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SUPPLEMENT

TO

HARROWER'S MONOGRAPHS ON THE INTERNAL SECRETIONS

Vol. 1 JANUARY, 1921 No. 1

EDITORIAL NOTE AND COMMENT

IT SEEMS ADVISABLE TO preface this first issue of *Harrower's Monographs* with a word of apology. We had hoped to have this finished and ready to send out at the end of 1920, but delay after delay, first with paper makers, then with type setters, and finally unforeseen experiences in our own office, has postponed the date of publication longer than we anticipated. We therefore apologize to those who have subscribed and who have been looking for this publication for considerably longer than they had expected to.

A LARGE PERCENTAGE OF the subscribers to this new publication have, at the editor's special request, merely subscribed "tentatively." That is to say, their subscription, while bona fide enough, was not accompanied by cash in advance because at the time their subscriptions were solicited it was not sure that this journal would be sufficiently self-supporting to warrant its publication; and, consequently, we had no positive assurance just when the journal would appear.

For this reason there will be found with this issue the usual form of subscription reminder which is permitted to be enclosed with second-class matter. Please fill out the form, giving your full address, and pin to it a check and mail it as soon as possible to this office, thus saving us further unnecessary work and expense.

A VERY LARGE AMOUNT of time, not to mention much money, has been involved in the production

of this first issue, and while it is quite a little bit larger than we had anticipated, it is believed that it contains a very fair consideration of the medical aspects of hyperthyroidism boiled down into such shape that it will be both interesting and practically useful as a work of reference.

SINCE THE SPOKEN WORD of a well wisher is so very much more efficient a means of advertising than all the letters or post cards of solicitation that we might write, it is hoped that many of our new subscribers who may appreciate just what is being attempted by the publication of this series of monographs will speak of this to their colleagues and invite their subscriptions. The subscription price, $3.00 per year, is very close to "cost." We do not expect that this will be a source of monetary profit, but we are hoping indeed that this publication may add materially to the prestige of the institution from which it emanates.

CRITICISMS REGARDING THE subject matter, the method of arrangement for publication, or in fact any comments of a constructive nature that may occur to the reader will be very acceptable by us here in the office, and we will look forward with pleasure to many such comments.

THE NEXT ISSUE OF this publication is to be called "Neurasthenia: An Endocrine Syndrome," and the manuscript for this monograph is virtually complete at this writing. It is surprising how many facts can be brought forward to connect the syndrome known as "nervous prostration" or "neurasthenia" with disturbance in thyroid, adrenal or ovarian endocrine function. Without a doubt neurasthenia has a very important endocrine aspect and it will be the aim of the editor to emphasize this aspect as may not have been done in medical literature heretofore.

PLEASE USE THE FORM that is subjoined for your convenience before this supplement disappears and before a reminder may be necessary.

THE EDITOR.

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HYPERTHYROIDISM:

MEDICAL ASPECTS.

INTRODUCTION.

1.—PRELIMINARY REMARKS.

THE CONDITION known as hyperthyroidism is one of the most common and most complex of the endocrine syndromes. It is also one of the serious problems of medicine, for a study of the very extensive literature on the subject quickly brings us to the conclusion that there is much diversity of opinion in regard to the origin, the clinical relations, and, especially, the treatment of this disease.

Many writers still insist that the origin of this disease remains a mystery, though to my mind toxemia—chemical, bacterial, endocrine or emotional—is the real cause. Yet, as we shall shortly see, the complicated associated factors are the chief sources of difficulty. The complexity of this disease and the frequent stubbornness of its response to treatment—whether medical or surgical—makes the study of the subject so much the more important. The fact that the prognosis is not good and that radical cures are by no means the rule, should be an incentive to the rank and file of the profession—the ones, by the way, who see the most cases of hyperthyroidism—to study this subject still harder.

The suggestions in regard to treatment differ widely. Some advise sedative drugs, others alteratives, still

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ρthers urge destructive measures as the X-ray, radium, or injections of boiling water or a solution of quinine and urea hydrochloride. Many other forms of treatment are recommended and an increasing number, like myself, insist upon a comprehensive routine which will neutralize not merely the thyroid dyshormonism, but simultaneously will care for all forms of toxemia, regulate the diet and alimentary conditions, and control the associated disturbances whether causative or resultant.

Two widely separated fundamental ideas will be found each with its adherents urging his particular viewpoint. The surgeon, on the one hand, cannot see eye-to-eye with his medical colleague, while many a statement in the literature emphasizes the superiority of the medical as compared with the surgical treatment of hyperthyroidism, taken as a whole.

One paper which I recently noticed apparently settled the matter of treatment very briefly. This writer says: "Treatment is in a word, of course, surgical." While on the other hand, in a discussion of a series of papers on goitre read at the American Medical Association, New York Session, June, 1917, Dr. Solomon Solis-Cohen, of Philadelphia, made the following statement: "Contrary to surgical opinion, I continue to believe that goitre in exophthalmic goitre being only an incident and not the main factor, should not be treated surgically except in a small proportion of cases—less than 10 per cent. But when the goitre is itself the disease, when the pathological change in the thyroid gland constitutes the main lesion, then the only right way to deal with it is to get rid of it by excision or ligature. Should toxic symptoms develop in these cases, then the indication becomes still more urgent to remove the goitre because that is the source of evil." This is the ideal viewpoint and altogether commendable, and coincides with the remark of another Philadelphia physician, A.

B. Webster, who wisely said: "Surgery has gone mad in treating end-results and not dealing with the primary cause." At all events, this monograph is concerned with the medical aspects only.

I have gathered many opinions into these pages, some of them are vitally important and altogether practical, while others are incidental and of adjuvant helpfulness. A study of the literature indicates that this subject has had a more scientific and extensive development in the past decade than in all the years since Parry made a report of his first case seen in 1786, and it is confidently believed that the successful control of hyperthyroidism will come only when all the various aspects of this disease are known and aggressively treated.

The technicalities of the physiology, histology and pathology of the thyroid properly are left to the text-books, where the subject is very fully considered. For concise, well-arranged and splendidly illustrated information the reader is referred to Crotti's monumental work. The records of the clinical and experimental work of McCarrison in India is very valuable, and mention should be made also of Bram's very recent book.

2.—Terminology and Synonyms.

The word "hyperthyroidism," as used in this monograph, is intended to denote a condition or symptom complex dependent upon or related to an excessive functional activity of the thyroid gland. It does not necessarily mean exophthalmic goitre, though it is a fundamental part of this disease, nor does it solely indicate the serious thyrotoxic cases which we occasionally see.

There are several other names for this disorder, and they should be mentioned here if only to show why they are not used instead of the term that it is proposed to use exclusively in these pages. The syndrome first discussed by Jacob Parry of Bath, England, as far back as

1786, is now connected with hyperthyroidism; but hyperthyroidism is not necessarily Parry's disease. The same is true of the syndrome of Graves or Basedow, which, in this country at least, is most often called exophthalmic goitre. Hyperthyroidism is present in exophthalmic goitre, but it must be emphasized that many hundreds of cases of hyperthyroidism show neither exophthalmos nor goitre. As a matter of fact, enlargement of the thyroid only occurs in about one-fourth of all cases; and ocular protrusion in a still smaller proportion.

As I see it, hyperthyroidism is a fundamental endocrine-metabolic disorder, while the exophthalmos and the goitre may be clinical results of it, the latter showing itself earlier and more routinely, and the ocular manifestations being found usually only in a certain class of severe cases.

The word "dysthyroidism" is used quite commonly and many early writers evidently intended it to mean hyperthyroidism, but to my mind this is not an advisable term, for dysthyroidism refers to perverted thyroid function, or dysfunction of the thyroid, and naturally this should include hypothyroidism, the *instabilité thyroidienne* of Léopold-Lévi (a condition in which the thyroid function varies periodically from insufficiency to excess) and, of course, hyperthyroidism.

The term "basedowefied goitre" is occasionally seen, especially in Continental literature, where the German name clings to this disease. By this is meant a simple goitre which has developed a train of hyperthyroid symptoms—a superimposed Basedow syndrome.

The word "thyrotoxicosis," mentioned above, is certainly correctly applicable to serious cases of hyperthyroidism, but it has come to indicate chiefly the maximal form of intoxication of thyroid origin, and is more usually connected with the disease known as "toxic adenoma of the thyroid" than with the condition which

we have in mind when the word "hyperthyroidism" is used. Adenomata, or real tumor growths of the thyroid, usually cause a condition of hyperthyroidism, but the pathology is different and one of the great errors in the finer diagnostics of dysthyroidism is the mistaking a simple enlargement or hyperplasia of the thyroid with hyperthyroid symptoms for an essential tumor and removing it, only to find later that the thyroid had been a victim of extraneous circumstances which had been ignored and were still irritating the remaining gland tissue and causing a repetition of the same sort of troubles.

"Toxic goitre" is another term which may mean both of the previously mentioned conditions, and, to my way of thinking, is a term to be eliminated from our literature, for an adenoma is indeed a source of toxemia, and so is an abnormally irritated thyroid with a very different pathological picture.

Finally, the term "thyroidism" is sometimes improperly used in place of hyperthyroidism, when it really indicates the conditions resulting from overdoses of thyroid extract, and is not a real disease.

II

THE ETIOLOGY.

3.—FUNDAMENTAL CONSIDERATIONS.

WITHOUT A basic knowledge of the causes of hyperthyroidism and the numerous predisposing factors, successful treatment is impossible. Since the etiology of the disease is not simple, some writers still insisting, like Hoover (1920), that its etiology is unknown, we must collate every fact concerning the numerous contributory factors, whether we may later pin the real cause to one or more of them, or not. A quotation from this writer is in order: "In expounding the medical treatment of Graves' disease, the first question to be answered is whether or not there is a rational basis for specific treatment. The etiology of this disease is wholly unknown. The suspected etiology rests entirely on fanciful speculation. No advocate for any kind of treatment has thus far proposed to combat the etiological factors, for the simple reason that the factors are unknown."

The chief reasons for the difficulties encountered in the control of this disorder, doubtless, are due to its complicated etiology. Hoover is right about the absence of any basis for "a specific treatment" of hyperthyroidism, and so far as I know there never will be, for there is no single uniform etiological factor as, for instance, the plasmodium in malaria, or the specific bacillus in typhoid fever. This complicates matters and should serve to urge us on to broader knowledge and the better service that this will make possible. But

I disagree with this distinguished internist when he states that "no advocate for any kind of treatment has thus far proposed to combat the etiological factors," for I know of at least one who has advised just this thing many times!

As I see it, there are three clearly established classes of causes—toxic, endocrine and emotional. Perhaps the one term "toxemia" might cover all of these three forms; for undoubtedly dyscrinism, no matter what may be the cause, involves changes in the character or the amount of the endocrine products and this virtually amounts to a toxemia, since abnormal amounts of a useful product may act as poison. The same is true of the emotional basis of hyperthyroidism, for here it seems that the abnormal chemistry automatically brought about by fear, rage, or any other emotion, amounts virtually to a subtle form of toxemia.

4.—Predisposing Influences.

For the sake of completeness, some of the older data which is to be found in all textbooks, must be briefly mentioned here:

Hyperthyroidism is essentially a disease of women, and too, of young women. From eighty to ninety-five per cent of all cases occur in women, and the disease is more often found during the period of reproductive activity, being rare in older persons, and still more rare in children.

The so-called "endocrinopathic inheritance," so well discussed by Timme, of New York, should always be sought in the anamnesis of hyperthyroidism, and it will surprise one how frequently there is a hereditary disturbance of that subtle thing which I have called the "physiological substratum" which permits a given exciting cause to initiate a hyperthyroidism in one individual, whereas, the same circumstances, or perhaps

even worse ones, make no impression whatever upon another individual.

Heredity certainly plays a predisposing part, and there are numerous reports of familial exophthalmic goitre, including that of Harvier, of Paris, who reports a case in a young man whose mother, grandmother, maternal aunt and also a paternal aunt all were "Basedowians." In his paper this author goes into the neuropathic and hereditary aspects of this disease quite fully.

Bumsted states that the direct inheritance of hyperthyroidism itself is not so uncommon as is generally supposed. He cites a case reported by Rosenburg, in which the patient's grandmother, father, two aunts and two sisters had suffered from exophthalmic goitre, and also Oesterreicher's statement that in a family of ten children, eight of them suffered from this condition. Bumsted, himself, has had four sisters under his observation during the last five years. Two of them have severe exophthalmic goitre, the third, early symptoms, while the fourth manifested symptoms when she had been for some time at home with her sisters after leaving school. I have repeatedly found an overlooked simple goitre in a mother who has accompanied her hyperthyroid daughter to my office for consultation.

It is hard to separate emotionalism from heredity, and perhaps, environment; but an emotional imbalance certainly makes a fruitful soil for the development of hyperthyroidism. Harry Campbell, of London, once said: "Many cases (of hyperthyroidism) occur in those of a markedly neurotic degenerate type, and while hyperthyroidism itself favors a condition of emotional instability, it is equally true that the reverse is also the case." This matter is given further consideration elsewhere in this monograph.

Location evidently predisposes to hyperthyroidism, just as it does to simple goitre, though probably not in the same degree. The causes for this probably are con-

nected with the local food or water supply, and in this connection the epoch-making studies of McCarrison, in India, must be mentioned, and this officer complimented for his excellent work and splendid book. The importance of his conclusions and their character are considered again under the heading of exciting causes.

Another interesting reference to the predisposing influence of location upon the etiology of hyperthyroidism is found in a paper by Yeardley, of Parkersburg, W. Va. He states that hyperthyroidism is endemic in his city, and that there must be a thousand cases of this disease of a moderate type there. He adds: "How widely it is distributed elsewhere, one is unable to say, but that it is much more extensive than is commonly realized, is a safe assumption."

5.—The Paramount Importance of Focal Infection.

The most common single cause of hyperthyroidism undoubtedly is focal infection, especially of the structures near the thyroid gland. It seems that bacterial toxemia not merely can arouse and irritate the thyroid through the blood stream (and indirectly through the adrenal mechanism, of which more later), but the transmission of irritating substances through the lymphatics is also possible, and many experiences of my own, as well as a few reports in the recent literature, emphasize this. Bergh, of Christiania, reports that in his own opinion the primary source of infection, which most often causes the thyroid derangement responsible for the exophthalmic goitre, is in the tonsils, nose, or throat. All of his own cases had this as a large measure of the etiology. He cites Sølling's report on ninety-seven cases, no less than sixty of which displayed a tendency toward infectious sore throat. In sixty-two of these ninety-seven cases, the hyperthyroidism began evidently as a local process in the thy-

roid. This sustains Bergh's assertions that chronic catarrh of the nasal mucosa is not a superficial harmless thing, but may spread along the lymphatics to the thyroid.

Pietrowicz, of Chicago, reports fifty-two cases of hyperthyroidism, forty-nine of which happened to be in women and three in men. A hereditary influence was noticed in five, on the mother's side. In fifty-two of these patients, i. e., every one of them, some infection of varying degree was present in the mouth, tongue, teeth, nose, tonsils, pharynx or larynx, and in thirty-five of this group, when the infection prevailed on the right side, the right lobe of the thyroid was found to be more enlarged than the left, and in ten of them, in whom the seat of infection was left-sided, an enlargement of the left lobe of the thyroid was noticed.

Tonsillitis is among the commonest of the causes of hyperthyroidism and, in no case of this disease, no matter how serious or insignificant it may seem to be, should careful study of the tonsils be omitted, not even if the history is negative and the patient assures us the tonsils have been removed or that nothing is wrong with them in this respect. Crypt infections of a chronic type without the acute flare-up of tonsillitis are almost as important as these more active infections. In my own estimation, the acute conditions are not much more vitally important or more fundamentally serious causes of hyperthyroidism than the chronic semi-inactive conditions. In both instances, surgery is the best treatment, and whenever I am asked if I believe in surgery for hyperthyroidism, I am always willing to say: "Yes, of the tonsils, if necessary!" Elsewhere attention has been called to a case of mine in whom tonsillar infection was but one of a series of infective foci.

The importance of studying bacterial toxemia is forcefully emphasized by Meredith, and its early con-

trol made an important part of the treatment of hyperthyroidism. An interesting illustration of this relationship is given by Barber, of Guy's Hospital, London, who records a case of a girl aged twenty-one, who had a hyperthyroidism associated with urticaria of eight years' duration. The condition was attributed to a chronic toxemia, probably of streptococcic origin, and this impression was confirmed as a complete cure of all the difficulties followed the removal of infected tonsils.

The ear, nose, and throat specialist has plenty of opportunity to find a latent, early hyperthyroidism as a complication of the conditions which interest him especially. There are many recent papers on this subject, a notable one being that of Squier. Infections of the naso-pharyngeal fossae and the related sinuses, including the eustachian tube and the middle ear itself, are among the most frequent causes of this disease. To put it succinctly, the study of the etiology of hyperthyroidism begins with a search for foci of bacterial infection, especially in the head.

Another common and similar cause is pyorrhea and sub-dental infection. Florence A. Stoney, of Bournemouth, in her essay, reports her war-time experiences in full confirmation of this. It is bad practice to leave such oral sepsis alone, "while the more needful therapy is inaugurated." Both measures are needful and rarely is it impossible to attend to both at the same time.

In this connection a paper by Sloan, a Cleveland surgeon, is of interest because this writer, having studied the case histories of a number of patients suffering from recurrences, has come to believe that in many instances, if not always, the exciting cause of the exophthalmic goitre and of its recurrence, will be found to be an infection—usually focal in character—which must be eradicated before cure is possible. He goes on to say: "When the removal of the maximum amount of the gland does not cure, then the exciting cause must

be sought and removed as any otherwise existing focal infection will continue to stimulate the remainder of the gland." Of course this looks all very well in print, but is not very pleasant for the patient. Why not seek and remove the existing focal infection before removing even a minimal part of the gland?

Bronchitis, an old pleurisy, and pulmonary troubles, are just as likely to cause hyperthyroidism, provided the "physiological substratum" previously referred to is favorable. One of the greatest obstacles to the cure of hyperthyroidism is tuberculosis, and *vice versa.* This aspect of the subject is taken up later.

Any other infection, whether it be near or remote from the thyroid, may aggravate it intensely. Pelvic infections must be controlled—endometritis is a distinct factor, either etiological or aggravating. An infected prostate more than once has caused a most unfavorable thyroid response. The chronic alimentary infections that are overlooked so often produce abnormal protein toxins, which must be considered in this connection. Sir Wm. Arbuthnot Lane, of London, while laughed at by some for his leaning towards short-circuiting on the colon, reports case after case of hyperthyroidism entirely cured by his surgical intervention.

The therapeutic value of the Bulgarian organisms in hyperthyroidism is probably due to their "friendly" control over the putrefactive bacteria so common in the lower bowels, and this explains the good results reported from this measure (see under "Treatment"). Space forbids more than a reference to cholecystitis, appendicitis and colitis as associated factors in the hyperthyroid syndrome; and we will not stop to discuss whether they are predisposing or exciting causes.

An old typhoid may underlie exophthalmic goitre—and it may be found that a gall bladder for years has been harboring these organisms with little or no indication of this chronic infection, but that the slow bacterial

toxemia is the elusive factor at the bottom of an obstinate dysthyroidism.

Still one other chronic and protein infection must be given considertaion in this connection. The importance of syphilis as an underlying cause of thyroid disorder is often entirely ignored. The subject is treated editorially in the *Medical Record* from which I quote: "Careful students of exophthalmic goitre, which is a condition of interest alike to ophthalmologists, neurologists, internists, surgeons, gynecologists, and endocrinologists, will be surprised, perhaps, to hear that it is often of syphilitic origin. Certainly the two have usually been kept apart in practice and theory as well, although Levy-Franckel assures us that since 1911 evidence of the association of the two diseases has been accumulating. Before that date Pierre Marie had noted the occurrence of syphilis in a number of subjects with Graves' disease. In 1911 the late distinguished Professor Gaucher, in association with the author, announced that sufferers from the latter malady might benefit by anti-syphilitic treatment. Sainton, and later Schulmann, noted that familial and conjugal cases of Graves' disease were sometimes due to the underlying syphilis shared by the subjects. It was probably not an entire coincidence that in these syphilitic goitrous subjects severe specific lesions had existed in the vicinity of the thyroid—mouth, throat, and rhinopharynx. The nearness here is not sufficient to suppose any extension to the thyroid gland, so that the connection is obscure. The gland is usually involved in the second year of the disease, although in some cases tertiary syphilis has preceded the lesion. Save for the possibility of specific thyroiditis in a few cases, the pathology is obscure. Apparently specific thyroiditis has never been known to cause typical Graves' disease, though quite recently the affection has been described in heredosyphilitics. The most striking fact is this, that while in ordinary Graves'

disease iodides are contraindicated because of the state of hyperthyroidism, in the luetic variety this drug does good. Another is the general statement that in certain cases of tabes, exophthalmos has been a forerunner."

Pfeiffer, of Dijon, records three cases of serious hyperthyroidism in which there was an emotional cause which sufficed to produce a permanent anatomical change. All three of his cases were accompanied by an important factor—an active syphilis—and Pfeiffer is convinced that the cause of exophthalmic goitre of so-called emotional origin occurs in a syphilitic soil. This is rather a serious judgment to make, especially as he records only three cases, but it is mentioned to emphasize the necessity for considering lues as a possible factor in these cases.

Acute infectious diseases are possible exciting causes of hyperthyroidism. I must call attention here to a fact which I have not seen in the voluminous literature on this subject—that in the history of the patient with hyperthyroidism, it is virtually the rule to find that in childhood, or later, the patient has suffered from whooping cough, measles, mumps, scarlet fever, pneumonia, or other of the acute infectious diseases. These, I believe, do play some part, however slight, in the preparation of the ground for the development of hyperthyroidism, for the thyroid gland undoubtedly is an important element in the organism's defense against toxemia as well as a vital part of the immunizing mechanism as originally shown by the illustrious Sajous. With such an important rôle in these two related conditions, it is easy to see why the thyroid may have become crippled and fundamentally altered in such a way that a later toxic or infectious strain upsets it altogether. Then, too, anyone of these acute diseases may be the chief exciting cause of hyperthyroidism, and there should be no need to quote almost scores of references to this effect. However, Todd, of London, calls attention to

the occurrence of hyperthyroidism as a sequel of influenza. He observed sixteen cases in a group of about 1,500 cases of influenza, five of which, having been quite marked, are recorded in detail. The thyroid signs and symptoms first appeared at times varying from the sixth to the twenty-first day of the illness, and in all but one fatal case they developed during convalescence. Their onset was sudden in all of Todd's cases, though I have seen several frank cases which developed gradually some little time after the active influenzal infection. The importance of the condition rests largely with the early recognition of the thyroid involvement of minor grade, for as Todd remarks, the condition responds favorably to a prolongation of the all-essential period of convalescence, whereas, if such were not provided, the cases might well have formed one of the groups of so-called "irritable heart."

6.—The Emotional Basis.

The aspects of hyperthyroidism that are related to the emotions are as prominent as they are important. Emotional instability practically invariably is a part of the syndrome, and it is one of its earliest manifestations. One cannot study this disease properly without a full knowledge of this phase of the etiology of this disease, nor can one treat hyperthyroidism successfully without taking this carefully into consideration.

Certain individuals of the emotional type—those high-strung persons who are unduly susceptible to all sorts of external impressions—are fit subjects for the development of hyperthyroidism. Fear, the tendency to worry, an unstable temper, and strain, physical, as well as mental, are predisposing causes. I admit that I do not know whether these factors favor a condition of hyperthyroidism or whether it is not a latent tendency to thyroid instability which favors the funda-

mental changes in the emotional balance and makes these persons especially emotional or temperamental. Suffice it to say that these two conditions—hyperemotivity and hyperthyroidism—are related very closely.

Quoting from a recent paper by Sajous: "As every clinician knows, many cases of exophthalmic goitre are due to terror or severe fright, particularly when associated with traumatism; also profound grief, violent excitement, rage, etc. There is no doubt that fright alone may cause the disease. In a case personally observed, the active symptoms of the disease began one week after an accident—the sudden fall of an elevator down eight stories without causing the previously-well male victim any physical injury, the elevator being supplied with a safety air cushion. In another, the patient, after an automobile accident, entailing only great fright, suffered, when almost well after treatment, a recurrence of all her symptoms as a result of another, though less serious, automobile accident. As Cannon, of Harvard, well states, 'Any high degree of excitement in the central nervous system, whether felt as anger, terror, pain, anxiety, joy, grief, or deep disgust, is likely to break over the threshold of the sympathetic division and disturb the functions of all the organs which that division innervates' (one of which is the thyroid gland). They entail also in the light of Crile's work a physical exhaustion of the cerebral nerve cells, the cell bodies of which show marked chromatolysis. We are evidently dealing, then, with a toxemia due to impaired metabolism in these cells giving rise to toxic wastes which provoke excessive thyroid activity."

In one of his numerous papers on the various medical aspects of hyperthyroidism, Bram, of Philadelphia, states that, "There is a remarkably clear indication that traumatic shock or fright is capable of bringing on Graves' disease in persons previously possessing perfect health. In one of my cases, a man was seated in his

back yard reading a newspaper one fine, warm day, when a 'friend' suddenly approached from the rear and poured a cup of ice water down his back. The sudden fright resulted in a well-marked picture of hyperthyroidism two months later. In another case, the syndrome asserted itself some weeks after extreme worry over the death of a mother; in another (a woman of fifty), the symptoms gradually appeared after a train accident."

I also have run across many cases in which the emotional or psychic etiology was clear. One man, previously perfectly well, woke up about four o'clock one morning in San Francisco and found the city falling around him. By ten o'clock he had acute exophthalmic goitre, with an exophthalmos that was as startling as it was sudden. Another case in a young woman was of especial interest to me because of the circumstances. She was riding in the open end of a Pacific Electric car. The car was run into by a truck and one of the iron bars at the side of the car was broken loose and struck her nose, breaking it. The nose was healed, but to this day she has a condition of hyperthyroidism, which only responds temporarily to treatment. My interest in this case was that of a medical expert, and I gathered together such an array of information that the surgeon evidently advised the Company to pay rather than fight, because the woman received satisfactory damages.

I recall also another case, referred to me by a Los Angeles physician, of a young woman who, after work one evening, was ardently discussing some matter, and happening to have her back to the edge of the porch, she stepped backwards rather suddenly, and fell two feet to the ground. Ordinarily, she would have merely suffered from a slight bump, but in her instance, a hyperthyroidism of such severity was initiated that all of the treatment of several physicians failed to control

it, and she died within a few months as a result of the heart effects.

"Fright, intense grief, and other profound emotional disturbances have been recognized as causes of this pathological condition, but I do not think that sufficient attention has been paid to the very close connection between the chronic symptoms of Graves' disease and the more immediate effects of terror. The description given by Darwin and Sir Charles Bell of the condition of man in intense fear almost might have been written with regard to a sufferer from this disease. The heart beats quickly and violently so that it knocks against the ribs. There is a trembling of all the muscles of the body. The eyes start forward, and the uncovered and protruding eye-balls are fixed on the object of terror. The surface breaks out into a cold, clammy sweat. The intestines are affected. The skin of the face is flushed, down over the neck to the clavicles. . . . Of all the emotions, fear is the most apt to induce trembling.

"Such being the condition resulting from severe terror, we have only to imagine the condition to become prolonged by a failure of the nervous system to recover its balance and right itself, and we have a more or less complete clinical picture of Graves' disease. We have all the well-known symptoms—trembling, palpitation, flushing, sweating, exophthalmos, relaxation of the bowels. There is no information that I know of in regard to the enlargement of the thyroid gland under the influence of profound emotional disturbance. All one can say on that point is that the enlargement which takes place in those cases where the symptoms develop rapidly after such disturbance makes it probable that this is actually the case. If this be so, we have had associated with one another, probably as long as the human race and its ancestors have existed, the symptoms which we find in Graves' disease. The existence of a certain abnormal condition of the nervous system

once having been established, we know how, in time, it becomes dissociated from its existing cause, rises to independence as a disease in its own right, and may require only a minimal incitement to set it off. In many cases the disease is started anew by severe mental shock; probably in a good many more it is the expression of an unconscious memory of the individual of some such shock in an ancestor."

The exigencies of the Great War enabled us to connect the emotional cause with the thyroid effect in many hundreds of cases, and many reports, both scientific in the medical literature, and of news value in the dispatches, show how frequently hyperthyroidism was related to emotional stress. Brooks, speaking of the information derived from studying numerous soldiers, says: "Very closely associated with these definitely circulatory symptoms are those of dizziness and fainting. Commonly these attacks are accompanied either by a marked paling of the face or by a marked hyperemia. Such attacks are directly precipitated by exercise or by emotional stress, such as, for example, occurs during a physical examination. Next to the tachycardia, the manifestations which seem most striking . . . are numerous evidences of emotional instability, which is an invariable accompaniment of the disease. Irritability of temper, headaches, and insomnia are almost constant, and during aggressive periods an intense feeling of fear, apprehension and terror, often quite beyond the control of the patient, is manifest." He then goes on to call attention to the fact that these outbursts of emotionalism are followed by a state of great exhaustion almost amounting to prostration.

Again, Florence A. Stoney, who served her country so well in the capacity of a Roentgenologist, in a conclusive paper "On the Connexion between 'Soldier's Heart' and Hyperthyroidism," makes this statement: "We know that the thyroid is excited by mental stress and

danger, fright being a not infrequent cause of the onset of hyperthyroidism. Such conditions are produced in a very severe degree by the war strain—by the responsibility, the danger, the noise, sudden explosions near by, with the accompanying horror and nervous shock, and the constant strain on the attention, added to severe physical strain. History tells us that for years after the Franco-German War the people who remained under the German heel in Alsace-Lorraine were, to a marked extent, subject to exophthalmic goitre. There are many cases of shell shock which show no signs of Graves' disease, and where one can only suppose the thyroid has not been adversely affected; but other cases show symptoms of hyperthyroidism definitely dated by the patient as commencing only after one such definite shock, or after the burial by an explosion."

Early in 1916, before very much had been written to connect D. A. H., and other martial cardiac conditions with the endocrines, the editor of *The Prescriber* (Edinburgh), invited me to express my ideas on the subject, and in my paper, "Shell Shock and the Internal Secretions," I paid special attention to the emotional basis of endocrine dysfunction, connecting it with hyperthyroidism and the consequent overstimulation and depletion of the adrenals. I referred to Rénon's paper, in which he described a symptom complex, which is due to *l'angoisse de guerre*, and this I definitely connected with dyshormonism in the following statement: "Among the usual symptoms enumerated by Rénon as being due to this 'war neurasthenia' are several which can be quickly connected with the endocrine organs. A progressive loss of weight is the rule—the glands of internal secretion control both nutrition and growth; the temperament is changed and the disposition becomes uncertain—mental instability and inactivity are commonly connected with ductless glandular dyscrasias; arterial tension is reduced—common both

in pluriglandular insufficiency and in hypoadrenia; dermography is reported to be nearly always present—one of the typical manifestations of severe adrenal depletion is the dermographic sign first mentioned by Sergent, and called by him *la ligne blanche surrénale.* I cannot but believe that the most constant single factor, and one that is quite susceptible to treatment, in 'shell shock' or 'war neurasthenia,' is a pluriglandular dysfunction."

Among scores of more recent communications upon this aspect of hyperthyroidism, especially in the French and British medical literature, the paper of Etienne and Richard is of especial interest. These physicians were in the city of Nancy while it was subjected to repeated violent bombardments from the big German guns and aeroplanes. This enabled them to study the effect upon the endocrine glands of emotional stress. In two women of 24 and 34 respectively, exophthalmic goitre developed in an acute form with high blood-pressure. In two other young women the blood-pressure was below normal. These writers note further that in some women menstruation was arrested by a bombardment; glycosuria was brought on in other cases. In one man of 36 symptoms of Addison's disease appeared, and these were followed by the symptoms of exophthalmic goitre. These latter symptoms subsided in three months, but the Addisonian symptoms persisted to a fatal termination in about eighteen months from the first signs of trouble. The nervous crises that were found in this case had appeared first after the destruction and bombardment of La Courneuve, near Paris. In four days the skin showed bronzing with patches of pigmentation of the mucous membrane, rapid pulse and low blood pressure. This case corroborates the possibility of an emotional origin of Addison's disease, and has been demonstrated for many cases of exophthalmic goitre under similar stress. In two other cases Addi-

son's disease became superimposed upon a preëxisting exophthalmic goitre. Hyperthyroidism of emotional origin may develop under the influence of adrenal hyperfunctioning, but it can also develop with hypoadrenia, and an adrenal difficulty may complicate a hyperthyroidism.

With the foregoing in mind, it is interesting to recall the experimental work of W. B. Cannon, of Harvard, on the innervation of the thyroid gland. Cannon and his associates succeeded in transplanting the ends of certain nerves so that certain stimuli would be continually passing through the thyroid, which, under ordinary circumstances, would have gone elsewhere. From the results of these numerous experiments he concludes that the nerves distributed to the thyroid cells belong to the sympathetic and not to the vagus supply, and that their effects are not indirect through alterations of the blood flow; indeed, that they are true secretory nerves. The thyroid gland is subject to that division of the nervous system which is brought into action in emotional excitement. After having made the above quotation, Lichty, of Pittsburgh, shows that the experiences in the recent Great War go far in confirming the work of Cannon. This explanation of Cannon's work points the way definitely from etiology to a rational treatment. It implies a condition of imbalanced nervous function which must be restored. This is a decidedly medical condition, and no one unto this day has better outlined such a medical treatment than S. Wier Mitchell, of Philadelphia, in his "rest cure." The possibility of restoring nerve function and mental balance by proper application of the principles laid down by Mitchell is beginning to be recognized by all.

This explains why so many cases of hyperthyroidism in women who have to take care of their homes and families do not benefit from "the rest cure"—they cannot rest. If they stay at home their children and home

cares keep them continually on edge, and if they go away they are in a perpetual state of fear and worry about their children, their husbands or their affairs. This is another very good reason for my somewhat pessimistic attitude as outlined in the chapter on Prognosis (Sec. V.).

Before closing this chapter, some reference must be made to the excellent remarks of Sajous upon the fundamental chemical causes brought about by emotional difficulties. In his presidential address before the American Therapeutic Society (1919), he asks: "Why, with the excessive stress due to fear, rage, etc., once terminated and entirely appeased, does the morbid process continue? Why do all the morbid symptoms, particularly those of nervous origin, persist?" He then goes on to explain that this is due to a vicious circle. The thyroid, powerfully stimulated to react against the intoxication, itself becomes a destroyer of the nerve cell. This becomes intelligible when we recall that besides the chromatin, the nerve cell is likewise rich in fatty substances, lecithin (containing stearic, palmitic or oleic acid), in particular. If we now recall the familiar fact that thyroid gland first attacks fats, breaking them down sooner than any other tissue, we can realize why it is that excessive thyroid activity so actively disturbs the nervous system. Briefly, a severe mental stress, fear, rage, deep grief, etc., causes excessive catabolism in the nerve cells, and the excretion by them of highly toxic wastes, including neurin; these poisons by provoking a defensive reaction of the thyroid, cause it to break down fats, including the fatty components of the nerve-cells, thus establishing a vicious circle, by perpetuating the catabolism of these cells and the formation of poisons. This accounts for the severity of such cases, unless they are treated, not symptomatically, but in such a way as to arrest the excessive thyroid activity.

7.—Associate Endocrine Disorders.

The well established fact that the glands of internal secretion are intimately related to one another predicates a pluriglandular syndrome in hyperthyroidism, and an extensive clinical experience establishes this beyond all question. I have never seen a single case of hyperthyroidism without an associated dyscrinism of varying extent and seriousness. Fortunately, my own experience is amplified by many hints in the literature.

The thyroid gland exerts an influence upon all of the organs of internal secretion, including even the liver and the duodenum (secretin). This "keystone of the endocrine arch," as the thyroid has been aptly called, also is influenced by the other endocrine glands, including the pancreas, parathyroids, pituitary, thymus, adrenals and gonads.

The Pancreas. There is a good deal of evidence to indicate that the pancreas and thyroid evidently produce antagonistic hormones. The thyroid inhibits the pancreas and *vice versa.* Parenthetically it will be recalled that the Langerhansian (pancreas) endocrine principle has been called by Gley, Schaefer and others, an "antihormone," for it is "a brake to the sugar mechanism," as von Noorden says, and does not "arouse or set in motion." In hyperthyroidism there is an increase in the blood sugar and occasionally even glycosuria. In the opposite condition, myxedema, the pancreas is allowed full sway and makes this privilege manifest by conferring a high degree of sugar tolerance upon the individual with this disease. In experimental thyroidism, produced by feeding thyroid glands to rats, the inhibiting action of the thyroid principle on the pancreas became evident, following microscopic section of the latter. It was noted that the alveoli became smaller and the cells themselves were reduced in size and contained many mitotic figures. These findings

promptly disappeared, however, when the thyroid treating was discontinued.

The Parathyroid Glands. The parathyroid glands are closely related to the thyroid, both anatomically and physiologically. Their proximity to the thyroid places them under pressure when that gland enlarges and symptoms of parathyroid disorder may result, such as a tendency to tetany, tremor, and a defective calcium metabolism. No doubt a parathyroid atrophy can result from pressure, but there may be similar symptoms when the thyroid enlarges in hypofunction. The physiological relation is shown by the fact that thyroid therapy relieves or, at least, improves tetany, which is one of the most usual findings of hypoparathyroidsm, although parathyro-thyroid therapy is still better.

The Pituitary. There is a very real but somewhat variable functional relation between the thyroid and the pituitary glands, but whether this could be called an antagonism or not, is hard to say. As a matter of fact, the dual function and structure of the pituitary body complicates our study of this subject. However, it is known that the pituitary enlarges in hypothyroidism, and further, that an extract of the posterior pituitary lobe *(Liquor Hypophysis—U. S. P.)* has been given by able physicians with considerable success in hyperthyroidism. When we remember that the thyroid and pituitary—especially the anterior lobe—are vitally concerned in the sexual development, and that atrophy of either gland causes many similar symptoms, we are bound to consider their early service to the organism as that of synergists, as they undoubtedly are, in many respects, the exception being, perhaps, in blood pressure control. Pituitary dysfunction may result in hyperthyroidism, though rarely, and acromegalia, a condition connected with hyperfunction of the pituitary body, may be accompanied by symptoms very similar to

hyperthyroidism and probably the symptom complex is due to a combination of these two disorders.

The Thymus. In many cases of hyperthyroidism an area of dullness will be found in the region of the second and third chondrosternal junction, that is, the thymus gland, which lies below the upper part of the sternum, is enlarged or hyperplastic. A good deal of theorizing and writing has been done to explain this enlargement, as well as to establish just what the normal function of the thymus really is. Sajous, of Philadelphia, believes that the thymus under the usual thyroid stimulation produces phosphorus, which is carried out by the leucocytes for the supply of the osseous and nervous structures during the period of rapid growth. It is well known that the thymus atrophies or disappears entirely—there is some difference of opinion as to whether it really disappears altogether—in fairly early childhood, and by five or six years the thymus is a negligible organ. It is possible that there is a demand for the substances produced by the thymus in conditions of hyperthyroidism and that the thymus is aroused from years, perhaps, of drowsy inactivity by the incessant demand caused by the excited thyroid.

Nordentoft, of Copenhagen, has been very interested in the use of the X-ray in the treatment of exophthalmic goitre, and in a comprehensive paper on the subject lends special emphasis to the importance of the consideration of the thymus aspect of this disease. Discussions of the value of this method and its influence both upon the thyroid and thymus are made elsewhere, but it should be stated here that many cases can be gathered from the extensive literature in which the symptoms of hyperthyroidism were present but the thyroid was of normal size, while the thymus was very much enlarged and marked improvement followed the removal of the thymus, surgically, or by means of the X-ray. This writer believes that the thyroid and thy-

mus under other conditions seem to work in concert. He quotes Sølling's postmortem examination of eighteen cases dying with hyperthyroidism where a persistent thymus was found in sixteen.

