible. Partial diabetes under careful dietary control permits of normal sex life of women (menstruation, normal pregnancy, normal child, lactation) and pregnancy under such conditions does not aggravate the diabetes. But in the absence of such dietary control the condition of pregnancy aggravates the diabetes in the mother, and uncontrolled diabetes in the mother is extremely injurious to the fetus. There is some evidence that in late stages of pregnancy the fetal pancreas may function for the mother.—Author's Summary.

(THYROID) Some Phases of the Differential Diagnosis of Exophthalmic Goiter. Plummer (W. A.) St. Paul Med. Jour. 1916, xviii, 297.

Although the article contains nothing strikingly new, it formulates and emphasizes some of the differential points between exophthalmic goiter and neurasthenia. Plummer considers the first salient and important symptoms to be increased appetite. This is constant and is in contrast to the poor and capricious appetite of the neurasthenic.

The fluctuation of symptoms in Graves' disease is typical. It is marked by a periodicity, measured in weeks and months while the symptoms of the neurasthenic vary from hour to hour and from day to day. The general demeanor of the ex-

ophthalmic goiter patient; the short, quick, nervous step; the bright, animated and at times prominent eyeball; the alertness and the intense restlessness, are in marked contrast to the languid, emotionless, complaining and introspective character of the neurotic.

The vasomotor disturbances are characterized by hyperhidrosis and warm hands, while in the neurasthenic they are hot flashes, cold sweats and cold hands. Bruits and thrills are present in 80 per cent of cases of Graves' disease. They are most intense over the superior thyroid vessels, whereas in non-hyperplastic goiters they are transmitted from the carotid and become more distinct as the clavicle is reached.—F. B. L.

(THYROID) Report of a Case of Adenocarcinoma of Thyroid. Campiche (P. S.) Cal. State Med. Jour. (San Francisco) 1916, xiv, 146.

The case report is one of metastatic adenocarcinoma of the thyroid with a comment on the relative benignity of this type. The author compares it with myeloid sarcoma. Hence this is the only instance in which a radical operation on metastatic foci might be attempted with the hope of cure. These so called "metastatic colloid struma" (Kocher) produce colloid substances, and even though a radical thyroidectomy be performed cachexia strumipriva never arises when they are present.—F. B. L.

(THYROID) The Inconspicuous Everyday Forms of Thyroid Insufficiency. Harrower (H. R.) Calif. State Med. Jour. (San Francisco) 1916, xiv, 184.

While perhaps the long list of symptoms attributed to thyroid insufficiency might lead one to believe the thyroid is the cause of most of the vague complaints of patients, nevertheless Harrower's paper impresses the reader with the necessity of being watchful for signs of thyroid deficiency when the patient's ailments are seemingly those of neurasthenia. Among the symptoms and signs that he traces to thyroid insufficiency are nocturnal enuresis, headache, cold feet and hands, chilblains, psoriasis, prurigo, eczema, herpes, rheumatism, nasal and bronchial catarrh, rough skin, defective speech, enlarged tonsils and adenoids. "The most important single remedy in the asylum," he quotes from an alienist, "is thyroid extract." Many of those persons who "catch everything" are found to be in a low state of metabolic activity, the result of diminished thyroid secretion.

He advises the French method of administration. They give small doses of 0.01 gm. per day in three doses, given in alternate weeks. Pluriglandular therapy is recommended in obesity. Corpus luteum should be added at the climacteric.

Pituitary gland (whole) should be given with thyroid in children.—F. B. L.

(THYMUS) Enlargement of the Thymus Treated by the Roentgen Ray. Friedlander (A.) *Am. Jour. Dis. Child.*, 1917, xiv, 41.

The author emphasizes the more frequent occurrence of enlarged thymus than is commonly realized and refers to Benjamin of Cincinnati, who found that out of 225 new cases in one year in his children's out-patient clinic, 19, or 8.4 per cent showed indisputable evidence of enlarged thymus. Quite a number of the cases occurred in babies suffering from congenital syphilis, but the author draws no conclusion from this observation.

Familial tendency has been noted, for in his recent cases four families had more than one child affected.

He calls attention to three definite symptoms of enlarged thymus, namely, dyspnea, continuous or remittent; suffocative attacks with cyanosis and stridor. The diagnostic physical signs are a detectable bulging mass in jugulum (more often absent than present) and enlargement of the area of normal thymus dullness or percussion. Definite information is afforded by the X-ray. Marked enlargement of the normal shadow, which is continuous with the heart shadow, is characteristic.

Out of 100 cases treated by the X-ray method there were four deaths as compared with seventeen deaths out of fifty cases treated by thymectomy (Parker).

The author uses Lange's technic, which he describes in detail.—M. B. G.

THYROID GLAND in Relation to Gynecology and Obstetrics. Marine (D.) *Surg. Gyn. & Obs. (Chgo.)* 1917, xxv, 272.

There is evidence in man of a thyroid sex gland interrelation recognizable in the female in association with the development of secondary sexual characters, with menstruation and pregnancy, and also in the male at puberty, but to a very slight degree. The meager evidence available would tend to indicate that the interstitial cells of the ovary, and perhaps also the adrenal cortex, play a major role in this relation in the female, as certainly the cells of Leydig do in the male.

The thyroid enlargement is of the nature of a work hypertrophy to stimulate metabolism identical in appearance so far as we know, different only in degree from that seen in simple goiter. Both of these reactions can be controlled and prevented either indirectly by giving iodine or directly by giving the iodine-containing hormone in physiological doses.—Author's Summary.

PINEAL GLAND, its Influence upon Growth and Differentiation with Particular Reference to Its Influence upon Prenatal Development. McCord (C. P.) Surg. Gyn. & Obs. (Chgo.) 1917, xxv, 250.

From the lack of unanimity in the literature any conclusions as to the details of pineal gland function must be made flexible rather than dogmatic. A survey of the available data leads to the following summary of internal secretion.

1. A clinical syndrome is to be associated with the disturbances of the function of the pineal gland. Because of the involution of the pineal at puberty, the constitutional manifestations of pineal pathology appear to be confined to pre-pubertal years. The essential characteristics, apart from pressure and neighborhood manifestations) are (a) early sexual development evidenced in the enlarged genitalia, pubic hair, general body hair, early change in voice; (b) precocious mental development, manifested in maturity of thought and speech; (c) general overgrowth of body to the extent that a child of six or seven years may have the appearance of a child near puberty.

2. The experimental extirpation of the pineal gland is surgically possible. The gland is not essential for the maintenance of life. The early symptoms of pinealectomy are attributable to severe brain injury. No changes attend the removal of the gland in adult animals. As to the effect of pinealectomy in young animals, Sarteschi, Foa and Horrax respectively state that the removal of the gland leads to precocity of development. Exner and Boese and Dandy report no changes after pinealectomy.

3. The administration of pineal substance to young animals is reported to hasten growth and sexual maturity. In unicellular organisms (paramoecia) pineal extracts increase the rate of reproduction to more than double that of controls. In larval forms (ranidae) both growth and differentiation are hastened as a result of pineal feeding.

4. The inference is allowable that the pineal gland is an organ of internal secretion whose functions, however, are of minor significance in the general activity of the endocrinous system.—Author's Summary.

PARATHYROID SYSTEM, its Relation to the Female Genital Apparatus. Pool (E. II.) Surg. Gyn. & Obs. (Chgo.) 1917, xxv, 260.

No direct relationship has been established between the parathyroids and the female sex organs; no morphological changes in the parathyroids have been noted during pregnancy; yet apparently there is a connection between the parathy-

roids and the sex processes in the female. Tetany, the clinical evidence of insufficient parathyroid function, is somewhat prone to occur in menstruation, pregnant and puerperal women, as well as patients suffering from gynecological diseases or who have undergone gynecological operations. The cause of maternal tetany is now referred to parathyroid insufficiency. The function of the parathyroids is apparently closely connected with calcium. There is no reason to believe that maternal tetany and lactation tetany are associated with calcium deficiency. Latent tetany, or a sub-tetanic condition, is much more common in pregnant and puerperal women than is usually assumed. Tetany in new-born infants, the offspring of tetanic mothers, is usually fatal within a short time after birth. In the treatment of maternal tetany the administration of calcium in large doses is followed by beneficial results in the great majority of cases.—Author's Summary.

(PITUITARY) The Relation of the Pituitary Gland to the Female Generative Organs; from the Experimental and Clinical Aspects. Goetsch (E.) *Surg. Gyn. & Obs.* (Chgo.) 1917, xxv, 229.

Perhaps between no two of the ductless glands is a closer interrelationship in function demonstrable than between the pituitary and the sex glands. There is abundant evidence available at the present time for believing that such a close association in function exists. We know from experiments in which the pituitary gland has been partially removed in dogs that a deficiency in pituitary secretion thus produced is followed by underdevelopment, genital inactivity and hypoplasia in young animals, and by impotence and sterility and retrogressive changes in the sex glands, together with adiposity in case the animals were adult at the time of operation. Conversely after primary alterations in the sex glands, as is seen in pregnancy or after castration, there is a consequent hyperplasia and hypertrophy of the pituitary gland. Overstimulation of young animals with the extract of pituitary anterior lobe is followed by overdevelopment and marked increased activity of the sex glands. Even histological evidences of such increased function are apparent, such as premature sex development evidenced by early and abundant ovulation in the female. It is the secretion of the anterior lobe of the pituitary which is responsible for these sex changes, whereas the posterior lobe secretion has an important function in regulating, certainly in part, carbohydrate metabolism, absence of this secretion being followed by a tendency to adiposity.

Clinical hyperpituitarism is well exemplified in the diseases, gigantism and acromegaly, now generally believed to be due to an overfunction of the anterior lobe of the pituitary

gland consequent upon adenomatous hyperplasia. In the early stages of these diseases we find an exaggerated sexual activity and libido, and in the late stages corresponding with pituitary involution and inactivity, a disappearance of the sexual function. The sex glands in this late stage show, histologically, atrophy and various forms of degeneration. Similarly inactivity and atrophy of the sex glands is seen in clinical cases of primary hypopituitarism, dependent upon pituitary underfunction following upon diseases of this gland or of its neighborhood compromising its function.

Pituitary extracts have gained wide usage in therapy. Thus "pituitrin" or "pituitary liquid," derived from the posterior lobe (together with pars intermedia) because of its stimulating action upon the smooth musculature of the uterus and bowel, is used very extensively and satisfactorily in obstetric practice and for the relief of abdominal distention and intestinal paresis following surgical operations in the abdomen or pelvis.

As a result of the facts learned from the experimental feeding of pituitary extracts, particularly of the anterior lobe, we should feel encouraged in our efforts to benefit clinical states dependent upon underfunction of this gland in the human. Thus, for example, a number of clinical cases showing among other symptoms, characteristic sexual disturbances (irregular menstruation, amenorrhea, sterility), dependent upon primary pituitary disease, have been so greatly benefited that there have been a return of menstruation and libido even when these had been absent for a considerable time.

It is probable that many clinical conditions showing genital aplasia, adiposity and underdevelopment and dependent upon changes in one or more of the ductless glands other than the pituitary, would be benefited by the feeding of pituitary extract in addition to the extract of the gland which is primarily involved. On the other hand, the feeding of extracts, such as thyroid and adrenal, combined with pituitary in clinical cases of pituitary diseases in which symptoms referable to these glands are present is advisable.—Author's Summary.

(THYROID) A Typical Case of Basedow's Disease. Tonsillitis as an Etiologic Factor. Hammill (R. C.) Med. Clin. of Chicago, 1916, ii, 85.

Hammill presents the case of a woman forty-one years old with a negative family history, who has had tonsillitis since the age of six. Enlargement of the thyroid was noticed at the age of eighteen, when it was much larger than at the present time. She had at that time puffiness of the eyes, shortness of breath, and was very nervous. Then the symptoms ceased up until at twenty-four she had another attack

and was afraid to walk because "her heart beat so hard." Ever since then any excitement has caused severe emotional strain. At the present time she has the symptoms of exophthalmos, Stellwag's positive, Moebius' negative, tremor of outstretched hand, perspiring freely under axilla, flushed skin around neck and over upper chest, marked dermatographia, swelling of the isthmus and right lobe of the thyroid. Marked palpitation of the carotid. Blood pressure 150-78. Temperature normal, blood count normal. Pulse 115-125. Tonsils enlarged; from the right pus was ejected. Hammill thinks that the tonsils either became infected with a microorganism whose virulence varied from time to time or else they became a locus minoris resistentiae to microorganisms such as we are constantly taking into our mouths, and hence reinfected at frequent intervals. He thinks that tonsillar infection stimulates the thyroid in many cases, as it produces acute inflammatory rheumatism and chorea in others.—C. E. E.

SCLERODERMIA (The Cause of) Bydrage tot de Kennis van de aetiologie der sklerodermie. Nederl. Tijdschr. voor Geneesk. (Haarlem) Koopman (J.) 1917, ii. 55.

Description of a case of sclerodermia, complicated with a tuberculosis of the knee joint. A year after the first symptoms, the symptoms of an insufficiency of the adrenal system and still some months after a classical Addison's disease was observed.

An emulsion of the skin produced tuberculosis in the guinea pig. Application of the thyroid gland and of hypophysis had no result whatever.

In this case the author believes that sklerodermia has been caused by tuberculosis, and that the Addison's disease is simply an effect of the same cause.

As it is well known that tuberculosis may cause pluri-glandular insufficiency and as it is absolutely certain that in many cases of sclerodermia the function of the thyroid gland or of the hypophysis is changed, the author suggests the idea that sclerodermia and insufficiency of the endocrine organs are both caused by a specific infection, and that in cases in which the organo-therapy has no success, this infection has not had an influence on these glands.—J. K.

(PARATHYROIDS) Relations between Epilepsy and Tetany. Bolten (G. C.) Geneeskundige Bladen (Haarlem) 1917, xix, 301.

Many authors have observed cases in which the patients showed epileptic symptoms as well as tetany, but there has never been described a case of epilepsy and tetany in which there was proof that both diseases had one common cause.

Bolten discusses these cases at length and comes to some very important conclusions which have a distinctly practical bearing.

Not all cases of tetany depend from the parathyroids. Especially in Austria and Russia there have been observed epidemics of tetany, which have most probably no relation with the parathyroid glands, but are caused by ergotin-intoxication. The tetany of children, however, is nearly always caused by insufficiency of the parathyroid glands. Epilepsy, too, shows very often no relation to the internal secretion. The traumatic epilepsy, the epilepsy in cases of tumors of the brain and the reflex-epilepsy have nothing to do with the endocrine organs. Only the "genuine" epilepsy is caused by insufficiency of the thyroid gland as is proved by the splendid effects Bolten has observed in administering fresh thyroid glands in cases of epilepsy.

Therefore, in cases of combination of epilepsy and tetany one has to examine carefully, whether the cause of these diseases is an insufficiency of the thyroid and parathyroid glands. Only in this case Bolten has observed very good results from rectal applications of fresh thyroid and parathyroid glands at the same time.

In other cases, however, not due to insufficiency of the thyroid-parathyroid system no effect can be expected from this treatment.

In the literature there is nothing to be found about this for the simple reason that in no case did the author investigate whether the tetany or the epilepsy really depended upon endocrine causes.—J. K.

(OVARY) Carcinomatous Ovarian Teratoma with Premature Puberty and Precocious Somatic Development. Harris (R. H.) Surg., Gyn. and Obst. (Chgo.) 1916, xxiv, 604.

The case of carcinomatous ovarian teratoma reported herewith is of special interest for the following reasons:

1. Malignant ovarian teratomata, including all solid teratomata, are rare; and those showing carcinomatous or sarcomatous areas are still fewer in number.

2. No other case reported as ovarian teratoma has been associated with precocious sexual and somatic development; although Fusino reports premature menstruation in a patient with a solid ovarian teratoma, and Askanazy has collected four cases of ovarian sarcoma, believing them to be cases of embryonal teratoma, in which there were in all cases genital hemorrhages, three times growth of pubic hair, twice mammary hypertrophy and twice abnormal height.

3. The patient was younger than in case of any of the published reports of ovarian teratoma excepting three cases

of malignant ovarian teratoma in girls fourteen years old and younger.

4. The growth of the tumor was associated with the beginning of puberty at five years of age and with rapid bodily development.

5. The tumor was a complex cysto-solid teratoma with definite adenocarcinomatous areas.

6. There has been no menstruation since the removal of the tumor, and no further precocious growth.

7. There was no discoverable recurrence when the patient was examined thirty months after removal of the tumor, a much longer time than the average freedom from recurrence.