Aikins, of Toronto, has written a very interesting paper upon exophthalmic goitre and in its course refers to the condition which is described by the French writers as "rejuvenescence of the thymus," which accompanies hyperthyroidism in a large proportion of the cases. Capelle and Bayer found a hypertrophied thymus in forty-three out of sixty cases at autopsy, or seventy per cent; Matti in seventy-five per cent out of one hundred thirty-three autopsies, while Berry found a hypertrophied thymus present in every case that has come to autopsy by his hands. Klose goes so far as to say that hyperthyroidism never occurs without enlargement of the thymus, and several writers explain the symptomatology of this disease not by disease of the thyroid, but of the thymus, and Garré, who treats the thymus in every instance, believes that it is largely responsible for the difficulty; while Hart, another German writer, agrees with this and believes that the thymus itself is capable of causing the symptoms usually ascribed to the thyroid.

Further experimental proof has been developed by several investigators including Downs, of Philadelphia, who produced experimental thyroidism in rabbits by feeding thyroid gland, and reports that he found a hypertrophy of the thymus in seven out of the nine animals thus treated. Of course, this is only a brief report, but taken in connection with other related facts, it furthers the belief that the thymus-rest may be stimulated to both hyperplasia and hyperfunction either by the same factors which cause hyperthyroidism or by the hyperthyroidism itself, thereby becoming a real feature in the hyperthyroid syndrome.

At any rate, numerous therapeutists reported their favorable experiences with thymus irradiation in hyperthyroidism, and this aspect of the subject is considered more fully in the chapter devoted to X-ray therapy.

The Adrenals. The relationship between the thyroid and the adrenal glands is another complex that is seriously disturbed by thyroid hyperactivity. I have repeatedly called attention to the frequency of hyperadrenia in hyperthyroidism and believe that either the factors which irritate the thyroid into excessive activity or the actual excess of the normal thyroid principle, suffices to stimulate the adrenal glands abnormally with a resulting irritability, sympatheticotonus, and, later, adrenal depletion with its typical asthenic syndrome. Experimentalists such as Herring and Hoskins have found that thyroid feeding causes a hypertrophy of the adrenal glands both in the cortical and medullary portions. Herring's experiments with cats, which were fed on thyroid, showed adrenal hyperplasia with an increase of the adrenin content. An application of this in practical form is found in the Goetsch test, or the injection of adrenalin in supposedly hyperthyroid cases, which is discussed elsewhere.

It may be stated unqualifiedly that in every true case of hyperthyroidism the patient is found to be oversensitive to adrenal activity. This adrenal aspect is of great importance in such cases, the symptoms are exaggerated by it, glycosuria may be brought on or increased, and the local reaction to the epinephrin sensitization test lingers over a longer period than in normal cases.

A further hint of the possible relation between the adrenal glands and the thyroid is the fact that not infrequently in hyperthyroidism there is a pigmentation of the skin just as there is in Addison's disease.

The Gonads. The relation of the thyroid to the sex glands and their function has already been touched upon in several places, but is sufficiently important to require some further consideration. It is well known that the thyroid is responsible for the initiation of sex function and that genital atrophy is one of the recognized results of inactivity of the thyroid and associated endocrine glands. The fact that hyperthyroidism is essentially a disease of women points to a definite relationship between this and ovarian function. It is also a well-known fact that there is a predisposition to the onset of hyperthyroidism at both puberty and the close of ovarian function about thirty years later, as well as a tendency to exacerbation of an already existing disease during menstruation and pregnancy. To my way of thinking, there are two aspects to this particular relationship: On the one hand, the thyroid gland may have to work overtime in order to attempt to establish a more nearly normal ovarian function in hypo-ovarism. Levi and de Rothschild refer to good results in hyperthyroidism from the organotherapy of an associated ovarian insufficiency. On the other hand, there may be a condition of ovarian irritability, or, as it has been called by Seitz, "ovarian poisoning," where the ovarian hormone is so depraved that it acts almost as a toxin to the various responsive organs of the body, and naturally this substance irritates the thyroid as do any other poisons. Obviously these two conditions are quite opposite from the standpoint of etiology, as well as of treatment, and only by careful consideration of the associated findings will a differentiation be made.

Eastman, of Indianapolis, reports two cases connecting hyperthyroidism with dysovarism. In one, 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 the thyroid. According to Eastman, the thyroid and ovarian secretions do not supplement each other; they neutralize each other.

Tilmant, a French physician, reported a most unusual instance of familial hyperthyroidism evidently based upon an ovarian foundation. He refers to a family in which of the seventeen members, four of the seven men and seven of the ten women have goitres. In six of the women, symptoms of exophthalmic goitre developed as the monopause became installed or the ovaries became insufficient from other cause. In all of the women the goitre subsided temporarily during their pregnancies. One of the sons, who had a goitre, married his cousin, who already showed signs of hyperthyroidism, and their three daughters have developed exophthalmic goitre, but their three sons seem to be sound.

The fact remains that the ovarian aspects of thyroid disease, including hyperthyroidism, are as worthy of careful consideration and treatment from this standpoint as the persistent thymus, and, unfortunately, I have found many cases in whom the associated dyscrinism had been ignored altogether.

III

THE SYMPTOMS.

8.—THE TYPICAL CASE.

THE SYMPTOMATOLOGY of hyperthyroidism has been very thoroughly studied, no other clinical entity boasting so large and comprehensive a literature. In considering the numerous symptoms, it is necessary to emphasize the fact that the number and character of these manifestations vary directly with the extent of the hyperthyroidism; and this can range from an insignificant hint of nervous and perhaps cardiac irritability, especially under stress, to the typical cases of ultimate Graves' disease. Perhaps it may be of interest to quote just what Graves wrote many years ago:

"A lady, aged 20, became affected with some symptoms which were supposed to be hysterical. This occurred more than two years ago; her health previously had been good. After she had been in this nervous state about three months, it was observed that her pulse had become singularly rapid. This rapidity existed apparently without any cause and was constant, the pulse being never under 120, and often much higher. She next complained of weakness on exertion and began to look pale and thin. Thus she continued for a year, but during this time she manifestly lost ground as a whole, the rapidity of the heart's action having never ceased. It was now observed that the eyes assumed a singular appearance, for the eyeballs were apparently enlarged, so that when she slept or tried

to shut her eyes, the eyes were incapable of closing. When the eyes were open the white sclerotic could be seen to the breadth of several lines all around the cornea."

Quite the most thorough and voluminous reports on this subject have emanated from the Mayo Clinic, where H. S. Plummer and his associates on the Medical Staff have reviewed many thousands of cases. According to their findings, the general symptoms and the order of their onset are as follows: Cerebral stimulation; vasomotor disturbances of the skin; tremor; mental irritability; tachycardia; loss of strength; cardiac insufficiency; exophthalmos; diarrhea; vomiting; mental depression; jaundice, and death.

It should not be necessary to extend these remarks, for every textbook on medicine gives the subject full attention, and the "four pathognomic signs"—exophthalmos, goitre, tremor, and rapid pulse—are known to every sophomore medical student. However, attention is again called to the distinction already made between exophthalmic goitre, or Graves' disease, and hyperthyroidism. We will now proceed to the consideration of the principal symptoms in the order of their clinical importance.

9.—Neurological Aspects.

For a good many years exophthalmic goitre was considered solely as a nervous disease and rightly so, since many of the symptoms are distinctly nervous in character, if not in origin, as we know now. The relation of the endocrine glands to the nervous system, and especially the sympathetic system, is particularly intimate, and in no condition is this better illustrated than in the symptomatology of exophthalmic goitre.

Much of the following information is taken from a paper by Lewellys F. Barker, of Baltimore, as I have

yet to see a more concisely comprehensive statement in the literature. Though we have to deal with an intoxication resulting from thyroid dysfunction, it is not surprising that the syndrome has been and still is described as a nervous disease since many of the symptoms recognizable in this disease admittedly are due to disturbances of the neural and psychic functions. According to Barker, of the four cardinal symptoms of exophthalmic goitre — tachycardia, struma, tremor and protrusion of the eyeballs—no less than three are due to abnormal innervations; and when the host of less striking manifestations of the disease are considered, it is clear that neuropathic and psychopathic phenomena predominate. Even in the disturbances often looked on as non-neural in origin—the changes in the blood, the metabolic disturbances, the disorders of endocrine glands other than the thyroid—later there may be found to exist a neural link. At any rate, at the present time, any study of the symptoms of hyperthyroidism, in addition to a study of metabolism, involve an extensive inquiry into the domain of the pathologic physiology of the nervous system.

Barker then divides the nervous manifestation under three headings: (1) Symptoms referable to disturbances of the vegetative nervous system; (2) Phenomena referable to the peripheral neurons of the cerebrospinal nervous system, and (3) Phenomena directly referable to the brain and spinal cord.

Before discussing these three classes of symptoms, let us recall the list of symptoms of hyperthyroidism as enumerated in Barker's paper:

1. In the head and neck:
   - (a) Von Graefe's sign.
   - (b) Dalrymple's sign.
   - (c) Protrusion of the eyeballs.
   - (d) Epiphora in some, dry eyes in others.
   - (e) Loewi's phenomenon.
   - (f) Excess, or lack, of saliva.

2. In the respiratory system:
   (a) Asthmatic attacks.
   (b) Dyspnea, or tachypnea.
3. In the circulatory system:
   (a) Tachycardia.
   (b) Pulsus irregularis respiratorius.
   (c) Vasomotor angina.
   (d) Subjective palpitation.
   (e) Transitory changes in blood-pressure.
   (f) Vasomotor symptoms, especially temporary crythemas and dermographism.
4. In the digestive system:
   (a) Gastrospasm and pylorospasm.
   (b) Gastric hyperacidity or hypoacidity.
   (c) Spastic constipation.
   (d) Unmotived watery, painless, diarrheas and unmotived vomiting.
5. In the urogenital system:
   (a) Pollakiuria, polyuria and oliguria.
   (b) Certain disturbances of menstruation and of lactation.
   (c) Certain disturbances of sexual libido and potentia.
6. In the cutaneous glandular system:
   (a) Profuse sweating (and Vigouroux's sign, which is probably dependent on it).

As a result of the work of the English physiologists, Gaskell and Langley, we know that there is a double innervation in all autonomic domains; each bit of involuntary muscle and each secreting gland is controlled by two sets of neurons, the two sets being apparently reciprocally antagonistic in their effects when stimulated. Thus, if one stimulates one set of fibers, the heart-rate is accelerated; stimulate the other and the heart-rate is slowed. Similar findings might be cited throughout all the domains under autonomic control. Normally, there seems to be a fairly stable balance between the innervations of one set and those of the other set of fibers, this balance being temporarily and adequately upset from moment to moment by certain stimuli correspondent to physiologic needs.

The above long list is sufficient to convince us of the prevalence of autonomic signs in this disease, but, of course, all could not very well be present in the same

patient. It will be remembered that the autonomic or vegetative nervous system (which includes the sympathetic and autonomic systems) innervates all the smooth muscles, including the cardiac muscles, as well as all the secreting glands. So any symptom in which any of the above are disturbed must be considered as in the domain of the vegetative nervous system.

In the second class mentioned above, phenomena related to the cerebrospinal peripheral neurons, one occasionally finds that toxic-degenerative processes have caused multiple neuritis, various palsies especially of the nerves innervating the eye muscles and, rarely, paralysis of Bell's (facial) nerve. In discussing this, Barker says: "What has always surprised me most in the study of patients exhibiting exophthalmic goitre, as far as the peripheral nerves are concerned, has been the constant presence of extensive evidence of disturbed function of the peripheral autonomic nerves in contrast with the apparent absence of evidence of disturbance of function (except in rare instances) of the peripheral cerebrospinal nerves."

It is not believed that gross organic nervous lesions of the brain and spinal cord (the third class mentioned previously) often result directly from a thyrotoxic cause, though the fine tremor so characteristic of hyperthyroidism is presumed to be of cerebral origin. Most interesting to every internist are the neurotic and psychic symptoms manifested by patients with exophthalmic goitre. The frequency of neurasthenic states, of anxiety states, and of phobic and obsessional states in patients suffering from the disease is notorious. Indeed, it is on account of the symptoms of such states that the patient most often applies, or is brought by a member of the family, to the physician for relief.

Outspoken psychoses (maniacal, melancholic, paranoid) are by no means uncommon in exophthalmic goitre, especially when there is a psychopathic hered-

ity. Even in the milder cases, complaints of nervousness, irritability, inability to concentrate, headache, insomnia, pains in the eyes, pressure in the head, throbbing of the vessels, internal quivering, hot flushes, fatigability, dyspnea, anorexia and nausea are very common.

10.—Eye Symptoms.

The ocular symptoms of those cases of hyperthyroidism properly classed as exophthalmic goitre are of unusual interest, and are included here, not because they are expected in every case of hyperthyroidism, but because one cannot tell when hyperthyroidism merges into the more comprehensive Graves' disease, unless one is acquainted with these ocular symptoms.

Exophthalmos, or proptosis, is the first and basal sign of exophthalmic goitre. The eye itself seems to be pushed forward from its socket and when the attempt is made to close it without special muscular effort, it is seen that the lids do not fully cover the eye, this condition being known as lagophthalmos. The majority of the other signs follow sequentially. The order in which the most prominent ones should be mentioned is: Exophthalmos, Dalrymple's sign, von Graefe's sign, and Stellwag's sign.

In the Dalrymple sign the sclera shows above and below the cornea and more markedly and frequently below than above. It may be absent above but present below, or *vice versa.* It is distinctly a sign observed in a condition of rest in the primary position of the eye.

The von Graefe sign is seen only when the eye is moved from above downward, and is more marked in all cases in movements below the horizontal. In order to demonstrate this sign, the eye should be made to move very slowly from above downward. This von Graefe sign is the inevitable consequence of the exist-

ence of the Dalrymple sign, even as the latter is the necessary sequence of the ocular protrusion. The findings in the von Graefe sign consist in the lagging of the upper lid in relationship with the upper edge of the cornea in motion from above downward. In health, if the eye is directed upward and then follows an object, say the finger, brought down *slowly* to the horizontal meridian, the relationship of the upper lid to the cornea is preserved constantly; but with the von Graefe phenomenon the upper lid lags, and if there is sclera showing between the upper lid and the cornea in the position of rest, the band of sclera is seen to be wider as the eye descends from above downward.

The Stellwag sign has been confused by some with the Dalrymple sign. The sign is simply infrequent winking, or nictitation, and is due, in all probability, to the exophthalmos.

These and some other ocular signs are mentioned in an excellent paper, "Ocular Symptoms in Exophthalmic Goitre," by J. H. Claiborne, of New York. One of these is a phenomena first mentioned by Gifford as an early sign of this disease. This is a difficulty in everting the upper lid on account of its retraction and rigidity. This is quite common and would be natural in view of the stretching of the lid and the crowding of the muscle fibres by the protrusion of the eyeball.

Another sign is named after its discoverer, Rosenbach, which consists in a trembling of the upper lid in closing the eye gently as though in sleep. It is noted that the trembling disappears as soon as the eyes open, and is not present in actual sleep. This sign is believed to be due to instability of the tone of the muscular fibers of the levator and the orbicularis muscles, caused by the stretching due to the protrusion and the exhaustion of nervous control. This, by the way, is believed to be analogous to the tremor which takes

place in the fingers when a delicate act is attempted after violent exhaustive exercise of the hand and arm.

In his discussion of Claiborne's paper, W. H. Wilder, of Chicago, called attention to a sign which he himself had elicited some years previously, and regarding which I have seen no remarks in the literature. I had best quote Wilder's remarks in full:

"I cannot agree with the view that all the ocular signs of this disease can be explained by the mechanical effect produced by the exophthalmos. Dr. Claiborne does not place enough value on the nervous influence. Exophthalmic goitre may exist without any noticeable exophthalmos. Some of the later signs like that of Stellwag, might be explained by the mechanical theory, but the peculiarity of the von Graefe signs seems to be the slight spastic action of the levator muscle of Müller. Excitation of the sympathetic nervous system by a toxin is a more probable cause of this sign and of a sign I first observed about twenty-five years ago. It consists of a peculiar little jerk or twitch of the eyes at the instant of changing the movement of abduction to that of adduction. This sign can best be elicited by having the patient gaze intently at the end of the finger or at a pencil held about 18 inches in front of the eyes and moved with a slow even pace from side to side so as to make the eye perform an excursion of abduction and adduction. When the eye reaches the limit of the excursion and changes from abduction to adduction, there will be seen a more or less pronounced jerk or twitching before it regains its steady movement. I have observed this as one of the earliest signs, even before those of von Graefe, Stellwag or Dalrymple, and I have never failed to get it in any case of exophthalmic goitre that I have studied. However, it may be observed in some nervous diseases, such as multiple sclerosis and lateral sclerosis, in which

one may also observe varieties of spastic tremors of which this seems to be an illustration."

One other ocular sign, first noted by Möbius, is occasionally mentioned in the literature, especially in Germany. Möbius' sign is an inability to keep the eyeballs converged, and is believed to be due to a disturbance of the innervation of the internal recti muscles.

A number of theories have been set forward as explanations of the cause of exophthalmos. It has already been connected in the previous quotations from Barker's paper with the overstimulation of the sympathetic fibers. Some believe that it is due to a deposition of an excess of post-orbital fat, but this does not seem to fit in with the increased metabolism and wasting one expects to find in hyperthyroidism. It is clear that Claiborne believes that an unusual tonicity of the ocular muscles may be responsible for this condition, while on the other hand, O'Day believes that the prolonged circulatory disturbance and tachycardia brings about a dilation of the superior and inferior ophthalmic veins. In this connection, he states, "The tachycardia of hyperthyroidism rightfully may be regarded as a tetany of the heart muscle. Its tendency is to hold the ventricles in systole. Every attempt at diastole is immediately caught in the spasm and hurled back within the narrow margin yet to be invaded. The ventricles thus being unable to fill, the auricles become engorged and furnish the first step in the general venous stasis which sooner or later involves the ophthalmic veins in the manner suggested."

11.—The Circulatory System.

Various cardiovascular and vasomotor symptoms usually are interspersed through the general discussion of symptomatology in treatises on hyperthyroidism. A more thorough knowledge of the blood-vascular picture

may be arrived at by singling out the information on that one subject and collating the latest findings that are considered.

Circulatory disturbances are the rule in hyperthyroidism, early or late, and much can be determined in regard to diagnosis, prognosis and treatment from their study; in fact, death in late hyperthyroidism is commonly due to a circulatory disturbance—cardiac failure.

The earliest circulatory symptom is tachycardia, appearing after muscular or severe mental exertion. Later, the palpitation becomes constant and causes the patient to assume the common symptoms of nervousness, irritability and insomnia. The "heart hurry" and palpitation are increased by lying on the left side, and therefore we find thyroid sufferers sleeping or trying to sleep, on the right side, or on the back. The palpitation has no relation to the severity of the tachycardia since mild tachycardia may be accompanied by severe palpitation.

Dyspnea is fairly common. The rapid and labored breathing often leads both patient and physician to a diagnosis of pulmonary disturbance; in fact, the loss of weight and weakness, coupled with dyspnea and diminished chest expansion are differentiated with difficulty from the findings of true tuberculosis. Function tests and basal metabolism determinations mentioned elsewhere only can establish the correct diagnosis.

In cases that exhibit marked palpitation and subjective precordial distress, an anginoid pain of a very severe nature frequently occurs. These attacks are sometimes severe enough to cause unconsciousness, but true angina pectoris is comparatively rare, occurring most often in men with a history of addiction to wine and women, and the unfortunately frequent habit of excessive worship at the shrine of "My Lady Nicotine."

The heart is not only unbalanced and rapid in hyper-

thyroidism, tuberculosis, Addison's disease, paroxysmal tachycardia, the serious anemias and the leukemias, febrile conditions, endocarditis, and several other diseases, but is accompanied by a rapid pulse and indeed may simulate hyperthyroidism as already mentioned in connection with tuberculosis. Bloch states that the heart-hurry of shell shock cases was due to thyroid overactivity from nervous shock in most cases, with a few individuals suffering from nicotine poisoning. Soldiers who were not accustomed to tobacco and were allowed liberal quantities of "smokes," developed a condition of chronic nicotine poisoning which simulated hyperthyroidism—they had not built up a gradual tolerance for that poison.

At any rate, tachycardia — continuous night and day—is a very constant symptom in hyperthyroidism, the pulse running from 90 to 180 or more beats per minute. The mechanism that brings this about is interesting: The thyroid principle stimulates the accelerator fibres to the heart which are derived from the sympathetic, the inhibitory fibres of the vagus being stimulated to a less degree.

This hurry and rush on the part of the heart must be compensated for, and as a result, the myocardium hypertrophies. According to Hoover, inspection will show us, then, a heaving and diffuse heart-beat with the apical area increased in dimensions. The shock from the systolic contraction of the heart shakes the chest as if it were smitten by a heavily gloved fist. This shock is not local, but diffuse—involving the entire left chest.

The palpating hand is moved noticeably by the strong cardiac impulses and detects a thrill in those cases that have developed a mitral regurgitation from the dilating chambers of the heart. This thrill is felt in a large area and is not localized as is the thrill of aortic stenosis.

Audible murmurs heard over an enlarged thyroid are not necessarily proof of hyperactivity of the gland. Hoover believes that these murmurs originate at the source of the thyroid arteries, and are transmitted along the course of the arteries over the body of the thyroid. The mechanism of the production of these murmurs is quite the same as that giving rise to the murmur of a dilated aorta. In dilatation of the lumen of the aorta beyond its origin, the eddies which a current with requisite velocity will produce in transition from a smaller to a larger lumen, are responsible for the audible murmur. This same author explains how to identify the character and source of various murmurs which may be heard over the thyroid. There are three sources for murmurs in this location: Stenosis in the carotid artery from pressure on the artery by an enlarged thyroid; encroachment of the gland on the jugular vein at the bulbus venosus or in its immediate vicinity; and enlargement of the thyroid arteries. The carotid murmur does not outlast the systole of the heart, but a murmur in the thyroid arteries will always outlast the systole and may persist during the entire cardiac cycle. A murmur within the bulbus venosus will cease when the internal jugular vein is compressed at the angle of the jaw. Gravity is an essential factor in the production of a murmur at the bulbus venosus, but the murmur within a thyroid artery is unaffected by the position a patient may assume. Such a murmur will be just as loud when a patient is in the horizontal position as when he is erect.

It is well to remember that there is no constancy in the relation between a murmur in the thyroid artery and the progress of a case of hyperthyroidism. The murmurs may entirely disappear and the symptoms show no improvement. On the other hand, the size of the thyroid artery and the palpable thrill and audible

murmur may persist unaltered when all the other signs show a very marked improvement.

Percussion in early cases is not very enlightening; fluoroscopy, in my estimation, is much more satisfactory; but in later developments the general cardiac area is found to be wider and the apex impulse is further downward as far as the seventh interspace, and outward to the midaxillary line. While percussing the upper limits of the heart, one may note thymic dullness (often noticed during fluoroscopic study), a fact that will lead to an early prescription for X-ray treatment to that offending organ.

Auscultation in the early stages shows a strong apex beat, a rapid rate, and sometimes a hemic murmur at the base; later, as the heart dilates the sounds are more feeble, a systolic bruit appears in the mitral area transmitted toward the axilla, and in severe cases with threatening decompensation, souffles occur in the aortic and tricuspid districts.

Sahli has described as a "gallop rhythm," a triple rhythm that is heard over the whole cardiac area. It is a one-two-three series of sounds; the second accentuated at the apex and the third increased over the great vessels. The extra sound is presystolic in time and is much like the third sound of mitral stenosis, except that it is heard too generally over the cardiac field. The two reasons for this phenomenon are, according to this famous Swiss internist, (1) "an abnormally quick diastolic reaction followed by a sudden passive tension of the left ventricular wall from the entering column of blood," or (2) "an increased contraction of the auricle."

The heart transmits its series of exaggerated impulses to the dilated vessels of the thyroid, where a throbbing sensation is felt by the patient and on palpation. This pulsation is often visible in the thyroid and

may be observed in other large vessels such as the carotids, femoral, and radial arteries.

Pressure of the enlarged gland on the carotid sheath causes congestion in the epipharynx and vasal mucosa with epistaxis as a fairly common resultant symptom.

A venous pulse, diastolic in time, can sometimes be observed in one or both of the jugular veins.

Auscultation over the thyroid will often reveal a systolic sound and rarely a diastolic murmur. These murmurs are found only in hyperfunctioning glands and never occur in non-toxic hypertrophic glands.

Of the more superficial vascular symptoms the important ones are: (1) a soft rapid pulse (occasionally dicrotic in late cases) that is commonly arrhythmic; (2) capillary pulse; (3) throbbing of superficial arteries; (4) a lowered blood-pressure (increased at first) reaching the point of 90 mm. of mercury in severe cases with cardiac weakness; (5) symptoms of vasomotor instability such as dermographia and patches of erythema.

The heart changes that one expects in hyperthyroidism, according to Goodall, of London, are as follows: (a) Tachycardia, 120 to 200 a minute, leading to (b) myocardial exhaustion associated with (c) atonia, with relative valvular incompetence; (d) dilatation; (e) myocardial degeneration; (f) auricular fibrillation.

Blood Findings. Kocher, of Berne, was practically the first to call attention to the blood changes in hyperthyroidism, and to show the value of these changes from the diagnostic and prognostic points of view. His associate, André Crotti, now of Columbus, Ohio, refers to the blood picture in the following paragraphs:

First of all, exophthalmic goitre does not give an anemia, as it is generally believed. In all cases, the proportion of the red corpuscles is either normal or even increased. But the white corpuscles are considerably reduced. The number has been found to be

3,000 instead of the normal 8,000. This diminution of the white corpuscles is called leukopenia. In normal blood the polynuclears reach a proportion of seventy-five per cent. In exophthalmic goitre this proportion is considerably diminished, and the polynuclears may fall as low as thirty or thirty-five per cent. But at the same time the lymphocytes are increased in number, and may even reach seventy per cent; twenty or twenty-five per cent being accepted as normal. Frequently, too, but not constantly, an augmentation of eosinophiles is noticed.

Such a blood examination has a considerable diagnostic and prognostic value. Cases in which the lymphocytosis is highly developed and where the number of polynuclears is reduced, are severe cases, and operation is not without danger. Such patients should be treated medically before attempting any surgical interference.

In mild or frustes forms, where the diagnosis is doubtful, the blood examination will be of considerable assistance in deciding whether we have to deal with an exophthalmic goitre or not. Of course, in such cases we might find (seldom, however) no lymphocytosis, but for that reason alone the diagnosis should not be discarded. If there is a lymphocytosis the diagnosis is almost certain.

W. A. Plummer, of the Mayo Clinic, presents a tabular report based on the study of the blood counts in 578 patients. The average count from the entire group is as follows:

	Per Cent
Hemoglobin	83.1
Erythrocytes	4,790,000.0
Leukocytes	6,973.5
Polymorphonuclears (relative)	58.3
Polymorphonuclears (absolute)	4,065.5
Small lymphocytes (relative)	34.8
Small lymphocytes (absolute)	2,426.7

Large lymphocytes	4.4
Transitionals	1.1
Eosinophiles	1.6
Basophiles	0.49

Blank, a German investigator, explains contradictory statements regarding the diagnostic value of the blood picture in hyperthyroidism as due to diagnostic difficulties, errors of technique, temporary variations in the count and a too narrow conception of the normal values. In seventeen cases of typical hyperthyroidism twenty-eight "Basedowoid" cases, i. e., those in which the cardinal symptom of hyperthyroidism (cardiovascular diagnosis) was present, but other symptoms were also pronounced, and forty-one cases of ordinary goitre. His findings were as follows:

(1) In about 30 per cent of cases of hyperthyroidism there was poikilocytosis. (2) Typical Graves' disease is distinguished from Basedowoid and goitre by thrombopena, which is present in forty-three per cent. (3) The hemoglobin content is normal in only twenty-eight per cent of cases of Graves' disease. Its diminution has no diagnostic significance, but its increase is more in favor of Graves' disease than of Basedowoid. (4) Hyperthyroidism and goitre show no difference from one another as regards the number of the red cells. (5) Individual cases of Graves' disease show considerable oscillations in the color index. (6) The leucocyte count has no value in differential diagnosis. (7) In fifty per cent of the cases of hyperthyroidism and goitre, polychromasia occurs, and basophil stippling occurs in fifty to seventy-five per cent.

12.—Hyperthyroidism in Children.

As we have seen, hyperthyroidism is largely a disease of women, and apparently it is quite rare in children. This I believe to be due in part to the absence

of the influnce of the sex hormones, and the infrequency of this condition before puberty, and its quite usual occurrence during the period of gonad functioning predicates a wider basis of dysfunction than the thyroid alone. But as Kastner, of Milwaukee, has said, "Even though the child under ten is not open to the disturbances occasioned by the sex glands, which, according to some, play such a rôle in hyperthyroidism in adults, still his is a period of growth and development which makes demands on, and makes liable an overthrow of the balance of the organs of internal secretions and the nervous system."

Of 1500 cases reported from the Mayo Clinic, only five, or 0.3 per cent, were in children under ten years of age. Sattler could only find records of 184 children under fifteen in 3,477 cases of exophthalmic goitre on record. This quotation is made by H. C. Gram, of Copenhagen, and in his comprehensive paper Gram remarks that excessive growth in height is connected with this rare manifestation in children, but calls attention to the fact that one not infrequently encounters in girls approaching puberty some slight enlargement of the thyroid with mild nervous manifestations and a tendency to tachycardia—evidently a pathologic exaggeration of the physiological hyperthyroidism expected at this time. Holmgren in 1906 called attention to the excessive growth which occurs in these circumstances. This growth seems to be whipped up and the bones settle prematurely into a condition which, normally, would occur only four or five years later. The epiphyses become consolidated earlier than usual so that growth practically ceases after this spurt, such children not being exceptionally tall when they reach their majority.

It has long been recognized that tonsillitis, acute infectious diseases, so-called rheumatism, and even carious teeth—in fact, any condition capable of producing

systemic poisoning—were in some way intimately connected with hyperthyroidism in various forms.

The symptoms occurring in the five cases of juvenile hyperthyroidism in the Mayo Clinic series cited before, were, in their order of frequency, exophthalmos and tachycardia, mental irritability, tremor and vasomotor disturbances of the skin. In children the enlargement of the thyroid is said to be frequently most marked on the right side. The tachycardia is pronounced. Frank exophthalmos, as exhibited in adults, is more rare in children, the eye symptoms being mostly confined to a staring, unwinking look, and the loss of the normal agreement between the motions of the lids and excursions of the pupil in looking upward and downward. (Stellwag's and von Graefe's signs.)

In children the tremor is remarkable, inasmuch as it is often coarse, partaking more of the nature of choreic motion than of the fine tremor of small amplitude commonly seen in adults. Sometimes both tremors are combined. Trembling may, at times, affect the whole body. The mental irritability and nervousness so present in almost every case are usually not so marked in severity as in adults. Very rarely will mental depression be shown. There may be excessive perspiration, and in long-continued cases the skin may be modified by vitiligo, purpura, edema, and pigmentations.

Since juvenile hyperthyroidism is rare, it may be of interest to report a recent case discussed by Frantz, of New York, before the New York Neurological Society, because of several suggestive points in the findings: "The patient, a girl of nine years, had come to the Neurological Institute a year before. She was fidgety, would get into rages, and had palpitation on violent exercise. Muscular asthenia, ocular manifestations and a distinct exophthalmus were present. Tachycardia and slight tremor of the hand were also noted. Labo-

ratory findings were negative; mental age was twelve and a half.

"The patient's father had had rheumatic arthritis, the mother suffered from hyperthyroidism. Goitre had been present in a maternal aunt. The child was born in a little town in Germany, where goitre was prevalent. At the time of the child's birth a goitre developed in her mother, and the same condition was diagnosed in the child at the age of one and a half."

The course of hyperthyroidism in children offers some departures from what we are accustomed to see in adults. The passing of a few days or weeks may witness the high point in the development of the condition, and in a few weeks more there is a disappearance of all symptoms. Some children with marked exophthalmos and tachycardia, such as would be attended by great disability in their elders, continue their customary strenuous activities. On the other hand, long-continued illness, incomplete recoveries, and a tendency to relapse have been observed.

IV

THE DIAGNOSIS OF HYPERTHYROIDISM.

13.—INTRODUCTION.

THE DIAGNOSIS of hyperthyroidism is supposed to be one of the easy things in medicine. The pathognomonic signs are so well defined and easily observed that "the diagnosis virtually can be made by a member of the family." This, of course, sounds very simple, but unfortunately is a dream, and if the discovery of the four cardinal symptoms were all that was needed to complete the diagnosis of this disease, it would be indeed easy. On the other hand, when conditions have reached a stage where the pathognomonic symptoms are clearly evident, the prognosis is quite bad, although, as will be explained in a later chapter, the outcome may not necessarily be fatal.

The diagnosis of hyperthyroidism involves much more than noting the symptoms, which already have been enumerated. Success in the control of this condition is dependent upon discovering its presence in the beginning of its development, and long before the pathognomonic signs have had a chance to show themselves; and here a prerequisite to success is a broad knowledge of physiology and an appreciation of the extremely important place that the laboratory holds in facilitating this work.

Naturally, the diagnosis of the various stages of hyperthyroidism is largely a matter of knowing the symptomatology, already discussed, and this, in turn, depends upon an appreciation of the influence of the

thyroid upon the organism and the control exerted upon this gland by other organs, especially among the endocrines. Frank cases, in which the pathognomonic findings are all fully developed, offer no difficulty to the observant physician; but conclusions about the minor or "*fruste*" forms are not so easily reached. It is in these atypical and early forms of this disease that the laboratory has come to our aid, and by means of various clinical and laboratory tests one can determine whether the thyroid is beginning "to work overtime." Also these methods serve in the differentiation of certain nervous and circulatory manifestations, which occasionally may simulate hyperthyroidism, but are of an entirely different character and origin. In the past few years it has come to be customary to apply these laboratory measures even when a diagnosis has been decided upon, for it has been found that mistakes often are obviated and, best of all, that by means of these tests we can arrive at the degree of the hormonic excess and its derangement of those metabolic and nutritional factors over which the thyroid presides. The laboratory also enables us to measure the response of the organism to our regulative measures and to serve as a guide to our therapeutics as well as our diagnosis.

14.—METABOLIMETRY.

The so-called "basal metabolism," or heat production of an individual at the lowest level of cell chemistry can now be determined with considerable accuracy by indirect calculation from the data of the gaseous exchange. The latter become available through determinations with comparatively simple respiration apparatus and the estimations are made fourteen or more hours after food, at complete rest, whereby the stimulus to heat production incident to muscular activity or digestive changes is avoided. As few pathologic con-

ditions that are not easily differentiated from hyperthyroidism show a rise in the basal metabolism, this feature serves as one of the most striking and characteristic manifestations of overactivity of the thyroid. Thus a novel index of the intensity of thyroid intoxication has been added to the hitherto recognized symptoms, including tachycardia, nervousness, loss of weight, and tendency to increased sweating. The foregoing editorial from the *Journal of the American Medical Association* aptly expresses the gist of this phase of the subject.

To DuBois, of New York City, is due the credit of pioneering metabolimetry in this country, though evidently the basic idea was first thought of many years ago by the German physician, Magnus-Levy. From that time on there accumulated a voluminous literature on this particular subject, but practically nothing appeared in American medical literature until 1916. At the present time metabolism studies are quite fashionable and metabolism laboratories have been established in many parts of the country. The simplification of the calorimeters, or "metabolimeters," as they are beginning to be called, has facilitated the work and the complicated estimations of times gone by are now very much more convenient. As an editorial writer in the *Journal of the Americal Medical Association* said, in commenting some years ago, upon DuBois' first paper: "At the present time (that is in 1916), the scientific status of the treatment of exophthalmic goitre is about at the point where we would be with diabetes if there were no laboratory tests for glucose and the acetone bodies."

The accurate technique of metabolimetry need not be discussed here. (The reader is referred to the papers of DuBois, Benedict, Means and Aub, and to the more recent books on laboratory procedure.) Briefly, the method consists in determining the gas exchange with

the Benedict universal respiration apparatus (or modifications of this basic calorimeter), and from this data the heat production is calculated in relation to the body surface, which, in turn, may be conveniently determined by DuBois' height-weight chart. The calorific value of oxygen is used to estimate the respiratory quotient obtained.

According to DuBois, exophthalmic goitre stands out *par excellence* as a disease of increased metabolism, and the increased metabolism stands out as the chief symptom of hyperthyroidism. The determination of the heat production seems to afford the best index of the severity of the disease. An increased basal metabolism is found with great regularity in exophthalmic goitre, and in severe cases reaches a level found in no other condition. All other diseases in which metabolism is increased are easily distinguishable from exophthalmic goitre, and they never approach the extreme found in this condition.

Measurements made by DuBois with the Benedict calorimeter, and confirmed by others, are highly significant, and inform us that very severe cases of hyperthyroidism show an increase of as much as seventy-five per cent., or more, above the normal average, while in severe cases the increase is fifty per cent., or more, and in moderately severe and mild cases, twenty-five to thirty per cent. In a few mild, and several atypical cases, or cases in which operation has been performed, the figure may be within the normal limit. In the serious cases the warmth of the skin and the sweating can be accounted for entirely by the necessity for increased elimination of heat. At least a part of the tachycardia must be due to the increased metabolism, and perhaps it might be possible to reproduce the extreme tachycardia, cardiac enlargement, emaciation, and mental irritability, if we were able to stimulate so notably the

metabolism of a normal individual for twenty-four hours a day over a period of months or years.

The most comprehensive studies on basal metabolism in exophthalmic goitre are those of Means and Aub, of the Massachusettts General Hospital. Quite full bibliographies accompany these papers. Another student of this aspect of hyperthyroidism, McCaskey, of Ft. Wayne, Indiana, emphasizes that there is a close quantitative parallelism between the thyroid secretion and metabolic weight, and that the estimation of the latter by means of the oxygen consumption, therefore, may be relied upon with certain reservation as an accurate index of the activity of the thyroid gland. The isolation and identification of thyroxin and its complete chemical study by Kendall, of the Mayo Clinic, together with its physiological and therapeutic study by H. S. Plummer of the same institution, have placed the entire subject upon an accurate and almost mathematical basis. McCaskey believes that we may confidently proceed on the following assumptions: (1) That the symptoms of hyperthyroidism are due to quantitative variations of thyroxin in the body cells; (2) that the present fundamental phenomenon which dominates the entire clinical picture from cretinism to "Basedowism" is a perversion of a metabolic rate; (3) that this metabolic rate has an absolute equivalent in accordance with fully established physical laws in the heat production of the entire mass of body cells; (4) that this heat production is essentially a process of oxidization and is equivalent to quantity of oxygen consumed, the latter being regulated by and dependent upon the metabolic rate; (5) that it is now possible with the comparatively simple Benedict Respiration Apparatus to determine clinically the oxygen consumption over a sufficient period of time, say five to fifteen minutes, with sufficient accuracy for all clinical purposes, and finally—(6), that if food metabolism is eliminated by twelve to fifteen

hours' starvation (this means the usual normal condition in the morning), and the metabolism of voluntary muscular effort is eliminated by absolute rest in a recumbent position (a half to one hour suffices), there remains only the energy output or heat production of metabolism of the circulatory and respiratory mechanism—a small and probably negligible addition for the phenomenon of secretions and entire chemical changes of the cells of the body while at rest—and this is called basal metabolism.

The basal metabolism is quite constant, not only in the same individuals, but in all individuals when calculated in proportion to the area of body surface, and the variation in health in a large majority of people probably is less than 10 per cent. from the average rate. The clinical estimation of this basal metabolism, therefore, is a very practical and reliable guide, and while comparatively easy, it requires the utmost care and accuracy.

Before making any final decision as to the functional state of the thyroid gland, clinical metabolimetry should be done; first having eliminated such other causal conditions, aside from variation in thyroid function, which may produce fluctuations of the basal metabolism, such as fever, severe cardiorenal disease, pernicious anemia, and, of course, age. These factors are all discussed in detail in the various papers on this subject and cannot be given more extensive consideration here.

As this method becomes less complex and the apparatus more convenient, the application of metabolism study will greatly facilitate the development of accurate knowledge in regard to the factors underlying hyperthyroidism, and eventually information will be at hand enabling us to determine the cause of certain variations in pulse, cardiac activity, and other manifestations which might be due to coincidental cardiac or renal disease, and will also serve to modify our conception of

conditions as, for example, in the instance where patients suffer from auricular fibrillation with hyperthyroidism, where the low pulse-rate might give a wrong impression, whereas, the metabolism remains high, no matter what the actual cardiac condition might be. In other instances, as recently reported by Sturgis and Tompkins, of Boston, emphasis is laid on this aspect of the advantage of comparing basal metabolism with the pulse-rate in cases with hyperthyroidism. They call attention to the point that in other instances low pulse might be accounted for by the fact that these patients had a normal metabolism and their pulse-rate was unusually slow, when, in reality, the metabolism was much higher than normal.

It should be clear, however, that metabolism study is but a part of the investigation of these cases, and as Hoover puts it: "The diagnosis of Graves' disease should be made quite apart from studies in basal metabolism. If the diagnosis is once made, then the study of the patient's metabolism may be of some value in criticizing his progress. It will give some indication as to whether the patient is growing worse or improving. It is, however, by no means necessary, for the size of the heart and the heart-rate are far more dependable in estimating the progress of the disease than any guidance that basal metabolism may give. It is our practice at Lakeside Hospial (Cleveland) to study the basal metabolism in all cases of Graves' disease and all suspected cases, but the measure is not really a diagnostic aid, and is not essential for guidance and criticism of the progress of the disease. Physicians in private practice who have no such laboratory facilities available are just as well situated as are clinicians who have well organized laboratories at their disposal.

"The writer does not wish to imply by this statement that the study of metabolism in Graves' disease has been of no value. It has been of very decided value in

contributing to the study of the subject, but research and practice are very different, and I am sure the writer is justified in making the statement that the clinician who requires a study of basal metabolism to make a diagnosis of Graves' disease, or who requires the basal metabolism for guidance in the criticism of the progress of his patients, must find himself in a very weak position, both for diagnosis and for treatment of the disease."

15.—Other Clinical and Laboratory Tests.

One of the most constant results of hyperthyroidism is a condition of sympatheticotonus, in which the nerve endings of the sympathetic and the vasomotor systems are markedly sensitized to the influence of adrenin; so much so, that slight doses of this principle give a more rapid and decided reaction than is seen in the normal individual. Several tests have been originated, which involve this effect, while others, equally or more efficient, no doubt, are outlined here.

Loewi's Mydriasis Test. Loewi discovered this test while experimenting with artificial diabetes in animals. He found that the instillation of a couple of drops of 1:1000 adrenalin chloride into the conjunctival sac caused the pupil to dilate within a half an hour, and that this condition remains from ten to eighteen hours after arriving at the maximum divergence, occurring within an hour after the adrenalin was applied. He reasoned from this that here was a possibility for forming a test to determine sympathetic irritability. The adrenalin stimulated the sympathetic, in turn controlling the dilator fibres of the pupil. Hence, the facts, when followed in order, argue for the application of this test in latent hyperthyroidism. The thyroid and adrenals are synergistic, and both stimulate the sympathetic; therefore, in hyperthyroidism the sympathetic

would be irritated and an abnormally early response would follow the entrance of adrenalin into the already irritable sympathetic system. This does occur and has become widely known. This test is not absolute, but as a routine is of some advantage in filling out a puzzling clinical picture. In Loewi's test it is well to remember that in addition to the mydriasis there is a diminution or total absence of convergence miosis, but the light reflex remains undisturbed.

Goetsch's Test. Another more popular adrenal test is that of Goetsch, of Brooklyn—a test also based on the excessively irritated state of the sympathetic in hyperthyroidism. Here the adrenalin is injected hypodermically. Eight minims of the 1:1000 solution are diluted with an equal amount of sterile water and injected into the arm. Immediately the area around the point of injection blanches and at the margin of this is a red areola gradually shading off into the normal skin color. In about half an hour the center of the area becomes lilac or lavender in color, and in from one and a half to two hours the red areola becomes lavendar color while the similar color at the center disappears. The lavendar areola is the characteristic part of the test and lingers for about four hours after the primary injection. The local reaction may be accompanied by augmented hyperthyroid symptoms, such as tachycardia, exaggerated tremor and anxiety.

Goetsch's test is particularly valuable in the group of cases in which the excessive functioning of the thyroid is responsible for psychoneurosis, psychasthenia and neurasthenia, without any appreciable ocular, vasomotor or cardiac symptoms. It is also especially helpful in establishing a diagnosis in latent cases, and has been recommended highly in the differentiation of incipient tuberculosis from early thyroid hypersecretion, as the response is negative in tuberculosis that is uncomplicated by hyperthyroidism. Goetsch believes that a posi-

tive reaction in a tuberculous case is accurate proof that hyperthyroidism is present. This procedure has been thoroughly tested at the Trudeau Sanatorium, and has been shown to be of value in determining borderline cases with thyrotuberculous symptoms.

As would be expected, many have attempted to belittle the Goetsch test. It is always thus in medicine. Mention might be made of the work of Peabody, Sturgis, Tompkins and Wearn, who used the test in twenty-six normal seasoned soldiers in which the test was not present. However, they found it in fourteen per cent. of twenty-eight medical students, and in forty-eight per cent. of 103 soldiers hidden evidence of organic diseases, but with the symptom-complex of the effort syndrome. Seven psychoneurotics all gave positive results. Among hospital patients seventeen per cent. of seventeen patients with organic heart disease, and fifty-seven per cent. of twenty-one patients convalescing from acute infections gave positive reactions. Positive reactions were found in only fifteen out of twenty-one cases of hyperthyroidism. This quartet believes that, owing to the wide distribution of the reaction among persons having no evidence of hyperthyroidism, that the test does not possess any specific significance in the diagnosis. In justice to Goetsch it should be said here that medical students may indeed have latent hyperthyroidism; that the effort syndrome is very definitely connected with sympathetic irritability and factors related to hyperthyroidism and allied endocrine dysfunctions; that psychoneuroses are commonly connected with thyroid disorder, and acute infections practically always involve the thyroid. Obviously, the Goetsch test is not infallible, but as a factor in the diagnostic procedure it it a well worth-while addition to our work.

Harrower's Thyroid Function Test. My own gland feeding test has been used quite extensively in determining the pre-hyperthyroid state, and also to check

up clinically on the capacity of the thyroid gland to respond to endocrine stimuli in a given case. A detailed explanation of this test is given elsewhere. It may be well to cover its most salient points here and let the reader's own desires and interests carry him further into the literature. The test is based on the fact that thyroid influence makes its early manifestations by way of the heart, i. e., an increased pulse-rate. If the thyroid is irritable and about to start out on a rampart hypersecretory campaign, the pulse will show an early rise and will continue to be rapid for two or more days following the test. A normal thyroid will be but mildly surprised and react accordingly—a slight, fleeting increased rate. The hyposecreting gland pays but little attention to the nudge given it by the ingested glandular substance, and little or no change is observed.

The recommended application of the test consists in giving four daily doses of thyroid extract for three days. The first day ½-grain is given; the second day 1 grain, and the third day 2 grains at each dose. The pulse is taken at regular intervals for one day preceding the test, during the three days of the test, and for two days following the discontinuing of the capsules. The printed instructions which accompany the chart are as follows:

Each package of "Thyroid Testing Capsules" contains 12 capsules of three graduated strengths and sizes. A pulse chart accompanies each, with explicit instructions as to how to fill out the record.

After the consultation, at which the first pulse-counting is done and recorded, the patient counts the pulse again at 6 and 9 o'clock; and the following morning commences to take the four small capsules at 8, 10, 12 and 2 o'clock with a swallow of water, recording the pulse five times a day—at 9, 12, 3, 6 and 9 o'clock. On the second day the four medium-sized capsules are taken at similar hours and the pulse is again recorded under as nearly identical conditions as possible, and at the same hours.

During the third day the four large capsules are taken at the same hours as previously and the pulse is again recorded as be-

fore. The fourth day, or the "first day after" finishing the ingestion of the capsules the pulse is recorded as before and again during the forenoon of the fifth day when the chart is completed (and plotted, if convenient), the physician is consulted and the data thus secured carefully studied.

It is important to watch for symptoms such as irritability (temperamental or nervous), twitchings (of the eyelids, lids, fingers, etc.), breathlessness and other nervous manifestations. If it should happen that on the second or third days these symptoms are present and prominent, the remaining capsules should not be taken; but the chart is completed, while on its reverse side a brief statement is made of the symptoms giving the time of onset and other related facts.

NOTE: Take the pulse under as nearly uniform conditions as possible, preferably before eating, after a ten-minute rest and sitting. Mark the chart in the proper space with a dot at approximately its relative position, e.g., 72 would be just above the 70-line, 86 would be about the middle of the space between the 80- and 90-lines, etc. Be regular and persistent. The information thus obtained is worth all of your trouble.

This Thyroid Function Test obviously is not a measure intended to be used in frank hyperthyroidism, for the pulse-rate in these cases already is high and often irregular. The test was developed by me in the study of latent dysthyroidism, especially those cases presumed to be complicated by a thyroid functional *apathy*. While it is true that latent thyroid *sensitiveness* also is discovered by this measure, it cannot be used when conditions have reached a stage of cardiac irritability and tachycardia. In early cases, however, it is useful, and the chart will show clear-cut evidence of the difference in the reaction of a case of thyroid apathy, as compared with one of thyroid sensitiveness.

A critique of this test is made by Bram, of Philadelphia, and his statement is willingly published here: "The administration of thyroid extract to a patient already suffering with thyroid toxemia nearly always aggravates the symptoms. It is for this reason that it has been administered in specified dosage at stated inter-

vals during three or four days or longer, in order to observe whether existing symptoms are aggravated, or vague symptoms rendered clearer. This test is mentioned merely to be condemned, for not only is its reliability as an accurate and useful supplement in diagnosis called into question, but a hyperthyroidism formerly more or less latent may be whipped up to become very active and malignant in its course." This merely emphasizes, in perhaps a somewhat exaggerated way, what I have repeatedly stated, e. g., that the Thyroid Function Test *is not a test for frank hyperthyroidism.*

Glucose Tolerance Test. Since the work of Tachau, in 1911, much has been done in the study of alimentary hyperglycemia in hyperthyroidism. The older methods of blood analysis were slow and complicated, and hence such investigation could not be carried out extensively until the simpler methods of blood sugar determination were brought into practical use by Lewis and Benedict, Meyers and Bailey and other technicians.

As in the estimation of the basal metabolism already discussed, it is necessary to eliminate all sources of error by fasting and resting, so in the blood analysis for glucose it is necessary that the patient fast, before the blood is taken. The patient is then given 100 grams of glucose by mouth. One hour following its ingestion a second blood specimen is taken, and in another hour a third sample is drawn from the patient's vein. It is well to examine the urine before the test and, at the time of withdrawal of each blood sample, although the glycosuria that may be present is not of such diagnostic importance as one might at first think, as the urinary sugar would only involve what is termed "the renal glucose threshold," rather than the thyroid function.

A normal individual who has ingested 100 grams of glucose does not show an increased blood sugar content that lasts an hour. However, there is an immediate increase of blood sugar, but this soon subsides before the

hour is up. A few exceptions occur to all rules, but the hour limit is a safe one to set for normal people. Probably half an hour is usually sufficient to lower the crest of the sugar wave. The techinque of the method is found in the papers of Wilson, Smith and Janney.

In hyperthyroid cases the sugar wave, plotted from the several findings, reaches its crest at the end of the first hour—falling to normal by the end of the second hour in the great majority of cases. So constant is this finding in hyperthyroidism that it corresponds favorably in diagnostic import with the basal metabolism test. It makes no difference to the diagnostician whether the findings of the basal metabolism test or the blood sugar results are due to a direct action of the thyroid or indirectly are brought about by the influence of that gland—the fact remains that these two tests are constantly positive in hyperthyroidism and are highly necessary to the physician in accurately determining the prognosis and treatment of his suspected thyroid cases.

McCaskey's final decisions regarding the value of the study of the alimentary hyperglycemia are as follows:

1. That alimentary hyperglycemia following 100 grams of glucose is present in probably every case of thyrotoxicosis.

2. That it is rarely, if ever, present at the end of the first hour in normal persons, although it may have occurred at the end of about thirty minutes.

3. Its presence, therefore, in one hour, and especially in two hours, always indicates abnormal carbohydrate metabolism unless the gastrointestinal function is delayed.

4. It occurs in latent, and, of course, in manifest diabetes, in alcoholism, malignant disease, arthritis, and very probably in a considerable number of infections—acute, subacute or chronic—in the same category with arthritis.

5. Before attaching a positive diagnostic value to alimentary hyperglycemia in suspected hyperthyroidism, these conditions and possibly others of which we are now learning must be excluded.

6. While its positive value can only be considered corroborative, its negative value in excluding hyperthyroidism is very great and probably exceeds 90 per cent.

7. In hyperthyroidism there is no constant direct ratio between its intensity and the height of the alimentary hyperglycemia, although in general the blood sugar values are high in severe cases.

8. Too much importance should not be attached to alimentary blood sugar values below 140 mgm. of sugar in 100 c.c. blood, although sharp lines of demarcation cannot yet be drawn.

The Quinine Test. Bram, of Philadelphia, recently reported a procedure which consists in the progressive administration of quinine by mouth: "The patient is given a dozen capsules, each containing ten grains of the neutral hydrobromid of quinine, with instructions to take one capsule four times a day, to be washed down by an ample quantity of lukewarm water, an hour or two after meals and at bedtime. By the time thirty, forty, or fifty grains have been taken by persons whose thyroid function is not excessive, there develops a sense of fulness in the head, impaired hearing with tinnitus, often dizziness and headache, and occasionally a feeling of slight gastric and bladder discomfort. Persons possessing a degree of susceptibility or idiosyncrasy will experience these symptoms after the first or second capsule, while those to a degree tolerant may not complain until sixty to one hundred grains have been taken. In the presence of a hyperactive thyroid, no symptoms develop from the daily administration of quinine hydrobromid, even if given during a period of weeks or months; on the contrary, improvement in the Basedowian syndrome is frequently observed." Subjects of

thyrotoxemia are exceptionally tolerant to quinine administration during the course of the disease, and for a long time, usually years after the cessation of the thyrotoxemic process. In fact, this toleration to the drug in moderately large doses practically amounts to an immunity.

According to Bram: "The quinine test seems valuable and quite reliable, because of its simplicity in application, its harmlessness, and the fact that it does not require an especially trained individual to make the observation. Though there may be a five per cent. to ten per cent error in its use, it is especially commendable since its interpretation does not depend upon an aggravation of the symptoms of hyperthyroidism, but there is rather an improvement of the Basedowian syndrome in many instances.

Abderhalden's Ferment Test should be mentioned, though I do not believe it to be practicable in the hands of the practitioner. Rosenbloom, of Pittsburgh, gives a recent and very comprehensive consideration of this subject and the somewhat complicated technique of the method. Lampé, of Halle, and others have thought that the serum of hyperthyroid individuals contains a specific antibody to thyroid tissue, and they suggest that this can be determined by following the somewhat complex system of determination originated by Abderhalden.

The Pituitary Test, originated by Boudouin and Porak, of Paris, is also used to determine the presence of excess thyroid principle in the blood stream. One milliliter of the extract from the posterior lobe of the pituitary gland (Liquor Hypophysis, U. S. P.), when injected into the patient causes the pulse to become slower within two minutes of the injection. In thyroid toxemia this effect disappears in about eight minutes. In normal individuals the injection of a similar amount of Liq. Hypophysis causes an acceleration of the pulse,

which shortly becomes stationary in five to seven minutes, and usually returns to the normal within fifteen minutes.

Marañon's Skin Reaction. A certain dermographic sign, believed to be quite commonly present in hyperthyroidism, has been described by Marañon, of Madrid. Since he noted it present in ninety-two out of one hundred cases, irrespective of their clinical type, it seems worthy of mention here:

"By slightly rubbing or pressing with the fingers the integument of the throat an intense vasomotor reaction may be provoked. It is not confined to the area rubbed but may extend to the anterior wall of the thorax. In goitrous subjects the distribution is markedly influenced by the area of the goitre, whether unilateral or bilateral. The red area may be continuous or dissociated, and in certain cases an urticarial component is evident, the area showing slight elevation. The mere fact that the practitioner is about to compress or stroke the skin may cause the phenomenon without actual contact. A blush may appear independently on the thorax or other distant point. A proportional or quantitative behavior has not been seen, and the vasomotor irritability is quite independent of the degree of hyperthyroidism in a given case. The author claims a certain priority in calling attention to this symptom, although Chvostek has called attention to the unmotived blushing of the hyperthyroid subject. The author believes that excess of thyroid or altered thyroid secretion has sensitized the vosomotor apparatus, and he would place the phenomenon under sympathicotonic manifestations. It is seen predominantly in women, in the young and at the menopause."

A French cardiologist, by name, Lian, believes that tenderness in the region of the thyroid is an early sign of a tendency toward hyperthyroidism. The cardiac symptoms in the minor forms of hyperthyroidism may

be mistaken for a cardiac neurosis. The tachycardia may be moderate and occur only when standing or working or under emotional stress. Certainty is attained in these questionable cases by the pain expressed when the thyroid region is palpated or explored with the point of a pin.

Berkeley and Koopman report a new test for checking up on a clinical diagnosis of tentative hyperthyroidism. From their statements it would appear that this test bids fair to be as reliable as the blood Wassermann for lues, having been used by them in hundreds of cases with controls to offset error. The reaction is thought to be due to a specific thyroid substance which combines with the antibody in the patient's blood.

16.—Differential Diagnosis.

There are many chances for error in the study of the various phases of hyperthyroidism, and the differential diagnosis of clinically similar disorders is extremely important.

Let us forget for the moment the typical, well-advanced case which has already been outlined with its four cardinal symptoms and obvious earmarks of well-defined or fairly well-advanced hyperthyroidism. Let us recall some of the earlier symptoms of hyperthyroidism and compare them with other conditions which, for a time at least, simulate quite closely these conditions which are presumed to be the result of excessive thyroid activity.

Neurosis. The nervous aspects of this disease are so constant and yet so varied that one must be sure to differentiate the neurotic aspects of hyperthyroidism from hysteria and "essential neurasthenia." The laboratory gives us the key to the differential diagnosis from hysteria. There may be quite a good deal of similarity between the symptoms of hysteria and cer-

tain aspects of hyperthyroidism, but the metabolism is not increased so markedly—usually not at all—and the other laboratory tests are negative. Again, in hyperthyroidism the sympathetic system is more definitely and extensively modified than is the case in hysteria, e. g., while at times there may be manifestations of great similarity between these two conditions, they are not so uniformly present and persistent in hysteria as in hyperthyroidism.

The differential diagnosis between neurasthenia and hyperthyroidism is extremely difficult for practically all cases of hyperthyroidism are neurasthenic. Here again the clinical and laboratory study is the only means of making a differential diagnosis.

Adrenal Dysfunction. Another condition which is quite similar to hyperthyroidism in some of its manifestations is hyperadrenia, and it must be remembered that the adrenal glands are always irritated by the same conditions which cause hyperthyroidism, and also by the excessive production of the thyroid hormone itself. In other words, hyperthyroidism predicates an associated hyperadrenia, and the two are found together so commonly that the differential diagnosis is almost impossible. When we recall that the adrenal glands cooperate with the thyroid and that the same factors stimulate both of the glands, it will be readily understood how rare it would be that the adrenals would not be irritated in conjunction with the thyroid. Parenthetically it may be remarked that the ardenal glands are susceptible to toxemias, are much more easily irritated and, consequently, are much more likely to play out first and, therefore, hypoadrenia may take the place of adrenal irritability while the thyroid continues on its rampage, and the asthenic hypoadrenal syndrome is interspersed with the hyper-emotive and excessively irritated mental, circulatory and nervous aspects of hyperthyroidism. The blood pressure is a means of

determining this with some degree of exactitude. In this connection it may be well to make reference to a statistical study of simple and toxic goitre which was made by Fred M. Smith, of Chicago, at the Jefferson Barracks during the war. His study embraced no less than 65,500 men and over 1,000 cases of goitre. Smith believes that "the blood pressure affords some assistance in the diagnosis. The systolic pressure has not usually been increased in irritable heart in which no organic basis could be found. On the other hand, seventy-three per cent. of the men with hyperthyroidism had a systolic pressure of over 130 mm. of mercury and fifty-one per cent. over 140 mm." According to this writer, in doubtful cases the history and eye signs have been the determining factor, and the presence of an increased systolic pressure was used as supporting evidence in favor of hyperthyroidism. To my mind this is additional evidence of the associated presence of hyperadrenia with a hyperthyroidism.

Tuberculosis. As has been mentioned in our consideration of the Goetsch test for "epinephrin sensitiveness," tuberculosis in certain stages shows a remarkable similarity to hyperthyroidism. The Goetsch test is one of the means of making a differential diagnosis, and has been used quite extensively for this purpose. Quite recently R. B. McBrayer, of Sanatorium, North Carolina, gives a report on the study of the Goetsch test and makes a comparative report of the symptoms and signs of hyperthyroidism, as compared with tuberculosis. He studied particularly the systolic and diastolic blood pressure, the pulse-rate and quality, tremor, nervousness, palpitation, diuresis, temperature, respiration, pupillary changes, the emotional aspects, vasomotor changes in the face, hands and feet, and the presence of sugar in the urine. Based upon this comprehensive and well-supported study, McBrayer draws the following conclusions:

The differential diagnosis of tuberculosis and hyperthyroidism could be made easier for the general practitioner if, after the subcutaneous injection of adrenalin as in the Goetsch test, between fifteen and ninety minutes after the injection, he finds the following:

1. A systolic blood pressure rising ten or more points and remaining above normal for fifty-five minutes or more.

2. An increased pulse-rate of ten or more points per minute proportionate to the systolic rise.

3. An increase of pulse-pressure (the difference between the diastolic and systolic blood pressure) of thirty-five or more points.

4. The pulse irregular and varying in volume.

5. An increase in respiratory rate of four or more points per minute.

6. Varying pupillary changes.

It should be remembered that frequently a latent or even active tuberculosis may coexist in a patient suffering from hyperthyroidism, thus complicating the diagnostic problem. Without a doubt, the metabolism study and the application of the various clinical and laboratory tests outlined elsewhere will clear up the diagnosis in these border line cases.

Much emphasis must be laid on the tendency of hyperthyroidism to simulate tuberculosis, especially in the female at puberty and the menopause. This is emphasized by Emile Sergent, of Paris, who points out that in both pulmonary tuberculosis and hyperthyroidism the symptoms may be found either separately or in combination, and this authority concludes that the possibility of hyperthyroidism should always be borne in mind at both extremes of the sexual life of woman and that the presence of tuberculosis should only be admitted if there are definite proofs of its existence. (It should be remembered that the toxemia of tubercu-

losis may cause real hyperthyroidism and both may be found simultaneously.)

I recall an interesting case of a physician who had spent some time to advantage at a nearby sanatorium. The tuberculosis was apparently arrested, but he developed a condition of sympathetic irritability which caused a set of symptoms "out of all proportion to conditions now present in the lung." He was frankly told that he was a neurasthenic. He was nervous, suffered from insomnia, tremor, and especially that indefinite "internal tremor," not infrequently complained of by these cases. The pulse was periodically rapid and quite variable. While he had gained in weight as a result of the successful treatment of the tuberculosis, he had recently lost several pounds, and his medical confreres were nonplussed by the absence of expected retrogressive intrathoracic changes. This man was suffering with adrenal irritability—hyperadrenia with the sympathetic findings that are expected in this condition. My Thyroid Function Test was negative, and pancreas therapy (the pancreas is the physiological antagonist of the adrenals and pancreas therapy, as will be seen later, helps to offset some of the symptoms of adrenal excess), gave him some symptomatic help.

Another somewhat similar case of "typical neurasthenia" came to me with a story of failure to secure results from the treatment of the ailment which several doctors had confidently diagnosed. Some years before he had succeeded in controlling a tuberculosis and, like many another, had remained here in California. He drove a laundry wagon for its outdoor advantages and during the past two years gradually had developed tuberculosis. His train of symptoms were quite like some cases of hyperthyroidism. I have seen mental irritability, insomnia, loss of weight, slight tremor, tachycardia, marked asthenia, and an unstable digestion. The Thyroid Function Test gave, no especially

noteworthy help, and further study convinced me that he had adrenal irritability rather than the hyperthyroidism for which, by the way, he was referred by his doctor. In this particular case organotherapy—Crotti's formula modified by the substitution of spermin in place of ovarian substance—"has done me more good than all the treatment I've taken in the last year."

Simple Goiter. Another very important condition which has to be differentiated from hyperthyroidism is the simple or non-toxic goitre. Too often thyroid surgery has been resorted to in the belief that the patient had hyperthyroidism when, in reality, there was a simple, comparatively small, non-toxic goitre, accompanied by a focus of infection somewhere, which was not merely a large element in the cause of the thyroid enlargement, but also of the associated adrenal hypersensitiveness—which caused an increased pulse, an increase in the systolic blood pressure, and a general sympathetic irritability which was more decidedly of adrenal than of thyroid origin. Hence, it is very necessary to differentiate between these two thyroid states. In simple non-toxic goitre the thyroid gland is usually quite large and the Thyroid Function Test does not indicate any change in the pulse. As a matter of fact the indication that thyroid apathy is present is the rule, and this, of course, is directly opposite to the conditions found in hyperthyroidism.

The mental and nervous aspects of simple goitre are diametrically opposed to those of hyperthyroid goitre. While the nervous aspects may be brought on or exaggerated by some coincident condition, if this happens to be the case these manifestations vary with their origin, and since the origin is not a persistent thyroid irritation, in simple goitre complicated by these additional findings, the symptoms vary materially and are absent a good share of the time, whereas in hyperthyroidism they are present always. In simple goitre

the pulse changes and vascular findings are never so protracted as in hyperthyroidism.

Toxic Goitre. The differentiation between hyperthyroidism and toxic goitre is very difficult. Hyperthyroidism is, of course, a condition of toxic goitre, yet, on the other hand, hyperthyroidism may be largely a non-thyroid condition in which the thyroid is merely the victim of circumstances, while, on the other hand, a toxic goitre is an adenomatous hyperplasia or tumor growth of the thyroid gland which is exerting a poisonous influence upon the body. The "feel" of the goitre is a means of making a differential diagnosis. A toxic goitre or thyroid adenoma is hard, rounded, lobular, and well defined. Again, in toxic goitre one does not expect the well defined evidences of hyperthyroidism as seen in the laboratory findings previously outlined.

A differential diagnosis between essential cardiovascular conditions and the cardiovascular symptoms of hyperthyroidism can be deduced from studying the section devoted to the cardiac manifestations.

In the careful study of quite a number of soldiers clinically diagnosed as suffering from hyperthyroidism, Fred M. Smith, whose article has already been referred to, shows that the clinical diagnosis must be supported by tests in order to prove the case. Every case must present the regularly recognized hyperthyroid symptoms such as rapid pulse, fine tremor, sweaty palms, eye symptoms, etc. Of the thirty cases presumed to be hyperthyroidism, an actual diagnosis was made in only six men. The sugar tolerance test was employed and also the epinephrin test of Goetsch, and the simple thyroid function test by feeding thyroid gland in graduated doses. Of all these tests, according to Smith, the thyroid feeding test was found to be the simplest and the only accurate test, the reaction being uniformly present in the six cases of true hyperthyroidism and absent in all the pseudo types.

V

THE PROGNOSIS.

THE PROGNOSIS of hyperthyroidism is not good. Despite the statements of some, I am pessimistic about the possibility of real and unqualified "cures." It is true that there are many reports in the literature giving figures which introduce a feeling of genuine satisfaction at the outcome of the treatment, especially if it is surgical; but I cannot bring myself to a state of enthusiasm about the end results of any method of treatment.

It is true that there are several stages in the progress of this disease and that we find differing degrees of severity which naturally respond differently to treatment, as well as many constitutions which oppose the development of the hyperthyroid symptom complex more vigorously than others; and, naturally, the stage in which we find a given patient, the complicating circumstances and conditions, and especially the "physiological substratum" referred to elsewhere, makes all the difference in the world to the prospects. While the *formes frustes* of hyperthyroidism doubtless are curable, the more marked and complicated cases can only be helped and are never cured.

The reason for my pessimism is based solely upon the uniformity with which hyperthyroidism involves many structures of the body. The thyroid is never involved alone. And, parenthetically, this is the chief bone of contention between those who urge surgical intervention and those who oppose it, save only under

special and comparatively infrequent conditions. Bram has this to say upon the aspect of the subject: "It has been emphatically concluded by men devoted to research work in endocrinology, that though the thyroid gland sends forth into the circulation a surplus of its product, the organ is merely one link in a chain of glands to be incriminated in the production of Graves' disease; and that this hyperfunction of the thyroid is but a fraction of the grand totality of events occurring within many or all of the other glands of the body. Not only the thyroid gland but the parathyroids, thymus, adrenals, pituitary, sexual glands, and even the spleen, pancreas, and pineal gland are not without fault and function in this disease. How can thyroidectomy, then, overcome a disease the pathology and pathologic-physiology of which are so widespread? Generally speaking, surgery should not be attempted in exophthalmic goitres unless there be dangerous pressure symptoms from the goitre or malignant changes in the thyroid gland."

In an interesting paper on the diagnosis and treatment of hyperthyroidism, M. H. Fussell, of Philadelphia, remarks: "While it is true that many patients with well marked exophthalmic goitre recover under rest and other measures, it is equally true that every patient who has the marked characteristics of the disease has undergone a change in the heart muscle, and other organs of the body, which may cause death or prolonged invalidism. The great difficulty in the treatment of many diseases is that we are constantly confronted with the end results of the disease when the chances of bringing about a cure are almost nil. Hyperthyroidism frequently is not diagnosed until the patient has all the characteristics of the typical disease." Herein lies our greatest source of difficulty.

I have seen case after case who have gone through from one to four surgical operations, or who have fol-

lowed most rigidly a well-thought-out medical routine and have kept it up for years, acquire a greater or less degree of health, and then following some mental shock, an acute infectious disease or a toxic ailmentary storm, reacquire their old trouble again with all its numerous symptoms. Treatment may reduce the toxemia of thyroid origin and thus mitigate its baneful effect upon the myocardium, the nervous structures and the endocrine balance; but the susceptibility to this dysthyroidism remains, and the right kind of a push assuredly will start the pendulum swinging again.

I do not wish to convey the idea that hyperthyroidism is a fatal disease for, as a matter of fact, it is not. Stanton, of Schenectady, collected nearly three thousand "true hyperplastic cases representing the typical symptoms-complex of Graves' disease," and believes that it can be stated with reasonable certainty, "that typical exophthalmic goitre of the Basedow type in a majority of cases is a self-limited disease." Plummer states that the height of the intoxication is usually recorded during the first year, and Stanton believes that towards the close of the second year we may expect about one-third of the cases to have so far recovered as to be able to continue at their normal occupation, while at still later periods others improve so that we may count on sixty to seventy per cent. of spontaneous recoveries after a period of five or six years. This writer goes on to state that his conclusions agree with those of W. Hale White, of London, who was able to trace eighty-five cases who had been treated in Guy's Hospital, and in his own private practice, and after a number of years found sixty-one of these patients cured and twenty-one decidedly improved, leaving only five of the eighty-seven unimproved. Stanton says further that the medically treated cases studied by him and his associates show a mortality of about ten per cent. during the period that they were under observation. He re-

marks that "Hale White found fifteen deaths among one hundred and two patients with exophthalmic goitre. The actual deaths were compared with the expected deaths in healthy insured individuals of the same age for the same period of time and the mortality was found among the exophthalmic cases to be only twice that of the normal death rate for healthy persons of the same age. This is not a high mortality, and in life insurance work is equalled by many occupations and conditions not ordinarily considered to be dangerous."

Nevertheless, in these cases, the sympathetic nervous system, as well as the cerebrospinal neurons, have been so sensitized (and, according to some, actually structurally changed) and the thyroid cells themselves seem to have been so modified, that recurrence is far more likely in a so-called "cured" case than in one who has never suffered from the metabolic and sympathetic imbalance of hyperthyroidism. Such individuals must eschew "the strenuous life," and they must keep a very watchful eye upon accumulating toxins, and they should be told these facts just as we warn a compensated cardiac case against undue strain upon the heart.

Before closing these remarks upon the prognosis of hyperthyroidism, it may be well to quote the first paragraph of the conclusions of the paper by Stanton from which I have already quoted: "Removal of a portion of the thyroid gland of patients suffering from exophthalmic goitre produces a profound immediate effect visible within a few days of the operation characterized chiefly by an improvement in the subjective symptoms of discomfort felt by the patient and also accompanied by a fall in the pulse rate, a diminution of the tremor, and an incrase in weight. This initial improvement, however, seldom amounts to a cure. The exophthalmos usually persists for months or years, the heart remains irritable, the pulse becoming rapid with exertion or excitement and at irregular periods we may expect acute

exacerbations of toxic symptoms, which may alarm both the patient and the surgeon."

All of which establishes me the more in my belief that the prognosis of exophthalmic goitre is not good.

VI

THE TREATMENT.

OBVIOUSLY THE treatment of hyperthyroidism always must be a complicated and difficult matter. The etiological factors are too numerous and their ramifications too complex to enable us to apply any given measure with invariable confidence.

From my own standpoint I am convinced that many a failure in the treatment of this disease is as often due to the omission of essential procedures as to the selection of "a wrong method." This is particularly true in regard to the various surgical procedures and the reasons for this attitude are given elsewhere.

The greatest satisfaction in the solving of this difficult endocrine problem comes from the studied application of all the prospectively useful measures, and fortunately they are of such a character that most of them may be used together. Rest, diet, hypdrotherapy, detoxication, the X-ray, organotherapy, and the use of certain drugs all may be fitted together and made a part of a routine treatment. Then, of course, associated causative elements, as focal infections, emotional factors, and disorders of other endocrine glands, necessarily must be taken care of in conjunction with the active treatment.

The greatest source of failure in the treatment of hyperthyroidism lies in ignoring overlooked causes; and this fault is the greater when the treatment is of such a nature as to be irrevocable.

18.—General Hygiene.

No method that has ever been recommended for the control of hyperthyroidism is likely to prove of lasting helpfulness unless the fundamentals of good hygiene are explained and one insists upon their being carried out. Rest, environment, diet, elimination and other simple hygienic measures are of paramount importance.

Rest. Scattered through this monograph are hints about the importance of rest as a means of reducing the excessive metabolism, calming the irritated sympathetics and restoring the disturbed mental and physical balance. And rest undoubtedly is the ideal remedy for overwork. The cardiac disorder calls for a thorough circulatory rest, the excessive metabolism demands the reduction of muscular tire to the minimum; and the nervous hypersensitiveness requires the removal of every possible source of mental and emotional stimulation. A changed environment is often the only way to enforce the rest cure, and the eradication of fear, worry, and introspection is equally essential. And this is a hard job! As Bodley Scott, of Bournemouth, recently said: "This can never be more than a compromise; the nervous affection is all against it, and with a pulse-rate of 120-140, it is more of an aspiration than a reality; but if by comparative rest the pulse-rate can be lowered five beats a minute, much is gained." Hoover warns against dependence upon rest as a uniform part of the treatment, and says: "As these patients are weak and the ability for both mental and physical labor is very greatly reduced, the only clearly logical method of treatment is to give them rest. What may be rest for one person is not rest for another. Confinement to bed may not amount to rest; it may be a mere annoyance. Confinement to bed may not mean rest to the patient any more than confinement in a strait-jacket will amount to rest. If the patient is

discontented and unhappy and is unwilling to co-operate on such a basis, rest will not be attained by confinement to bed. I recall one patient with severe Graves' disease who grew decidedly worse after two weeks' confinement to bed. She was then allowed larger liberties and made a complete recovery."

However, rest is not all by any means, despite Hoover's statement that "The only medical treatment which has seemed of value is physical and mental rest," or the dictum of Stanton that "We can state, with reasonable certainty, that typical exophthalmic goitre of the Basedow type in a majority of cases is a self-limited disease." For instance, I recall the case of a young woman who came to me after staying in bed thirteen weeks at the suggestion of a prominent internist. She had had her appendix removed the year before. She had taken many drugs for the control of her typical hyperthyroid syndrome, and her last effort—complete rest and hyperalimentation—was suddenly ended by her physician who happened to hear a paper I read at the meeting of the California State Medical Association, and promptly advised her to consult me. Six separate and distinct focal infections were discovered, all or most of which had been overlooked. Her tonsillar crypts were badly infected. Dental radiography showed eight of the largest subdental abcesses the radiographer had ever seen. Her antra were both filled up. She had ethmoidal sinusitis. She had a bad infection of the uterus and adnexa—incidentally how rarely do we see references in the literature to endometritis and "pelvic adnexitis" as factors in the cause or at least the aggravation of hyperthyroidism—and, too, she had a severe mucous colitis.

Remember that all these sources of bacterial poisoning were in bed with her during those thirteen long weeks. The teeth were then removed, the tonsils later, and the pelvic difficulty was attacked. As a result of

this the improvement was the greatest noted in five years of treatment by a dozen physicians. When, however, her ethmoids were drained she developed meningitis and died before we could cure her hyperthyroidism entirely. The point I wish to make here is that while rest is good and imperative, it is useless to prescribe it when essential factors in the etiology, such as those just mentioned, are left alone.

Diet. If we recall that the metabolic rate in hyperthyroidism is increased from twenty-five to seventy-five per cent., and that malnutrition at times to the point of emaciation is the usual concomitant, it is clear that hyperalimentation should be a part of the treatment. Every effort should be made to increase the weight, or at least to hold it steady. In his paper, entitled "Curative versus Symptomatic Treatment of Exophthalmic Goitre," Sajous has this to say on the subject of diet: "Another aggravating factor in such cases is the use of inappropriate foods—those rich in protein. Thyroidectomized dogs suffer severely when fed on meat, and recover when fed on milk. Carnivora in general suffer seriously; herbivora, least from the same operation. Obviously the thyroid must contribute to the breaking down of meat protein. Indeed, while Falta found that protein increased the activity of the thyroid, Rudinger, his associate, observed that a diet free from protein and rich in carbohydrates tended to the opposite. Our aim being to inhibit thyroid activity, we should therefore prohibit all meat—butcher, fowl, fish, oysters even—and feed the patient only on milk and its various products—butter, cheese, cream and buttermilk—with vegetables and ripe fruit, watching out for acidosis and using alkalies freely." Harry Campbell, of London, differs in regard to the free use of milk and believes in a diet rich in fats and poor in nitrogenous constituents. Meat juice should be prohib-

ited and milk should be taken sparingly, as both of these act as excitants to the thyroid gland.

The necessity for a generous diet and a careful fitting together of the various foods should be emphasized to the patient, preferably in writing. The diet should really be that of forced feeding, somewhat akin to the mistaken method that used to be in vogue in the treatment of tuberculosis. The patient should be trained to masticate the food and the appetite should be tempted as best we can, and special efforts should be made to increase the amount of carbohydrates and fats; at the same time, according to Weiland, possibly supplementing the treatment by some pancreas preparations to increase digestion and assimilation.

Another very important dietetic point must not be omitted. Coffee must be proscribed. The same thing applies to tea, meat extract, and, in fact, all poisons, for caffeine and other similarly acting xanthin-bodies irritate the thyroid as well as the adrenal mechanism which, in turn, can and does stimulate the thyroid. The atoxic, purin-free diet is an essential part of the treatment of every case of hyperthyroidism.

The regimen of a "cured" case, as of a patient undergoing treatment, must be carefully watched. Ochsner, of Chicago, gives his discharged patients a printed slip of instructions which is subjoined:

1. You should avoid all excitement or irritation like attending receptions, shopping, church work, or politics.

2. You should get an abundance of rest by going to bed early and taking a nap after luncheon.

3. You should have an abundance of fresh air at night, consequently you should sleep with wide-open windows or on a sleeping porch.