The patient was a girl of five years and ten months. The family history presented three cases of carcinoma. The patient weighed six pounds when born, and grew normally until the age of four. The physical changes usually observed at puberty began to be noticed soon after the first menstrual period. The breasts grew larger, the areolae darkened, the pubic region became covered with dark brown hair, hair appeared in the axillae, and the whole body developed rapidly.

The growth of the ovarian tumor was well advanced by the time of the third menstrual period, seven months before operation, when its presence was discovered by the family physician. An inverted pear-shaped mass was then palpable slightly to the right of the median line of the lower abdomen. The examination was made on account of symptoms suggestive of appendicitis. The presence of the tumor apparently was not considered sufficiently important at that time to demand surgical consultation. As the tumor gradually increased in size, it caused a corresponding enlargement of the abdomen. Bodily movements, such as those involved in buttoning the shoes, became difficult to perform and caused discomfort. The patient no longer cared to play, and was more and more inclined to sit about and to rest with the head on a table or other support. She complained of being nauseated and her appetite became capricious. Her bowels moved regularly, except during the menstrual periods, when enemata were found necessary. During the last week before the removal of the tumor, the patient slept only two or three hours at a time, with intervals of wakefulness, when she groaned and seemed to be in pain.

There were no abnormal findings in the case except the signs of puberty, precocious somatic development, and the physical changes caused by the comparatively large size of the ovarian tumor. The bodily development was symmetrical.

Reference to the standards determined by Bowditch in an examination of 24,500 children attending school in or near

Boston, shows that the patient at five years and ten months was actually larger than the average girl nine years of age. She was 49.8 inches tall and weighed 58 pounds; while the average girl of nine is 49.39 inches tall, and weighs 57.07 pounds inclusive of clothing. Seaver gives the average height as 49.7 inches and the average net weight as 54.9 pounds for a girl of nine.

A laparotomy was performed, and the mass, which proved to be a tumor of the right ovary, was removed. It weighed 68 ounces, or about one-fourteenth the body weight of the patient. Microscopic examination showed areas of definite dermoid character, such as hair, sebaceous and sweat glands, fetal living tissue, etc. The larger part, however, presented the appearance of adeno-carcinoma.

The patient was examined twelve, eighteen, and thirty months after operation. She has been well, and has grown at a normal rate since removal of the tumor. There has been no menstruation since then.—E. N.

Relation of Glands of Internal Secretion to Female Pelvic Organs. Vest (C. W.) *Am. Jour. Obst.* (New York) 1916, lxxv. 366.

This paper, which is a brief resume of the gynecological relations of the internal secretions, is summarized by the author as follows:

There are definite conditions associated with the female pelvic organs, which are indicative of an abnormal condition of some of the glands of internal secretion. The hypophysis, thyroid, and ovary are intimately associated; that gland therapy is of value in cases of lactation atrophy of the uterus, in certain cases of amenorrhea, and in women at the menopause. It has been observed that the breasts react to changes in the pelvic organs when there is a disturbance in the internal secretions of the latter, as is evidenced by their accumulation of fat. Furthermore, they are often painful, and in certain cases of amenorrhea, after the ingestion of the luteum extract, they secrete an opaque, watery fluid. Finally, the author reports two instances of cessation of the menses, associated with an accumulation of fat, following an acute infection, thought to be measles, which had occurred early in menstrual life.—E. N.

(ADRENALIN) L'action de l'adrenaline sur le tractus digestif.
(Action of Adrenalin on the Digestive Tract.) Loeper (M.) and Verpy (G.) *C. r. Soc. de Biol.* (Paris) 1917, lxxx, 703.

Intramuscular injection of one milligram of adrenalin in human subjects caused an increase in secretion of HCl in the stomach as well as augmentation and acceleration of the con-

tractions in the digestive tract. They suggest that there may be digestive syndromes originating from the adrenal.—F. A. H.

(PANCREAS) Spontaneous Diabetes in a Dog. Krumbhaar (E. B.) *Jour. Exp. Med.* (New York) 1916, xxiv, 361.

Krumbhaar reports a case of typical diabetes occurring spontaneously in a dog. The autopsy performed immediately after death showed the pancreas to be large, soft and with no signs of old or recent inflammation. Histologic examination, however, showed striking changes in the islands of Langerhans. Not only were these scarce but every island showed degeneration of one or more kinds. There was extreme hydropic degeneration and exhaustion of the granules involving both the alpha and beta cells but especially the latter. Some of the islands were replaced by fibrous tissue.

In addition this dog showed a sarcoma of the thymus.

J. R. G.

(DIABETES) The Effect of Exercise upon Carbohydrate Tolerance in Diabetes. Barringer (T. B.) *Am. Jour. Med. Sci.* (Phila.) 1916, cli, 181.

In speaking of the effect of exercise upon carbohydrate tolerance in diabetes, he reminds us that this tolerance is increased in the mild cases and decreased in the severer forms. Experimentally he gave patients dumb bell exercises one hour daily three times a week. In one mild case the patient whose tolerance was 150 grams of white bread daily, after eight months of such exercise, showed an increase of the tolerance to 270 grams. During the summer months the patient stopped these restricted exercises and led an active outdoor life, chopping trees and working with a pick. The tolerance decreased steadily so that by September it was 120. Resuming the exercises the patient was able to tolerate 190 grams by January.

In another case the tolerance was increased from 60 to 90 grams while in a third no such effect was noticed.—J. R. G.

(THYROID) The Alleged Detoxicating Power of the Thyroid Gland. Bassinger (H. R.) *Jour. Infec. Diseases* (Chgo.) 1917, xx, 131.

The author gives a good review of the work which has been done as regards the detoxicating power of the thyroid. Not being satisfied with previous results he has attempted to solve the problem by injecting a minimal, sub-minimal and repeated sub-minimal lethal doses of diphtheria toxin into the thyroid of a dog. In a second series of cases he used tetanus toxin. He finds that minimal lethal doses cause death more rapidly than in the control dog. Sub-minimal doses, that is,

about one tenth of the former, produce only the slightest symptoms of toxemia. The colloid in the glands was the same as in the controls. Repeated sub-minimal doses produced no hyperplasia nor increase of colloid. He concludes that the thyroid has no detoxicating properties that can be demonstrated by the injection of diphtheria or tetanus toxin into the thyroid. Microscopic examination showed no increase in colloid, repeated injections caused some resorption of colloid but no active hyperplasia.—J. R. G.

(DIABETES) The Influence of Acidosis upon Hyperglycemia in Diabetes. Epstein (A. A.) and Felsen (J.) *Am. Jour. Med. Sci. (Phila.)* 1917, cliii, 58.

Acidosis as known manifests itself in a variety of ways. (1) By increasing the acidity of the urine, (2) By increased hydrogen ion concentration of the blood serum, (3) Diminished combining power of the serum for carbon dioxide and hence (4) Reduced carbon dioxide tension in the alveolar air, (5) Increased ammonia output in the urine and the elimination of ketone bodies.

Recent observers have shown that acidosis not only is associated with diabetes but in itself may produce glycosuria. This is also true in acid poisoning and again after removal of the pancreas sodium carbonate when given diminishes glycosuria. The acidosis may be affected in two ways: (a) by action upon the liver and muscles immobilizing glycogen and (b) it may interfere with renal elimination.

The hunger treatment in diabetes shows that some cases improve remarkably; others develop a severe acidosis. The author studied four cases and showed that (1) the withdrawal of food from certain cases of diabetes provokes and aggravates an acidosis, (2) this acidosis causes an increase in blood sugar content, (3) a liberal but judicious administration of carbohydrates may control the acidosis provoked by carbohydrate withdrawal or complete fasting and lead to general amelioration of the symptoms, (4) a progressive rise in the blood sugar content associated with a gradual fall in the alveolar carbon dioxide is indicative of impending coma.

J. R. G.

(INTESTINE) Has Secretin a Therapeutic Value? Carlson (A. J.), Lebensohn (J. E.) and Pearlman (S. J.) *J. A. M. A. (Chgo.)* 1916, lxvi, 178.

Secretin is the product of the action of the acid duodenal contents upon the duodenal mucosa. It can be prepared artificially by macerating the duodenal mucosa in a 0.4 per cent hydrochloric acid solution, neutralizing the boiling mixture and filtering. A few cubic centimeters of the filtrate after

injection invariably produces a powerful secretion of the pancreatic juice. Secretin excites not only the pancreas but also the liver and intestinal mucosa. It stimulates markedly the flow of bile and the succus entericus. Remarkable it is that the pancreas is not fatigued but has been observed to maintain undiminished flow for eight hours. Secretin seems to be a specific substance much like adrenin, both being non-specific in distribution, relatively simple in composition, of low molecular weight and subject to rapid oxidation.

In diabetes, it has been employed with conflicting results. It is apparently of no definite value. Likewise in digestive disturbances and in a variety of ailments it has been tried but with no definite basis for its use.

Direct introduction of secretin even in large quantities into the intestine of an anesthetized dog is with no effect. It apparently cannot pass the digestive tract. Experiments with human gastric juice also prove that secretin is destroyed. Experiments upon dogs with duodenal fistulae reveal no specific results from the administration of secretin by mouth. The authors then examined two proprietary preparations, Secretogen and Duodenin. These also were found to be without effect in their experiments.

The authors conclude that secretin is of value only when given intravenously, and its action is transient like that of adrenin.—J. R. G.

(DIABETES) Clinical Significance of Glucose Nitrogen in Diabetes Mellitus. Janney (N. W.) *Am. Jour. Med. Sci. (Phila.)* 1917, cliii, 44.

By means of improved experimental methods the writer establishes the fact that in the fasting subject, the glucose nitrogen ratio of severe diabetes mellitus is about 3.4 to 1. The glucose-nitrogen ratio is therefore to be regarded as a definite index of the severity of the disease. In association with other factors the ratio is a valuable prognostic sign.

J. R. G.

(DIABETES) Observation on the Starvation Treatment of Diabetes. Martin (C. F.) and Mason (E. A.) *Am. Jour. Med. Sci. (Phila.)* 1917, cliii, 50.

In offering 100 grams of glucose to a normal person, there is of course an increase in blood sugar but this drops below normal in from two to three hours. In diabetes the rise is sustained much longer. This very slow decline suggests possibly a kidney block. While it is not an absolutely established point, considerable evidence suggests the importance of kidney block in these conditions. Thus an insidious

and progressive diabetes may be entirely overlooked. Experience shows that the best time to make estimates of blood sugar is two hours after the meals.

In some cases test diets repeated at short intervals show great variations in the patient's tolerance. As regards acidosis, the ferric chloride reaction is sometimes absent in the presence of acidosis. Starvation in an ordinary individual results in acidosis, but in a diabetic usually the reverse. However, in the latter acidosis may at times be initiated by hunger.—J. R. G.

(PITUITRIN) The Action of Pituitrin upon the Surviving Human Uterus. Charteris (F. G.) Glasgow Med. Jour. 1917, lxxxvii, 65.

The author criticizes much of the work in animal experimentation by saying that drugs are too often given in toxic doses and secondly that animals are selected not for their resemblance to the human but for the ease of experimentation. Accordingly, he used strips of human uterine tissue about one inch in length and one eighth of an inch in thickness. The material was obtained from non-pregnant tissue, from tissue removed after early abortion and from tissue removed by Caesarean section at full term. These strips were suspended in balanced salt solutions and curves taken indicative of their contraction. There was no difference in the response to pituitrin of the pregnant and non-pregnant uterus. Both responded by increased activity. Contractions became more numerous, the tonus was markedly increased and the individual contraction shorter with more rapid relaxation. The action is prompt, occurring within a minute and lasting several minutes. Neither adrenin, ergotine, fluid extract of ergot, nor quinine produced the same prompt effect. In these experiments added to the solution made a concentration of about one to five thousand.—J. R. G.

(PITUITARY) A Case of Diabetes Insipidus with Peculiar Necropsy Findings in the Posterior Lobe of the Pituitary Body. Weber (F. P.) and Schmidt (H.) Am. Jour. Med. Sci. (Phila.) 1916, clii, 892.

The relation of the pituitary to polyuria has long been known and indeed some authors have described polyuria in cases where the lesion did not directly involve the pituitary but was simply in that region. These authors describe a very interesting case of a woman 73 years of age. Polyuria started suddenly, following the removal of a lymph node in the neck. Upon admission to the hospital two years later the patient was found to be suffering from tuberculosis. She was pass-

ing ten liters of urine daily, blood pressure was 90 and the Wassermann and eye-ground examinations were negative.

Post-mortem showed the usual findings of miliary tuberculosis except for the pituitary. Here the pars posterior (pars nervosa) was relatively enlarged over the anterior lobe (pars glandularis). The posterior lobe almost enclosed the anterior lobe and contained large clumps of granular cells rather large and with small nuclei which stained deeply with hemotoxylin. The cytoplasm was granular and Sudan III showed these granules to be droplets of lipid substance.

J. R. G.

(KIDNEY) Renal Glycosuria. Murlin (J. R.) and Niles (W. L.) *Am. Jour. Med. Sci.* (Phila.) 1917, cliii, 79.

The authors describe a case of renal diabetes, with glycosuria and normal glycemia, relatively independent of diet. The case was of interest in that only one day of hunger was needed to clear the sugar from the urine.—J. R. G.

(PANCREAS) A Contribution to the Study of Pancreas Intoxication. Goodpasture (E. W.) *Jour. Exp. Med.* (New York) 1917, xxv, 277.

This study was undertaken with the idea of purifying as far as possible the toxic part of the autolysing gland. It was found that the fresh pancreas extract in salt solution is toxic and when injected intravenously produces symptoms of poisoning analogous to those resulting from the duodenal loop fluid and other toxic materials of protein nature. As little trypsin could be present in a gland rapidly extracted, it seemed probable that the toxic agent was some other substance. The beta nucleoprotein fraction of the gland seemed toxic and produced reactions identical with those following the salt solution extract. Further studies showed this toxic agent to be thermostabile. It is destroyed by autolysis but can be obtained in a gland which had autolyzed twenty-four hours. It is probably protein in character. Intravenous injection of 0.05 to 0.1 grams per kilo is usually fatal and elicits symptoms in dogs comparable to those of hemorrhagic necrosis of the pancreas. After autolysis of the dog's pancreas this toxic protein and guanylic acid may be separated and obtained in relatively pure form.—J. R. G.

(PITUITARY) Diabetes Insipidus and the Hypophysis. Von Meyenburg (H.) and Mason (E. A.) *Beitrag path. anat. u. allg. path.* 1916, lxi, 550.

They remind us that the majority of evidence points to the involvement of the pars posterior in polyuria and polydipsia. They quote two cases. In the first, a very marked

case, autopsy showed a small tumor of the optic chiasma. Histologic examination proved the tumor and also the hypophysis to be tuberculous. In a second case a man 21 years old with severe diabetes insipidus, frontal headache, abducens and oculomotor paralysis, died eight months after the onset of the symptoms. Autopsy showed a malignant tumor at the base of the skull in the region of the hypophysis. Both cases showed especial involvement of the pars posterior but he believes that the best explanation is not a hypo- or a hyper-functioning of one part but a dys-function of the entire gland.—J. R. G.

(THYMUS) Syphilitic Disease of the Thymus in Infants and the Mode of Origin of the Dubois Abscesses. Oliver (J.) *Amer. Jour. Dis. Child. (Chgo.)* 1917, xiii, 158.

Abscess-like cavities in the thymus were first adequately described by Dubois in 1850. These cavities are characterized by a lining of stratified squamous epithelium and contents that are puriform in appearance. There are three theories as to their origin: that they are derived from the Hassall bodies; that they come from the primary cavity of the developing thymus; and that they arise by a necrosis of the medullary tissue. In addition to the "abscesses," in many instances there is a preponderance of reticulum and a disappearance of the lymphocytes in the thymus as a whole. Oliver reports a case in which the origin of the cavities by a cystic dilatation and coalescence of the Hassall bodies appeared to be unquestionable. The syphilitic etiology of this condition is universally recognized, although Oliver was unable to demonstrate spirochetes in the tissues of the case reported, probably as a result of improper fixation.—J. P. S.

THYMUS Disease in Children. With Report of a Case of Thymus Hypertrophy. Sheffield (H. B.) *Pediatrics*, 1917, xxix, 5.