4. You should eat and drink nothing that irritates the nervous system like tea, coffee, or alcohol. Of course, you should not use tobacco in any way.

5. You should eat very little meat. If you are very fond of meat, take a little beef, mutton, or breast of chicken, or fresh fish once or twice a week, or at most, three times a week.

6. You should drink a great deal of milk or eat things that are prepared with milk, such as milk soup, milk toast, etc.; cream and buttermilk are especially good for you.

7. You should avoid beef soup or beef tea, or any kind of meat broths.

8. You should eat an abundance of cooked fruits and cooked vegetables or very ripe raw fruits, or drink fruit juices prepared out of ripe fruits.

9. You may eat eggs, bread, butter, toast, rice, cereals.

10. You should drink an abundance of good drinking water, or if this is not available, you should boil your drinking water for twenty minutes, or drink distilled water.

19.—HYDROTHERAPY.

Hydrotherapy is always a useful adjuvant measure in the treatment of disease. Its control over the circulation and elimination has been admittedly defined and classified by Kellogg, of Battle Creek. In hyperthyroidism the treatment can be rendered more efficient by suitable hydriatic measures. The use of cold compresses and the ice bag to the thyroid permit of the further promotion of the vasoconstriction made possible by the drug treatment referred to later. In addition, by its very weight, the bag exerts a slight continuing pressure upon the goitre while the patient is lying down. The ice collar sometimes lessens the circulatory headache and throbbing by contracting the widely dilated vessels in the neck. The ice bag to the heart for intermittent periods is an accepted measure in controlling tachycardia, but care should be taken not to overdo its use.

The warm or even the neutral bath are indicated for their neurosedative effect, and the latter is especially useful in insomnia, provided that the patient can

be properly cared for, or has been instructed to care for herself, in order to prevent chilling on leaving the bath.

The cold rub or cold mitten friction in the morning not merely is a good circulatory regulator, but also exerts a beneficial influence upon the hyperidrosis which not uncommonly bothers these people, the general toning of the skin tending to lessen this uncomfortable symptom.

Nellis B. Foster, of New York, refers to the pack as another useful measure. He says : "Hot or cold packs, or alcohol rubs, are best reserved as an aid to sleep at night. Some patients respond best to hot packs, the majority better to cold ones."

Hydrotherapy may increase very decidedly our control over the toxemia, and the high clyster is of splendid service in reducing the toxemia of colonic origin. It may be well to quote from a little printed slip which is used in directing the home treatment of my patients:

The lower bowel is often a source of much toxemia and its proper care may greatly help other treatment which may be needed. The high enema, consisting of a quart of luke-warm water in which a teaspoonful of common salt has been dissolved, is an excellent preliminary treatment.

This may be introduced into the colon from a fountain- or a bulb-syringe and should be allowed to pass in very slowly and be retained for at least five minutes by the clock, preferably while lying down. During this time it is best first to lie on the back with the hips raised and later on the right side and to manipulate the abdomen gently commencing at the lower left side, running up to the ribs, then across to the other side and down to the lower right side. Often this procedure merely loosens the easily removed feces and an oil enema is advisable, for the oil gets into the kinks and crevices. This is given with a bulb syringe preferably following the cleansing enema referred to above.

Secure one pint of any vegetable oil—olive, almond or cotton-seed. Place the bottle in warm water until the oil is at body heat, divide the bottle into thirds by marks on the outside, then place one end of the bulb enema outfit into the oil, squeeze the bulb to empty the air, insert the nozzle and slowly inject one-

third of a pint of oil into the rectum. The previously mentioned positions should be taken and the oil held in all night (sometimes it is necessary to use a cloth to prevent soiling the clothing). Repeat this procedure on the two following nights, noting the amount and character of the stools.

In cases of severe intestinal irritation it is an advantage to replace one ounce of the pint of oil by one ounce of ichthyol (or ichthyonat), as this has an antiseptic and soothing influence.

Massage. Massage is a useful means in the control of the restlessness, and also the insomnia, however, it should be superficial and not of the type which is a substitute for muscular and circulatory exercise.

20.—The X-Ray and Radium.

Since it is known that in hyperthyroidism there develops an unusual vascularization of the gland, a part of the treatment, therefore, should be aimed at the reduction of this excessive vascularity. It appears that this may be accomplished through the instrumentality of the X-ray, and numerous writers have reported encouraging results since 1914, when several reports appeared in German literature. Among the first to apply this method in America were C. A. Simpson, of Washington, D. C., and W. A. Halsted and his associate, Waters, at Johns Hopkins University.

The favorable influence of the X-ray is believed to be brought about in two ways: First, it is known that the cells of the ductless glands are highly radiosensitive and easily destroyed by the Roentgen rays. We know also that the cellular hyperplasia of the parenchyma is encroached upon and choked to death, as it were, by the resultant increase of fibrous tissue of the capsule, interstices and blood vessels. The logical conclusion is that the constricting effort involving the gland will bring about a reduction in the thyroid principle manufactured, thus causing an amelioration of the distressing symptoms. Yet, may it not be possible that roentgen-

ization in addition to this brings about certain chemical changes in the glandular secretion or even in the blood serum, thus exerting a detoxicating effect? Pfender, of Washington, D. C., is inclined to give more and more credence to the theory that the X-rays, to some degree at least, effect chemical changes which alter the thyroid secretion, thus producing a normal or approximately normal state in the individual.

Another advantage in the use of the X-ray in hyperthyroidism is the convenience with which the frequently associated hypertrophy of the thymus can be controlled. Attention already has been called to the frequency with which this condition accompanies hyperthyroidism, and practically all of the technique that has been published shows that not merely has there been a thorough-going irradiation of the thyroid itself, but that the thymus also comes in for treatment. To my mind, this is fully as important a part of the treatment, and I also believe that treatment, medical or surgical, which ignores the persistent and therefore abnormally functioning thymus is wanting and likely to fail. As a matter of fact, there is no other reasonable method for disposing of an active thymus than recourse to the X-ray—surgery is quite out of the question because of its complexity and danger.

Boggs, of Pittsburgh, believes that Roentgen treatment offers a good prospect of cure without operation in a large percentage of cases of exophthalmic goitre. The principal treatment should be directed to the thyroid, but in many cases the thymus should also be rayed; this, of course, is major work, and should not be attempted by any one unfamiliar with the technique and the physiology of the ductless glands. The first symptoms of improvement are a decrease in the pulse-rate and an increase in weight; the reduction in the size of the thyroid is not always marked, even after the disappearance of all symptoms, and the exophthalmos

is the last to show improvement. Even if operation is found to be necessary later, the mortality will be lessened by a preliminary X-ray treatment, the aim of such treatment being to produce sufficient atrophy of the thyroid so that it may produce a normal amount of secretion, and no more.

Several papers refer to technique—notably those of Simpson, Pfender, Boggs and Stoney, and also Robert Knox, of London. Hubeny, of Chicago, makes some very concise statements, and as his paper happens to be the most recent one on this subject that has come to my attention, I will quote his outlined methods here:

The writer has practiced two techniques:

Technique 1. Interrupterless machine, broad focus Coolidge tube. Parallel spark gap nine inches. The rays filtered through four mm. of aluminum and 1 mm. of leather. The skin focus distance was eight inches. Three areas were treated at each sitting, each area receiving two-thirds of an erythema dose. Areas treated: 1, right half of goitre; 2, left half of goitre, and 3, thymic region. This constitutes one treatment. Repeat in three weeks.

Give such treatments, then stop for three months; this is considered one series. Then give a second series. If necessary, a third series may be given after waiting three months.

Technique 2. Interrupterless machine. Broad focus Coolidge tube; nine-inch parallel spark gap, four mm. of aluminum filtration. One mm. of leather filtration. Skin focus distance fourteen inches. Sitting, three to six. Six areas, 1, right anterior thyroid; 2, left anterior thyroid; 3, right anterior thymus; 4, left anterior thymus; 5, right posterior cervical ganglion area; 6, left posterior cervical ganglion area. Dose, one-half erythema over each area. The same frequency of repetition as technique 1 applies. The technique as given in 2 is one of choice when patient is not highly toxic, permitting a gradual recrudescence of symptoms with less tendency towards recurrence. The areas over the cervical ganglia are included, based on the observations of Cannon that stimulation of these centers causes secretory activity in the thyroid; conversely, the effect of the X-ray seems to inhibit their action.

If, for any reason, such as cardiac debility or marked thyrotoxicosis, immediate results are desired, technique 1 is to be employed.

If operative interference becomes necessary it is desirable to give an intensive course several weeks prior to operation.

The earlier the cases receive treatment the sooner their response to roentgenotherapy.

The favorable signs are the abatement of the nervous symptoms, gain in weight, slowing and stabilizing of the pulse, with a lessening or disappearance of exophthalmos in about forty per cent, of the cases. The goitre may or may not decrease in size.

In ambulatory cases no interference with the daily occupation is necessary; in marked thyrotoxicosis regulation of diet and rest, both physical and mental, are essential.

Some of the undesirable and dangerous possibilities are hypothyroidism, telangiectasis and atrophy of the regions treated. These patients are particularly susceptible towards atrophy and telangiectasis, and as the majority are young women, the resulting disfigurement (when it does occur), is of considerable import. These changes are more liable to occur when unfiltered rays are used or repeated erythema produced.

The first treatment may increase the toxemia to a dangerous degree. To guard against this, start with small doses, and precede same with rest in bed. Where surgery has been employed but no complete cure effected, great caution should be used, as the danger of hypothyroidism is then greater.

Hector MacKenzie, of London, believes that X-ray treatment may prove to be by far the best means of treatment at our command, but it must be applied in no half-hearted way. The treatment must be persevered with and, in many cases, continued for a long period of time. It is most likely to prove beneficial in cases in which the thyroid enlargement is moderate and the patient not so seriously ill as to necessitate confinement to bed. In cases of an unusually severe type and rapid course this method, as have other remedies, has seemed to fail. The present trend of experience in this respect is decidedly in favor of a further extended trial of X-ray treatment.

Radium, with its subtle destructive influence over certain cells, has been used by a number of writers.

Claggett, of Chicago, and Aikens, of Toronto, write in favor of it and claim a similar effect to the X-ray, and that the administration of radium treatment is simpler, takes a shorter time to accomplish the results, and that there can be no discoloration of the neck, though I know of no reports of this condition following properly applied Roentgen therapy.

By using the basal metabolism as an index of toxicity, Means and Aub, at the Massachusetts General Hospital, have come to the following conclusions:

1. In the majority of cases the results, after two or three years, are equally good with Roentgen-ray treatment as with surgery.

2. That after surgery the metabolism shows a rapid preliminary fall, a secondary rise followed by a final fall; that with Roentgen-ray treatment there is a gradual progressive fall.

3. That in securing the same end results with surgery or with the Roentgen ray, a lesser rest factor is necessary with the Roentgen ray. With the Roentgen ray there is practically no mortality. With surgery there is a definite one.

4. That patients treated surgically do better, and the risk of operation is less, if they have previously had their thyroid and thymus glands irradiated.

5. That the risk of operation is greater and the need for pre-operative Roentgen-ray treatment is greater in cases with a very high metabolism and moderate tachycardia than in those with an extreme tachycardia and moderate metabolism elevation.

6. That the safest program for the treatment of exophthalmic goitre, as a whole, is the routine irradiation of thyroid and thymus glands, in all cases, with surgery held in reserve for patients who do not then do well.

7. That surgery is contraindicated with patients whose metabolism is rising in spite of complete rest in

bed, and also with patients of the type with moderate tachycardia and great metabolism increase, except when they have previously had thyroid and thymus glands treated by the Roentgen ray.

8. Finally, we believe that in the management of exophthalmic goitre, periodic determination of the basal metabolism should be quite as much a routine as is the examination of the urine for sugar in diabetes mellitus. Further, that in border line cases the basal metabolism furnishes very valuable aid in differential diagnosis.

21.—Drugs.

While there are many references to the use of various drugs in the treatment of hyperthyroidism, it is very clear, first, that the majority of these drugs are directed at the symptoms rather than the cause; and, second, that their influence is not curative but merely temporarily palliative. Bearing this in mind, the drug treatment of hyperthyroidism resolves itself into the use of accepted remedies for the opposing of conditions as they come up. This explains why so many different drugs have been used and recommended.

Naturally, sedatives have come in for extensive application, and for years chloral, chloretone and the bromides have been used to overcome the sympathetic irritability and nervousness. The most acceptable form of bromide is the hydrobromate of quinine which constitutes a part of the one-time "Forchheimer treatment," which consists of quinine hydrobromate, with ergotin. This salt was chosen because it is better borne by patients than the other salts—i.e., cinchonism is not produced so easily. Forchheimer's experience was very extensive in the use of this drug. Quinine hydrobromate is given in doses of 0.3 Gm. (grs. 5), in gelatin-coated pills, four times daily; to each pill is added

ergotin, 0.065 Gm. (gr. 1), when the quinine alone does not give results in forty-eight hours.

It will be seen that ergotin, which, by the way, was first recommended by the French physician, Huchard, is associated with the bromide, and this is because of the vasoconstrictive influence of this remedy and its consequent lessening of the circulation of the thyroid and the mechanical reduction of the thyrotoxicosis.

Sajous recommends a combination somewhat similar to the Forchheimer formula, but including sodium salicylate, which was originally recommended by Babinsky for its sedative circulatory influence. Sajous' formula is as follows:

℞
Ergotinae .....3ss (2 Gm.)
Sodii salicylatis
Quininae hydrobromidi aa...3iiss (10 Gm.)
M. et ft. capsulae No. xxx
Sig.: Two capsules three times daily, one hour after a meal.

The importance of this vasoconstrictor influence has not been considered as much as it should be. According to Sajous: "The main remedial role of the vasoconstrictors in the process, however, is that they tend through their direct stimulation of the vasomotor center, to restore the vessels to their normal caliber, including the arteries of the thyroid. As a result, the volume of arterial blood admitted into the organ is reduced, thus restraining directly its functional activity."

The reduction of toxemia being of such prime importance, the value of every eliminative measure is emphasized. Sodium phosphate in doses of three or four grams daily, in a ten per cent. solution, has become an essential part of the treatment in some clinics. This was a routine with the famous Kocher, of Berne, who recommended the neutral sodium phosphate in doses

up to six grams a day. It is important to emphasize here the disadvantages that follow the use of certain alimentary stimulants. Calomel, for example, is known to be a direct stimulant of the thyroid and is contraindicated, and quoting from my own article, "If laxatives are prescribed, they must be of the gentlest-acting nature. Cathartic pills, pills of alcin, belladonna and strychnine, and active alkaloid-containing stimulants, are not advisable, because of their vigorous action, and also because of a frequently undesirable simultaneous effect upon the heart."

Our efforts for the control of toxemia of alimentary origin include the various intestinal antiseptic measures that are quite generally used. Too much importance cannot be placed upon reducing toxemia of this nature, and in addition to the antiseptic remedies a number of writers have called attention to the advantages derived from lactic acid bacteria and milk products containing them.

Pietrowicz put all of his patients upon lactic acid ferments, and a marked influence after the administration of these ferments was noted upon the general condition of the patient, in which there was marked slowing of the heart and a decided diminution of the nervous symptoms, giving great relief, and producing a marked sedative effect. At this time it is proper to instruct the patient's attendants to prepare fresh, home-made buttermilk, which Pietrowicz considers preferable to any of the chemically prepared products, but in the absence of such, lactic acid ferments from artificial media may be employed as a substitute. The gastrointestinal symptoms were also greatly relieved by this method.

The serum treatment has been tried by various clinicians and many enthusiastic reports are to be found, but it is clear from the study of current literature that the serum treatment of hyperthyroidism is not generally a success. Harry Campbell remarks that: "The

serum treatment is based upon the view that normally the thyroid secretion acts as an antidote to certain autotoxins developed elsewhere in the body, and, conversely, that these autotoxins serve to neutralize the thyroid secretion. If this hypothesis, and it is only a hypothesis, be true, then when the thyroid secretion is present in excess it is only necessary to inject autotoxins obtained from thyroidectomized animals to neutralize this excess and so to again establish equilibrium."

Antithyroidin, originally produced in Germany, is a serum product obtained from thyroidectomized goats. Thyroidectin, made in this country, is a reddish-brown powder prepared from the blood of thyroidectomized sheep and occasionally has been of some advantage. Rogers and Beebe, of New York City, have prepared a serum by injecting into rabbits two protein substances —a nucleoproteid and a thyroglobulin—and the use of this serum has seemed to counteract the toxemia temporarily, but the general impression about the value of this class of remedies is unsatisfactory, although it is fair to quote from a recent paper by Sydney Kuh, of Chicago, as follows:

"Many years ago I reported a series of some twenty-odd cases of hyperthyroidism treated with the serum of thyroidectomized animals. Most of my patients were women of the poorer classes, dispensary cases, with large families and unable to employ servants. In order that the results of the experiments might be as clear as possible, they were encouraged to continue with their housework, nothing was said to them about diet, general hygienic measures, etc.; in other words, the only change that was made in their lives consisted in the administration of the serum. A marked gain in weight, a decrease in the pulse-rate, etc., gave encouragement. This method of treatment has been continued since then and my experience now is based upon the observation

of hundreds of cases. Only recently I saw the first woman to whom I gave the serum seventeen years ago. She is still in splendid health. In these years I have learned one thing, however, about the treatment of such cases. The doses recommended by Möbius and used by me in the earlier cases, were altogether too small for the best possible results. In place of the fifteen drops given three times daily, I now usually go up to fifty or sixty drops, and I believe that this serum is by far the best remedy we have for the disease under discussion."

Many other drugs have been mentioned. Some are used occasionally; others very rarely. Arsenic has had a vogue since it is a hematinic and, in addition to its tonic effect, is said to exert a direct depressing action on the thyroid. Moretti speaks highly of sodium cacodylate in doses of 1½ grains by intramuscular injection for twenty-five days, then a break during which some iron preparation is given, then the injections are resumed in slightly increased dosage. He finds much benefit from this treatment and, in cases of moderate severity, the cacodylate is said "to be sufficient to effect a cure." Belladonna and hyoscine are of value when the tremor is very troublesome. Campbell found it of some use locally, but he thinks its internal use is inadvisable, as it may aggravate the mental excitability. Calcium is of great value, not merely as a remineralizant, but because it seems to have a selective effect upon the thyroid. Referring to this Leonard Williams, of London, says: "One of the many functions of the thyroid is concerned with the metabolism of the calcium salts, and I have often thought that patients have shown very definite improvement after taking chloride of calcium (10 grs. *ter die).* The salt seems to give the thyroid some definite and useful work to do, and thus in some degree to preserve the patient from the effects of its furious raging."

On the assumption that exophthalmic goitre is more common in districts in which the water is deficient in lime, treatment by the administration of calcium salts has been recommended. Campbell states that during the last eighteen months he has been in the habit of treating his cases in this way, and has had better results than from any other form of medication. He gives a dose of ten grains of chloride of calcium daily.

Digitalis is quite generally used, and is of value when the cardiac condition indicates, but like many other drugs that have been recommended, it is required not for the disease but for its effects. Personally, I am much more satisfied with the posterior pituitary principle for this particular effect. (See *Liq. Hypophysis)*.

Iodine is generally conceded to be a thyroid stimulant, yet Delgado, of Lima, Peru, relates that he has obtained excellent results from the use of potassium iodide in certain cases, and he urges others not to be withheld by their prejudices from its use with hyperthyroidism. In the especially striking case reported, the exophthalmos, tachycardia and enlargement of the thyroid, with hallucinations and distress, had developed after a period of emotional stress and financial worry. He applied psychotherapy and gave daily four gm. of potassium iodide, and in two days nearly all the symptoms had disappeared!

The Eclectics speak highly of Fucus and Iris, and undoubtedly there is some prospect of value in suited symptoms. Another plant-remedy, by name, Proteogen, developed by A. S. Horowitz, of Cincinnati, is now being tried.

22.—ORGANOTHERAPY.

The use of glandular extracts in the treatment of hyperthyroidism may be divided into two categories:

Those measures which have a direct action, as the influence of the posterior pituitary principle upon the circulatory and cardiac difficulties, and those that influence fundamental underlying factors as the use of pancreas preparations or anterior pituitary substance.

Liquor Hypophysis. Pal was led to apply the posterior pituitary principle (now known as *Liquor Hypophysis, U. S. P.)* in the therapeutics of this disease because of the experimental discovery that the influence of this principle on the arteries was the opposite of that of thyroid. It is well known that Liquor Hypophysis raises blood pressure and also that thyroid extract many times reduces blood pressure. Pal found that hypodermic injections of a solution of this principle apparently had no influence on the normal thyroid, or on ordinary goitre, but displayed a pronounced action when the thyroid gland was functioning excessively. Sixteen cases of Graves' disease were treated, and while the advantage was not equal in all cases, the general benefits were good. In the course of these clinical experiences this writer's chief interest became absorbed in the cachectic cases with serious cardiovascular manifestations and low blood pressure. In nine such cases, in which an operation could not be performed, the tachycardia showed a gradual improvement but returned as soon as the treatment was suspended. There was also improvement in the restlessness, tremor and hyperidrosis. In seven of his cases there was a gain in weight, although all showed every token of deep intoxication.

An interesting point in the remarks of this writer concerns the fact that in three of the severest cases a paradoxic symptom—swelling of the thyroid gland—was seen, and in a fourth case, in which the thyroid was very small, but in which there was profound thyrotoxicosis, this symptom was not only overcome, but evidently the patient acquired new thyroid tissue, and

there is no doubt that his life was saved by the pituitary treatment. Experiments on animals has shown that the thyroid and pituitary principles are, in part, antagonists, and it is assumed that the latter inhibits in a degree thyroid hormone secretion. It may also be that some antagonistic substance, normally held in check by the thyrotoxic bodies, appears to be generated in excess, and thereby to produce the swelling of the gland.

Galloway reports a case of Graves' disease of fifteen years' standing to whom he gave fifteen minims of pituitrin daily for forty days, during which time the patient gained twelve pounds, the tachycardia and tremor were controlled entirely, and the exophthalmos was markedly reduced. This writer calls attention to the fact that twice since the treatment was discontinued the tachycardia has returned, due to worry or overwork, but each time seven daily injections of fifteen minims of the pituitary preparation sufficed to control this symptom.

The use of Liquor Hypophysis properly may be a part of the routine treatment of the tachycardia so common in this disease, but the dosage should be small at first as it is possible to produce vascular spasm, especially where there are symptoms of arteriosclerosis. I have frequently used three minims daily with much benefit, and seven or eight minims, to my mind, is a maximum daily dose. It is by far the most important remedy in my experience. "I have had occasion to use numerous sedative remedies, and none seem to exert so particularly beneficial an effect upon the pulse-rate and cardiovascular irritability as this organotherapeutic wonder-worker. The usual effect of these injections is to reduce the pulse rate from thirty to seventy beats a minute, while by its remarkable influence upon so many functions it also favors the intestinal activities as well as increasing diuresis. Whether the pituitary

gland contains a principle that exerts an effect opposite to that of the thyroid gland (an 'anti-hormone') has not been established clinically at least. Pituitary therapy is as profitable an advance in the treatment of hyperthyroidism as any measure suggested in the past ten years, and deserves much wider study, application and practice."

Thymus. Elsewhere attention has been called to the not infrequent complication of hyperthyroidism by a reëstablishment of thymus activity and the enlargement of this gland. There are also a number of references in the literature to the value of thymus extract in hyperthyroidism, and it is believed by Dor, of Lyons, France, that the thymus enlarges itself in an effort to offset the thyrotoxicosis, and after conditions have reached a certain degree of seriousness, the enlarged thymus itself becomes a detrimental rather than a beneficial factor. At all events, Dor goes so far as to say that nothing ameliorates exophthalmic goitre as well as thymus extract, and this author and his son have made many clinical tests of this measure which happens to be one of the oldest organotherapeutic measures in hyperthyroidism, for as far back as 1895 Owen administered thymus to a case of hyperthyroidism by mistake, and the results were quite unusual, and when the mistake was discovered, it naturally prompted this author to try it again. with further encouragement.

Recently Hawk and his associates in the University of Pennsylvania have studied the effects of thymus feeding upon the metabolism in goitre, and in their last communication they give scientific proof that a certain influence actually is exerted by thymus therapy. They studied the metabolism of a number of elements, dividing the day into five periods and gathering accurate figures of the metabolic changes. The usually increased metabolic activity in exophthalmic goitre was watched and under thymus treatment the retention of all ele-

ments was seen to be depressed, while on its removal the elimination of these elements increased again. Quoting from Hawk's paper: "Thus thymus treatment appeared to depress the stimulating effect upon metabolism (caused by thyroid excess), which supports the view of a possible antagonistic action of these glands, such as has been suggested by others on the basis of indirect evidence." It was also noted that thymus administration led to a greater retention of water and an increase of weight.

Evidently there is enough accurate scientific basis for the use of thymus when an excessive metabolism with emaciation and the usual findings of hyperthyroidism are present. At least the enthusiastic reports of some writers now have more than an empirical foundation.

Anterior Pituitary. In December, 1915, George Richter, of St. Louis, read a paper on "A New Treatment for Graves' Disease," in which he refers to the value of the oral administration of the anterior lobe of the pituitary which he found to be a satisfactory means of controlling the symptoms in a number of cases.

In his recent Prize Essay, Leigh F. Watson, of Chicago, reports seventy-five cases with varying degrees of hyperthyroidism, to whom he gave a pluriglandular formula, the principal ingredient of which was anterior pituitary substance. The reports were unusually good, when the character of this disease is considered, and the complexity of its associated disorders.

Corpus Luteum. Ovarian therapy is specifically directed at disturbed ovarian function, and it is possible that the ovarian hormone functions may be sufficiently disturbed to aggravate hyperthyroidism. Hoppe, of Cincinnati, has developed a theory that hyperthyroidism actually may be caused by a defective secretion in the interstitial sex glands and that the hormones of these glands exert an inhibitory and regulating influ-

ence upon the thyroid secretion; that when the function of these glands is deficient there ensues a lack of physiological inhibition of the thyroid, with a resulting excessive secretion, and therefore, hyperthyroidism. In other words, Hoppe believes that hyperthyroidism and hypo-ovarism are closely related conditions and emphasizes the fact that organotherapy directed at the ovarian aspects sometimes controls the thyroid manifestations. He states that the ordinary Forchheimer treatment (which is referred to in the previous chapter) often is attended with only indifferent success, while on the other hand, the combination of quinine hydrobromate, extract of belladonna and ovarian extract was found to be rapidly beneficial in many of the cases, and the improvement usually was so rapid and marked as to convince this writer that rest, diet, and the hygienic measures, all of which he had used for twenty years, could not account for the results, but that the ovarian product was the active therapeutic agent.

Crotti, of Columbus, Ohio, has also emphasized the frequency with which there is an ovarian aspect to hyperthyroidism, and his pluriglandular sympathetic sedative formula contains a suitable dose of ovarian extract for that very purpose. From my own standpoint I agree with these writers, and while there may be some question about Hoppe's theory that ovarian dysfunction is a direct cause of hyperthyroidism, assuredly it is a common complicating factor, which should be taken care of simultaneously with other associated difficulties.

Pancreas. Another useful remedy in the treatment of hyperthyroidism is pancreatin, or preferably, total pancreas substance. It is believed that this may exert a dual action, not merely increasing digestion, and hence favoring the assimilation of much-needed food, but also acting upon the sympatheticotonic condition characteristic of hyperthyroidism. This is explained in

the following manner: Toxemia having its origin in the thyroid gland, or from any other associated cause, gives rise to a hyperadrenia, which I am convinced is responsible for a share of the symptoms of hyperthyroidism. The dry mouth, the tremor, the heart-hurry, and some of the other nervous manifestations seem to be as much of adrenal as of thyroid origin. Now it will be recalled that the internal secretion of the pancreas exerts a decided antagonistic effect upon that of the chromaffin cells, and, in fact, for this reason, this principle has been called by some "the pancreatic antihormone;" hence, any means of facilitating this endocrine function of the pancreas, in addition to increasing its external secretory powers, is distinctly in order. The administration of pancreas preparations not merely assists digestion but favors the increase in its output into the blood of these chemical substances which are physiologically opposed to the conditions present in hyperthyroidism.

In a note by Leviton, of Chicago, an interesting reference is made to clinical results in this connection. He was treating several cases of diabetes mellitus and gave fifteen to twenty grains of pancreatin by rectal administration two or three times a day. In two of these there was a complete cessation of the manifestations of an exophthalmic goitre which was associated with the diabetes, and while these experiences were virtually accidental, and similar cases fortunately infrequent (for the combination of diabetes mellitus and hyperthyroidism is both rare and very serious), they indicate that still more consideration should be given to these associated endocrine factors.

Adrenal. Another adjuvant organotherapeutic measure should be mentioned here. The late Professor Gibson, of the University of Edinburgh, was strongly in favor of adrenal therapy in hyperthyroidism. For a long time he persisted against the discouragements of

his colleagues. Years after his death it began to dawn on the profession that there was indeed an adrenal aspect to every stage of hyperthyroidism; and that while in the early stages the adrenals are irritated and a condition of hyperadrenia obtains, as has been mentioned previously, it also followed "as the night the day" that the long-continued overstimulation of the adrenals necessarily produced a hypoadrenia which, in turn, complicated the case and demands treatment just as do other basic or associated disorders. There are now many references to the value of adrenal support when it is indicated in hyperthyroidism, or when the patient is asthenic and in a typical condition of hypoadrenia (with low blood pressure, marked muscular asthenia, and diminished elimination, especially of the urinary solids).

Crane reports his experience with this treatment and states that the patient was progressively benefited. The edema slowly disappeared, the mental condition was improved, and the size of the thyroid was reduced, and eventually the tachycardia, tremor and struma entirely disappeared. The exophthalmos, while improved, was not fully controlled. The dose used by Crane was one grain of adrenal substance three times a day.

I have frequently been asked why adrenal gland and pancreas can be given together in hyperthyroidism (it may be mentioned that the formula originally suggested by Crotti contains both adrenal and pancreas). This is easily explained when we recall that adrenal substance consists largely of the cortex and does not contain a very marked dosage of the adrenal medullary principle. Adrenal extract is a cardiac tonic and slows and strengthens the heart. Further, when administered in this form, its influence upon the adrenal glands and the factors controlled by them is supportive rather than stimulative. It must be remembered, too, that in the complex hormonic mixture in the blood all the hor-

mones, both antagonists and stimulants, are to be found and the remarkable selective capacity of the organism to avail itself of those which are needed and in proportion as they are needed, explains why, when antagonists are given simultaneously, benefit may accrue in both the directions represented by the apparently opposing principles. Suffice it to say that the tonic value of adrenal gland is an advantage in the atonic circulatory conditions of hyperthyroidism, and that the antagonistic value of pancreas over adrenal *medullary* irritability as well as the thyroid itself makes this pluriglandular idea not so unreasonable after all.

Thyroid. Quite a number of writers have indicated that thyroid extract itself has some place in the treatment of hyperthyroidism, and this paradoxical statement occasionally really has some basis of good sense, for unquestionably the thyroid gland is a dual organ, and its service to the body is not limited to the production of one single hormone; and it is possible that the condition of thyroid hyperplasia involves more definitely the one part of the thyroid as compared to the other. At all events, in Graves' disease there often ensues a condition of thyroid exhaustion where small doses of thyroid gland are a distinct advantage, and this has been taken advantage of by Leigh F. Watson, of Chicago, who uses a combination of anterior pituitary and thymus (both of which have a place in the treatment of this condition as indicated above), with thyroid, the varying doses of which are usually, however, small ones carefully fitted to the circumstances. Usually the administration of thyroid in the earliest stages of hyperthyroidism causes an exacerbation of the symptoms and this measure has been used as a diagnostic test, and is referred to more fully in the chapter on diagnosis.

23.—My Routine in Hyperthyroidism.

When a colleague, going over some of the statements collated in the manuscript for this monograph, said, "There are so many differing ideas gathered here that some of the men will not thank you for leaving them to decide what to select in the way of medical treatment," I resolved then and there to reprint at the conclusion my short paper with the above title. These remarks, however, are not intended to be considered as a hard and fast statement of therapeutic policy in hyperthyroidism, but are offered as entirely suggestive.

The great idea in the treatment of hyperthyroidism is to do everything possible for the patient—and do them as nearly at once as circumstances permit. Bearing this in mind, I wish to direct attention in closing to the following:

One of the frequent puzzles encountered by general practitioners is the complex related to disturbed function of the thyroid gland. Perhaps every other day I get a letter reading something like this:

"Please suggest treatment for a woman aged 28, very nervous, anxious and restless. Marked insomnia. Slight tremor when hands are extended. Pulse at times as high as 140 and much worse after excitement. Menses irregular and always associated with exacerbations of her other symptoms. There is a slight enlargement of the thyroid, but it is not nearly as great as I expected it would be. I do not notice exophthalmos in this case, but believe that the patient is suffering from hyperthyroidism, and will be glad to hear from you," etc.

To my way of thinking, cases of the type just mentioned are properly diagnosed as suffering from *thyroid irritability*, and I have found that the following therapeutic routine is satisfactory in a great many cases:

Absolute Rest Imperative. As soon as possible, and during your efforts at treatment, prescribe as complete

muscular and mental rest as circumstances permit. In serious cases rest is so imperative that nothing must be left undone to favor it. Care and worries must be left and quiet insured.

An Extra Good Diet. Naturally patients in this category always are in a state of metabolic imbalance, and while it is advisable to simplify the diet as much as possible, since the chemistry is usually increased in these individuals, obviously the food should be generous in amount and of an easily assimilable character. In addition to three well-balanced meals, it is proper to add an extra lunch and perhaps give a glass of hot malted milk, or some such thing, at bedtime. In addition to its nutritive value, sometimes this latter is an advantage for the control of the insomnia which sometimes is found in these cases.

While acidosis is more common in hypothyroidism than in hyperthyroidism, I have found considerable advantage from the administration of the alkaline mineral salts which replace the reserve so often depleted in the chronic endocrine difficulties. For this purpose I use three grams of a mixture of magnesium phosphate 2, calcium phosphate 8, calcium glycerophosphate 8, potassium bicarbonate 32, and sodium bicarbonate 50, with much water, an hour before food, twice a day. (It is very necessary to give this on an empty stomach in order that the gastric acid may not nullify the alkalinity, and vice versa.) I usually advise the continuance of this part of the treatment for at least three or four weeks, and thereafter advise the tablets on alternate weeks.

Crotti's Sedative Formula. Another procedure in the line of active treatment involves the use of a pluriglandular formula which frequently exerts a sympathetic and sedative effect. This is a modification of a formula suggested some years ago by Dr. André Crotti, of Columbus, O. This formula contains pituitary

(total), adrenal, pancreas (not pancreatin) and ovary, and the main difference between my modification of the Crotti formula and the original lies in the fact that the amount of pancreas substance is increased threefold. The fundamental value of this preparation lies in its capacity to slow and strengthen the heart action, to modify the tendency to dysovarism, not unusual in cases of this character (it may be noted that no objection can be found to administering this formula to men, despite the fact that the ovarian element may not be of particular value), and to antagonize or sedate the sympathetic irritability, which is the chief manifestation of hyperthyroidism. Such treatment needs to be carried out for several months, and, naturally, the influence is purely symptomatic.

Find and Remove Focal Infection. In this connection, I cannot lay too much emphasis upon the fact that hyperthyroidism is not merely an irritability of the thyroid gland, with a corresponding increase in the production of its hormones. As a matter of fact, it is really a manifestation of a much more subtle and deeply laid disturbance in the functions of the body. As I see it, there are three fundamental causes, any or all of which may be related to the onset of the thyroid irritability. The first of these may consist of various foci of infection, and every case of hyperthyroidism should be very carefully examined from every possible standpoint so as to exclude conditions which would favor the absorption of bacterial poisons into the system. The teeth, tonsils, sinuses, lungs, gall-bladder, intestines, appendix, and pelvis all should be carefully studied from this standpoint, and if it is believed that there is a condition of focal bacterial toxemia, obviously it must be taken care of, for no treatment, whether surgery of the thyroid or the very best medical regimen—with or without such measures as I have mentioned here—could possibly have any direct influence upon a focal

infection. Incidentally, herein lies the great sin of some surgeons! The thyroid gland is so obviously at the root of the serious sympathetic imbalance that of course it must be removed forthwith, *while the real underlying cause remains* to cause just as much trouble later on by irritation of the remainder of the thyroid, which must necessarily be left behind. This is wrong, but my remark does not mean that I am opposed to surgery under certain circumstances, for undoubtedly it is occasionally necessary and decidedly helpful, but I have seen too many postoperative cases to believe that the thyroid is the chief offender. *It is merely the victim of circumstances.*

Study Possible Endocrine Causes. Again, the intimacy of the relation of the glands of internal secretion enters very definitely into hyperthyroidism, both from the standpoint of cause as well as of effect. The function of the thyroid gland is bound up with that of the other endocrines and two of these glands in particular are likely to enter into the etiology of hyperthyroidism. The one is *the thymus,* which may be both persistent and enlarged, thereby adding to the complex by what properly should be called hyperthymism. At all events, a number of prominent investigators have found that a goodly percentage of patients suffering from hyperthyroidism have a persistent thymus and that treatment calculated to reduce the thymus (the suitable exposure to the X-ray, perhaps half a dozen times) not merely disposes of the thymus, but mitigates the symptoms of the hyperthyroidism very materially. Hence a condition of this kind should be looked for in every case and disposed of when it is found.

The other endocrine organs often closely related to dysthyroidism, are *the ovaries,* and when one appreciates the close dependence of the thyroid upon the ovaries, and the ovaries upon the thyroid, it is clear how any disturbed function of the ovaries may react upon

the thyroid sufficiently to derange its normal routine. Personally, I do not believe that hyperthyroidism is related to ovarian dysfunction as often as ovarian dysfunction is related to hypothyroidism, but there is a relation and when there is a disturbance of ovarian function it should be sought for and controlled, and this is usually best accomplished by suitable organotherapy. It was evidently with this in mind that Crotti added the dose of ovarian substance to this formula, which has been referred to above.

An Emotional Basis Is Common. Finally, the emotional aspects of hyperthyroidism are extremely important. Indeed, the thyroid function may be unbalanced solely as a result of a mental shock, and without any question, instability of the nervous system is not merely the result of hyperthyroidism *but may be the cause of it as well.* This complicates matters very much indeed and explains the necessity for rest and a congenial environment as well as the removal of all factors which might aggravate conditions which act through the medium of the emotions. It also explains the good results that we often secure from a change of circumstances and cessation of all work and worry.

No matter what may be the cause of hyperthyroidism, and whether one uses medicine, organotherapy or the X-ray, the suggestions made above are perfectly in order, for while they may not directly attack the cause, they have many hundreds of times brought about a satisfactory control of the effect. This undoubtedly is rational provided that whilst this is going on the cause is being sought for and eradicated as far as possible. I cannot refrain from emphasizing this because many physicians have fallen down on cases of this kind, and on analysis of the circumstances later on I have found that some subtle irritating element—infective, endocrine or emotional—is still at work undoing the good that might come from organotherapy, or whatever else

may be used. I have even been criticized for failure to accomplish as much as was hoped from the pancreas therapy just mentioned, and have been able to justify myself by showing up allied disorders which, when cared for, later permitted the organotherapy to become useful.

Remarks on the Prognosis. I might as well say here that I do not think that the prognosis of frank hyperthyroidism is good, either from the surgical, medical, or the organotherapeutic standpoint. Practically always there has been a fundamental derangement of the whole endocrine balance, and no matter what we may do, recurrences are very likely to come when the causes, which we may be able to remove for a time, are permitted to reassert themselves. In other words, we can accomplish a great deal for a given case and a year or two later the development unchecked of some focus of infection may undo all our hard work, or mental conditions may interfere, as they did in a case which I recall: A young married woman had a long siege of difficulties with hyperthyroidism which culminated in surgery. About nine months later she came to my attention with "my trouble just about as bad as it ever was." We found a bad appendix, which was removed. We neutralized a very decided acidosis and gave her the sympathetic sedative treatment (already mentioned). The results were splendid. The pulse practically never went above eighty and the patient obviously had improved so much that she considered herself well. But—she had a near accident in an automobile. Nothing really happened, but for a fraction of a second it certainly looked as though she were going to be wrecked, and within a day or two all of her troubles were back again —proof of the emotional aspects of this difficulty.