Hypoplasia of the thymus and the associated hypothyroidism, "produces not only arrest of growth and frailty of bones and general debility, but also lowered mental capacity." There are three groups of cases associated with hyperplasia of the thymus: In the first, hyperplasia of the thymus with the accompanying increased activity of the thyroid, may cause the clinical picture of exophthalmic goiter. In the second group, the child shows no definite manifestations of any pathological condition, but may die without any apparent reason as a result of some slight cause, such as an injection of serum, narcosis or a slight operation. In the third group, an enlarged thymus is demonstrable on percussion and is associated with enlarged lymph glands elsewhere in the body. These children suffer from so-called thymic asthma, and may

die suddenly during a paroxysm of asphyxia. The case reported very briefly by the author is of this type.—J. P. S.

(PITUITARY) Alleged Antitoxic Action of Pituitary Extracts. Houssay (B. A.) and Giusti (L.) *Semana Médica* (Bs. Aires) 1916, xxiii, 559.

The pituitary body extracts have no antitoxic properties against veratrin, strychnin and morphin.—G. P. G.

MENSTRUATION, Cholesterinemia Variations during. Goncalons (G. P.) *Semana Médica* (Bs. Aires) 1916, xxiii, 639.

The author recorded the findings in twenty-seven complete menstrual cycles. They show that the cholesterin content of the blood rises abruptly five, six or seven days before the menses and then gradually declines a little. It rises again as the menses become established, keeping at this same level, somewhat below the early peak, until the close of the menses and then gradually dropping back to the ordinary level where it remains till it runs up abruptly anew from five to seven days before the onset of the next menses. One woman with exophthalmic goiter and one with postpuerperal amenorrhea showed this same curve of the cholesterinemia although there was no uterine discharge and another with a probable depressed ovary gave an irregular curve. The author believes that this curve is not due to the internal secretion of the corpus luteum alone.—G. P. G.

PITUITARY Body. Esposel (F.) *Revista dos Cursos de la Facultad de Medicina* (Porto Alegre, Brazil) 1917, iii, 28.

A general summary of the knowledge of this ductless gland.—B. A. H.

(MAMMA) Chronic Inflammation of the Mamma and Treatment with Mammary Extracts. Navarro (A.) *Anales de la Facultad de Medicina de Montevideo* (Uruguay) 1917, i., 323.

Navarro obtained the cure of four patients by mammary organotherapy.—B. A. H.

PITUITARY, Tumor of the. Adiposo-genital Syndrome. Ricaldoni (A.) *Anales de la Facultad de Medicina de Montevideo* (Uruguay) 1917, ii, 328.

The author describes the first case that has appeared in the Uruguayan medical literature. There were present absolute blindness, headache and adiposity. The height was 172 cm. and the weight 75 kg. Amenorrhea has persisted during the six years since the incidence of disease. X-ray of sella showed a greatly enlarged hypophysis. Radiotherapy had no effect.—B. A. H.

(THYROID) Tuberculosis and Hypothyroidism Co-existent.

Albina (E.) Rev. de la Assoc. Med. Argent. (Bs. Aires) 1917, xxvi, 967.

Girl, fourteen years of age, with profuse menses lasting eight days; temperature reaching 38 degrees C, perspiration often profuse, severe pains in the ankle and in the hand. Infiltration tuberculosis of the vertex of the lungs. As the treatment by sodium salicylate was unsuccessful she was given thyroid and the following menstruations were normal and the other symptoms disappeared.—B. A. H.

(MAMMA) A Remarkable Hypertrophy of the Breasts. Novaro (R.) Anales del Instituto Bodelo de Clinica Med. (Bs. Aires) 1915, i, 61.

I. S. A., twenty years old, single, with irregularity of menses and sometimes severe menorrhagia. Hypertrophy of the breasts had begun six months before she was examined. It increased during the menses. Constipation, headache and insomnia were present. The breasts reached almost to the pubis; the nipples had nearly disappeared; the diameter of the right areola was 11 cms and of the left 13 cms. The Wassermann reaction was positive. After operation, the left breast was found to weigh 6700 gms and the right 5,900 gms. Novaro believes that this remarkable mammary hypertrophy is due to abnormal functioning of the ovary.—G. P. G.

(ADRENALS) Cortico-adrenal Virilism. Guemes (A.) Semana Médica (Bs. Aires) 1917, xxiv, 207.

Woman, years old, bald, with a dense beard and moustache; amenorrhea of three years; gained twelve kgrs. in six months; pigmentation of the face.

At autopsy it was observed that the right adrenal was hypertrophic, weighing 141 gms. The tumor was made up of spongiocyte cells and there were metastatic cells in the liver. The cholesterol content of the adrenals was 11 per cent. No adrenin content was detected.—G. P. G.

(THYROID) Pathogenesis of the American Trypanosomiasis.

Chagas (C.) Memorias do Instituto Oswaldo Cruz. Rio de Janeiro (Brazil) 1916, viii, Fac. ii, 5.

A general summary of our knowledge of this disease, discovered by the author and produced by the Trypanosom *cruzei*.

This disease begins, according to Chagas, by an acute state lasting thirty days, more or less, after which the Trypanosomes disappear from the blood and the disease becomes chronic. The evident symptoms are: myocarditis and ar-

rhythmia, injuries of the nerves, goiter, etc. Chagas modifies his previous classification of the clinical forms, leaving only the cardiac, the nervous and adrenal forms, and suppresses the pseudo-mixedematous and mixedematous forms and the chronic with acute exacerbations because he has found that these are mixed with the aforementioned forms.

He believes that the infantilism he has observed is different from cretinism. He has found cysts of leismaniform corpuscles in the heart, muscles, nervous system, thyroids, adrenals and testicles. Chagas discusses the water theory of endemic goiter and offers some objections to the theory, because he thinks that it is probable that Trypanosomiasis exists in association with the other, endemic, form of goiter.—B.A.H.

(GONADS) Genito-Glandular Dystrophy. Souza (O. de) and Castro (Aloisio de). *Annaes da Policlínica General Do Rio de Janeiro* (Brazil) 1916, i, 9, 121; 1917, ii, 5, 79.

Souza and Castro offer an excellent study of the diseases produced by endocrine dysfunctioning in which the main symptoms are atrophy of the gonads and general trophic alterations. Their observations comprise twenty cases. The common link of them is atrophy of the sexual organs. Three of the cases had tumors of the pituitary body (one is Ricaldoni's case). The authors believe that the principal factor in these cases is functioning of the gonads. They classified their cases in these divisions: (A) Sexual-Gland Dystrophy of an infantile type. (B) Sexual-Gland Dystrophy of gerodermic type. (C) Genital Dystrophy of eunuchoid type. (D) Sexual Dystrophy of adiposo-genital type. (E) Associated types of genital dystrophy (pluriglandular syndromes).

Their other classification is commented on by Dr. Housay. Simple Types: Where there are genital disturbances alone. Infantile Types: Which term they say, with reason, must be limited to the patients who retain infantile characteristics till puberty or later. The authors take issue with those who believe that the genital insufficiency is able to produce the infantilism. A given cause they say could produce both the somatic infantilism and the arrest of development of the sexual organs. Also, experimentation has given us no reason to believe that removal of the gonads will produce arrest of somatic development. Gerodermic and Eunuchism Type: Souza and Castro group, reasonably according to us, those cases in which are observed singly or together the senile type of skin, alterations in growth and distribution of the hair, adiposity of breasts and hips, abdominal adiposity of the eunuch and sometimes the thin type of eunuchism. Since the injuries of the pituitary often produce indifferentiable syndrome with alterations of the sexual organs, Souza

and Castro believe that Frohlich's syndrome is a genitoglandular dystrophy due to pituitary tumor. They affirm the manifestly hazardous hypothesis, that injury to the sexual glands might produce the disorders secondary to the pituitary body. This theory is opposed by the experimental fact that sexual atrophy is produced by removal of the pituitary body. Associated Types: The authors group all those cases known by the term of pluriglandular syndromes and most probably due to disorders of the internal secretory activity of the gonads.—B. A. H.

(THYROID) Chronic Thyroid Rheumatism. Servetti Larraya (J). *Revista Médica del Uruguay*, 1916, xix, 829.

Servetti Larraya gives a summary of the etio-pathogeny of this condition and a discussion of the literature pertaining to it, followed by a description of his case. A. L., man, forty-two years old, without syphilitic history. (Gonorrhoea was not inquired about.) For the past four years has had painful (gouty) attacks in several joints, with deformities and rigidity. All medication employed was unsuccessful. Then Dr. Servetti Larraya gave him thyroidine (Tyrénine Grémy) 0.02 cgms. daily during eight days. After a week's interim thyroid treatment was resumed for twenty-seven days, 0.04 cgms. daily. Treatment was then discontinued two months, but a new attack having occurred it was necessary again to give him thyroidine during twenty-four days. The patient again improved.—G. P. G.

EXOPHTHALMIC GOITER, The Treatment of, by Injections of Boiling Water. Ceballos (A.) and Bacigalupo (G.) *Rev. de la Asoc. Méd. Argent.* 1917, xxvii, 236.

The authors give the remote consequences of the treatment of six patients by Porter's method. Two of the patients were men and the remainder women. As many as thirty injections were administered. Some of their patients were observed for two years, the others for one year following the treatment. They noted a decrease in the size of the thyroid. In three patients, after two years of treatment, the pulse rate diminished from 130 to 100 beats per minute. The exophthalmos was unaltered. The subjective symptoms were decreased by the treatment and the patients felt better.

Two patients were presented at one of the meetings of the *Asoc. Med. Argent.*, but we have not seen all the improvements of which the authors speak.—G. P. G.

EXOPHTHALMIC GOITER. Basedow's Disease. Cesesia (A. F.) Thesis of Professorship of Faculty of Medicine of Buenos Aires, 1916.

The author gives a fairly complete study of the literature of the subject. He claims much for his treatment of this disease on the results obtained in one mild case of exophthalmic goiter, in which he used a homo-graft of the ovary. In another case he made a testicular graft in a pederast. The grafts were successful. (Manuscript read before the Society of Surgeons of Buenos Aires, July 14, 1915.)—G. P. G.

(OVARY) Etio-pathogenesis of Uterine Fibromata. Piccardo (T. J.) *La Prensa Médica Argentina* (Bs. Aires) 1916, iii, 65.

Piccardo is convinced that excessive function of the ovaries (hyperovarism) is directly concerned in the etiology of uterine fibromata. He promises a later paper concerning the histology of the ovaries removed during their operations.

He has found, as have other observers, that in patients with these tumors, the ovaries are increased in size, sometimes being as large as a plum, with elongation of the thrompes. He believes that these fibromyoma are produced by a hyperactivity of the ovary because of the size of the ovaries, the elongation of thrompes and the profuse menses. He believes also, that this ovarian activity can begin in the early states of puberty. In these cases the tumor remains single, or as a nucleus and does not occupy the whole uterus, as often occurs in the latter states of feminine sexual life when the tumors become numerous. He suggests antagonistic organotherapy as treatment, the thyroid gland being his choice.—G. P. G.

(PITUITARY) Hypopituitarism in a Boy with Positive Wassermann. Cockayne (E. A.) *Brit. Jour. Dis. Child.* 1917, xiv, 52.

This patient was 9 years old and had appeared normal, healthy and intelligent until 2 years ago, when he complained of severe headaches, became languid; later muscular weakness was noticed. Became fat 6 months ago. He was dull, apathetic and showed continual tremors of hands and legs. He talked intelligently for a time and then lapsed into baby talk, speech becoming slurred and indistinct. The gait became unsteady and the knee jerks exaggerated; pupils: right reacted to light and accommodation, left reacted to light slightly and sluggishly. Both discs were chalky white with optic atrophy. The forehead was bulging. Marked deposit of fat occurred all over body. The testicles were small and the penis was very small.

Two Wassermans were positive.—M. B. G.

PITUITARY Gland and Idiocy. Cornell, (W. B.) *Medical Ass'n, Greater New York*, Oct. 15, 1917.

The speaker presented a case of a hyperactive idiot, 7 years old, but who measured up to less than 3 years mentally. An x-ray picture of the head, which was markedly microcephalic, showed the anterior clinoid process almost doubled on itself and encroaching on the pituitary gland. Treatment with pituitary extract resulted in some slight improvement.

M. B. G.

DUCTLESS GLANDS, Practical Experiences With. Black (S) N. Y. State Jour Med. 1917, xvii, 125.

The writer's experience is very different from that of Dana and Berkeley in the treatment of feeble-minded children with pineal substance. He has not found a single case where he could state positively that the improvement was due to this medication.

He also thinks that the use of the parathyroids in paralysis agitans and tetany has been made more of lately than is warranted. In 9 old persons with typical paralysis agitans absolutely no results could be attributed to the treatment with this gland. He has not used it in a genuine case of tetany.

In obesity, Black recommends the use of thyroid extract in large doses, carefully watching the blood pressure and heart. He has given as much as 30 grains a day in conjunction with the Bergonie treatment.

He refers to a case of goitre that disappeared entirely with adrenalin chloride solution: 1-1000, ten drops three times a day in water. Various combinations of hormones as ovary plus adrenal or pituitary, adrenal and ovary worked no better in his hands than the adrenals alone. Recurrences he found to be common.

In absolute contradiction to many experts, he believes that most of the conclusions as to the relationship between thyroid hormone and diabetes to be theoretical only, and from practical experience thinks it is a good plan to give diabetics thyroid. He refers to a marked case in which 30 grains of thyroid per day were given for several weeks, keeping down the sugar in the urine and the woman appearing stronger.

In cases of rickets, he considers the administration of calcium by mouth to be superior to that of thymus.

The reviewer feels that the value of this paper would have materially increased had the author included case histories and statistics to prove his views, many of which are at variance with those held by other observers and investigators. In their present form, they are at best but broad statements.

M. B. G.

MONGOLIAN IDIOCY, Etiology of. Herrman (C.), Arch. Ped. 1917, xxxiv, 494.

The author concludes that there is no positive evidence that worry, emotional shock, illness during pregnancy or congenital syphilis are important or essential factors in the causation of Mongolian idiocy. The evidence that Mongolian imbecility is a unit character and recessive, although not conclusive, is certainly suggestive.

He believes that distinct manifestations of disturbed function of the endocrine organs are not present in Mongolian imbeciles and post-mortem examinations have not shown any characteristic changes in the thyroid, thymus or supra renals. The administration of extracts of these glands in this disorder has not been followed by marked improvement.

M. B. G.

(PITUITARY TESTIS) Dystrophia Adiposa Genitalis with Congenital Lues. Langmead (F.) Brit. J. Child Dis., 1917, xiv, 55.

The author describes a case in a boy of 15 years. He did not walk until the age of 3 years and could not speak distinctly until 4 years of age. He was stunted, obese and feminine in build and his mentality measured up to about 7 years. The external genitals gave an appearance of a feminine character because the scrotum was divided by a deep groove but not by an actual cleavage; the penis was small and the testicles rudimentary. Luetic stigmata were shown by eyes, Hutchison teeth and scars about angles of mouth. X-ray showed small pituitary fossa and prominence of posterior clinoid process. The sugar content in the blood was about normal. The father died of general paralysis at 45; the mother had Tabes Dorsalis.

(From "La Pediatria." May, 1917.)

(PITUITARY) Su tre sogetti adenoidei con femminilismo ipofisario. Citelli (S.) e Caliceti (P.) La Pediatria, 1917, xxv, 278.

The authors found three cases of hypophyseal feminism in three soldiers, who had had adenoids in their youth. Through neglect their mental development was considerably reduced.

Skeleton and genitalia were normal, so that they are not eunucoids. Hypothyroidism, delicate skin, development of the mammae, distribution of the hair on the pubis and sexual frigidity show hypophysary type of feminism.

X-ray examination shows absence of thymus and of the cranio-pharyngeal canal; no visible alteration of the hypophysis, so that it must be dystrophy of the gland brought about by the adenoids (?). All three are very sensitive to hypodermics of "endo-ipofisina."

The absence of thymus and the lymphatism shows that their causative action of the syndrome, when present in cases like these, is about nil. G. V.

(THYMUS) Grave osteo-porosi Infantile Associata a sclerosi del timo. (Lansarini.) *La Pediatria*, 1917, xxv, 302.

A girl 26 months old with dystrophy of the bones died of bronchitis. The post-mortem examination showed increase of weight of all the endocrine glands; osteo-porosis of all the bones; precocious involution of the thymus with sclerosis and sclerosis of the adrenals. G. V.

(PITUITRIN) La prova dell'ipofisi nelle malattie delle ghiandole a secrezione interna. (Porak) *La Pediatria*, 1917, xxv, 499.