This does not deny the value of the routine mentioned above, and to it may be added such other drug and sedative treatment as circumstances may demand.

VII

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TABLE OF CONTENTS

NEURASTHENIA:

AN ENDOCRINE SYNDROME

INTRODUCTION

1.—PRELIMINARY REMARKS

THE OBJECT of this monograph is not so much to collate interesting points about neurasthenia, as to attempt to establish by the published experiences of many others the opinion that I have long held that neurasthenia is indeed fundamentally an endocrine syndrome. It will be my attempt to show that from the underlying, predisposing, physiologic strata to the direct, exciting causes there is a large endocrine aspect to its etiology, and that, therefore, the consideration of this disorder from this particular viewpoint is likely to broaden materially our possibilities for therapeutic success.

My interest in these problems is not so recent. A number of years ago I published a book entitled, "Practical Hormone Therapy," in which several hints of the endocrine phases of presumably non-endocrine disorders were disclosed. In a later article entitled, "The Internal Secretions in 'Run-Down' Conditions," I remarked:

"Many a chronic and intractable disorder is due to an overlooked defect in the production of the hormones of the internal secretory glands. Increasingly greater stress is being laid upon the importance of these chem-

ical messengers and there is now little doubt that in health as well as in disease they regulate and correlate the metabolic activities of the body.

"Many a patient under treatment for some more or less obscure trouble has associated with it a condition of hormone deficiency; for when an individual is 'run-down' with the usual manifestations of this condition—nerves on edge, oxidation poor, elimination low, muscles easily tired out, and, almost invariably, the digestion and assimilation faulty—it is not conceivable that when practically all the other activities of the body are below par, the internal secretory organs are working normally and producing their necessary quota of hormones. In fact, this lack is often the sole cause of many conditions of this character, and pluriglandular insufficiency should be sought for more generally than it is at present, and its importance appreciated in a more practical way."

To-day the medical profession is appreciating as never before the truth of the above statements; and this monograph, I hope, will serve to broaden this appreciation still more.

Any consideration of a subject as complex as neurasthenia involves an understanding of what sort of a condition it is supposed to be; and when the subject is to be considered from the endocrine aspect, it becomes doubly complex because all endocrine problems are complex and neurasthenia, of all conditions, is one of the most indeterminate and variable.

As a matter of fact, the term "neurasthenia," or, perhaps, the current usage of the word, has been criticized by a number of physicians and according to Tom A. Williams, the neurologist of Washington, D. C., "the term 'neurasthenia' is a convenient cloak for failure to investigate a case sufficiently." Unfortunately this criticism of the profession is all too well founded, and a large number of cases labeled "neurasthenia" really

only have a latent and secondary neurotic aspect. In an article on the dietetic treatment of neurasthenia, Paton makes the following comment on the character of this disorder: "As everyone knows, 'neurasthenia' is not the name of a specific and definite disease, but merely a convenient term for a very varying congeries of symptoms produced by many different causes." As I see it, Paton, Williams, and others holding this view are right, although the position taken by Cobb, whose recently published "Manual of Neurasthenia" is to be commended, differs from my own view, and while he does not claim that this condition is specific, he states that "it gives the same signs and symptoms (albeit the range is large) in every case, and, when the diagnosis of the condition is made with care, it is as positive in its status as that of any organic lesion."

To my mind, the condition that is usually called typical neurasthenia is a symptom-complex based upon a generalized asthenic state which may be the result of widely varying etiological factors, in which not merely are the nerves asthenic, but there is associated with it a mental tiredness, or psychasthenia, and the common muscular asthenia or fatigue syndrome, with circulatory stasis, poor elimination and the general state so commonly known as "the run-down condition."

Just what circumstances determine when and where a tired patient becomes neurasthenic is difficult to state, and just why there should be a difference in the name or treatment of a run-down individual's disease is not clear to me, and the attitude of many authorities in discarding the term "neurasthenia" is quite in harmony with the clinical experiences and physiological facts. In other words, my personal opinion is that neurasthenia, as such, cannot exist alone, and nerve-tire is but a part of a more complicated and fundamentally important condition.

Whether it happens to be an individual disease

entity or not, neurasthenia has been considered by innumerable writers, medical and lay, for many years. One author says: "It is the custom in writing about neurasthenia" to do so and so, while another remarks that "the language of some writers implies that we have gone far enough with the explanation of neurasthenia by calling it a fatigue neurosis," and again, "a majority of writers declare that the causation is not to be found in tangible—structural or anatomic—changes," etc.

We will now retrospect a little and set down a few historical and preliminary facts that may serve as a foundation for our contentions.

2.—DEFINITIONS

The name "neurasthenia" originated in 1868 and was fathered by an American physician named G. M. Beard, and later was written about by Weir-Mitchell, of Philadelphia, and a hundred and one others. However, Cobb, in his excellent book, informs us that before the condition was named it had been described by G. Hersch in 1843. It is probable that even more remote authorities can be found who recognized what some have called "general debility" and recorded their observations and treatment. From approximately 1870 until 1896 the disease was known and classified as "hysteria" in spite of the mass of literature, mostly American, that was piling up in defense of neurasthenia as a separate and definite disease. Therefore, we must give Beard the credit for discovering and naming this neuro-asthenic disturbance.

It is needless to state that Beard's ideas met with anything but open arms on the part of his fellow practitioners. He published a book (following three papers on Nervous Exhaustion (Neurasthenia)" in 1880, and in 1869, 1878 and 1879) entitled "A Practical Treatise

another in 1881, the title of which, "American Nervousness: Its Cause and Consequences," connected this "new disease" with conditions essentially American.

At the present time books, magazine articles and briefs bearing on this subject are quite numerous, with more and more emphasis being placed upon the endocrine causes of neurasthenia; otherwise, present-day discussions show a fairly close similarity to Beard's original treatise.

If you were asked to define "neurasthenia" you would probably ward off the embarrassing situation by saying that you were not a walking encyclopedia, that you never wasted time on definitions, or in some other way you would let the questioner know that you knew but did not have words to express yourself. Dorland's dictionary defines neurasthenia as: "Nervous prostration, depression due to the exhaustion of nerve energy. The name for a group of symptoms resulting from some functional disorder of the nervous system, with severe depression of the vital forces. It is usually due to prolonged and excessive expenditure of energy, and is marked by tendency to fatigue, lack of energy, pain in the back, loss of memory, insomnia, constipation, loss of appetite, etc." Mott's definition in the Practitioner's Encyclopedia of Medicine and Surgery is: "A condition of irritable nervous weakness. The term was introduced by Beard to cover a large group of symptoms pointing to either general exhaustion or special exhaustion of some particular function of the nervous system, e.g., cerebral, cardiovascular, sexual, gastro-intestinal."

Thomas D. Savill, of London, in his book "Neurasthenia" comments on the difficulty of giving a single and satisfactory definition and says: "In order that we may have a common train of understanding, I may say that I regard neurasthenia as a generalized irritable weakness of the entire nervous system, characterized (when the brain is affected) by hypersensitive-

ness of the sensorium, loss of mental and bodily vigor, inaptitude for work, disturbed sleep, and irritability of temper; and (when the spinal cord is chiefly affected) by general muscular weakness, restlessness, nervousness, and vague pains; and usually accompanied (in both forms) by various phenomena referable to the vasomotor and sympathetic systems."

In the masterly work, "Diseases of the Nervous System," by Jelliffe and White, neurasthenia is said to be "a condition known as a primary fatigue neurosis and has certain quite characteristic and constant symptoms which are in the main a feeling of pressure on the top of the head, more or less insomnia, spinal irritation, with perhaps pain in the back, certain paresthesias, easy fatigability, emotional irritability and some depression."

After considering the matter of definitions from all standpoints, Cobb gives his ultimatum as follows: "Neurasthenia is a condition of nervous exhaustion, characterized by undue fatigue on slight exertion, both physical or mental, with which are associated symptoms of abnormal functioning, mainly referable to disorders of the vegetative nervous system. The chief symptoms are headache, gastro-intestinal disturbances, and subjective sensations of all kinds."

Beard, himself, admitted that neurasthenia is (or was) "the central Africa of medicine" and when it comes to forming a definition that is explicit and has no need of dragging in a "characterized by" string of symptoms, we begin to feel the "headache, fatigue, loss of memory, and subjective symptoms of all kinds" and deem it wise to stop right here—urging the reader, if possible, to form a better definition from those given above—and mail it to me!

Perhaps I may be permitted to give an incomplete definition of my own: Neurasthenia is a variable syndrome which constitutes a part of a symptom-complex

dependent upon disordered endocrine function, and its chief characteristic is as the name indicates, "neur-asthenia," or nerve tire.

It should be emphasized that neur-asthenia never is found alone. Myasthenia accompanies it practically always, for "the fatigue syndrome" involves the muscles as well. Psychasthenia, too, is commonly present. Chemasthenia—a term that I coined some years ago to indicate an asthenia, tiredness or inactivity of the chemical processes of the body—is usual in these cases, and this is quickly discovered by laboratory tests, principally the quantitative uranalysis. Finally, and logically too, there is an "endocrinasthenia"—in fact, why might not the well-known neurasthenia be due to, if not actually identical with, the less well-known endocrinasthenia, or hypocrinism?

This subject is discussed more at length in a chapter entitled, "The Asthenias: Neurasthenia, Psychasthenia, Myasthenia and Chemasthenia—Endocrinasthenia," in my book, "The Internal Secretions in Practical Medicine," published a few years ago.

II

THE ETIOLOGY

3.—Predisposing Influences

The literature on neurasthenia is sufficiently comprehensive and easily accessible to make it unnecessary for me to go into the fundamentals as usually discussed in medical writings. For the moment, we are more interested in the endocrine aspects, and consequently the predisposing influences will be given consideration largely from this standpoint.

Generally speaking, neurasthenia occurs in the sedentary classes, those who do not buffet weather conditions or strive with their muscles for eight or ten hours a day. Those who acquire neurasthenia usually live in towns or cities under all sorts of strain in business competition, social "climbing," and in attempting to accomplish all that their ambitions demand of them. Their environment, as well as their physiology, is such that it favors toxemia—their alimentary conditions usually cause autointoxication, the emotional factors tend to overwork those physiologic elements concerned (of which more later), and exercise, and consequently elimination, is deficient, with the resulting toxemia which wears out those subtle factors which "break" at or before the "nervous breakdown" which, as we all know, is a common name for neurasthenia.

Heredity, of course, plays a very important part. The physiological substratum of an individual is determined very largely by heredity. Someone has well said that to treat neurasthenia, one must treat the patient's

ancestors—and also the physician in charge of the case? The ancestor with imperfectly developed nerve tissue and mental feebleness, or who has overworked the material that nature supplies along that line, most assuredly can transmit tendencies which favor neurasthenia to his progeny for at least one generation. In these cases, to use the words of the famous Osler: "There is something wrong with the blastoderm." This tendency should be described best as a weakness that permits a breakdown in the nervous make-up under a strain that otherwise could have been sustained with little injury. All cases of neurasthenia evidently are the result of a poor balance between personal capacity and the task or strain applied. In other words, the strenuous life, which is the cause of neurasthenia, and daily adds to the long list of those whose nerves and endocrine structure cannot withstand the high pressure, breaks down those who do not have the stamina to withstand the stress. This stamina is dependent upon heredity, although it is modified both by physiology and environment.

George M. Butler expresses some interesting notions about functional nervous diseases which I feel justified in quoting here. He says: "The peculiar characteristic of the physiologic pathology of all functional nervous diseases is that the neurons themselves are not primarily at fault. They are merely scapegoats. They bear the brunt of some other morbid condition, and the nervous disturbance is an end-result. These neurons may be likened to a workman fretting because of a lack or poor quality of tools; and one might as well expect to get good work out of a workman in such a plight by drugging him into stupefaction, as to expect to remedy the neuroses with narcotics. They merely add one form of toxicosis to another. The essential morbid strain in all of these diseases is that of a nervous residue which is not adequate to the ordinary demands of living. The

rational principle of treatment is to bring the expenditure as far as possible within the income either by decreasing the former or by increasing the latter, or both. These patients are physical ne'er-do-wells just as some persons are financially shiftless. It is almost as impossible to make solid, prosperous individuals out of either type as to change the leopard's spots. The most that can be done with the physical as well as the economical ne'er-do-wells is to educate and help them to live within their modest income."

Elsewhere, some comments have been made in regard to what I consider to be the abnormal methods of present-day education. At puberty, or just after it, there is a physiological stress upon the organism which cannot be helped. Too often there is added to this an emotional stress as a result of examinations, "cramming," etc., which serves to unbalance the mechanism and thus favors "a nervous breakdown."

Conditions that tend to produce hypertension, such as faulty elimination by way of the kidneys, bowel and skin, are listed as prominent etiological factors in neurasthenia; but whether they are really a cause or an attendant symptom would be difficult to explain. At present, there is a tendency to class these findings as symptoms, and there is more than a grain of sense in this, as it is perfectly possible for a neurasthenic to have high blood-pressure; also just as possible for him to have low blood-pressure—in fact, the latter is the commoner of the two findings. In the matter of autointoxication, however, we can readily see that the toxic products from the ceptic gastro-intestinal tract can debilitate the nervous system and no doubt produce symptoms identical with those of neurasthenia, as we shall shortly see.

Acute infections, such as pneumonia, influenza or typhoid, assuredly predispose to neurasthenia; and chronic invasion by the treponema pallida, bacillus

tuberculosis or the malarial organism, readily favor a condition which has all the characteristics of neurasthenia—in the acute conditions as a sequela and in the chronic states as an attendant woe.

Since the recent influenzal scourge, there has been a noticeable increase in the number of serious neurasthenias. It did not require this epidemic to prove that influenza was an able progenitor of neurasthenia —that fact long has been understood and widely recognized. The influenza toxin is capable of depressing the cellular activity of every body tissue with the mechanism controlling the sympathetic nervous tissue early involved, as shown by the vasomotor paralysis and peripheral stagnation of the blood, with deep purple color of the subcutaneous area, even in those who succumbed to the overwhelming infection in the first 72 hours. Incidentally, the reports from autopsies on all influenza cases, as, for example, the careful paper by Kime and his associates, showed a regular adrenal involvement with hemorrhage and cloudy swelling—macroscopic in a high per cent of cases, and microscopic findings of a serious nature, without exception.

It is difficult to say just where a cause ceases to be "predisposing" and becomes definitely "exciting." The other chief etiological factors—toxemia, emotional imbalance and dyscrinism—are more often direct causes, and will be considered as such, and separately.

The war neuroses are a definite form of neurasthenia, and the etiology was the constant onslaught of stimuli that were applied to the kinetic system of Crile—the brain, the adrenals, the liver, the thyroid and the muscles. Psychiatrists and neurologists believe that the brain was primarily at fault as it was the seat of activity of the condition fear, and its variant—anxiety. Fear and anxiety are common in the minds of all, but were greatly increased in the training of war, raised to the four plus degree at the red battle line. There is

no doubt that the brain and psyche were upset extraordinarily; but of this more later.

4.—The Endocrine Basis

Many students of the endocrine glands are now convinced that changes in the normal output of the endocrine principles or hormones cause a reduction in the metabolism and what might be called a "half-speed action" on the part of many functions in the body. In no condition is deranged cellular chemistry more important, and its regulation more advisable, than in neurasthenia. Hence, in addition to the removal of as many predisposing and immediately exciting causes as possible, the need for the reëstablishment of hormone production upon as nearly a normal basis as possible is a rational and successful aspect of both the study and the treatment of these cases.

Swale Vincent, of Winnipeg, in his book "Internal Secretions and the Ductless Glands," refers to the relations between the internal secretions and the nervous system in the following words: "The nervous system is no longer the only controlling influence to be reckoned with in explaining bodily function, and especially is this the case with the coördination and interaction of many of the chief functions of the body. It is even possible that the nervous system itself may be controlled by these chemical stimuli. . . . Conveyed in the blood stream to different parts of the body these products may act as agents of augmentation or possibly inhibition in regard to the special activities of various organs and tissues." Since this book was published, we have perhaps come to some more definite conclusions, and it is now believed that many nervous factors are directly controlled by these hormone stimuli and that disturbances in the character of these stimuli or the receptivity of the organs or cells to be stimulated pave

the way for the syndrome of neurasthenia which interests us for the moment.

According to an editorial writer in *American Medicine*, "The glands of internal secretion are being connected with the causation of the neurasthenic syndrome more and more frequently, and rightly so." This writer then goes on to state that "recent confirmation of the position taken in our editorial columns that 'it would appear that the organs of internal secretion are to be charged with causing many of the disorders which together cause the neurasthenic syndrome' is found in the article on 'Therapeutics' in the *Journal of the American Medical Association*, entitled 'Neurasthenia—Suprarenal Insufficiency.'" (This editorial is mentioned in the next chapter.—H. R. H.)

In his article, "The Rôle of the Blood Plasma in Disease," Harry Campbell, of London, gave an early hint in regard to the possible endocrine aspects of neurasthenia. He says: "There is sufficient opportunity for the plasma to become faulty in respect of its hormone constituents; it may contain too little, too much, or a perversion of any one hormone, and these individual defects may be combined in endless ways, producing an endless variety of plasmic imperfections, each of which has its own peculiar effects upon metabolism. There can indeed be no doubt that disordered hormone function is responsible for numerous functional nervous disorders. . . . Whenever a disease is due to a hormone defect, treatment obviously consists in treating that defect."

Bernheim, the French internist, remarks that "it seems plausible to assume that neurasthenia is the result of toxemia from some upset in the nutritional biochemistry or in the endocrine system."

M. Naamé, of Tunis, in his monograph, "Etudes d'Endocrinologie," definitely attributes many of the symptoms that are commonly classed together as neu-

rasthenia to hypocrinism—deficient functioning of the endocrine glands as a whole. He calls particular attention to the frequency with which the adrenal glands and the gonads are incriminated. He believes that the insomnia and headache associated with arterial hypotension arise from pluriglandular insufficiency which is related chiefly to hypoadrenia, and the commonly accompanying insufficiency on the part of the thyroid and pituitary. He suggests that the temperamental irritability so common in these cases may be due to a deficiency on the part of the parathyroids which, it will be recalled from Koch's recent work, are functionally useful chiefly through their faculty of destroying, or favoring the destruction of, poisonous products of cellular chemistry which have a particular predilection for the nervous system. The cerebral depression so common in neurasthenia is suggested as probably more definitely due to hypothyroidism than to any other aspect of the pluriglandular difficulties. Naamé is heartily in favor of the organotherapeutic control of the endocrine bases for neurasthenia, for, translating one of his statements which is particularly pertinent, he says: "I can speak with authority because I, myself, am a definite example of a serious neurasthenic state which for ten years has been accompanied especially with insomnia and mucomembranous enteritis. I have personally used opotherapy, and have made myself over from an endocrine standpoint; and am now in perfect health."

Déjérine and Gauckler, neurologists of Paris, discuss a certain fatigue syndrome which they term "periodic asthenia." This condition varies in severity, and occasionally so-called "crises of fatigue" may aggravate the whole symptom-complex. They show that these periodic crises result from a disturbed endocrine equilibrium, and that the best method of controlling such conditions, after removing as far as possible actual

causative elements, is to replace the deficient hormonic products with pluriglandular therapy. Their clinical experience is stated to be more satisfactory when *"opothérapie combinée"* was substituted for the administration of various indicated single glandular extracts which previously had rendered little or no service whatever.

Campbell Smith, of Tunbridge Wells, believes that neurasthenia is a complex manifestation of cellular degeneracy; and that in many cases the changes are most apparent in functions which are under the control of the ductless glands. Later in the same paper this author emphasizes the advantage of treating conditions of this character by means of suitable pluriglandular therapy.

5.—Adrenal Neurasthenia

Of all the glands of internal secretion related physiologically and in the literature to neurasthenia, the adrenal glands stand out as the most important. There are literally scores of comparatively recent references to the relation that adrenal dysfunction plays to the instability of the nervous system. In one of the chapters of Professor Laignel-Lavastine's work on "The Internal Secretions and the Nervous System," entitled "Asthenia: An Endocrino-Neurological Syndrome" and translated in *The Journal of Mental and Nervous Diseases*, are some statements which are especially interesting and from which I will quote several paragraphs: "Asthenia is abnormal fatigue. It is either general or, more especially, motor or psychic. Motor asthenia is extremely commonplace, due to various causes—infectious, toxic or psychic.

"Among the motor asthenias of endocrine origin, the first to be recognized was the asthenia of Addison's

disease. It is connected with adrenal insufficiency, and is accompanied by arterial hypotension.

"Certain asthenias allied with adrenal insufficiency are not Addisonian. This fact is well known to-day. They were very common and usually, but not always, are accompanied by arterial hypotension. Their recognition and, consequently, their organotherapeutic treatment will permit the cure of a large number of sick, ticketed as neurasthenics, cyclothymiacs, melancholics and even hypochondriacs."

One of the comparatively few American writers on this subject, Tom A. Williams, of Washington, D. C., makes the following trite remarks: "Neurasthenia is a structure of the imagination, highly embellished with additions that have been made from time to time by many individuals, until it has become a huge edifice of which the characteristic features are weakness, lack of endurance of mind and muscle, and all the possible results of that weakness in its effects on internal organs, and all the possible complications that follow the bodily and intellectual inactivity and insufficience incidentally accompanying it." He goes on to say that hypoadrenia as a cause of neurasthenia is far more common than we have believed. He outlines the usual symptoms of neurasthenia and also the symptoms of hypoadrenia, all of which are referred to in the section on Diagnosis. "Hypoadrenia may result from the wasting of old age, the toxins of the infectious diseases, hemorrhages into the substance of the gland due to high blood-pressure, or perhaps from exhaustion by long-standing emotions. Neurasthenia, we may realize, *is* hypoadrenia." This writer tells of an interesting example in an official in a responsible position whose mental depression, asthenia, languor, flabby muscles, feeble heart, and incapacity of decision made a very good picture of neurasthenia. He feared dementia. There was some tremor, hypotension was evident—the systolic blood-pressure being 100 at

forty years of age. Adrenal therapy improved this gentleman so much that he was able to accomplish the work that he formerly could not do.

In an article of my own entitled "Adrenal Dysfunction in Sanitarium Practice," published some years ago, I emphasized the endocrine aspect of neurasthenia in the following terms: "Again, what about the neurasthenic? Toxemia is the great cause, dyscrinism the great effect. . . . It is my own personal opinion that the neurasthenic exhibits a perfect sequence of endocrine symptoms and that neurasthenia, of all conditions, deserves to be studied and treated as a condition in which dysadrenia is the most important fundamental factor. . . . In fact, hypoadrenia is the most common single symptom in the gamut of cases that comes to a sanitarium for treatment."

Cases often labeled psychasthenia because of their feeling of inadequacy, may be classed in a separate category. To me, this is really another form of neurasthenia—more serious, perhaps—and according to Tom Williams, whereas the genesis of this mental inadequacy is a real physical tire which occurs only during exertion, the origin of the inadequate feeling in phychasthenia is from a besetment or apprehension; and it always passes off while the patient is actively exerting himself with muscles or mind. Williams is confident that when we are confronted with patients who have great asthenia, lack of concentration and more or less of the long list of symptoms heretofore assigned to neurasthenia, "we must not be content to stop with the latter as a diagnosis. If, in addition, there are low blood-pressure, subnormal temperature, and pigmentary changes, hypoadrenia may be the cause of all the depression."

One of Tom Williams' papers was made the subject of an editorial in the *Journal A. M. A.* Here are two paragraphs from this communication: "The typical

neurasthenic generally, if not always, has a disturbance of the adrenals on the side of insufficiency, the blood-pressure is almost always low and the circulation poor. Mental exertion often causes extreme weariness and exhaustion. There may be a vasomotor paralysis which causes chillings, flushings, cold or burning hands or feet, drowsiness when the patient is up and wakefulness on lying down.

"It is believed that many individuals presenting the classical symptoms of neurasthenia with low blood-pressure, decreased mental elasticity, mental and physical depression with the fear that they cannot now accomplish their usual good mental work, with the story that they have 'lost their nerve,' with a vacillating and indecisive frame of mind, are suffering from functional hypoadrenia. In many cases of this character Williams has found that two to four grains of desiccated adrenal gland, three times a day, has caused improvement, and the administration of this substance by mouth has frequently raised the blood-pressure as well as controlled the physical and mental derangements."

Paul Carnot, recently elected Professor of Therapeutics in the University of Paris, in his well-known treatise on "Opothérapie," speaking of the use of adrenal therapy in the various phases of asthenia (myasthenia, neurasthenia, etc.) recalls the fact that Dufour was the first to employ adrenal substance on a neurasthenic woman affected with muscular depression, who, after being cured, was still well eight years later. This writer also mentions a case of myasthenia observed by Claude and Vincent, in a hale blacksmith, who, upon awakening one morning in January, was seized with muscular impotence, and was unable to raise his head; then a paresis of the muscles of the face, the pharynx, the tongue, and the eyes developed; in short, it was a case of generalized myasthenia. The

patient also presented pigmentation of the face, arterial hypotension, the white adrenal line, and anemia, which led to the supposition that there was hypoadrenia. He was placed upon continuous adrenal treatment. The improvement during treatment was pronounced. The urotoxic coefficient, which at one time was very high (1.21), fell to 0.25—a rather low figure—under the influence of the treatment, subsequently rising to 1 after abandoning the opotherapy. Mention is also made of the fact that Sicard, in a case of Erb-Goldflam disease (myasthenia), was successful with thymus and adrenal opotherapy.

At a recent meeting of the British Medical Association, Arthur Hurst, of Guy's Hospital, London, called attention to the necessity for securing a clear conception of what is meant by such terms as functional neurosis, psychoneurosis, neurasthenia, etc. In his opinion, a functional disorder is one which does not depend upon organic change; it may be either biochemical or nervous in origin. Neurasthenia generally has been classified as a neurosis, but it really depends upon definite, though evanescent, organic changes in the central nervous system *and the adrenal glands*, and possibly other endocrine glands resulting from mental and physical exhaustion and chronic intoxication. According to Hurst, therefore, neurasthenia is really a temporary organic condition and not a functional disorder. From my own standpoint, neurasthenia is still a functional neurosis because, despite the fact that the endocrine glands are very definitely involved in its etiology, this influence is of a temporary functional character, and the changes in either the nervous system or the endocrine system rarely seem to be of a structural variety.

Another prominent London physician, Leonard Williams, some years ago wrote an interesting paper in his inimitable style entitled, "The Real Neurasthenia."

It contained many pertinent statements connecting neurasthenia with the ductless glands. Unfortunately, Williams' articles do not lend themselves easily to abstracting, but I am taking the liberty of quoting several direct and unusual statements from his article:

"The real neurasthenia or shock is a circulatory matter. Graves' disease has been described as a chronic condition of fright, fight and flight—a good enough description if you will look beyond the bulging eyes and tremulous hands, to visualize the overactive adrenals, behaving chronically to produce the disease, as they behave suddenly in the presence of these emotions. Shock is an arterial matter, and the adrenals hold intimate converse with the arteries.

"The proper circulation of the blood is second only in importance to its proper composition. Its composition is determined by the efficiency partly of the excretory organs, and partly of the ductless glands.

"In the true neurasthenia, a very wide divergence between the pulse-rates in these two positions (standing and recumbent) is always present! and, what is worthy of note, is the fact that this is the only objective phenomenon which is present.

"When the bulb (medulla) is in watchful health this control (of the 'tone' of the vessels) is active and unerring. When it is out of health, things happen. One kind of toxemia may give rise to an undue pressor effect; another kind, to depressor. These biochemical questions are functions of the endocrine system. . . . If you hit the medulla in the face, or shake it, as a terrier shakes a rat, it falters. The contractile power is impaired, the vascular tone is lowered, the vessels dilate, the blood-pressure falls, the various organs are insufficiently supplied, and there emerges the real neurasthenia; a tremulous, elusive, emaciating phantom, full of subjectivities.

"As to treatment—how is one to treat a battered

bulb except by the sedative of a purified and well composed blood supply? The purification refers to drainage, and the good composition to the tribute of the endocrine glands. Of the former I will say nothing; it is so banal that few ever consider it! With regard to the latter, I permit myself to fling wide my restraint in a parting shot, and boldly call attention to the practical identity in the symptomatology of the real neurasthenia with that *of adrenal insufficiency.*"

John J. McNulty, of New York, in a very recently published article, enphasizes the endocrine basis of the fatigue syndrome and the neurasthenia so often imposed upon this: "Fatigue, of course, is merely a fashionable name for asthenia, and asthenia, as we know, is the most common syndrome resulting from adrenal insufficiency." In other words, endocrine weariness, as McNulty calls it, is really another name for neurasthenia, and as this writer puts it in his opening sentence: "The present state of psychophysical fatigue seems, to our present understanding, to be largely the expression of lowered functioning of the endocrine chain of glands—the so-called autoprotective mechanism." In his concluding statement he says: "The prevention of fatigue is the correction of social and economic abnormality; but the therapy of fatigue —endocrine weariness—is the rôle of the physician of inclusive understanding in the administration of associated gland substances bearing internal secretions and enzymes. These are given as catalysts to activate resident reactions, not to stimulate or spur already jaded functions."

In conclusion it may be fairly stated that the adrenal aspects of neurasthenia are of paramount importance, first, in the study of these difficult cases, and second, in their successful treatment; and the matter becomes doubly interesting when the clinical test is applied, for undoubtedly the success which so often follows adrenal

support emphasizes the reality of the adrenal depletion which it is rightly claimed underlies so many of these cases.

6.—Thyroid Factors

The fact that the thyroid gland is so largely concerned with the cellular chemistry and that disturbance in its function causes widely varying changes in the activity of these cells, could easily be an underlying causative factor in the neurasthenic syndrome, and it is.

Askenstedt, of Louisville, in an interesting communication shows that she has carefully considered the fundamental part that the thyroid plays in neuroses. She has gathered together many facts which show that a more or less insufficient function of the thyroid, just as in those who are victims of a slight excess in secretion, are fit subjects for the superimposition of a neurotic imbalance which is absolutely identical with the neurasthenia of current medical literature.

Further attention to the importance of the psyconeurotic syndrome as it is related to hyperthyroidism has been referred to by a number of writers, especially Woodbury, of Clifton Springs, New York, whose paper on this subject shows conclusively how easily the imbalance of thyrotoxicosis can develop into a neurasthenic state. The overstimulation of cerebration and the motor system by the excessive thyroid activity brings about not merely neuroses, but true psychoses and a line of symptoms including nervous hypertension, depression, apprehension, worry, insomnia and vertigo that are well known by those who see many cases of hyperthyroidism. The mental aspects of these cases are quite complex. Woodbury calls attention to the frequency with which a deficient concentration, which is usually regarded by the patient as an impairment of memory, is a source of annoyance. He has seen a

number of instances of impairment of consecutive thought which is referred to by Reynolds as "mental chorea" and is accompanied by a rather unusual but characteristic type of speech. In the early progressive cases there is a remarkable increase in general efficiency with added aptitude for detail. Loquaciousness is also common, as is the state of excitability, in which patients are easily startled. In advanced cases marked nervous fatigue is always constant and a history of one or more nervous breakdowns is usual. Emotionalism, agitation, obstinacy, failure to think clearly and logically—all are seen with sufficient frequency of relation to be significant. I am convinced that those individuals of the neurotic type who are always going to do things in a wonderful way, who are going to be movie actresses or to write novels, and who start out to accomplish wonders and then "fizzle," very often are in the very beginning of the stage of hyperthyroid neurasthenia which Woodbury discusses so well.

Charles Reeder, of Tulsa, Oklahoma, has been carefully noticing the relation of the thyroid gland, and especially its deficient function, to neurasthenia during ten years of practice. Whenever he finds individuals with mental depression, insomnia, faulty assimilation and intestinal indigestion, with painful nervous headaches or other symptoms which are commonly classed as neurasthenia, a close examination discloses to him some abnormal condition of the thyroid gland in at least fifty per cent of these cases. Reeder emphasizes the necessity for the careful study and early discovery of this condition, for thyroid treatment proves of very great value and to ignore this aspect of treatment is a source of considerable dissatisfaction, both on the part of the physician and of the patient. In all cases of pronounced neurasthenia Reeder urges that the common symptoms of hypothyroidism be sought for, and when found and treated with carefully regu-

lated thyroid therapy it will be surprising how much better results are obtained in this perplexing class of cases.

It will be recalled that the chief result of thyroid insufficiency is a condition of cellular infiltration with various forms of apathy both mental, physical, muscular and chemical.

One of the most interested students of thyroid disorders, and an authority of considerable prominence, Léopold-Lévi, of Paris, has gone quite fully into the various minor forms of thyroid insufficiency. In his book, "La Petite Insuffisance Thyroidienne et son Traitement," he takes up the relation between thyroid disturbance and neurasthenia. It appears that Lévi differentiates a special form of neurasthenia which he calls *neurasthénie fragmentaire,*" or a syndrome of partial neurasthenia which is a result of a combination of conditions—apathy, indolence and depression—which result from the markedly slowed cellular chemistry brought about by the lack of the arousing or exciting influence of the thyroid upon metabolism. In these subthyroid individuals this neurasthenic aspect is aggravated by an accompanying diminution of the vital reactions and a lessening of the nutritional exchanges. Fatigue, especially in the morning, is very common. Individuals of this type usually are loath to get up, and they are not at their best in the morning. They usually brighten after having breakfasted and they have begun to move about. These neurasthenic individuals sometimes say that they were "born tired," and the symptoms which they may show are very diverse.

In fact, ridicule has been heaped upon some well-meaning physicians who have emphasized the wide range of the symptomatology of hypothyroidism. As a matter of fact, the fundamental infiltration of the individual cells resulting from the slowed chemistry, the accumulation of wastes, the solution of these wastes by

the body fluids (which are drawn into the cell itself by the process of osmosis and the consequent swelling of the cell unit—"thyroid infiltration") may indeed cause a very comprehensive list of symptoms. Those of them which are related to neurasthenia involve the brain—cerebral infiltration with mental inactivity, disinterestedness and loss of memory; the circulatory system, in which there develops an exquisite hypersensitiveness to cold, as first emphasized by Hertoghe, of Antwerp; and constipation—alimentary muscular atonicity—with the inevitably resulting toxemia.

The above reference to susceptibility to cold is really an important neurasthenic manifestation because these individuals become terribly concerned and perturbed by any discomfort that this sensitization may favor. The slightest draft provokes rheumatoid or neuralgic pains, or brings on a lumbago, a torticollis, or even a migraine, and naturally this susceptibility to these various troubles quickly unbalances that subtle factor which prevents the normally balanced individual from becoming neurasthenic.

Léopold-Lévi calls particular attention to the importance of constipation in these individuals. He calls constipation "the stamp of the subthyroidic temperament." Now the degree of "neurasthenia, myasthenia, or other troubles, may far exceed that which characterizes the symptoms of thyroid insufficiency, yet these signs may be due to thyroid insufficiency, and in that case will respond to thyroid treatment." The above quotation from an English article by this writer directs attention to an aspect of these hypothyroid, neurasthenic individuals that is a little difficult to explain. Certain individuals may be suffering from a minor form of thyroid insufficiency which develops a major form of neurasthenia, whereas, a very much more serious thyroid insufficiency in another individual carries with it practically no neurasthenic manifestations. The differ-

ence lies in the physiological substratum. Some people are born to be neurasthenics. Their heredity, environment and temperament all favor the development of this condition, and in these unfortunates the factor which has brought about the hypothyroidism plus the results of the hypothyroidism itself, are the direct causes of the neurotic condition.

According to Léopold-Lévi, when one has established a diagnosis "it should be confirmed by treatment with thyroid extract. This is essential, for when the results are immediate, continued, constant and pronounced, they may be regarded as a diagnostic factor." Quoting still further from the same paper: "In the case of pluriglandular syndromes, the results of thyroid treatment serve to distinguish between symptoms of thyroid origin and those provoked by derangement of other endocrine glands. Even in cases where thyroid insufficiency is proved, the endocrine balance must be maintained and the coexistence of other endocrine insufficiencies and instabilities (testicular, ovarian, parathyroid, adrenal, pituitary) must be allowed for. . . . . Where thyroid insufficiency is associated with other endocrine insufficiencies, the glandular therapy should be equally complex. Pluriglandular combinations may be employed with advantage in suitable cases."

The minor forms of thyroid insufficiency often cause marked changes in the mental balance. Hertoghe, of Antwerp, in his paper on thyroid insufficiency, refers to this in the following statement: "The psychic condition is expressed by an extremely disagreeable tendency to profound pessimism. Women of this type get into a state of panic about nothing, see everything through black glasses, and live on the edge of a species of chronic despair. . . . Misunderstood by everyone, the sympathy of their intimates alienated by incessant complaining, they live on in a state of complete indifference to their surroundings."

The mental aspects of these cases of thyroid neurasthenia vary much in degree and also the time of their incidence differs in different individuals. According to Hertoghe, "In adults the usual infiltration brought about by hypothyroidism may involve the nervous centers, thus determining the slowness of ideation, a partial or entire loss of memory and a difficulty in expression. These patients may know what they desire to say but the cerebral image is clouded."

One can readily understand how so insidious and progressive a change in the chemical functions of the body might lead to a typical neurasthenic condition. The state of mind of such a person is vividly portrayed in Hertoghe's words: "On the psychic side, melancholy is the predominating note of the myxedematous subject. He is the victim of a resigned and silent sorrow. His reason, on the other hand, is never clouded, and his better self preserves its full perceptive powers; but the expression of his opinion is so fatiguing to him, that he ceases to attempt it. These people are frequently reproached for their general negligence and their inattention to the duties of their occupation. This is unjust, for, as a matter of fact, the obligations of daily life are more than they are fitted to perform."

7.—Toxemia the Chief Cause

Unquestionably, the chief underlying cause of neurasthenia, as of most forms of endocrine dysfunction, is toxemia. A careful study of these cases will show this, and in most of them the evidence of the relation between toxemia and neurasthenia is very clear. Practically without exception the neurasthenic patient for years has had some alimentary difficulty, and a study of the gastro-intestinal canal will indicate a general atonic condition, a tendency towards ptosis and an autointoxication which is found so routinely that Kel-

logg, in his book "Neurasthenia or Nervous Exhaustion," charges a very large share of the etiology of neurasthenia to alimentary, and especially colonic disease.

On page 99 of the above book, we read: "The most common form of colitis, pseudomembranous colitis, has long been looked upon as a nervous disorder. It is a very frequent accompaniment of neurasthenia, and was thought to be due to some nervous disturbance. This view was doubtless the outgrowth of the fact that this disease generally accompanied very marked neurasthenic symptoms. The truth appears to be, however, that colitis is simply another consequence of the same causes which produce neurasthenia. . . . In general, the germs which produce putrefaction are capable of giving rise to this condition. The chronic intestinal toxemia which accompanies neurasthenia, a dominant factor in a majority of cases of neurasthenia, is also associated with colitis, both as a cause and a consequence. Colitis, by producing a diseased condition of the mucous membrane, lessens its ability to resist the poisons which are produced in abnormal quantities in the cavity of the intestine, since these toxic substances readily pass through the congested, irritated or abraded mucous-membrane. Colitis is, then, a cause of neurasthenia and not a result of this condition. Colitis can be cured only by changing the intestinal flora."

The point that I wish to make is this: Toxemia of alimentary origin is the most common form of toxemia that we have to meet in general practice. This is not denying the possibility of many other sources of poisoning, but the alimentary source transcends all the others in frequency and severity. This poisoning very definitely influences the endocrine system as a whole, and especially the thyroid and adrenal glands. Consequently, alimentary toxemia cannot but stimulate the adrenal glands, and when it is at all severe or pro-

longed, it will overstimulate them until they are played out, with the result that the functions which they are supposed to control are also played out.