The reaction of normal individuals to hypodermics of pituitary is widely different from the reaction shown by those sick with diseases related to the endocrine function. G. V.

THERAPEUTIC EXPERIENCES

(PITUITARY) The Present Status of Pituitary Extract in Labor. Mundell (J. J.) J. A. M. A. (Chgo.) 1917, lxviii, 1601.

Mundell states that pituitary extract should be given only late in the second stage of labor, when the pains have become slow and weak, owing to uterine inertia, with a normal presentation, a ruptured bag of waters, a fully dilated cervix, and the head moulded and through the brim just above a relaxed perineum.

For 1916 (1914 statistics reported, Amer. Jour. Obstet. 1916, xxvii, 306) he reports 1293 cases, with a ruptured uterus in 12 cases (1 in every 106), 34 fetal deaths (1 in every 38), and 41 cases of asphyxia pallida (1 in every 32).—F. C. P.

(TESTES) Sterility Studies with Particular Reference to Weak Spermatozoa: Diagnosis and Treatment. Lespinasse (V. D.) J. A. M. A. (Chgo.) 1917, lxviii, 345.

The author divides the subject of sterility into five groups, viz: (1) obstruction in the sexual tract of the male, and (2) the female; (3) absolute failure of, or imperfect development of, essential male elements, or (4) of the essential female elements. (5) alterations in the secretions of the female sexual tract, so that her secretions are destructive to the life of the spermatozoa. The study is devoted chiefly to group three and the spermatozoa were examined for motility, size, shape, and staining reactions. A few cases with no obstructive lesions and with weak or imperfectly developed spermatozoa were treated with desiccated anterior lobe of pituitary and suprarenal cortex with good results. The remainder of the paper deals chiefly with group five and is not of particular interest from an endocrinologic viewpoint.—F. C. P.

(PINEAL) The Vineland Experience with Pineal Gland Extract. Goddard (H. H.) J. A. M. A. (Chgo.) 1917, lxviii, 1340.

Goddard makes a brief additional report of the work with pineal gland extract described in collaboration with Cornell (Med. Rec. (N. Y.) 5-10-13) and concludes, "It is thus seen that the Vineland experience, as far as it goes, is wholly negative."—F. C. P.

(OVARY, PLACENTA) Ovarian and Placental Extracts, Their Preparation and Standardization. Morley (W. H.) Surg. Gyn. and Obs. (Chgo.) 1917, xxv, 234.

A more uniform method of preparing extracts must be instituted. Some method for the standardization of these ex-

tracts must be discovered, in order to facilitate the comparison of the results of the different laboratory workers and clinicians. Many results obtained in the laboratory or in the clinic are due to the faulty preparation of extracts. The isolation of the active principles of the ovary and the placenta will clear up many, if not all, of these mooted points.—Author's Summary.

PITUITARY Extract in Obstetrics. Kinnear (J. A.) *Canad. Pract. and Rev.* 1916, xli, 141.

Kinnear discusses the use of pituitary extract for the following indications:

(1) **To Induce Labor**—For this purpose the author considers pituitary unsatisfactory, preferring the use of bougies. From the latter he has never seen any bad effects. With pituitary, on the other hand, the patient experienced labor-like pains lasting perhaps an hour, then disappearing.

(2) **In the First Stage of Labor**—Kinnear says he has had both good and bad results in administering pituitary when the cervix is slow in dilating, as in an occipito-posterior position. He speaks of the danger to the child when the drug is used at this stage. The child's circulation is affected, so that it is sometimes still born, or may die of cerebral hemorrhage.

(3) **In the Second Stage of Labor**—It is in this condition that the best results are obtained, especially in multiparae. The method is most satisfactory when the child is born within a few minutes after the administration of the extract. Bad results may be obtained if the baby is delivered after the effect of the pituitary has worn off.

(4) **In Cases of Slight Contraction of the Brim, So That the Head Sticks Above the Latter**—If there is doubt about the head's coming through, the pituitary should not be given.

(5) **In Cases of Placenta Previa and Post-Partum Hemorrhage**—Here Kinnear's experience has been favorable. The placenta usually soon becomes detached. For hemorrhage the author usually uses ergot hypodermically, but where pituitary has been employed, it has quickly brought about uterine contraction and cessation of the bleeding.

(PLACENTA) The Use of Desiccated Placenta, with Special Reference to the Vomiting of Pregnancy. Cary (E.) *Surg., Gyn. and Obst.* (Chgo.) 1917, xxv, 206.

The theory on which Cary suggests the use of placental extract is based primarily on the work of Loeb, who in 1909 showed that the corpus luteum sensitizes the endometrium for the reception of the fertilized ovum. This action is the lowering of the resistance of the host to this foreign protein

(the ovum), thus making it possible for it to exist and not be absorbed. Now that the ovum is imbedded and growing, a relative immunity must be established by the pregnant woman against the products of conception.

The growing ovum acts as an antigen and stimulates the host to the formation of anti-bodies. This is in accordance with Ehrlich's theory of immunity with which we are all more or less familiar.

A. H. Curtis demonstrated the death and absorption of living ova in the uterus of the guinea pig and the rabbit, following the subcutaneous injection of placental extract. The results of his experiments may be explained by the fact that the injection of placental extract increases the resistance or raises the immunity of the host to such a degree that the existing balance is altered, causing death and lysis. Even in older pregnancies the action is sufficiently strong to cause death of the mature fetus and resulting still-birth.

Cary advises desiccated placental extract in the vomiting of pregnancy because (1) if the condition is due to a lowered immunity of the host to the growth of the syncytium, as seems probable by the work of Acconci, it may stimulate by acting as an antigen. The work of Curtis would also bear this out. (2) If the proteolytic ferment is lower than normal, as demonstrated by the negative Abderhalden reaction, it may increase the ferment content of the blood. (3) The placenta may be a gland of internal secretion, and it may increase the action of the thyroid and adrenals, and by so doing hasten the oxidation of partial protein split-products being thrown into the circulation.

Cary has collected thirteen cases of vomiting of pregnancy, which have occurred at different periods during gestation. One or two of these developing later in pregnancy, as they did, might have developed into the pernicious type had they been allowed to continue. Of these thirteen cases two were lost sight of. Of the remainder, seven stopped vomiting within a day or two and the nausea soon disappeared. Two improved and remained fairly free from nausea, although the administration of the extract had to be continued over a longer period of time. In the remaining two cases the results were not satisfactory; one was definitely neurotic.

At the author's suggestion Dr. De Lee has used the extract in six cases, with good results in three, and varying success in the remainder. He has also used it in two cases of urticaria of pregnancy, from which prompt and lasting relief was obtained.—E. N.

ORGANOTHERAPY in Gynecology. Block (F. B.) and Llewellyn (T. H.) *Am. J. Obst.* (New York) 1917, lxxv, 357.

This paper is a report of the experience of the authors in the treatment of various gynecological disorders with corpus luteum extract, thyroid, and pituitary. The most useful extract they have employed is, in their opinion, that of corpus luteum. They consider that the extract made from the ovary of the cow and that of the sow are of equal potency. They see no necessity for the large dosage which some have recommended, most of their own successful results having been obtained with small doses. They divide the cases treated with corpus luteum into four groups, as follows: (1) Hyposecretion of the ovary due to pelvic inflammatory disease, (2) Natural menopause, (3) Surgical menopause, (4) Functional insufficiency of the ovary.

In the first group, the ultimate results have shown that eight patients were markedly improved and have remained free from the symptoms of which they complained at the inception of the treatment; one was well as long as she took small doses of the drug, but the symptoms gradually returned when the drug was stopped. The remaining patient was in no way improved although she was no worse as a result of the treatment. The treatment consisted of the internal administration of corpus luteum extract in doses of two grains three times daily for periods varying from one to six months, the average being three months. This was supplemented by appropriate local treatment such as the judicious use of hot douching and local applications of a solution of magnesium sulphate in glycerine.

Two cases were treated in which the natural menopause was approaching. In one the chief symptom was pruritus of the vulva and relief was obtained after the administration of six grains of corpus luteum daily for two months; the other case presented vasomotor symptoms which disappeared after the administration of corpus luteum in a daily dose of fifteen grains for one month, at the end of which time the menses returned and lasted six days—this being the first menstruation that the patient had had in four months.

In one case of surgical menopause with marked symptoms, there was no improvement as the result of treatment; it might be stated, however, that this patient had been operated upon eighteen months before the authors saw her.