It will be recalled that among the very important services rendered to the organism by the adrenal medullary principle, is the maintenance of the muscular tone, especially in the unstriped muscle fibres, and this includes in addition to the cardiovascular department the walls of the alimentary canal. Hence, aside from any direct influence that the poisons produced in the alimentary canal may exert upon the walls of this extended organ, it is clear that the tone of the muscular coat of the bowel is modified by the adrenal insufficiency, and we thus find ourselves face to face with one of the most common and most difficult of the vicious circles of disease. In other words, any condition which tends to alimentary autointoxication also tends to deplete the adrenal glands, and these, when played out, cannot maintain the normal tone of the unstriped muscle, including that in the bowel, so that a condition of alimentary atonicity obtains, with the result that the food is delayed in its passage and putrefies still more, with an increased production of these alimentary poisons and a still further depletion of the adrenal function and all the things dependent thereon.

It is no wonder, then, that Kellogg emphasizes so definitely the importance of colon hygiene in the treatment of neurasthenia, and without any question it should be among the chief measures which should be recommended.

I believe that in addition to attempting to remove the alimentary toxemia by mechanical measures, by hydrotherapy, by diet, and by changing the intestinal flora, as previously mentioned, some special effort should be made to increase the tone of the alimentary musculature, and while certain exercises are really valuable the encouragement of a more nearly normal

adrenal activity seems to me to be equally important, and, to my mind, always should be a part of the treatment of every case of neurasthenia.

The toxemias of bacterial origin, especially those due to focal infection, exert an identical influence upon the hormone producing organs, and there is really no difference in the mechanism or its results worthy of special comment here.

Specific intoxications of the nervous system with alcohol, lead, phosporous, arsenic and other cumulative poisons taken deliberately or unwittingly, occur in miners, painters and alcoholics. Alcohol and lead are the most important of the group, alcohol producing the well-known condition of peripheral neuritis and also central degeneration in advanced cases; lead showing its definite choice for nervous structures by producing even a genuine encephalitis.

Such metabolic disturbances as gout, diabetes, and the lithemic diathesis are frequently associated with neurasthenia, and the more rapidly progressing cachectic conditions like cancer, Addison's deases and Graves' disease are a prolific cause of that condition. In all these conditions the asthenia is general and not local; and there is, quantitatively speaking, as much myasthenia or chemasthenia, for instance, as neurasthenia. The depletion of body reserve supply is marked, continuous, and seriously debilitating.

It is not difficult to determine whether the adrenals are at fault in neurasthenia. The history will very quickly determine this, and the patient will show a train of symptoms and sensations which are related to hypoadrenia, and which will be discussed more fully in another chapter.

8.—Emotional Imbalance

The work of Walter B. Cannon, of Harvard University, and his associates, has established quite definitely the fact that emotional stimuli, such as occur in fear, rage, or pain, bring about many of the phenomena which result from stimuli of this character through a remarkable influence upon the production of adrenin in the adrenal medulla. We know now that these emotions stimulate the adrenal glands and result in the production of a hidden physiology, due to the excessive amount of adrenin liberated and later form the glandular depletion which one would naturally expect to follow excessive functional activity.

An increased output of this chromaffin hormone causes increased sympatheticotonus, overbalancing the work of the vagus or pneumogastric nerve and increasing the reactivity of the organism to all sorts of impressions. The cardiac action is augmented, the arterial tension is raised, intestinal motility is increased, and the pancreas function is lessened, especially as regards its internal secretory capacity, with a possible glycosuria, since the adrenal principle is the direct antagonist of the pancreatic internal secretion..

Kinnier Wilson, a London neurologist, in his monograph, "The Clinical Importance of the Sympathetic Nervous System," makes the following pertinent remarks: "Many of the common symptoms of neurasthenia and hysteria are patently of sympathetic origin. Who of us has not seen the typical irregular blotches appear on the skin of the neck and face as the neurasthenic subject 'works himself up into a state?' The clammy hand, flushed or pallid features, dilated pupils, innumerable paresthesias, the unwonted sensations in head or body, are surely of sympathetic parentage. In not a few cases of neurasthenia symptoms of this class are the chief or only manifestations of the disease.

Here, then, is a condition of defective sympathetico-tonus; may it not have much to do with impairment of function of the chromophil system? . . . There does not appear to be any tenable distinction between the asthenia of Addison's disease and the asthenia of neurasthenia. Cases of the former are not infrequently diagnosed as ordinary neurasthenia at first. It is difficult to avoid the conclusion that defect of glandular function is responsible for much of the clinical picture of neurasthenia. . . . Sympathetic tone is dependent on adrenal support, and until the glandular equilibrium is once more attained, sympathetic symptoms are likely to occur."

The phenomena of fear are adrenal in origin. Stage fright, with its dry mouth, weak knees and circulatory imbalance, is purely the result of an excessive overstimulation of the adrenals. And the all-gone feeling which follows experiences of this kind is the natural reaction due to the functional depletion of these glands.

On the other hand, these chromaffin cells may have been so unduly stimulated by various factors, such as have been mentioned elsewhere, or by the emotional stimulus alone, that they are temporarily or even permanently played out. Such a condition of hypoadrenia is responsible for reduced sympathetic tone, lessened muscular excitability and capacity, with exhaustion on the slightest exertion and an asthenia which extends to all the muscles controlled by the adrenal glands or the sympathetic system. This means an actually reduced cardiac power, with a lowered blood pressure, or in extreme cases, shock, collapse with pallor, clammy, cold skin, dilated pupils, respiratory excitement and even failure.

That emotional stimuli irritate the adrenal glands must be accepted as a fact, and that the effects of the emotions upon the organism are by no means mental, is clear to any who have studied the subject. It is through

the adrenal portal that emotional elements can modify bodily physiology and, therefore, since in neurasthenia in its varying shades there often is a history of an emotional imbalance of some kind, or there is a perpetual emotional susceptibility which is continuously bringing about an undesirable adrenal stimulation, it is easy to see how all sorts of asthenias naturally follow conditions of this kind.

Unfortunately, worry is in the same category as fear or rage, and as we all know all too well, the neurasthenic is a most introspective, concerned worrier. These patients, therefore, ordinarily, are in practically a perpetual state of hypoadrenia.

The experiences during the war, which are given quite full consideration in a subsequent chapter, have confirmed these findings, and as I wrote a number of years ago, "This may be visionary, but I still insist that we are going to connect the adrenal glands with numerous conditions encountered in general practice, particularly those connected with the emotions, more and more as we come to understand their functions and interrelations better."

9.—War Neurasthenia

Nearly one hundred papers bearing directly or casually upon various aspects of various neuroses and their relation to the exigencies of war indicate that what properly may be called neurasthenia very commonly results from the strenuous emotional imbalance which accompanies the experiences of the soldier or the refugee.

Conditions variously known as shell shock, post-traumatic asthenia, neuro-circulatory asthenia, and war neurosis, have been referred to in these papers and, in many of them, especially in those published in France,

the glands of internal secretion are incriminated as important factors in the etiology as well as the treatment of these disorders.

There is a good deal of practical helpfulness in some of the papers by Emile Sergent, of Paris, who, for years, has intensively studied the adrenal functions and during the great war has successfully applied his ideas in his military practice. For many years he has insisted that the adrenal glands played a much more important rôle than was admitted by the majority of his colleagues, and it is largely due to his efforts that our present knowledge and our clinical use of adrenal substance has become established upon so solid and practicable a basis. The collection of articles in his book entitled, "Etudes Cliniques sur l'Insuffisance Surrénale —1898-1920," includes a number of important communications emphasizing the relationship between neurasthenia and allied neuroses and depleted adrenal functions.

Sergent, from whose communications I have taken the liberty of making some extensive translations, found innumerable opportunities in his war service to verify previous opinions and experiences relating the adrenals to the asthenic and neurasthenic syndromes. In his studies at a base hospital in France he was able to confirm the fact that acute hypoadrenia, such as might follow toxic infectious influences, serious emotional imbalance, hemorrhage and shock, was related in some way to fundamental abnormalities in the physiological substratum of his patients. In his valuable work, "Etudes Cliniques sur l'Insuffisance Surrénale— 1898-1920," he devotes an entire chapter to "Adrenal Insufficiency and the War." He recalls that adrenal therapy was successfully applied during the war in cases of typhoid fever, paratyphoid, typhus, choleriform diarrhea, as well as gastro-intestinal toxi-infections with icterus infectiosus. Incidentally, reference

is made to a condition which he terms "acquired adrenal debility," corresponding to a more or less precarious and unsteady functioning of the adrenals where they have been previously affected by chronic lesions, superficial or partial (sclerosis, post-infectious chronic adrenalitis and degeneration, tuberculosis, etc.)

He cites the case of two soldiers who, on being returned from the front, reached Paris in a state of complete asthenia. One was an *"Addisonien fruste,"* only slightly pigmented, who was not at all asthenic before the war, and who probably had partial tuberculosis of the adrenal glands. The other was not pigmented, but, following a typhoid fever contracted several years previously and which doubtless had bequeathed chronic adrenalitis, he had become especially prone to fatigue and frequently manifested crises of transitory asthenia. Both were knocked out by the overstrain of field work; their adrenal function, which had been regulated to a medium service, wavered when faced with the required effort. They both reached headquarters in a state of pronounced adrenal insufficiency and manifesting all the symptoms thereof (asthenia, hypotension, white adrenal line, hypothermia, tendency to collapse, vomiting, etc.) ; and, fortunately, both were rapidly relieved from their acute crisis of adrenal insufficiency by means of organotherapy.

Speaking of the wounded, Sergent states that, suffering as they are, more or less, from the shock incident to traumatism, depressed by hemorrhage and anguish, exhausted by the long and fatiguing journey, by the prolonged inanition in case there should have been some delay in picking them up, they will be unable to stand the new shock of an operation and will succumb under chloroform if the surgeon is not advised of the help which can be afforded him by adrenalin before and after his intervention. He continues: "It goes without saying that we must always take into consideration,

in such cases, earlier lesions—more or less latent—of the adrenal glands. This adrenal debility may explain why certain wounded men suffer to a greater extent from traumatic shock or are easily subject to complications under chloroform. Be this as it may, all those injured in the war present an ensemble of conditions favoring those complications which are incident to adrenal insufficiency, and here, more than in other cases, preventive precautions are absolutely indispensable."

In another chapter Sergent states that it is not to be wondered at that the intensive overstrain of the combatant should have been the contributing cause which so often set in motion the complications incident to adrenal insufficiency favored by a previous anterior adrenal debility. Laignel-Lavastine shows that war asthenics and psychasthenics are essentially subjects of fatigue; that "their syndromes are the neuropsychic expression of a physiopathologic disturbance," and that this is evidenced by the ergograph, the arterial tension curves, and the graphics of the psycho-motor, circulatory, respiratory and glandular reactions. An asthenic subject, with arterial hypotension, due to adrenal insufficiency, will derive much greater benefit from resting in bed, if combined with suitable opotherapy.

Loeper, and his associates, believe that adrenal dyspepsia is a minor syndrome frequently observed in war cases of overstrain and in convalescents, and have shown that this form of dyspepsia resists the customary digestive medication while it yields to adrenal substance. Emphasis is placed on the fact that this gastropathy, which is accompanied by constipation, is by no means peculiar to war pathology; but is observed in all those suffering from overstrain.

The various forms of traumatism, according to Sergent, are another frequent cause of adrenal insufficiency, and it is therefore by no means surprising that

war traumatism has often brought about complications incident to hypoadrenia. Continuing, this author states: "It may be admitted that, in some measure, the same idea should be taken into consideration in interpreting the pathogenesis of the condition known as shock. This interpretation is not in contradiction with the theory sustained by Prof. Quenu at the Société de Chirurgie; . . . it is found to be complete and is, moreover, justified by the good results which have often been obtained from adrenalin, provided it was given in adequate doses. Corbett, too, has published an interesting study of the adrenal glands in shock, and noted a diminution in their adrenin content."

Note that Sergent calls particular attention to the possibility of individuals having a latent tendency to this adrenal insufficiency which, under the stress of some acute circumstance, such as toxemia, fright, or stress, is suddenly aggravated, with serious results. Similar conditions are encountered almost daily in general practice. Undoubtedly this kind of an endocrine collapse is more likely to supervene in patients who previously have been depleted by such conditions as typhoid fever, influenza, pneumonia, or other acute infections. The adrenal depletion which Sergent insists must accompany an acute infection, may not be entirely remedied, although the patient may be seemingly well, and when some other sudden stress further overstimulates these glands they play out with greater facility and more thoroughly than though they had not previously been depleted. In other words, a susceptibility to hypoadrenia may develop and conditions which previously have served to overwork and deplete these organs may leave them in such a state that the renewal of the stimulation brings about a more serious let-down more easily and more completely. All of which is applicable in present-day general practice.

Further emphasis will be found in a paper by

Ramond and François devoted to the study of adrenal disorder resulting from conditions of war. They write: "This protracted war, demanding of all our fighting men a continued moral and physical tension, forces overexertion upon all the organs, especially the adrenal glands. The literature already contains manifold examples of weakness (asthenia), low blood-pressure, and acute dyspepsia from Addisonism, as well as in various acute infectious diseases. All of these bear the imprint of hypoadrenia. It is probably also an important feature in the clinical picture of the gassed." In the service of these two physicians, in as short a time as four months, they have seen no less than twenty-six cases of actual Addison's disease, all of whom died save four, the origin of the trouble in each case being "the stress of war." Merklen, in a consideration of neurasthenia in military hospital practice, calls attention to the frequency of hypothermia especially in soldiers who may be recovering from pneumonia or other acute illnesses. This hypothermia was accompanied by extreme weakness and depression—a combination of symptoms quite similar to that which is found in many cases of neurasthenia brought about by causes other than those resulting from war—and while Merklen does not specifically relate the adrenal glands to the origin of this condition, he mentions that it possibly may be due to adrenal insufficiency.

There are many other writers whose attention has been called to various endocrine aspects of the "war neuroses." Frank P. Norbury, of Jacksonville, Ill., who was in a prominent consulting position during the war emergency, has written several papers. F. W. Burton Fanning, an English neurologist, reports 509 cases out of 1600 British soldiers of the home forces reported sick, as suffering from neurasthenia—due chiefly to emotional and toxic causes, which acted through the adrenal glands. John C. Rowley, of Hart-

ford, Conn., prefers the term "neurocirculatory asthenia" first advanced by Thomas Lewis, an American medical officer, and among others who have published articles upon the subject are Atkinson and Friedlander.

A paper of my own, "Shell Shock and the Internal Secretions: with Suggestions as to Treatment," was written in 1916, at the request of the editor of *The Prescriber* (Edinburgh), and served to draw early attention to the endocrine features of many war neuroses. Besides referring to the earlier writings of Sergent, I quoted from other authorities in confirmation of my attitude. For example, from an editorial in *American Medicine,* I quoted: " 'One can quite easily understand that just such a condition would be present in individuals driven from home and subjected to exposure and hunger. Similarly, men returning from the trenches, where they have been subject to extreme fatigue and the tenseness of the atmosphere, as well as the mental effects of losing their comrades and themselves suffering from wounds and shock, must also be considered to be in a state of adrenal insufficiency.' This condition of hypoadrenia was a prominent factor in 'the vivisection of a nation,' so well explained by Crile during his service in France." I also mentioned that "this subject was recently referred to by Rénon in a paper read before the Société de Thêrapeutique, Paris, and the symptom-complex which he describes as due to *l'angoisse de guerre* is almost typical of dyshormonism, and especially that form in which hypoadrenia is well marked. Rénon finds that a neuropathic or arthropathic physical substratum is common in individuals subject to the more marked effects of 'war shock,' and that the use of alcohol is a pronounced predisposing factor."

Carles, of Bordeaux, has also studied a number of neurasthenic soldiers and, in the course of a more recent report, tells of having seen within a year no less

than fifteen cases of what seemed to be typical Addison's disease in men on active service, except that the disease displayed a tendency to spontaneous subsidence even in the apparently gravest cases. These depleted soldiers, after a few weeks of rest and quiet, abstention from excitement and treatment with adrenal substance, were soon apparently in their normal health again. In each of the cases the predominant symptoms had developed after a period of exhausting fatigue, a serious infectious disease, or gassing. In all of them, asthenia and neurasthenia were the most striking symptoms and their trouble for the most part seemed to be more mental than physical. For months some of these men were incapable of reading a paper, writing a letter, or even answering questions that required any thought.

The fact that these individuals were considered from an adrenal aspect and treated as cases of hypoadrenia, gave these investigators a splendid opportunity to determine definitely whether the adrenal element was as prominent as they imagined. According to Carles, the administration of adrenal substance to the series of cases which came under his notice, brought about an improvement that was very rapid and satisfactory. It was the "touchstone." In all of them the blood-pressure was low but, according to Carles, one may expect this phenomenon among all the men at the front, due, in all probability, to the emotional factors which, through their important influence upon the adrenal glands, tend to modify this particular condition.

It seems that this is the proper place to make some practical deductions from the foregoing clinical experiences. The same fundamental conditions assuredly apply in ordinary practice as they do in war practice. If the emotional stress of war and the toxemias which inevitably accompany it can so uniformly cause endocrine neuroses, why may not stress of other origin cause the same thing during peace? It may be that the seri-

ousness of the emotional factors concerned in the war cases is greater from the standpoint of degree, just as the seriousness of the neurasthenia may be less than the types which Carles and others have called "Addisonian." The point that deserves to be appreciated is this: Severe toxemia, severe stress, and the consequent severe adrenal irritation, cause an adrenal depletion which favors if it does not actually produce a state of asthenia which is very similar to the neurasthenia which originally was emphasized by Beard.

Recall particularly that these war experiences indicate that certain individuals who previously have had some serious adrenal upset are much more susceptible to conditions of this type than others. Note also that the response of this type of neurasthenia to organotherapy is sometimes spectacular. In fact, it may be concluded that if indeed neurasthenia is akin to hypoadrenia, as I believe it to be, no treatment can be so efficacious as that treatment which controls adrenal depleting conditions and, simultaneously, no treatment can be so efficacious as that treatment which includes adrenal support, or organotherapy.

III

CLINICAL TYPES

10.—Cerebral Neurasthenia

Perhaps it is not proper from the standpoint of the neurologist to use the above term; but it is intended in this chapter to gather some of the statements in the literature emphasizing the cerebral or cephalic aspects of neurasthenia, and to connect them, where possible, with disturbed endocrine function.

The Mental Aspects. The mental aspects of neurasthenia are somewhat varied in their manner of making themselves known. The neurasthenic is first, last and all the time busily occupied in focussing his attention upon himself and his apparently abnormal conduct and physiology. Such individuals are introspective to a marked degree, and those suffering from this condition tell of their own cardiac, gastric, intestinal, and other physiologic processes with minutely detailed exactness, and new findings are sure to be reported from time to time as the patient develops the acuity of his introspective powers.

The process of digestion, naturally an unobtrusive element in everyday physiology, becomes a noxious, flatulent uproar occurring regularly after each meal. The heart makes its presence decidedly known, every beat being registered in the patient's sensorium, sometimes being attended by a synchronous thump in one or both ears. The fact that the heart is presumed to be becoming "diseased," worries the patient into a still more accurate study of self. The nerve-endings in the

skin have learned to report promptly indications of such sensations known as paresthesias—itching, burning, crawling, etc.—which really do not exist.

These neurasthenic patients are not "mental" in respect to their findings. They are sincere. They are not reporting these symptoms for effect alone. The real cause of the introspective interest in themselves is a real dysfunctioning of the organs that progresses with the development of the symptom-complex. In persons who are naturally of a nervous, irritable nature, the worry over this disturbed functioning becomes greatly exaggerated and is the real feature of that individual type of neurasthenia. In others of a more temperate, phlegmatic nature the abnormal state of affairs within causes more or less concern, but in general, introspection is a primary mental finding in neurasthenia. Worry is an emotion akin to fear or anger. As we have seen, it is the chief etiological element in most neurasthenics, and its effects on the physiology are brought about through its influence on adrenal functioning.

In most neurasthenics the will is weakened, and many writers bring out the truth of this statement. Déjérine, the Parisian neurologist, states that: "The neurasthenic may preserve what is virtually a will, which he no longer uses, because previous experiences of his weak, moral condition have impressed him with his sense of helplessness. He has reached the point where he does not make any effort, because he is certain beforehand that no results can be obtained." Morton Prince says: "Fear plays so large a part in the psychogenesis and symptomatology of the neuroses and psychoses that it is desirable to have a clear realization of its physiological and psychological manifestations and of the disturbance of the organism which it induces."

Now, Cannon, in his book, "Bodily Changes in Pain, Hunger, Fear and Rage," has shown the relation of

bodily changes to the powerful stimuli of emotional excitement, which, as this eminent physiologist has shown, act chiefly through the adrenal mechanism. Before long the mental overstimulation will deplete these vital regulators, and when they "give up" the original emotional and neurotic elements are supplemented by the train of symptoms dependent upon hypoadrenia.

The physiological processes are brought about through Crile's "kinetic chain," and the continued examination of many cases has shown a distinct endocrine character in the physical findings. A casual study of the usual symptoms will convince the observer that they are very similar to the symptoms found in disorders of the endocrines. Hence, we find the neuroses which are related to thyroid symptoms, others with adrenal symptoms predominating, and still others with a mental aspect—all depending on the individual's make-up—before the final exciting cause becomes "the last straw that breaks the camel's back."

Headache. The disturbed functioning of the intracranial apparatus is not attended by mental changes alone. A definite and characteristic headache is common. Not only does the head *ache,* but there arises the sensation as of pressure or weight upon the vertex of the cranial vault. In fact, many a neurasthenic who complains of headache will, after a thorough questioning, describe in his own peculiar terms a pressure discomfort and not a true ache. Some, however, have a headache of a decidedly real nature—painful in the extreme and persistent both in location and severity. The same variation that manifests itself in the mental phase of this condition is also evidenced in the varied types of cephalalgia. As Cobb puts it: A headache routinely may appear at nightfall and in one class of patients tortures away anything like slumber for hours. On the other hand, another type of headache greets the neurasthenic as he awakes and lingers until the middle of the

day, when it disappears until after the midday meal, returning with renewed vigor and fairly "racks the seams" in the sufferer's head. Again the subject may be set upon by a racking headache that will persist for an hour or so, depart, and return at another time unknown to the patient, and yet expected by him.

There is a tendency on the part of the examining physician to blame the headaches directly to the condition neurasthenia; to consider them an added symptom only. This is true, no doubt, in many cases, and if not true, can be made to appear that way, for, by the time the patient has half completed his customarily detailed account of his troubles, the physician wearily nods his head and thinks, "I must discount the value of all these findings about ninety per cent, for this is a neurasthenic."

In his "Etudes Cliniques sur l'Insuffisance Surrénale," Sergent, the eminent French medical authority, devotes an entire chapter to what he terms "adrenal encephalopathy." After citing various syndromes of acute adrenal insufficiency, he writes: "In a certain number of cases, we find predominating symptoms, such as headache, delirium, agitation, convulsions, apoplectiform crises, and coma, which savor of cerebral intoxication and permit our believing that adrenal insufficiency may assume the aspect of a genuine encephalopathy, comparable to the encephalopathy of exogenous and endogenous intoxication and susceptible of masquerading as an attack of apoplexy, coma, or, for that matter, meningitis, the first demonstrative case of which was reported by me. This adrenal encephalopathy is still little known to medical men. Its most characteristic expression is found in the acute syndromes, but the outline is found first of all in the slow forms of hypoadrenia. In Addison's disease the brain, in general, experiences no injury apart from acute complications or the concluding phase of the disease. The

intelligence and memory remain intact; but the subject, who has weakened progressively, sinks gradually into a state of semi-somnolence which ends more or less rapidly in complete prostration. This is merely one of the elements of the state of profound asthenia, into which he is plunged. This condition of constant semi-sleep, at times calm and tranquil, at others interspersed with broken dreams, nightmares, continuous subdelirium, ends sooner or later in coma. It was by taking as a basis a case of this kind, and the histological lesions which he observed in the brain and which recalled those which Ettlinger and Nageotte had already described in decapsulated animals, that Klippel described for the first time Addisonian encephalopathy. The crises which thus successively occurred in his patient must be considered as complications incident to acute adrenal insufficiency during the course of the slow—Addisonian—syndrome. For this reason, and to avoid a confusion which has too long existed between the two terms 'Addison's disease' and adrenal insufficiency, I prefer the designation 'adrenal encephalopathy,' which I suggested in 1903.

"Subacute encephalopathy, which accompanies habitual prostration in persons affected with slow adrenal insufficiency (Addison's disease or a syndrome of pure insufficiency without melanoderma) is often but the prelude of the more obstreperous complications of acute encephalopathy. But the latter, after the fashion of all manifestations of acute hypoadrenia, likewise may supervene at a moment's notice, whether it breaks out in subjects who have chronic capsular lesions which had hitherto been quiescent, or whether the consequence of acute lesions, or a faltering in the antitoxic function of the adrenal glands which find themselves powerless to destroy an excess of poisons suddenly introduced into the organism. Thus, capsular hemorrhages are accompanied by acute complications for which Arnaud

suggested the name of adrenal apoplectiform syndrome, by analogy with the irregularities of cerebral apoplexy. Arnaud, it is true, looks upon these irregularities as arising from the irritation of the pericapsular nervous plexus. It is, however, easy to recognize that they are attended by the habitual signs of the syndrome of acute insufficiency, from which they are only distinguishable by the predominance of the nervous symptoms (convulsions, delirium, coma). If the nervous symptoms dominate the situation, this merely signifies that the syndrome is evolving (or, evolves) into a nervous, encephalopathic form, in the same way that cerebral uremia exists side by side with gastro-intestinal uremia, for instance. The adrenal apoplectiform syndrome, having as its substratum the common groundwork of irregularities attributable to acute adrenal insufficiency, is a modality of the syndrome which characterizes it."

For the purpose of studying the clinical modalities of adrenal encephalopathy, the writer then proceeds to divide them up into categories, according as they are slow (subacute) or acute. The remarks reproduced below may not be devoid of interest in this connection. Speaking of the case of an unmarried woman of 42 years, suffering from a psychopathic form of subacute adrenal insufficiency, he states: "What may surprise us and cause us to hesitate is precisely the vital interest of this case, namely, the prevalence of an ensemble of neurasthenic symptoms with a cerebral, psychic aspect. There is, with the sensation of fatigue and progressive lassitude, a constant state of gloominess which, at times, intensifies itself to such a degree as to bring about crises of despair; there is profound amnesia, accompanied by headaches, eccentricities, dreams, minor hallucinations. For instance, at the time a robbery was committed in the patient's room, the resultant shock suddenly induced wandering, complete asthenic depression, and the crisis of acute adrenal encephalopathy. We here find the

characteristics of a toxic psychopathy, and were it not for the fact that we are able to trace back of them the common groundwork of the syndrome of hypoadrenia, we might fail to recognize their origin. These psychopathic irregularities incident to hypoadrenia, first described by Klippel, in Addisonian subjects, have within the last few years assumed an important place in psychiatry and are now the subject of interesting articles by Laignel-Lavastine, Juquelier, as well as Vigouroux and Delmas.

"Beneath this psychasthenic or depressive melancholy form of adrenal insufficiency, a place easily could be found, if need be, for a neurasthenic form of adrenal insufficiency. But it is well to emphasize that we are here dealing with a neurasthenia symptomatic of a sort of adrenal debility and that it is not a matter of further generalizing and looking upon neurasthenia in general as always arising from hypoadrenia.

"It may be admitted that certain individuals who are constantly tired, listless, lazy, morose, hypotonic, have a precarious adrenal function, especially if they respond to adrenal feeding, as is very often the case. I have observed the good effects of this medication on quite a number of people, more often than not children or young people, unduly fatigued by a hasty growth and for whom the least exertion constitutes real overwork. These facts should be taken in conjunction with the cases of neurasthenia successfully treated by means of adrenal opotherapy by Dufour and Roques de Fursac and the findings of Laignel-Lavastine."

In closing this interesting chapter, for the privilege of translating which I am indebted to Dr. Sergent, he states: "From this consideration of the principal clinical forms of adrenal encephalopathy, I think it well to emphasize the practical interest of certain of the remarks contained therein and upon which I laid stress as we proceeded. In conclusion, let me point out how

important it is for medical men to familiarize themselves with the various forms which hypoadrenia may assume, and to know them all. It is not only the satisfaction of making a diagnosis which makes it worth while to get them fixed in the mind; it is the certainty that if we know how to make this diagnosis, or, at any rate, if we know when to suspect it, that we sometimes will be able to save our patients and often curtail the duration of an illness which adrenal therapy alone can mitigate. Thus an acute adrenal insufficiency, when not connected with an irremediable lesion of the capsules, can be cured by means of adrenal therapy."

Hertoghe, of Antwerp, in his pamphlet on "Hypothyroidie Bénigne Chronique, ou Myxedème Fruste," speaking of cephalalgia, states that this symptom is more or less constantly noticeable in benign chronic thyroid insufficiency; that thyroid impoverishment manifests itself in headaches, which for a long time have been attributed to cerebral anemia. He continues: "This hypothyroid cephalalgia consists principally of two forms. Sometimes it seems to come from the frontal sinuses, extending above the orbits and remaining frontal. It resembles the pains which occur at the beginning of acute coryza. At other times it originates in the back part of the head. A painful spot at the level of the occipital nerve gives it the aspect of neuralgia. From the occipital region it invades the corresponding half of the skull and is termed 'migraine.' It differentiates itself from real migraine in that it is more intense in the morning, when the patient rises, and disappears towards evening after a hearty meal. Patients get so accustomed to this continual cephalalgia that they hardly refer to it, and the question has to be put to them before they will admit they are suffering from it. Loss of hair is often attributed by patients to these continuous pains. The doctor, who is quite often powerless to cope with them, encourages the patient in this method

of interpretation and styles the complaint 'epicranial rheumatism.'

"The least fatigue, the slightest perspiration, a draft of air, brings about the return of the occipital pain. Add to this the fact that the sorry condition of the teeth easily brings on attacks of neuralgia in the region of the trigeminal nerve. Supraorbital and suborbital neuralgia is most frequent in hypothyroid diathesis."

This same authority states in the conclusion of this article: "As I have already stated, dysthyroid migraine, which is intolerable in the morning, after the coolness and inanition of the night, improves towards evening and disappears after a good meal. It is perhaps well to recall at this point that patients instinctively seek for the 'whip' afforded by wine and liquors, although in reality alcohol is extremely harmful to them, in the sense that it is the antidote of the thyroid principle and aggravates the distress of the organism resulting from thyroid insufficiency."

11.—Alimentary Neurasthenia

Practically every neurasthenic has some alimentary difficulty or another, and perhaps it is not correct to classify an alimentary form of neurasthenia *per se*, yet a great many individuals have a form of indigestion of a neurotic character, which is more nearly neurotic than it is alimentary, and which does not respond to the dietetic, eliminative and hydrotherapeutic measures directed at the digestive organs. In fact, many chronic disturbances of digestion have as a part of the syndrome a subtle and frequently ignored neurotic aspect which, to my way of thinking, may be the one factor that the best gastroenterological regulation cannot reach.

For instance, I recall the case of a young lady who

had been a sufferer from digestive difficulties for years. She had recently spent six weeks in a very prominent Eastern hospital under an internationally known gastro-enterologist, without benefit. After this she got into the hands of a Pittsburgh physician, who saw fit to apply some of my ideas in her treatment. He had read a little article of mine connecting digestive difficulties with ovarian dysfunction and advising the most careful study and control of these matters as possible. It was found that this girl had a serious amenorrhea and, as a result of this, she was both neurasthenic and asthenic. The dysovarism was treated with suitable organotherapy, and not only was the amenorrhea and accompanying neurasthenia benefited, but the gastro-intestinal difficulty was cured entirely, though it had been in existence for years, and throughout this long period had been impervious to the best efforts of the best men. I might extend my remarks along these lines for many pages, but will refrain.

Undoubtedly adrenal dysfunction is capable of causing digestive disorders. George W. Crile, of Cleveland, has shown experimentally that among the functions of the adrenals is the power to inhibit intestinal function provided these glands are working to excess. Cannon confirms this, and his experiments have shown that a forced output of adrenin—due to emotional, toxic, or endocrine causes—produces an increase in the arterial tension by shifting the blood from the comparatively less important abdominal viscera to the immediately essential organs, as the brain, lungs and heart. Adrenal excess inhibits both pancreatic digestion and intestinal muscular activity, and thus favors toxemia which, as we have seen, is one of the most common causes of neurasthenia.

It is clear that the alimentary neurasthenia is a very unfortunate, vicious circle, in which whatever factor may be causing the emotional imbalance favors a dis-

turbance in the mechanism both of the secretory and muscular portions of the digestive tract, thereby bringing about an increased production of toxins which still further aggravates the adrenal difficulty and continues year in and year out to resist all efforts at treatment. Of course indigestion and dyspepsia have a place in the etiology of neurasthenia. For instance, Hayden believes that neurasthenia is a result of a poor or incomplete assimilation of food rather than auto-intoxication, and this is quite possible. I should imagine that all of these factors exert their influence together. Another writer says that he has seen many cases of neurasthenia follow along a history of dyspepsia with fermentation, flatulence, etc., while still another is equally sure that the rule is for neurasthenia and indigestion to originate simultaneously. What do we care which is initiated first, provided we know the physiological mechanism and are thereby offered a means of modifying its dysfunction?

The adrenal dyspepsia discussed by Maurice Loeper, of Paris, need not be of the severe type which forms a part of the clinical picture of Addison's disease, for similar digestive disturbances may result from a less serious involvement of the adrenal glands. Many soldiers suffering from the strain of war or convalescing from disease or wounds, have manifested most serious digestive difficulties. So do many other individuals whose adrenal dyspepsia is brought about by other similar emotional or toxic stimuli. Loeper found that the practice of himself and his associates of using adrenal therapy in these cases brought about such changes that in some instances "the patients were transformed by it. The digestive discomfort disappeared, the stools became regular and assimilation more perfect, so that the man soon increased in weight." They explain this benefit by the tonic action of the adrenal principle upon the nervous system.

An excess, as well as a deficit, of adrenin may generate abdominal trouble. We know that adrenin acts upon the smooth muscle fibres of the vessels and bronchi and probably the smooth muscle fibres of the stomach and bowel do not escape this influence. Hypoadrenia may influence the secretory activity of other abdominal glands, and the study of these adrenal dyspeptics seems to confirm this assumption.

12.—Ovarian Neurasthenia

The frequency of the relation between neurasthenia and dysovarism is sufficiently important to warrant its discussion under a separate heading. In fact, some writers have definitely classified a condition which they call "ovarian neurasthenia," and whether disturbed ovarian function is a direct cause of the neurasthenia, or the neurasthenia may be a factor in bringing out the ovarian dysfunction, need not concern us. The point is that dysovarism and neurasthenia are frequently found together, and the physician who is in the habit of considering the endocrine aspects of his patients will find himself a much more competent master of the situation in a complex neurasthenic syndrome than the one who has been in the habit of considering neurasthenia as more or less of a temperamental or hereditary neurosis, which can be modified only by the direct intervention of Providence.

If, indeed, it is permissible to classify a special type of ovarian neurasthenia, then this particular disorder should be subclassified into the neurasthenia of puberty, the neurasthenia of actual ovarian disease, and the neurasthenia of the menopause; and it may be well, under the circumstances, to make this tentative classification and give some consideration to each of these.

Neurasthenia During Early Ovarian Life. Ordinarily speaking, neurasthenia is not a disease of children.

It is quite a rare experience to find a thoroughly neurasthenic child, but at or near the onset of puberty the incidence seems to increase and "the nervous breakdown" of the high school or seminary student is quite a common neurological syndrome. In these cases the predisposing influences previously mentioned, especially the abnormal heredity which, unfortunately, is so frequently passed on to the young of this generation, as well as the extreme importance of toxemia as an underlying cause, and also the direct or indirect influence of emotional imbalance—all should be given consideration in the study of a nervous breakdown in a girl in the teens.

Without any question, our methods of education are seriously at fault and the educators do not seem to have acquired the kind of intelligence which appreciates the comprehensiveness of the revolution which is going on in a youth or maiden at and immediately following the establishment of the sexual life. The circumstances of our so-called civilization certainly are not favorable to our young people. Indoor life, the conditions in our schools, the unfortunately common practice of "cramming" for examinations, and several other things which might be mentioned—including novels of the Robert W. Chambers type, the movie sex-drama, etc., all play a very important part in the preparation of the soil for the implantation of the neurasthenic syndrome. It is not possible to lay the blame upon any one thing. It is merely the sum total of the numerous abnormal circumstances which favors the nervous breakdown. Whoever heard of a nervous breakdown in an American Indian girl? Why is neurasthenia, in the particular phase under discussion, practically never found in the rural and perhaps semi-civilized districts?

At puberty, as we know very well, a new factor enters into the endocrine balance. The thyroid gland is largely concerned in initiating ovarian activity, and if

emotional, toxic or infectious circumstances have weakened or overburdened the thyroid, it may not have sufficient physiological reserve at its disposal to render to the full the all-important service that it is supposed to offer to the ovaries at this particular time. So, in addition to any dysfunction which may result from a minor hypothyroidism, there is added an imbalance resulting from an incomplete establishment of ovarian function, and every physician and neurologist knows how commonly dysovarism—amenorrhea in its various degrees, dysmenorrhea, etc.—is related to the neuroses of puberty and young womanhood.

One cannot state definitely that an improperly initiated ovarian function is a positive and unquestioned cause of neurasthenia. To my mind, it undoubtedly may be, but cases in which this single factor brings this condition about are so rare as to be practically never found. In other words, those endocrine factors which have not served as they should, and as a result of which ovarian function has not been initiated and established in a normal way, have at the same time been falling down on their other physiological services to the body and, therefore, a "true ovarism neurosis" cannot very well be found, for there is practically always also a thyroid, and an adrenal, and perhaps a pituitary aspect to this complex. To put it plainly, pubertial neurasthenia has a pluriglandular aspect which deserves consideration and treatment from the pluriglandular standpoint.

Many of the headaches of girlhood are really the result of a well-meant attempt on the part of the body to establish or reëstablish a more nearly normal ovarian function. I am personally convinced that the pre-menstrual splitting, rending headache which comes on without warning and is mitigated or ended by the establishment of the menstruation is really the result of a pituitary effort to help out the lagging ovaries.

I am not prepared to place this in the classification of Pardee as pituitary headache, but it is not unreasonable to presume if the ovaries are inefficient and the pituitary is capable of encouraging them—and, of course, the pituitary has a very obvious relation to ovarian function—that the body would naturally attempt to secure ovarian encouragement from every possible source. Again, in some instances, an enlargement of the thyroid gland is seen at this particular time, thus emphasizing the unusual demands that are being made upon all of the gonad-stimulating endocrines. This special kind of headache may complicate matters, and the principal aim of treatment is to make it unnecessary for the thyroid to have to work so hard or for the pituitary to have to be over-engorged ever so slightly and, therefore, to cause a pressure condition because of the limitations of its bony sellar confines.

If we can reasonably consider a nervous breakdown in a girl or young woman as related to ovarian function—it is not difficult to connect them very definitely, provided the menstrual manifestations are abnormal—then a part of the treatment of the nervous breakdown is an attempt to reëstablish ovarian function, and here is the great reason for the good results which have followed the pluriglandular treatment of menstrual difficulties both with and without neurasthenia.

Many times I have been brought in touch with heart-breaking cases of neurasthenia, some of which have begun to acquire that serious aspect which comes with the metamorphosis of a neurosis into a psychosis for whom the very best efforts had been previously made by competent neurologists. Not infrequently, to my delight, I have succeeded in uncovering and emphasizing some endocrine aspect, and as is my wont, I invariably urge the regulation of the endocrine condition on the principle that sedatives were not curative, environ-

ment was merely an incidentally useful measure, and rest was but negative treatment. Parenthetically, I do not wish to belittle the importance of rest as an important factor in the treatment of neurasthenia, but it is perfectly clear that rest merely tends to prevent the aggravation of the condition, and it is for this reason that I choose to call it "negative treatment." That is, it is not aggressive treatment, but merely a favorable factor in the indicated therapeutic regimen. Environment again must not be minimized, and the above statements apply to it as well as to rest. In fact, a change of environment is but an application of the principle of rest to the emotional and psychic aspects of a given case. The value of sedatives should not be minimized as temporary expedients. Their value, however, should not be depended upon as really remedial.