The last subdivision consists of two cases of functional insufficiency of the ovary, only one of which was traced. In this case, the patient had an infantile uterus and complained of bilateral ovarian pain at the time of the menses, associated with a very scanty flow. Her symptoms were relieved by taking six grains of corpus luteum daily for two months.

Thyroid extract is probably the most abused of the organic extracts. The author believes that the action of

thyroid is synergistic with that of the ovary and it is indicated in cases where either the thyroid or ovarian secretion is below normal. In cases of ovarian hyposecretion, the first choice is always corpus luteum, but many times the cost of this drug is prohibitive and in such cases thyroid extract has been substituted with the hope that a good effect would be produced. The results, however, have been only moderately encouraging. It was given in three cases of pelvic inflammatory disease. One was markedly improved, another was moderately improved, while the third showed no improvement. In two cases of natural menopause, there was seen a great improvement in one and no improvement in the other; a case of surgical menopause was slightly improved while taking the drug but the symptoms returned after the cessation of its administration. In two cases diagnosed as ovarian hyposecretion without demonstrable cause, associated with amenorrhoea, the results were brilliant. One of these cases, a girl of eighteen years, who had never menstruated, who was physically and mentally a child of twelve years, showed improvement from the very beginning. She became mentally active, began menstruating, and showed enlargement of the breasts, growth of pubic hair, and other secondary sexual characteristics. Here also, as in corpus luteum therapy, the authors use small doses of thyroid extract, never over six grains daily and often only one and a half grains a day. The average duration of these treatments has been about two months.

The authors believe that the secretion from the pituitary body is antagonistic to that of the ovary in so far as its effect upon the uterus is concerned and the chief indication for the use of pituitary substance has been in the treatment of uterine bleeding of uncertain etiology. They have had six cases in which they have tried the drug, but unfortunately have been able to trace only four of them. Two of the patients were suffering from menarchial hemorrhages (profuse menorrhagia and metrorrhagia occurring at puberty) and were both promptly cured by the administration of small doses of pituitary substance, one receiving one-half grain three times daily, and the other one grain three times daily. Another case of closely allied origin was that of a young woman twenty years old, who was having profuse menorrhagia, severe enough to confine her to bed for two days at each period and the menses were recurring every two weeks. She was showing signs of weakness as the result of the loss of blood. The history and pelvic examination threw no light on the subject. A diagnosis of ovarian menorrhagia was made and she was given one grain of pituitary substance three times daily. Her last report was that she had not

menstruated for three weeks and her general condition was markedly improved.

In conclusion, the authors emphasize the importance of individualization in the study and treatment of these cases.—E. N.

(THYROID) Treatment of Dysthyroidism by Roentgen Rays.

Palmer (M. B.) N. Y. State J. Med. 1917, xvii, 425.

Provided the case be given the proper treatment nearly every case of dysthyroidism should show improvement and others should be symptom free.

Cases which are to be operated upon should have at least one treatment four weeks previous to operation and unless imperative, the second treatment should be given in cases showing a high pulse rate.

The avoidance of surgery is essential in a large proportion of cases showing toxic symptoms.

Large goitres giving no symptoms of dysthyroidism should best be removed by the surgeon, rather than be given Roentgen treatments.

M. B. G.

(ENDOCRINE GLANDS) The Pathogenesis of Some Non-Psychogenetic Types of Functional Nervous Disorder. Williams, T. A., *Alienist and Neurologist*, 1916, xxxvii, No. 4.

Of the illustrative cases two are of endocrine interest.

The first had been diagnosed and treated for two years for neurasthenia. The chief symptoms were drugged sensation, inertia, congested head, neuralgia, sensitiveness to coffee and digitalis, gastric contraction, impotence, pilocarpine vagotropism, positive Abderhalden reaction to pituitary, marked enlargement of the sella turcica, and the sphenoidal sinus. The diagnosis was dyspituitarism. Therapy by didymin was unsuccessful; other extracts gave further discomfort.

Case II. Paresthenia and ocular asthenia, with neuralgia pseudo-paralysis, history of migraine and ereutophobia, tremor, great fatigueability, hyperhydrosis, slight dermatographia, mild tachycardia, enothalmos, marked increase of weight, slight leucocytosis, tenderness of subcutaneous fat.

Diagnosis, pluriglandular dystrophy.

Therapeutics, mixed hormones of adrenal, pituitary, thyroid, and ovary; great improvement, but a relapse in three months aggravated by pituitary; but great improvement under adrenal since publication of the cases. (Author's abstract.)

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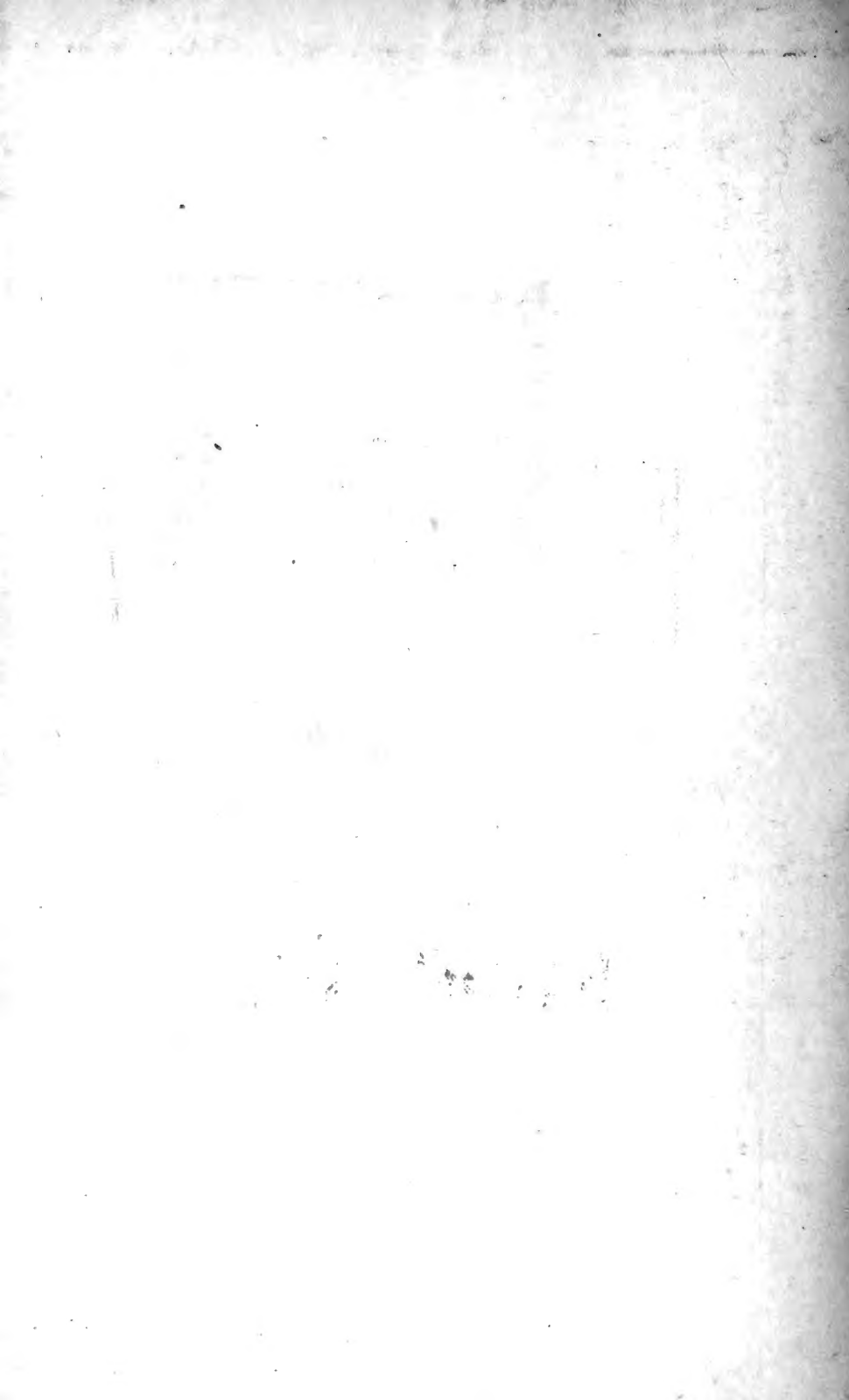
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