It happens that the endocrine method of treatment can very conveniently be fitted into the rest cure, or whatever may be advisable from a hygienic standpoint. For that matter, most of the cases of this type of neurasthenia that have come to my attention, already have been inmates of various institutions or have visited from one to a dozen or more physicians who have prescribed the milk cure, the Weir-Mitchell method, a sea trip, or what-not. My point, which I contend is based upon good reasoning, is simply that if rest is good, and a change of environment an advantage, it will make our pluriglandular treatment of the disturbed endocrine function so much the more efficacious, just as the regulation of the dyscrinism should accompany the other obvious measures and every effort should be made to normalize those factors which influence the ovarian function and its service to the body as a whole.

Neurasthenia With Ovarian Disease. The second condition in our tentative subclassification is very rarely of purely ovarian origin; yet must be considered as such because to ignore this is to fail in the treatment.

Certain individuals acquire a definite change in the structure as well as the function of the ovaries. Some writers have suggested a disorder with the name "ovarian poisoning," since it seems that the normal ovarian hormones are perverted and these changed chemical principles act exactly as poisons. Such cases call for surgery, in addition to the other indicated regulative measures.

Another form of ovarian neurasthenia is that which follows aberrant ovarian functioning. If the flow ceases, morbid fears of a pregnancy or serious disease bring on a neurasthenic state. Usually the amenorrhea is related to other associated endocrine dysfunctions, all of which must be considered together and treated. One can readily see how easily a neurasthenia can develop in the right kind of soil when some abnormality of ovarian activity—menstrual, sexual or developmental—can prey upon the patient's mind with dire results.

In a paper on "The Relation of the Internal Secretions to Neurasthenia in Women," read before the Los Angeles Obstetrical Society, some years ago, I said that it is not possible to treat gynecological disorders effectively without in every case carefully considering each individual from the endocrine standpoint. The ductless glandular system in women is more sensitive to physiologic impressions than the nervous system; hence, one must expect to encounter pluriglandular disturbances very frequently.

There is a comparatively small number of women whose neurasthenic manifestations are associated with ovarian and menstrual superactivity. Their periods are prolonged and excessive, they have so little freedom from the inconveniences of menstruation, and their economy is so depleted by the undue loss of blood and strength, that they easily become neurasthenic. Often they brood over their condition; and, rarely, the onset of a heavy flow prostrates them not merely physically

but mentally. All too often these cases are called "endometritis," for convenience, and are treated surgically, with mediocre results; while many would be benefited by the exhibition of mammary extract.

Recourse to suggestion, psychotherapy or any other measures, except the indicated organotherapy, necessarily falls short in attaining the desired results. These essentially ovarian cases absolutely must be treated first and foremost as dysovarism and the neurasthenia considered as coincidental.

Neurasthenia at the Climacteric. Menopausal neurasthenia is a very common disorder. It is not a far cry from the circulatory and nervous instability of the change of life to real neurasthenia, and to my way of thinking, the principal cause of a nervous breakdown at this time is preëminently endocrine. At this period in life an endocrine factor to which the organism had been accustomed for thirty or more years is removed with greater or less suddenness. This permits of an imbalance which may cause varying degrees of trouble, depending upon the physiological substratum of the individual in question, and also upon the character of the withdrawal of this factor. Some individuals have a good heredity, a well-cleansed system, and are largely "mistresses of themselves" and not victims of their own disturbed physiology. In these well-balanced individuals the menopause may be of no consequence, but in the opposite class it sometimes takes on very serious aspects. Then, again, the character of the ovarian functions and life must have something to do with the closing of the ovarian books. I believe that the ovarian life determines the character of the menopause, and when the menopause fortunately is brought about gradually, and the cessation of the menses does not come suddenly, the chances for endocrine imbalance and the circulatory and nervous troubles which may accompany it, are very much less. Perhaps, on the other hand, an

individual whose menses are suddenly cut short, is likely to have as much menopausal difficulty as the individual who actually goes through a surgical menopause.

Alfred Gordon, of Richmond, Va., enjoins caution in advising operation on the generative organs. He noticed a tendency of the pituitary, thyroid and adrenals to undergo hypertrophy after removal of the ovaries, and in 112 patients he observed functional nervous disturbances, such as restlessness, lack of self-control, dissatisfaction with everybody and everything, moroseness, indifference and indolence. There were outbreaks of anger and a tendency to attack other individuals. Some of the patients suffered from insomnia, headache, gastro-intestinal troubles and obsessions.

Without a doubt, neurasthenia is commonly found in women at the change of life, and one of the important reasons for this extends beyond the actual removal of this ovarian principle from the hormone-complex. It will be recalled that hypothyroidism of the major type, or myxedema, is essentially a disease of women (it is said that ninety per cent of all cases of myxedema occur in women, and according to Oliver T. Osborne, of Yale University, ninety per cent of all cases of myxedema occur in women between forty and fifty). In other words, myxedema really may be a menopausal difficulty. At all events, the correlation between the thyroid and the ovarian hormone activities is so intimate that the removal of the one may bring about a condition of "laying down on the job" on the part of the other, and in myxedema it will be recalled there is a very serious inactivity on the part of the cellular metabolism with a resulting toxemia and infiltration which alone might bring about neurasthenic manifestations, such as already have been discussed elsewhere in this monograph.

The same thing may be said in regard to the cessation of ovarian function and adrenal instability. It is believed by a number of competent authorities that the

circulatory difficulties of the menopause, and especially the flashes of heat, the periods of chilling and burning, as well as some of the circulatory skin manifestations, really are largely dependent upon an adrenal imbalance.

Sajous, of Philadelphia, in his monumental work, "The Internal Secretions and Principles of Medicine," referring to ovarian organotherapy, makes the following statement: "There exists, as has been shown by Sir Edward Schaefer, a close homology between the interstitial cells of the ovary and the same cells in the adrenal glands; both sets of organs are derived from the Wolffian body; ovarian extract raises the blood-pressure and slows the heart, as shown by Feoderoff, Jacobs and others. Removal of the ovaries, moreover, reduces the oxygen intake ten per cent, as shown by Loewi and Richter, while the administration of ovarian extract restores it; it has been, therefore, regarded as an oxidizing ferment. Neumann and Vas noted that ovarian extract enhanced metabolism; but Senator observed that ovarian preparations increased diuresis and the excretion of urea and phosphoric acid. Its physiological effects are those of adrenal preparations, therefore, in every respect."

This position thus emphasized renders more important the ovarian aspects of neurasthenia, provided we are willing to accept the suggestion already outlined that hypoadrenia and neurasthenia are closely akin to one another. As a matter of fact, the ovarian form of neurasthenia very commonly is associated with just such metabolic and functional insufficiencies as have been quoted by Sajous, and a large number of cases may properly be called suffering from hypocrinism, including the adrenal glands, the thyroid, and the sex glands.

With all this in mind the obvious thing to do for neurasthenia at the menopause is to treat the dyscrinism which accompanies or causes the menopause, and trust that it may be sufficiently intimately connected

with the neurasthenic symptoms to permit of their modification as the disharmony is lessened or controlled entirely.

13.—Sexual Neurasthenia

One of the quite common forms of neurasthenia has acquired an undue prominence because its usual name is applied to any mental or nervous aspect connected with the sex glands, and "sexual neurasthenia," as it is called, is a not unusual condition, which is quite frequently referred to in the literature.

Whether this disorder essentially is based upon disturbed function of the sex glands, which are, of course, glands of internal secretion, or whether it is a mental or a toxic disturbance, is very hard to state. To my way of thinking, most of them are more psychic than endocrine, although, of course, it must be remembered that any disturbance of function of the sex glands is an endocrine disturbance, consequently, sexual neurasthenia deserves consideration here.

According to Lydston, this condition "implies an ordinary neurasthenia with a sexual element, either psychic or physical in character." This writer goes on to say that organic disturbances of the gonads hardly can exist without a strong incidental psychic element, and emphasizes the fact that a purely psychic sexual element in sexual neurasthenia is rare. In these cases there is practically always some functional derangement of the sexual apparatus behind which may lie a varying degree of organic disorder.

Since Lydston, in his book, "Impotence, Sterility and Sex Gland Implantation," takes up the subject of sexual neurasthenia so satisfactorily and sequentially, I propose to make a number of quotations from this chapter rather than to hop around in a really tremendous

literature, much of which does not lead us anywhere. Lydston believes that neurasthenia in the male is associated with prostatic hyperemia and hyperesthesia and with inflammation of the prostatic urethra more than with any other condition. When one recalls the comprehensive sensory and sympathetic nerve supply of this gland, it is easy to understand why nervous symptoms may develop in patients suffering with prostatic disease. If to this is added the profound impression made upon an individual by a knowledge of his sexual disability, there is a very satisfactory reason for the frequency of sexual neurasthenia. This authority is one of those who believe that the prostate gland is a gland of internal secretion, and I thoroughly agree with him. I recall that during my experiences in Denmark I got in touch with some information from Prof. Rovsing's clinic in Copenhagen, which indicated that he differentiates a special form of neurasthenia, called "prostatic neurasthenia." At all events, Lydston believes that the prostate secretes a hormone which may be perverted as a result of local infection and which, conjoined with the absorption of the toxins of the infection, often has much to do with the etiology of sexual neurasthenia. If to this is added disturbances of digestion, the abnormal mental attitude and the emotional strain make way for a combination of conditions which Lydston properly believes might be called "prostateria"—an analogue of hysteria.

Too often well-meaning physicians "are wont to waive the sexual neurasthenic away with a bluff, 'My good friend, forget it, there is nothing the matter with you,' and as a result the individual seeks someone who will sympathize with him and goes to the quack," who promptly finds plenty to occupy the patient both mentally, physically and financially. The mechanism of the prostatic origin of sexual neurasthenia will take a little more space than we have at our disposition.

Lydston's book contains some splendid information and there is more of a similar character in Vecki's "Sexual Impotence," to the value of both of which I am glad to call attention here.

This disturbed function of both the prostate and the gonads, plus the emotional imbalance which cannot well be avoided under the circumstances, brings about quite a degree of asthenia and with it, of course, a neurasthenia which is very real to the patient. It may be that there is no basic *organic cause,* for a patient can be very sick functionally without any manifest anatomical trouble, and the prostatic irritability, the erethism, the impotence or any of the other more or less serious manifestations accompanying sexual neurasthenia are perfectly real to the patient.

These cases are very difficult to handle. Of course, the discovery of fundamental causative elements is imperative and naturally treatment must be directed to the relief of local conditions. The essential principles of good hygiene are applied, but success is quite elusive, at least in the experiences of some physicians, merely because they forget that these cases all have a depleted endocrine reserve and their patients are merely given some advice and treatment calculated to remove the causes. If a man is impotent, and as a result is neurasthenic, every effort to control the neurasthenia which ignores the functional condition of the sex glands, is bound to be a failure. Consequently, organotherapy has a very definite place in the treatment of sexual neurasthenia where there is a physiological call for the endocrine stimulation which is possible by organotherapy.

Prostatic neurasthenia, and neuroses associated with prostatic hyperesthesia and hypertrophy, are sometimes regulated very nicely by the use of prostate extract which exerts a somewhat intangible but none the less encouraging, steadying effect. The anterior lobe of the

pituitary is given with advantage in hypogonadism because this particular organ exerts a stimulating effect upon the sex nutrition and mechanism. Spermin, the principle prepared from the interstitial cells of Leydig originally by von Poehl, of Petrograd, is a sex tonic and has been recommended times without number in sexual neurasthenia—not, however, for any influence that it exerts upon the neurasthenia *per se,* but rather for its gonado-stimulant effect and the indirect advantage which might come to the neurasthenia by the reëstablishment of the gonad functions on a more nearly normal basis.

Finally, and to my way of thinking, most important of all, since all forms of neurasthenia are related in greater or less degree to adrenal dysfunction, the sexual neurasthenic should be studied from the standpoint of the adrenal glands, and if there is evidence of muscular weakness, poor circulation and low blood-pressure, deficient cellular activity, and perhaps hypothermia, sufficient grounds have been found to add to the neurasthenia syndrome a hypoadrenia, and, naturally, to give it the benefit of the indicated treatment, or adrenal feeding. A pluriglandular treatment of this combination of circumstances has proved to be quite an advance over the less comprehensive single extract.

Of course, many cases of impotence and the resulting sexual neurasthenia have no real endocrine basis—they are endocrine only in that the reproductive function of the gonads (which, by the way, is a different proposition from its hormone-producing capacity) is involved. But the real trouble is an infection, a psychic matter, or at least not a purely endocrine problem; but it will be clear to those who have read the previous chapters that both the emotional factor as well as the toxic factor that may accompany such troubles may have played upon the adrenal system sufficiently long to have worn it out. In which case we have exactly

the same kind of a neurasthenia as in the other forms which have been previously mentioned; and, naturally, the fundamentals of treatment are identical.

IV

DIAGNOSIS

14.—Usual Symptomatology

To those who have read the preceding pages, the diagnosis of endocrine neurasthenia will not be difficult. In fact, the diagnosis of endocrine neurasthenia consists in discovering the endocrine dysfunction and the neurasthenic manifestations. In other words, it is a dual diagnosis, and the difficulties are lessened because many of the symptoms in these two previously distinct and separate categories are really the same thing.

In Tom Williams' article, entitled "A Form of Neurasthenia Due to Hypoadrenia," referred to previously, he suggests that we compare the now well-known symptoms of hypoadrenia with some of the accepted findings in neurasthenia. The former include asthenia and the fatigue syndrome, circulatory inefficiency, resulting from a lack of the necessary stimuli to the cardiovascular musculature and resulting in sensitiveness to cold and cold extremities, low blood-pressure and weak cardiac action, nutritional manifestations such as anorexia, anemia, and a reduced metabolism (practically always hypoadrenia is accompanied by hypothydroidism, for it is now well known that the adrenal and thyroid principles stimulate one another mutually), and, finally, as a result of the lack of muscular tone there ensues constipation, stasis, and alimentary toxemia. On the other hand, the typical symptoms of neurasthenia include rapidly failing

strength, prostration after exertion, circulatory imbalance with a tendency to cold extremities, loss and control of the attention, weakness of memory and willpower, constipation, etc.—a combination remarkably similar to the findings in hypocrinism.

We have not space for a complete list of all the symptoms of each of the forms of neurasthenia—it would take many pages of this monograph—but if I have succeeded in relating many of the ordinary symptoms and signs with disturbed endocrine balance, I will have accomplished my task.

15.—Differential Diagnosis

The differential diagnosis is perhaps more important since neurasthenia simulates many conditions from which it must be differentiated. Perhaps the first of these is what is called psychasthenia—a state of affairs which is characterized by a tendency to give way to impulses. Janet and others believe that psychasthenia is a definitely inherited characteristic, while, as a rule, neurasthenia is an acquired condition, though as we have shown, the soil upon which the neurasthenia is implanted may be very favorable as a result of hereditary influences. It is believed that psychasthenia may be a part of a neurasthenic syndrome, or at least a border-line condition between neurasthenia and actual insanity. It is differentiated from actual neurasthenia by the fact that the neurasthenic is not impulsive although very nervous, and is often depressed but rarely considered insane, whereas the psychasthenic is really considered "peculiar" in manner of thinking and living, while the neurasthenic suffers more from lack of willpower and mental laziness.

Neurasthenia often may be confounded with hysteria, especially in women. One should not diagnose hysteria save only where there are convulsions, con-

tractures, paralyses, anesthesias and other toxemic or marked emotional characteristics. The hysterical patient ordinarily has none of the introspection, tendency to study medical literature, and constant sadness that unfortunately dominate the scheme of existence of many a neurasthenic.

Another neuropsychic condition—hypochondria—should be considered in this connection. The hypochondriac "is the victim of actual delusions regarding his condition," whereas the neurasthenic has no delusions, but, contrary to the belief of some physicians, really suffers from pain and other symptoms.

A very useful diagrammatic table facilitating differential diagnosis between neurasthenia, hysteria and hypochondriasis is taken from Savill's book "Neurasthenia," and is given here in order to clearly outline the points of difference between these three overlapping conditions.

Information regarding the differential diagnosis between neurasthenia and certain organic nervous and mental diseases, such as tabes, paresis, multiple sclerosis, etc., may be secured from an already comprehensive literature on the subject.

According to Tom Williams, of Washington, D. C., the incapacity of hypoadrenia is distinguished from melancholia by the absence of the retardation of thought and movement always present in the true melancholic, in whom, furthermore, the responsiveness increases in speed and effectiveness as the day goes on and when the stimuli are augmented and longer continued; whereas, in hypoadrenia the patient is at his best early in the day and the more work he does the worse he becomes.

A word or two may be added here in regard to the drug takers, for practically all of them are neurasthenic when they come for treatment, and most of them had this disorder before acquiring the habit. Anyone who

	NEURASTHENIA	HYSTERIA	HYPOCHONDRIASIS
SEX	Both sexes almost equally.	Female sex almost exclusively.	Male sex almost exclusively.
AGE	Any age. Young male adults slightly predisposed.	The first actual manifestations always appear before 30.	Very rare under 30. Predisposition from 30–50.
MENTAL PECULIARITIES	Intellectual weakness; memory defective; deficient power of attention.	Deficient will power (i. e., vacillation, indecision). Want of control over the emotions.	Great determination and perseverance towards one end, viz., cure of imaginary disease.
CAUSES	Overwork, dyspepsia, other causes of malnutrition, autotoxemia, traumatic or nervous shock. (Why not hypoadrenia?)	A patient is born with the hysterical diathesis. The determining cause of its active manifestation is generally an emotional upset or shock.	Solitary, sedentary life.
ONSET AND COURSE	Starts somewhat gradually and runs a fairly even course.	Hysteria essentially a paroxysmal disorder. All phenomena (healthy or morbid) vary from hour to hour, day to day, and paroxysmal outbreaks are frequent.	Starts very gradually and runs a very even course of most indefinite duration.
MENTAL SYMPTOMS	Mental exhaustion and inability to think or study. Inattention. Memory deficient. Restlessness; temper, irritable.	Wayward, hard to please, emotional, laggy, restless. No introspection, nor living by rule, nor study of medical works.	Introspective habit. Close study of medical books. Observing all accessible organs and secretions.
	Prostration and sadness. Not equal to the exertion of amusement; sometimes suicidal.	If sad, it is transient (excepting in the male). Fond of gaiety and amusement. Usually joyous, but laughter and tears may alternate with great rapidity. No tendency to suicide.	Habitual sadness. No taste for amusement, but little tendency to suicide.

	NEURASTHENIA	HYSTERIA	HYPOCHONDRIASIS
SOMATIC AND GENERAL SYMPTOMS	Occasional attacks of vertigo; syncope rare, convulsions never. Attacks of flushing and other sensations after meals.	Seizures of different kinds frequently arise. Always flush very readily at any time. Convulsive attacks in 75% cases (Briquet). Syncope very frequent. A great variety of symptoms occurring in paroxysms.	No attacks of any kind.
	Easily tired, easily startled. State of debility and exhaustion. Constant headache. Restlessness and sleeplessness. Long-drawn sighs.	Between the attacks no symptoms usually present. But symptoms referable to the nervous and neuro-muscular system may be present. Thus:	The digestion is often deranged, but in the patient's belief he has some grave disease either of the alimentary tract, abdominal or other viscera.
	Hemianesthesia never. General hyperesthesia and dysesthesia common. Pain in the back and sometimes limbs. Reflexes may be increased or normal.	Hemianesthesia very common (though may be undiscovered) or other anesthetic areas. "Ovaric;" tender spots around the mammal and in other positions. Reflexes usually increased. Borborygmi, globus and other spasms of the involuntary muscles are frequent.	Small and insignificant symptoms, or even normal sensations, are endowed with great and perhaps lethal significance. Patient tries an endless succession of remedies and doctors, always straining for a cure (which distinguishes hypochondriasis from the hopeless and suicidal tendencies of neurasthenia and melancholia).
TERMINATION	Lasts many weeks or months. Curable.	The diathesis lasts a life time, but the active manifestations come on suddenly, and after lasting a short time usually disappear. Semicurable.	Once established, the condition is very difficult to ameliorate, impossible to eradicate, and therefore incurable.

has seen a drug addict after removing his supply of opiates readily can understand that his symptoms might properly be called "acute neurasthenia." Since it is now very difficult to secure these drugs, many habitués depend upon medical aid for their sufferings and are a most distressing class to meet and treat. Too often time is wasted in investigating conditions, for ordinarily these individuals are inveterate liars. The study and treatment of the neurasthenia in drug cases cannot be extended in this article, save only to say in the most positive terms possible that there never was a drug fiend whose endocrine balance remained unscathed. Is not the drug taker subjecting himself to a tremendous toxemia? Do not the drugs ordinarily taken—cocain, heroin, morphin, or even alcohol—act upon the endocrine system, and particularly the adrenal glands, exactly as any poisons? If the adrenal glands are supposed to respond to these poisonous stimuli in order to facilitate the body's defense reaction, will not such overstimulation deplete these glands?

I have rarely seen a drug addict in whom hypocrinism, including hypoadrenia, hypothyroidism, hypogonadism and hypofunction of practically every endocrine organ was not present and prominent, and I have repeatedly stated and written that the successful control of this class of difficulties necessarily must involve the support of these terribly overworked and badly broken down glands. To my way of thinking, the neurasthenia of drug addicts is merely an incidental factor. The two great things to give consideration to are the poisoning and its results upon the poison-regulating mechanism of the body—the endocrine system.

In the differential diagnosis of endocrine neurasthenias it may be well to mention some of the statements of Walter Timme, of New York: "Stripped, these patients frequently show dystrophies of skeletal growth. The arms may be too long for the body, the

thorax too short for the legs, or *vice versa*. The teeth are somewhat anomalous in that the lateral incisors are small and the canines have attributes of incisors; caries is very common. The hairy growth may disclose a feminine pubic distribution in the male, and *vice versa* in the female. The reaction of the skin to stroking frequently will show, especially on the abdomen, a dermographic line which is white on the abdomen and pink on the thorax." Timme also calls attention to the frequent irregularity of the blood-pressure readings. It may be found to be normal or even slightly higher when taken casually, but if taken as it should be, in two or three successive systolic readings at intervals of a minute, a rapid systolic drop may be seen, the final reading being below normal. He has seen systolic readings taken in this way to differ as much as 175, 130, 105, with a fairly uniform diastolic reading of 70 mm. These individuals show a general relaxation of the smooth muscle organs and also of the tendons; flatfoot, visceroptosis, and a sacro-iliac backache are commonly present. To quote from this same paper: "Even with these few salient points in our examination, it will be seen that our attack is quite different from the old method. The interpretation of this picture is a faulty compensation of an adrenal inefficiency. This adrenal inefficiency has arisen as a result of some general causative factor such as infectious disease, but on a preformed basis of endocrine instability. The life history of the patient gives manifold evidences of such disturbances in growth and metabolism, especially. Such hypoadrenia may remain latent until the patient subjects himself to stress and strain beyond his narrow limits of fatigue, or may be partially compensated for by other glandular structures, such as the pituitary. Overcome this compensation and we have manifestations of neurasthenia, psychasthenia, and the psycho-neuroses."

As will have been noted elsewhere, one of the most important diagnostic points in the differentiation of the endocrine aspects of neurasthenic states is the response of the individual to presumably indicated organotherapy. This, to my way of thinking, is an extremely important measure. It is neither unscientific nor empirical, as some would have it, for in many cases I have succeeded in demonstrating the all-important endocrine factor in a given case of neurasthenia by assisting in its disposal by means of suitable organotherapy. What does the patient care, anyway, whether we know in advance the exact nature of his disabilities and can assure him positively of the outcome of our treatment? Frankly, I have yet to find the physician or specialist who has this happy faculty. We are not prophets. We cannot predict the future. We do not know the responsiveness of these endocrine glands even though we may be sure that they are not functioning normally, and such limitations make it impossible for us to predict in advance the outcome of treatment. Incidentally, I always make a point of this in my discussion with these individuals. Since they have the neurasthenic manifestations already outlined, they are introspective to a degree and find themselves looking very carefully for some of the changes that we expect to find as a result of the therapeutic diagnostic measures. They discover that their blood-pressure is increasing and that their muscular tone is better as a result of the endocrine support which we prescribe, and this in itself exerts a wonderfully salutary influence upon the all too prominent mental aspects. These people who have always been in the habit of magnifying their symptoms, now find themselves magnifying their progress, much to their relief and to that of their physician. In other words, the very unfortunate introspective attitude that these people hold toward their symptoms, now begins to serve both them and their

physician in good stead, for as they have magnified their troubles heretofore, they magnify the slight progress which may result from giving these glands a chance by removing the causes of endocrine depletion—and a boost by means of organotherapy.

V

THE TREATMENT

16.—General Measures

It has been almost impossible to refrain from referring in previous chapters to quotations and hints regarding treatment, in order to leave all of this information for proper segregation under the above head.

If neurasthenia is indeed a condition with a large endocrine aspect—and I believe we have established this with a fair degree of reasonableness—then the best treatment should include all measures calculated to antagonize or offset these particular troubles.

It will be clear that causative factors, as well as those associated troubles which are not actually causative but are aggravating, must be taken care of as best one may by diet, elimination, hygiene, environment, psychotherapy, and any other available therapeutic measures.

If it is true that toxemia is the chief cause of neurasthenia, general measures in the treatment of this latter condition necessarily must involve every detoxicating procedure which conveniently can be brought to bear upon it. The routine treatment of neurasthenia must include rest—the most effective means of reducing the production of wastes due to activity, whether muscular, nervous, or mental—and complete rest, usually including a change of environment to free the individual from the nagging circumstances of his routine existence, is customary whenever possible in the treatment of neurasthenia.

Alimentary detoxication by diet is naturally of para-

mount importance and it will not be my object here to dilate upon this aspect of the treatment of this disease. Kellogg, in his book, "Neurasthenia," connects the colon with the etiology of neurasthenia, and properly so. Colon hygiene is as important a part of the treatment of neurasthenia as any other single measure, and dietetic control is another important factor in perfecting conditions which oppose alimentary toxemia. It should not be necessary to emphasize the advantages of saline purgatives, judiciously used, of increasing the amount of water that is drunk and antagonizing alimentary atony and stasis by various measures, including massage, hydrotherapy and suitable exercises.

17.—PSYCHOTHERAPY

Where the emotional imbalance is serious, greater difficulty will be encountered because often these individuals have come to be unreasonable in their attitude to their well-meaning friends, but nevertheless, every effort must be made to remove emotional stress which, as we have seen, further depletes the regulatory endocrine glands and leaves the patient in the played-out asthenic, neurasthenic condition which has been described.

Moliére's famous "Le Malade Imaginaire" evidently was a bad case of neurasthenia, and like a good many other individuals with both real and fancied troubles, might have been benefited from psychotherapy. In fact, I recall having mentioned this matter in a paper which I read some years ago before the Pasadena Medical Society, entitled "The Adrenal Glands and Their Significance in General Practice." In this paper I called attention to the reactions which result from adrenal irritability and stated that the influences of fear, rage and emotional stimuli, including worry,

"possibly explain the occasional effects of psycho-analysis, suggestion, and even Christian Science in certain neurotic states. One can readily see that a calmed mind—reduced emotional overstrain—obviates the excessive psychic stimulation of the adrenals; and the hypertonic state of hyperadrenia, or the later asthenic state of hypoadrenia, thereby are allowed to right themselves by nature."

Undoubtedly this is an explanation of how the Eddyite can promptly disabuse the minds of the emotionally overwrought individual who has broken down—and "heal" him. If an individual insists on allowing his affairs and troubles, real or imaginary, to overburden those physiological functions which are influenced by such factors, and somebody comes along and says, "There is no such thing as worry; pain does not exist; there is nothing the matter with you anyway," etc., he is really receiving some valuable encouragement, because, provided there is nothing organically the matter with these people, such reassurance is exactly what was needed, and with that reassurance, the fear and worry are dispelled, the adrenals have a chance to reassert themselves, and the neurasthenia melts away as dew before the morning sun.

I really think that somewhat of the same thing may be said of psycho-analysis. The patients are reasoned with and shown the futility of their present mode of action and the reality of the recuperative powers of the body. They see the error of their ways, regulate their emotional affairs as best they can, and this, supported, of course, by the indicated measures, causes their neurasthenia soon to disappear. At all events, I am a firm believer in the paramount importance of controlling the underlying factors of an emotional and mental character, no matter whether the patient has a real neurasthenia or not. The old adage, "*Mens sana*

in corpore sano" applies nowhere with such force as it does in neurasthenia, and this can be read backward or forward, as one may wish. In other words, when the body is functioning normally detoxication is maintained properly and the metabolism and endocrine control of the chemistry is right, there is no chance for the development of mental and nervous imbalance that has come to be called neurasthenia.

18.—ORGANOTHERAPY

All of the foregoing treatment will have its salutary effect upon the underlying endocrine basis of neurasthenia, but only indirectly. That is to say, the removal of these elements will permit, if other conditions are favorable, the gradual reëstablishment of a normal endocrine activity on the part of all the ductless glands. The most successful treatment, however, takes into consideration the fact that these glands, after having been ill-treated, not merely need to be freed from the stimuli that have depleted them, but to be enabled in every possible way to regain their normal functional activity as quickly and as thoroughly as possible, and here is where organotherapy plays a tremendously important part in the treatment of all forms of neurasthenia.

In the most common type of all—adrenal neurasthenia—in addition to removing the toxic, emotional and endocrine etiological factors, the adrenal glands should be supported by means of organotherapy, and the hypoadrenal patient treated just exactly in the same fundamental manner as we treat a hypothyroid cretin. If, as it not infrequently happens, a neurasthenic sufferer really has nothing the matter with him but a disturbance of metabolism, which is either the cause of or the result of a hypoadrenia, the principle of adrenal support which I have discussed quite fully in a pre-

vious article certainly applies. The administration of adrenal substance to these individuals purveys to the organism a specially prepared pabulum which the depleted glands are capable of taking from the blood in a ready-to-use condition, and that they do so is evident by the spectacular results seen in some cases of hypoadrenal neurasthenia. It is easy to understand that the support of the adrenal glands, even though demanded by circumstances and accomplished most carefully by the physician, will only be of temporary value provided the underlying causes are allowed to remain unappreciated and uncontrolled. In other words, organotherapy is but a part of the treatment.

The same fundamentals naturally apply in the treatment of neuroses of thyroid origin. If the neurasthenia is based on a lessened thyroid activity and a consequent accumulation of unoxidized wastes which irritate and deplete the nervous chemistry and reactivity, this hypothyroidism must first be discovered and then treated as any other hypothyroidism. Attention has already been called to the advantage of my Thyroid Function Test as a means of determining the presence of an early thyroid apathy, and if this test indicates that such a condition is present, thyroid therapy is the only rational method of treatment. It is impossible to replace the missing thyroid hormone, no matter how small or how large the deficiency may be, in any manner that can compare, both in logic and results, with organotherapy; and the importance of the minor thyroid aspects of neurasthenia, to my mind, are next in importance to those of dysadrenia, and thyroid therapy many times can be added to adrenal therapy and the pluriglandular insufficiency involving both of these glands may be treated simultaneously with better results than though only one of these two aspects were discovered and attacked.

So to all the fundamental measures add a well-bal-

anced thyroid therapy, and by this I mean enough of the thyroid extract to encourage the thyroid without driving it. On the other hand, if the thyroid gland has already been overstimulated and is functioning to excess, and there is a psychoneurotic element due to a latent or obvious hyperthyroidism, then the treatment should be directed at the endocrine cause as well as the other causes of this case, and I know of no better routine than that which has been discussed before in the previous issue of *Harrower's Monographs on the Internal Secretions.*

In the chapter, "Sexual Neurasthenia," the treatment has already been referred to and is essentially the same as the above. In ovarian dysfunction accompanied by neurasthenia obviously the necessity for regulating the dysovarism is of paramount importance. In many of these individuals we find such a combination of circumstances that it is difficult to determine which of the causes is first in importance. In such cases no matter whether the neurasthenia is a result of this dysovarism or is an independent, entirely dissociated condition, the thing to do is to treat them both at once. Never mind whether the organotherapy has the credit for the ultimate benefit or whether it is due to the other regulatory measures that you have advised. Literally thousands of women who have acquired a neurasthenic habit in conjunction with an amenorrhea or other form of dysovarism, have found their neurasthenic tendencies disappearing as soon as suitable treatment, including indicated pluriglandular organotherapy, has modified the disturbed hormone function of the ovaries, and the related glands. I have met hundreds of neurasthenic individuals who have taken the Weir-Mitchell treatment, who have been at some "milk sanatorium," who have even been to Battle Creek and gone through the gamut of detoxication, diet and whatnot, who were found to have a more or less insignificant

endocrine aspect which was made the excuse for organotherapeutic regulation, with the entire removal not merely of the disorder at which the organotherapy was directed, but of the neurasthenia as well. I am reminded of a case I heard of in Canada last summer: The patient was a neurasthenic and had been at a sanitarium for a number of months. Her neurasthenia was accentuated by a very severe muscular weakness, or asthenia, and for years she had had an ovarian dysfunction which caused an aggravation of all her symptoms for some time prior to the expected but delayed flow, and much dysmenorrhea. She left for the northern part of the province generally benefited, but not specifically so. She was still quite neurasthenic and her ovarian dysfunction had not been abated worth speaking of.

In course of time the doctor received a letter from this lady's mother asking if he could not suggest some home treatment, as the benefits from the sanitarium experiences were being lost and she was getting back to where she was before she came there. Suitable pluriglandular therapy was recommended—a combination of thyroid, ovary and pituitary gland—and as a result of this the young woman became entirely well. Not merely was her disturbed ovarian dysfunction completely changed, but the flow became more regular in time and practically free from pain save for a few hours in the earliest part of its onset; the neurasthenia disappeared; and this doctor said to me: "You know we did more good for that girl by correspondence and at a distance than all our treatment here at the sanitarium."

The reason for this experience was that this woman was in need of definite hormone stimulation, and while good hygiene, electricity, hydrotherapy and diet exert a general beneficial effect upon the body as a whole, and, therefore, upon the endocrine glands also, no single

measure can so definitely influence endocrine dysfunction as endocrine therapy.

An excellent thing about the organotherapy of neurasthenic states is the diagnostic advantages which sometimes come with this treatment. As Léopold-Lévi has so aptly stated, if one finds that "thyroid treatment suppresses various symptoms one must admit that a thyroid insufficiency has been present, and in a certain measure that the results of this have been acting upon those functions controlled by the thyroid gland and that thyroid therapy is, therefore, of diagnostic value." And, naturally, this applies to other similar measures.

So in the treatment of all neurasthenias by means of organotherapy, if one has the impression that a certain glandular aspect is prominent and there are sufficient reasons for applying a treatment directed toward its modification and this treatment is efficient, we have established on a much firmer basis the reality of the endocrine basis in that given case. And this, to my mind, is by far the most convincing evidence of the importance of the endocrine aspects of neurasthenia, for I have come in contact with literally thousands of individuals, either personally or through many correspondents, whose neurasthenic picture has been entirely painted over and whose whole aspect has been changed as by a miracle merely by the removal of some factor which was causing dyscrinism and the active effort to reëstablish the endocrine functions that had been deranged—and overlooked perhaps for years previously.

Taking it by and large, when one acquires the habit of studying the endocrine aspects of any case, neurasthenic or not, the first method of treatment is to remove obvious causative factors, and the second is to restore the deranged hormone-producing capacity; and

this, in short, is the *open sesame* to real results in the treatment of neurasthenia.

The treatment of every neurasthenic involves the establishment of his confidence in his physician and his skill and good judgment. He must be reasoned with; he must be educated away from his mental attitude, and I do not think that this is ever accomplished by the old-fashioned attitude of superior knowledge and reserve rather than the more recent educative, friendly, coöperative attitude which the intelligent physician manifests to all his patients. In the control of neurasthenic patients one finds more than ever the necessity for living up to our real title—"Doctor"—*doceo*—"I teach."

VI

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EPILEPSY

As an Endocrine Disorder

FUNDAMENTAL CONSIDERATIONS

1.—General Remarks

IT HAS been said very aptly that there is no clinical entity older in the history of medicine than epilepsy, and no other that has been the subject of so much speculation. "Epilepsy," says Spratling, "is the strangest disease in human history." A consideration of the many causes to which it has been attributed goes back to the superstitious beliefs of the ancients, who thought those afflicted to be possessed of devils. From such beliefs to the more modern idea of bacterial infection is a long step, and yet the etiology of the disease has remained largely an unknown quantity.

Epilepsy is no respecter of persons, but has afflicted those of high and low degree. It is said that Cæsar and Napoleon both had it, and it is told how Charles Lamb, feeling the oncoming of attacks, was wont to take his strait-jacket and, accompanied by his sister Mary, hurry to the asylum. Many persons brilliant in the arts and sciences have been subjects of this disease; and it has cast many into the mental mires of insanity.

Medicine has emerged from under a cloud of darkness and ignorance, and entered well upon a period of brilliant research. Exact studies in physiology and

I am indebted to Dr. W. G. Parker, of Mt. Vernon, Illinois, for assistance in preparing the manuscript for this issue.

physiological chemistry, pathology, bacteriology, and the numerous newer methods of examination have developed a mass of data of tremendous importance. To become available to the individual physician this must be systematized and so arranged that he may have at hand the substance of the many publications relating to particular subjects. It is the purpose of this monograph to deal with such available data as relate to the endocrine aspects of epilepsy, together with personal experiences and numerous case reports in current literature.

Epilepsy as an endocrine disorder is a pertinent subject. It is a disease which has not lent itself to ready investigation; there has been a long search for some factor that would serve as an adequate basis of approach to an understanding not merely of the pathogenesis but also of the treatment of the disease.

Those small and separated structures which comprise the endocrine system long were neglected for lack of adaptable methods of investigation. They are now known to exercise a profound influence upon the development and physiological activity of the body. These influences are manifested in every tissue, and indeed many psychic phenomena are now known to be dependent upon changes in the internal glandular secretions. There is little doubt that the study of the endocrine glands in their relation to certain obscure states is going to enable us to solve many problems, and point the way to rational treatment of many conditions which heretofore have been subject only to empirical attack.

Among obscure disorders epilepsy takes a prominent place; it is a disease whose etiology has been a matter of great uncertainty. In this discussion so-called idiopathic epilepsy alone is considered. This excludes those forms due to head injuries with motor cortex involvement, and birth apoplexies in which convulsions

are due to tension of the traumatized areas consequent to later growth and expansion of the brain. Certain forms of injury to the base of the cranium will be included, however, for these frequently involve the pituitary gland and are fruitful sources of epilepsy.

2.—The Hormone Balance

In the discussion of the internal glandular functions we have come to understand and refer quite frequently to "the hormone balance." This is expressive of a normal interrelationship existing between the various endocrine glands. That disturbances or "upsets" may occur in this relationship is confirmed by numerous clinical observations. Such disturbances may take the form of physical or nervous and psychic states. Ordinarily they are functional in character, though they may become organic. It is obvious that perversion of specific functions related to certain hormonic physiology may cause serious impairment of metabolism, and thus lead to toxic conditions which are at this time not always definitely recognizable as such. Although a wealth of knowledge already has been unearthed, it seems quite certain that even as much more remains to be searched out and studied, especially relating to the complexities of the interrelationship existing in a functional way between the various ductless glands.

The vane of medical opinion is turning, and we are getting away from the older ideas of uniglandular function and pathology. Not long ago it was thought that abnormal states resulting from endocrine disease were largely due to individual gland involvement, and depended upon single gland pathology for the various stages of the disease manifested. Certain writers, notably David Marine, then of Cleveland, O., declared that there was no evidence to prove a selective relationship between the various endocrine glands. That new

ideas are being adopted is shown by the following quotation from Walter Timme of New York: "From observation and clinical examination of many patients throughout the past six years at the Neurological Institute of New York City I have come to the conclusion that the so-called types of endocrinopathies, such as status thymolymphaticus, gigantism, infantilism, acromegaly, and a host of unnamed others, are not static states, as one would be led to suppose from descriptions in the literature, but are simply cross sections taken at intervals in a dynamic, progressive, and widespread disturbance of the internal glandular system."

Francis M. Barnes, of St. Louis, discussing neuropsychic reactions in endocrine dyscrasia, says: "Another phase of the situation must be mentioned because of its very fundamental and general importance. One endocrine gland must not be looked upon as an isolated functional unit, but rather as a member of a series of organs interacting upon each other. As a rule, disturbance of function or loss of function of one gland does not long exist before that of others becomes involved secondarily. In other words, we must in many cases substitute for the uniglandular disorder a pluriglandular aspect. To be sure, in most cases, the dyscrasia in one gland is dominant, while that of others is secondary in character, although it is frequently found difficult to determine in which gland the difficulty lies. Especially good examples of secondary pluriglandular involvement are to be seen in the combinations of disorder of ovary and thyroid." In the article from which this quotation is taken this author describes a number of cases of neuropsychic reactions in endocrine disturbances in which the proper therapeutic application of glandular substances was productive of curative results.

In epilepsy, as manifested idiopathically, the ten-

dency has been to consider the etiology, whatever its nature, as a definite entity. We believe this to be an erroneous idea, and expect to show that while epilepsy in many instances may be an endocrinopathic disorder, nevertheless it varies in type from an endocrine standpoint, and cases which may respond to one form of treatment are not adequately influenced by another. For this reason the subject will be considered according to the various endocrine aspects, and a number of case reports summarized in a subsequent chapter to contrast the types.

Epilepsy has been found clinically to arise from diverse causes, and this has led to some insight into its varying etiology. In a discussion of its pathogenesis Cotton, Corson-White and Stevenson, of the New Jersey State Hospital, said, "It must be emphasized in considering epilepsy that it is not a unit or distinct homogenous disease process, but rather a symptom of several pathological conditions."

Long before the endocrine system was definitely considered as having to do with epilepsy, certain authors did not look upon epilepsy as a fixed clinical entity. Frederick Peterson, in a text published twelve years ago (1909) said, "Epilepsy can scarcely be considered a distinct disease. It is a syndrome of mental and nervous symptoms appearing under a variety of pathologic states. In many instances it is associated with morphological cellular changes in the cortex. In many more cases the anatomical basis still escapes detection."

3.—The Psychic State

In an article published in 1915, L. Pierce Clark, of New York, set forth the contention that neither the present accepted pathological anatomy of margino-cortical gliosis, nor its postulated pathogenesis, a still earlier *chemotoxic state,* is sufficient to account for essential epilepsy; that one must seek for an alteration in some more fundamental process . . . . etc. Such a phrase as "chemotoxic state" must of necessity be very indefinite as related to an unknown matter. Nevertheless, there are probably no more highly specialized functions in the human body than those of the endocrines, manifesting themselves, as they do, not only in physiological activity, but also in the transmission of hereditary characteristics. Endocrine perversion is a marked factor in many epilepsies, and although we do not know all of the intricacies of the chemistry of these glands, it is very apparent that such perversions are chemical in nature, and may result in what may as well be called a chemotoxic state as by any other name. This chemotoxic state will certainly vary according to the given involvement, just as other toxic states vary according to their causes. We see the results of toxic states of one kind and another every day: attacks of delirium, convulsions, manias, hallucinations, delusions, and so on, almost without end. These arise from known and unknown causes, all of which in the ultimate consideration are chemical in nature. It is not surprising to see mental and psychic conditions which may be considered analogues of the marked physical states from endocrine disorder; nor to observe minor as well as major forms. Samuel W. Bandler, of New York, puts it very nicely: "We must distinguish between the somatic and the mental or psychic side of pathologic states due to endocrine relation . . . . I have seen in so many of my patients attacks of mental

depression and blues, so many cases of excitement and states of exaltation of minor degree . . . that long ago I came to the conclusion that we must grant variations in intensity in mental diseases. If we have the forms known as manic-depressive insanity, dementia praecox, melancholia, etc., why may we not have the minor types of the same conditions confronting us in our gynecologic obstetric work? . . . All these variations . . . have convinced me that mental diseases of extreme type may have the same relation to the milder forms and to the so-called neuroses and psychoses, and to the so-called neurasthenia and hysteria, that the major forms of exopthalmic goitre and myxedema, gigantism and dwarfism, etc., bear to the minor variations noted every day."

Viewed in this light, with respect to its endocrine cause, epilepsy with its varying manifestations and types, becomes a significant subject for profitable study.

The psychic make-up of the epileptic thus comes to be most interesting as relating to the effect of impaired metabolism upon this higher sphere. Lacking a known cause of epilepsy, certain neurologists have studied the epileptic psyche and laid a certain stress upon its characteristics as being perhaps causative factors. Clark, previously quoted, in a paper read before the New York Neurological Society, analyzed the character traits of the potential epileptic, excluding feeble-minded subjects from his study. This paper will be briefly quoted before proceeding to a consideration of the individual endocrine aspects:

"The potential epileptic as a rule possessed a super-normal output of energy which was constant and fairly productive of good developmental results as far as the organic make-up was concerned. There was a poorly repressed or thinly inhibited outcropping of egotistical tendencies. These characteristics of pathological self-

love were far beyond the bounds of physiological variation. As a rule, the potential epileptic was illy adapted to his environment and could not easily change the same. He co-operated badly in economic settings. For the most part he was frank; the subtleties of mind were not his; on the contrary he had a simple, child-like pattern of emotional life. He never had the scruples nor doubts of the obsessive neurotic; not being hindered with the inhibitions and prohibitions of the latter class, he was often permitted to become engrossed with the lower animal instincts and passions. With the inhibitions reduced and with an over-emphasized estimate of his own importance and ability, the potential epileptic found himself in conflict with the outside world. While the normal individual had his infantile struggle with reality and made the life compromise, the potential epileptic youth kept up the baffling struggle; hence his deep-rooted dislike and even hate of the outside world. Individuals who possessed the epileptic constitution lacked real general interests. The libido was rigid, self-centered and crude. There were small religious promptings; the meaning and ends of life rarely engrossed the potential epileptic. His friendships were perfunctory; the egotistic traits prevented a free range of emotional expression. The parental attachment of the potential epileptic to his own sex was the rule, and this was especially marked in girls. The love fixation to the mother in the majority was more or less prominent throughout life. The potential epileptic's attitude toward the opposite sex was very significant; it rarely possessed the higher love attributes and more frequently evolved little beyond the simplest and grossest sexual demands. That fact alone, independent of the superadded convulsive disorder, made marriage among epileptics almost invariably a failure. . . ."

In connection with the foregoing, attention is once

more called to those mental variations noted by Bandler as characterizing minor forms of endocrine disturbance, since there is very possibly an analogy between such states. Dr. Clark goes into the subject of dream analysis, and characterizes the convulsive movements of the epileptic seizure as a probable reversion to infantile strivings, a subconscious desire to return to the intrauterine state. It must be frankly stated here that although dream analyses show novelty of thought they are of interest only in that respect, and do not appear to represent any progress toward the actual solution of a very real condition.

Joughin, of New York, in an article on "The Epileptic Syndrome and Glandular Therapy," starts his consideration of the subject by emphasizing the fact that a uniglandular symptomatology does not exist; that a pluriglandular symptomatology, dominated perhaps by some one or more glands, always exists,—which is a great step in the right direction.

There are many intricate features of interglandular relationship which are not fully understood, and yet this relationship is to-day so apparent that it is being studied on every hand. One of the apparently paradoxical things which we note in connection with endocrine epilepsy is the fact that it seems to occur, not so often in those marked degenerative states represented by such end results as myxedema, acromegaly, etc., but in the lesser, or rather, earlier states represented by minor forms of perversion. This has been noted in numerous instances. That some form of toxemia or other systemic condition results from a lack of glandular harmony is very apparent. There are possibly factors in different individuals, which in the presence of dyscrasia permits the occurrence of convulsions, while in others they do not occur before the organism becomes adjusted to the condition, or an improvement takes place. When idiopathic convulsions do occur we

recognize the condition as "epilepsy." The mental characteristics of the potential epileptic as described by Clark are of great interest, as they show a distinctly abnormal psychic attitude. That they represent a constitutional or physical abnormality (glandular), which is later manifested by certain effects (convulsions), the two states being but different phases or stages, seems a reasonable hypothesis. The varying intensity of the different types of epilepsy, as well as the fact that there are different types, seem to indicate this.

II

TYPES OF EPILEPSY

4.—Preliminary Remarks

Epilepsy is usually classified according to its manifestations; in other words, according to the type of attack, such as the grand mal and petit mal. A newer, though limited classification according to etiology is possible, but because of certain factors which are often interrelated a thorough differential classification should perhaps not be attempted at present. However, there are certain well-defined causal types, among which are the pituitary, thyroid and gonad forms. The various types and their differentiation will be taken up briefly, after which separate chapters will be devoted to the individual endocrine aspects of the disease.

It should be understood that the various forms of attack are in themselves merely symptoms. Whether the disease is a basic physiologic entity, manifesting itself by certain forms of convulsion, or whether what we know as the chief symptom—the attack—is merely an expression of a varying constitutional condition, remains to be seen. It would seem that this latter conjecture is true, for the epileptic state does not always manifest itself in the same manner; thus we may have a grand mal attack, a psychic equivalent or other form as the outward symptom.

5.—Prodromes and Aurae

It is well known that in many cases of epilepsy distinct premonitory warnings of attack are experienced by the patient. It is probable that the grand mal form is more often preceded by aurae than are other forms. The aurae may take the form of distinctive sensations in certain parts of the body, such as a tingling or sense of heaviness in a limb. Some patients hear ringing sounds; others see bright flashes of light; there may be a feeling of depression and vague discomfort, or respiratory oppression. No certain form of aurae is present in all cases, but in a given case the aurae is usually the same in all attacks. Nurses and associates are sometimes able to tell when an attack is imminent by the appearance or actions of the patient, who may be pale, irritable or depressed, although himself unconscious that anything is wrong.

Whatever form the aurae may take, it is supposed that it takes origin in that part of the brain in which the wave of stimulation begins. The wave spreading soon involves the cortex, resulting in immediate loss of consciousness and intense muscular stimulation. Many epileptics have no aurae of any kind, the fit coming on with lightning suddenness without warning.

6.—Forms of the Attack

Grand Mal. This form of attack constitutes a complete convulsion. The patient experiences his individual prodrome or aurae and may have time to lie down. Rarely the aurae is experienced some considerable time before the convulsion appears, though as a rule there is but a short lapse of time. Consciousness is suddenly lost and the patient's entire body becomes rigid, the muscles being in a state of tetanic contraction. This extreme rigidity fixes the limbs and the

patient falls, or may be thrown to the ground and thereby injured. The epileptic cry which has been so much discussed is not always present, but when it is present it is usually a gutteral sound resulting from fixation of the chest and laryngeal muscles, and is not the result of any conscious effort on the part of the patient. Muscular spasm rendering respiration impossible, the face becomes congested and then cyanotic. The stage of muscle fixation is usually brief, but may last as long as two minutes. During this stage the blood pressure rises and vascular accidents may occur, such as apoplexy in those predisposed. Small peripheral hemorrhages are sometimes seen in the skin and conjunctiva. The temperature begins to mount and may reach two or three degrees above normal. It has been stated that if the hand is placed upon the muscles in tonic spasm a thrill or vibratory impulse may be detected (Peterson). The unequal contraction of sets of muscles causes the patient to assume various attitudes, a detailed description of which will not be attempted here.

This stage is followed by the stage of clonic spasm. The muscles relax, to be suddenly contracted again. All movable parts of the body seem to be alternately contracted and relaxed; the limbs, eyes, face and other muscles are agitated by sharp twitchings. The tongue may be bitten, and the saliva which is frothy from jerky respiration may be blood stained. The cyanosis persists because of insufficient respiration, and the temperature continues to rise. This stage may last from one to five minutes, and is followed by a period of great relaxation. The bladder and bowel may be emptied during the spasm or at the time of relaxation.

During the period of extreme relaxation which follows the patient breathes stertorously, resembling in this respect a case in which there is an intracranial pressure. He lies in a deep coma, and if left alone may

sleep for some time, and gradually recover consciousness without having any recollection of the attack. If the attack occurs during sleep the period of stertor may merge into natural sleep. Following an attack the patient usually feels sore, weak and depressed.

It is said that attacks during sleep *(nocturnal epilepsy)* are most likely to occur just after going to sleep or just before awakening, and be induced by emotional and physical disturbances, such as fright, anger, menstruation, fatigue, etc.

A series of convulsions may occur without the patient recovering consciousness. This state, known as *status epilepticus,* consists of a period of convulsions and a period of prostration analagous to a single grand mal attack. The convulsions are not usually of such great severity, but may follow one another until hundreds occur. Great prostration and collapse may follow and prove fatal.

Petit Mal. This form of attack is in reality an abridged grand mal, in which the *petit* attack may consist of any part of the grand mal attack. The aurae alone may be experienced; the patient may become dizzy; he may "faint"; he may sink to the ground and become stertorous, in coma. In many instances the attack is but momentary, and may pass unnoticed. The patient may cease speaking for a moment, or if playing music he may miss a few bars. He may be driving his car and without warning may run off the road, as a patient of mine did just the other day. There may be a slight untoward movement of the body, or a slight twitching of the face. The face may suddenly become pale and the eyes have a vacant look. There are so many varieties of petit mal that it would be useless to attempt to enumerate more than a few. The one constant feature of the attack which is to be borne in mind is the fact that the consciousness is disturbed during the attack. An analysis of a supposed

petit mal attack should reveal this feature to substantiate the suspected nature of the trouble.

Psychic Equivalents of the Epileptic Attack. This is one of the most interesting of mental disturbances, and has often been the subject of fiction writers. The grand mal attack is replaced by a state of psychic automatism in which the patient is unconscious of his actions in the ordinary sense, and yet carries out many concerted and apparently conscious acts. The period of attack may be short or extended. The subject of the attack may go upon a long journey and transact business without exciting undue attention. On the other hand, the attack may be characterized by excitement and unruliness, and the patient become dangerous to others. The epileptic automatism may last for a considerable time (a sort of status) ; it may be terminated by the onset of a major convulsion; self-consciousness is usually abruptly restored, the patient having no recollection of what has transpired.

Jacksonian Epilepsy. This term is used to indicate localized irritations of the motor areas of the cortex, in which convulsions occur. The significance of these localized convulsions was first pointed out by Dr. Hughlings Jackson, of London, hence the name. This type of so-called epilepsy is found in depressed skull fractures involving the cortical areas, and other forms of mechanical irritation. Tumors of the motor cortex by their gradual growth involve increasing areas and result in various progressive symptoms and signs of such involvement, as monoplegia, hemiplegia, disturbances of tactile sensation, etc. Convulsions may occur, beginning in muscles or groups of muscles corresponding to the motor area affected, and gradually spreading to adjacent parts. Loss of consciousness with general convulsions may or may not occur.

Myoclonus Epilepsy. This is a variety which is not common, and one with which we have but limited concern. It consists of a certain association of epilepsy with myoclonia *(association disease)*. It is characterized by lightning-like contractions of certain parts of muscles. It is a progressive disease and the myoclonia is the most conspicuous element.

Larvated Epilepsy. This term has been given to epilepsy which remains dormant or hidden for long periods of time. It cannot be said that it is a distinct form; in fact, such lapses in the frequency of attacks depend upon changes in the causative factors in a qualitative or quantitative way. This will be better understood in the light of the endocrine studies which follow.

III

THYROID ASPECTS

7.—Hypothyroidism and Infiltration

Whatever insufficiency exists on the part of any vital organ affects the organism as a whole, as well as the vitality of the offending organ itself. Thus an endocrine insufficiency may tend to act in a vicious circle. In minor forms of glandular insufficiency the manifested effect is proportional and clinically may not be obtrusive. An explanation of this condition is very nicely set forth by the "egoistic and altruistic cell function theory" of Harry Campbell, the London neurologist, who regards the former as consisting of the maintenance of individual cell activity, while the latter concerns the supply to the organism as a whole. In discussing this theory, I once remarked: "This altruistic cell function is of extreme importance, for the cell itself may seem to all intents and purposes quite healthy, and yet still gravely fail in its altruistic functioning, a failure which, small though it be, may suffice to disorganize the delicate hormonic balance." The administration of glandular substances in cases of insufficiency, obvious or presumed, may thus correct the vicious circle and be productive of beneficial results.

Cellular Infiltration. The thyroid has a direct influence upon numerous physical and nervous states. It possesses the power of accelerating cellular activity, acting as an oxidizing agent and stimulator to the tissues. This action or failure of it is well exemplified

by those extremes of functional perversion represented by hyperthyroidism and myxedema. A lessening of thyroid activity permits of retrogressive changes in the tissues—a slackening of cellular activity. Myxedema is a striking example of this. In this disease there is an *infiltration* of the tissues, an exudation of fluid which, according to Halliburton and Unna, appears to be mucin. Thyroid insufficiency may manifest itself in a number of other ways, the tendency to infiltration and edema resulting in changes in the voice, nasal obstruction, headache, a dry rough skin, thinning of the hair—especially the outer third of the eyebrows—coldness of the extremities, abnormal chilliness, dullness and backwardness, menstrual disturbances, etc. (Hertoghe). Careful search will usually reveal some of these changes in minor hypothyroidism.

It is worthy of note that the insignificant, but none the less important signs of the slighter forms of thyroid impairment are very commonly found in individuals who have epilepsy.

A few years ago my friend, C. A. L. Reed, of Cincinnati, called attention to certain marked characteristics seen in idiopathic epilepsy, which were emphasized, namely, (1) that intestinal stasis is almost without exception present; (2) that a prominent result of the associated toxemia is a varying degree of acidosis which produces a condition of edema of the brain to which a part, at least, of the characteristic manifestations of epilepsy are due; (3) that in operating after the manner of Sir W. Arbuthnot Lane on cases of pronounced intestinal stasis, a marked infiltration of the peritoneal glands is usually encountered, and that from these glands an organism, named by Reed the *epileptococcus,* frequently may be isolated. After much investigation by various authors (Wm. B. Terhune and others), the germ theory of epilepsy seems to have been dropped or disproved.

In a previous communication I suggested that "the cerebral edema which Reed and Fischer, of Cincinnati, held to be the result of a toxic acidosis, may just as likely be of thyroid origin as of intestinal origin, for not only may the acidosis of systemic hypoalkalinity result from the loss of full hormonic service of the thyroid, but the essential infiltration which is the typical pathognomonic feature of hypothyroidism affects all the tissues of the body, for the thyroid exerts a cellular influence which is not limited to any organ or set of organs; hence, not only the brain, but also the peritoneal and mesenteric glands may be infiltrated as noted by Reed. . . ." Further, many clinicians have discovered the extreme intimacy of hypothyroid states with intestinal infiltration, alimentary stasis and ptosis and constipation.

Bolten, of Holland, states that epilepsy may be caused by thyroid insufficiency, as evidenced by several of his cases who were relieved by the feeding of fresh thyroids given per rectum.

Collier, of Rochester, N. Y., in a letter published in the *Medical Record,* discussing intestinal stasis and the germ theory, says: "We cannot hold with Dr. Reed that epilepsy is the result of a specific infection from the intestinal canal, but we do believe that there are a large number of idiopathic epilepsies due to chronic intestinal stasis, the condition so beautifully described by Sir Arbuthnot Lane. The idea of an 'unknown' organism whose habitat is the intestinal canal is untenable, we believe, but 'stasis,' that condition produced by a delay in the passage of the intestinal contents and its subsequent toxic action, we feel can produce and does produce conditions which, when associated with an instabliity of the central nervous system, are responsible for the production of the epileptic manifestations. We do not feel that anyone who will take the time to visit an institution caring for epileptics can go away

without being convinced that such condition as chronic intestinal stasis exists, and on these premises we have for some time past been 'short-circuiting' some of our cases with very favorable results . . ."

Alimentary Atonicity and Toxemia. It may be well to reiterate some facts concerning the relation of the thyroid to the picture of intestinal stasis. The man to whom we are indebted for directing our attention to the minor forms of thyroid insufficiency is Eugene Hertoghe, of Antwerp, who called attention to a syndrome identical with that so prominently brought forward at a much later date by Lane. Quoting from a resumé of his work on "Chronic Benign Thyroid Insufficiency or *Myxædême Fruste*," we read: "The entire gastro-intestinal system reacts very strongly to the infiltration of its elements, whether muscular, nervous, secretory or mucous. Infiltration of the muscular tissues induces peristaltic paresis, leading to retention of waste materials with consequent fermentation and constipation. In delicate subjects with weak abdominal walls this results in ptosis of the viscera, notably of those organs which are most heavily loaded, namely, the stomach and large intestine. . . . Imperfect intestinal drainage gives rise to intestinal toxemia, which reacts upon the already enfeebled thyroid and intensifies the prevailing conditions of inadequacy. As a matter of fact, many of the symptoms attributed by Lane to chronic intestinal stasis are identical with those which, since 1899, I have included in the symptom-complex of benign chronic subthyroidism. These are hypothermia, uncontrollable headache, rheumatoid pain and neuralgia, mental depression, dyspnea, asthmatic attacks, premature grayness and baldness, dental caries, cholelithiasis and brownish pigmentation of the skin."

A case of epilepsy with thyroid deficiency and associated gonad deficiency, in which constipation was marked for years, is reported by W. G. Parker (1920).

Appropriate endocrine treatment caused cessation of the convulsions and the patient was relieved of the necessity of taking enemas and cathartics altogether.

It is apparent to one who has observed such cases that the constipation is due to some depressed state of the intestinal tract or of the nervous mechanism controlling it. Léopold Lévi, of Paris, the greatest French authority on thyroid disorders, says that constipation of thyroid origin is common, and believes that it is quite the most frequent form of constipation.

8.—Nitrogenous Metabolism

There is in some cases a connection between the thyroid-parathyroid apparatus and states of subnormal function with epilepsy. Timme (1920), in discussing the criteria of endocrine epilepsies notes a group of persons "in whom the attack is secondary, in all probability, to retained nitrogenous products—presumably split protein and amino-acids. The retention in the tissues, in fact in the individual cells, of these partial decomposition products, acts as an irritant which finally produces the epileptic seizure as a purposeful act, for the convulsion, accompanied by its profuse sweating, increased kidney and bowel action, tends to relieve this condition. The reason for the retention of the amino-acids—partial decomposition products—in the cell, has been described ably by E. C. Kendall of the Mayo Foundation. He has shown that the iodo-thyroid product of the thyroid gland is instrumental in converting the amino-acids into ammonium carbonate, carbon dioxide and water, the ammonium carbonate probably being changed by parathyroid activity into urea. In these final forms the protein combustion products are ready for excretion by the emunctories. Failure of the thyroid-parathyroid apparatus, then, means failure in the removal of the toxins. This situation determines the seizure."

The Metabolism of Urea. This confirms the work done years ago by Professor Slosse, of Brussels, who definitely connected hypothyroidism with a disturbed function in the metabolism of the amino-acids. In view of this it is interesting to follow up the relation that disturbances in the elimination of urea have on the one hand to epilepsy, and on the other to dyscrinism. Routinely, in my consultation work, where I find an individual with hypocrinism either a condition largely of a hypothyroid character or, more often, a pluriglandular disturbance involving both the thyroid and the adrenals, in addition to finding malnutrition and subnormal temperature, poor circulatory tone and especially a low systolic blood-pressure, we also find that the elimination of the urinary wastes is considerably below par—and this is particularly true of the urea index. I believe that a deficient elimination of urea is a clinical finding of interest in the study of the epileptic and that if this phase of the metabolic activities can be encouraged there are better chances of controlling the epileptic seizures provided they are of functional origin.

Falta, in his textbook, refers to and comments on the report of McCarrison, of the Indian Medical Service, upon epidemic tetany in certain valleys among the Himalaya Mountains, the disease being prevalent in places where there is epidemic goitre. The disease is most prevalent in women, more marked in the spring and is increased during pregnancy and lactation. The goitre that predominates in these regions is of a marked degenerative character.

G. C. Bolten, the Dutch neurologist, already referred to, says that many authors have observed cases in which the patients showed epileptic symptoms as well as tetany, but there has never been a case described in which there was proof that both diseases had one common cause. However, more recently Bisgaard and

Norvig, after examining several thousand bloods and urines from epileptics, found that there was a remarkable increase in the ammonia content of the blood about three hours before convulsions or psychic equivalents, and this could be foretold by noting the increasing ammonia content in the urine. They profess to see an analogy between tetany and epilepsy. They believe the treatment, instead of consisting of sedatives which merely reduce reflex action, may well be directed to the endocrine disturbance presumably at fault.

This is supplemented by the comprehensive report of Dufour and Semelaigne, of Paris, who have made many studies of the blood urea in relation to epilepsy and epileptic attacks. They report several cases from which it is clear that the blood urea index is considerably increased prior to the attacks. This is in harmony with the previous work of two Roumanian physicians (Obregia and Urechia), who studied variations of the urea in epileptics and noted that prior to the convulsive onset an increase in the blood urea took place in the majority of the cases.

It may not be possible to make comprehensive estimations of the urea variations in connection with the study of epilepsy in general practice, but at least it is suggestive, and prompts us to remember that when there is a deficient elimination of urea and an accumulation of its precursors and other metabolic waste products, the epileptic condition is aggravated and it is reasonable to deduce from this that any procedure that will favor the metabolism of the body, increasing the burning-up process and favoring the removal of these waste products from the blood and tissues will be good treatment in all epileptics. I believe, therefore, that this particular phase of the study and treatment of epilepsy has a broad endocrine aspect, as outlined elsewhere.

Incidentally, this is still further emphasized by the

report that Laurès and Gascard find as a result of many clinical and experimental trials, that the urea content of the cerebrospinal fluid is increased in relation to an epileptic attack while, interestingly enough, during crises of hysteria it is decreased. Again Krainsky, many years ago, experimentally injected the blood of epileptics taken just before attacks or in cases of status epilepticus, into animals, caused their death, and states that the poison was carbamate of ammonium.

The Vascular Theory of Epilepsy. In his interesting little monograph on epilepsy Dr. Jules Pech, writing from Damascus, makes a proposition that is of interest here. He suggests that essential epilepsy is due to a stoppage of the blood stream in the cortical zone of the brain; that this stoppage is spasmodic and naturally transient, and that essential epilepsy is also entirely based upon disturbances of the great sympathetic system. The harmonious equilibrium and general functional solidarity of the organs regulating this is disturbed. His clinical experience emphasizes his opinion that there is a syncope or circulatory stasis in the brain; and, further, that there is an undue and spasmodic stimulation of the sympathetic.

In this connection it is well to recall that Hertoghe refers to the "thyroid infiltration of the brain" in hypothyroidism. I am personally convinced that hypothyroidism does indeed exert a very decided influence upon cellular chemistry and, as I have explained elsewhere, in an attempt to show how intimate the thyroid is with the mechanical elements in producing functional high blood-pressure, there is no reason why this fundamental principle should not be involved in epilepsy. It will be recalled that the thyroid initiates intracellular chemistry, that hypothyroidism causes a deficiency in this, as a result of which there accumulates in the cell which is involved (and there seems to be no limitations to the cells that may be involved) an

excess of wastes which by osmosis draws more fluid into the cell and thyroid infiltration results.

This does not have to be an infiltration of the skin or myxedema, nor an infiltration of the precapillary areas, which favors a mechanical obstruction to the blood-pressure in these remote cells, thus raising it; but it can and does affect the encephalon, thus lending greater emphasis to the need for studying the thyroid aspects of this disease and regulating them whenever this is desirable and possible.

It will be recalled that Prof. Kocher, of Berne, expressed the opinion that the convulsive attack in epilepsy is brought on through an opposition to the circulation in the brain and consequent rise in the intracranial pressure. This is in harmony with the Hertoghe dictum as well as that of Pech, just related.

Marburg and Ranzi have demonstrated surgically that during an epileptic seizure the brain swells and there is usually also an intense hyperemia of the dura and an infiltration of the meninges—all of which is in harmony with the impression gathered from other sources.

The vascular theory of epilepsy, as well as the probability that there is indeed an intracranial hypertension, is favored by Bram, of Philadelphia, who frankly believes that epilepsy is the result of an abnormally high intracranial pressure plus a sudden increase in the general blood-pressure. He recommends venesection in the immediate treatment of the attack and believes that iodides or thyroid extract are useful supplementary measures.

9.—Thyro-Parathyroid Relations

The relation that the parathyroid glands bear to thyroid functioning has been considered by many investigators. Undoubtedly, they are both related, vital parts of the detoxicating mechanism.

The parathyroid aspects of epilepsy have been given some consideration by a number of writers. It is fairly well known that paralysis agitans and various forms of tetany are connected with a disturbed parathyroid functioning, and among several writers on the subject, the French physician, Jeandelize, suspects that epilepsy in men should be classed in the category of convulsive conditions which are due definitely to parathyroid insufficiency. Certain it is that the parathyroids are concerned in destroying certain metabolic products which have an irritating effect upon the body, and particularly the nervous mechanism.

In a series of very careful experiments at the University of Michigan, Wm. F. Koch, of Detroit, has connected the parathyroids with the destruction of the guanidin bodies. Others have found these toxic waste products in excess in epileptic cases. This may be a lead to a better therapy later, but at present it is not being very extensively or successfully used.

10.—Epilepsy in Defective Children

It is well known that epilepsy is a disease of youth, making its appearance most frequently in children and young adults. This would indicate that something which takes place during the developmental stages may be at fault. That some endocrine factor is responsible is a premise worthy of careful investigation, for it is in the young that developmental processes are active and those glands which have intimately to do with development exert their most important service and may show evidences of imperfect action.

What is meant by the term "defective children?" The textbooks on children's diseases refer to a number of conditions, such as malformations of brain and cord, hydrocephalus, inherited taints, idiocy, imbecility, paralytic conditions following infectious diseases (anterior poliomyelitis, etc.), and some other similar conditions, but there are few specific discussions of endocrine defectives except those who are cretins. The chapters describing epilepsy in children usually offer no explanation for the condition.

Those defects considered in works on pediatrics are not in a general way very productive of epilepsy. Some of them are unrelated to endocrine imbalance. The signs of dyscrinism are not marked in the young, except of course in cretins, Mongols, etc., and yet this is the time when such dyscrasias are beginning to develop. One of the most important matters to consider in the diagnosis of endocrine dyscrasia is a review of the incidents of the developmental years, noting the occurrence of severe infectious diseases or other prostrations, the rate of growth, the time of walking, of cutting of teeth, the onset of puberty (age, irregularities, etc.), and other significant features. In these factors are often found the criteria of abnormality. Thus we may see in retrospect the onset of metabolic changes of abnormal nature, the development of endocrine toxemias from imbalance, etc., all of which may lead to the development of obscure states, among which epilepsy takes an important place. Thus we may note gonad deficiencies with menstrual irregularities accompanied by epileptic convulsions; thyroid changes, often secondary in nature; pituitary hypofunction from an abnormal closure of the sella turcica or other causes; upsets in adrenal function leading to hypergenitalism, and so on. The toxic states which seem to come from glandular imbalance, or consequent disturbed functions dependent upon gland action, are highly important.

Heredity as a Predisposing Factor. The factor of heredity which justly has been given so important a place in the etiology of epilepsy recently has been studied by Thom, who reviewed 157 cases of "hereditary epilepsy," noting the relation between the genetic factors and the age of onset. Thus, "named in the order of their potency in the production of the early onset of the epilepsy in the offspring, feeble-mindedness came first, followed by migraine, epilepsy, alcohol, and insanity. With the exception of alcoholism, all the maternal defective factors were manifested in the offspring at an earlier date in the form of epilepsy than those factors transmitted by the father."

As the above-named defective traits are frequently related to endocrine perversion, with the possible exceptions of alcoholism, one may see how there may be a distinct endocrine factor in heredity. The effect of alcoholism upon the organism may result in the transmission of inferior qualities to the offspring, because of alcoholic debasement in the parent. In passing, it may be mentioned that the two great toxemias—syphilis and alcohol—undoubtedly deplete or even destroy endocrine function and, as some hint, this may be the manner in which defects are transmitted to the children of these unfortunately numerous individuals.

Thymic Epilepsy. The thymus is a gland which is active in childhood. It appears to inhibit the sex hormone, and when abnormally active later in life to be antagonistic or at least disturbing to the thyroid. The thymus should have retrogressed by the time of puberty. Persistent thymus is one of the abnormalities of the young adult and apparently has been responsible for the development of epilepsy. William Browning, of Brooklyn, describes such a case, which will be briefly noted here since it is suggestive of certain other thymic abnormalities. The family history was negative, but the early personal history of the patient was significant.

"The patient was a Russian 25 years of age; he had bronchopneumonia at the age of 1 year, and 'very often' thereafter (significant of endocrine trouble); 'spasms' when 2 years old (quite the rule in thymic rickets); persistent enuresis until 9 (common in thymism); and nasal block ('lymphatism'). The first attack occurred in 1916 when he 'fainted'; no more attacks until 1919 when he fainted again; in April, 1920, he fell while standing on the street; had convulsions. The patient was a vigorous man weighing 142 pounds; 65 inches high; pulse 72; systolic pressure 127. The thymus was enlarged to physical examination and x-ray; there were enlarged cervical glands; skin capillaries over the region of the hands showed 'tache cerebralé'—reaction to pressure (status lymphaticus); no tremor; teeth short, faint cross markings of lower incisors; slight signs of early rachitis; clubbing at the wrists; knees 3½ centimeters apart. Three treatments of deep x-ray therapy, with no seizures from April to August. Cervical glands smaller to normal 1 month later. A case of thymism [epilepsy] from persistent thymus."

Bryant, of Boston, thinks that there is an element of failure of nutrition in many cases of epilepsy. He states that in addition to faulty heredity, malnutrition seems with considerable frequency to precede the onset of epilepsy. He suggests that there is a deficiency of calcium absorption, and mentions many "poverty rations," such as white bread and potatoes as being deficient in calcium. It would seem, however, that there may be a deeper significance in the malnutrition, which indeed is often noticeable. Poor elimination, toxemia, and disturbances in different important functions from internal glandular dyscrasia are capable of causing conditions which may be taken for simple malnutrition.

Epileptic Asymmetry of Form. A point of much in-

terest is noted in an editorial entitled "A Physical Token of Epilepsy" in the *Medical Record:* "At a recent session of the Royal Imperial Medical Society of Venice *(Berliner klinische Wochenschrift,* June 28, 1915) Benedikt drew a contrast between ordinary and epileptic asymmetry. The normal skull is hyperplastic to the right in the retroauricular portion of the temporal and parietal bones and the ear is placed slightly to the rear. When this arrangement is disturbed we have an anomaly, and in epilepsy this region instead of being prominent may show a flattening. Again, in the normal subject the distance between the occipital protuberance and the vertex is the same as the distance between the vertex and the bregma, while in the epileptic the entire distance between the occipital protuberance and the bregma may be shorter than the normal by 3 cm. When a shortening of 3 cm. is obtained the subject is very probably epileptic."

11.—Minor Hypothyroidism as an Aggravating Factor

With the more marked perversions of endocrine function most of us are familiar. They are nearly all late stage types; that is, of disease states that have progressed to such a degree that they may be looked upon as we view the well-developed stages of better understood conditions—fully developed tuberculosis, for example, or marked deformities, such as kyphosis. Such conditions are easy to recognize—and hard to treat. Minor degrees of endocrine malfunction are difficult of recognition but certainly offer considerably better prospects for cure.

In considering the predisposing factors of epilepsy one notes both general and specific varieties. Some of these already have been mentioned. Minor hypothy-

roidism is a condition which occurs very often if, indeed, in the past it often has not been, and is usually secondary to some other gland involvement. Minor hypothyroidism may represent an early stage of a later major condition; or, on the other hand, it may be merely an aggravating factor in the derangement of associated endocrine functions. Gonad and thyroid deficiencies illustrate this.

Landon D. Walker quotes Osborne and Fishbein concerning the relation of epilepsy to menstrual disturbances as follows: "Epileptic attacks developing during some disturbance of menstruation, whether at the time of puberty or at the time of the menopause, and especially if repeated only at the time when the menstrual period should occur and does not, shows that the cause has something to do with the thyroid. The thyroid gland hypersecretes normally at or before menstruation. If it does not something in the system cannot work as perfectly physiologically. In the kind of epilepsy just described thyroid is the treatment. . . . Many cases are on record in which this kind of epilepsy has been cured by this treatment."

Thyroid enlargements are more often seen in women than in men. Some of the reasons for this are given elsewhere in this Monograph. Hyperthyroidism also is more frequent in women than in men, but a larger percentage of goitres in men are of the hyperthyroid type than are the goitres in women. The frequency of hypothyroidism in women is doubtless due to the intimate relation between the thyroid and the menstrual function, involving the exhaustion of the parenchyma from the increased demands upon the gland at these periodical times and during pregnancy.

Thyroid enlargements are often noted at puberty, during pregnancy and in certain states dependent upon ovarian depression. Simple goitre in young girls is an expression of hypothyroidism incident to the increased

demands upon the gland at this time. The routine administration of potassium iodid (some are now favoring sodium iodid) for a short period each autumn, as practiced in the public schools of certain cities, has shown a lessening in the incidence of goitres in subsequent years. The disappearance of secondary enlargements of the thyroid have been noted clinically following hormone treatment of both primary and secondary insufficiencies.

The factor of heredity is strongly marked in both epilepsy and thyroid disorders. Cretinism, of course, is not an acquired disease. Hereditary tendencies to hypothyroidism are very frequently seen in successive generations. W. G. Parker reports a case of large cystic goitre in a woman whose babies all had goitre at birth. The goitres in the children later disappeared. Falta says that "it has been shown by animal experimentation (Halstead) that partial extirpation of the thyroid does not prevent normal carrying of young. In such cases the thyroids of fetuses seemed to act compensatorily. In other words, Halstead observed in the new-born pups an enormous hypertrophy of this organ. The thyroids were about twenty times as large as in the normal new-born pup."

Variations in the Subthyroid State. It has been emphasized previously that the activity of the endocrine glands is not constant; that there are variations in function in a quantitative way according to the demands of the interglandular harmony. Few of the important organs of the body are constantly and uniformly active: the liver secretes rapidly during intestinal digestion; likewise the other digestive organs are called upon periodically. The relationship of the thyroid to the parathyroids, adrenals, pituitary and others of the endocrine chain, as well as the well-known periodical action of the ovaries, leads one to suppose that here variations may be expected likewise. In this

connection Timme says: "I do not believe that there is a constant subthyroid state that is the goal of our quest. Such a state would determine a generalized hypothyroidism, a partial myxedema. A myxedematous state, more or less is self-compensatory, in that the person is sluggish, slow of mentality and activity, with a much lower basic metabolism than is normal. He burns less tissue and there is less to excrete. But our dysthyroid epileptic is one in whom either periodically or after a period of excessive oxidation, the thyroid-parathyroid apparatus is insufficient. In other words, an instability of this glandular activity must be predicated. Such instability, however, is almost never primary, depending on its covariants among the other endocrine organs for its production. A marked ovarian disturbance, an adrenal outpouring, an underfunctioning pituitary—all may serve to make excessive demands on this thyroid-parathyroid organ, allowing insufficient secretion for its catalytic activity. This constellation of the units of the internal glandular system determines the attack. It is not a condition of pure hypothyroidism as pictured by some authors. Hence, the stigmas of hypothyroid states are not successively found in these subjects. One may just as frequently find ovarian or adrenal or pituitary characteristics. The main points to determine are the endocrinopathic family history and the presence of glandular disturbances in the early life of our patient. The treatment also would vary considerably, depending on the result of our investigations into the primary disturbing element. If this could be found and corrected the seizures would cease. Frequently this can be done. Ovarian or gonad disturbances are often amenable to treatment. Emotional states, fright, fatigue, anger, serve to call out epinephrin in too great amounts not to involve overactivity of the thyroid, but these conditions are difficult to combat."

IV

PITUITARY ASPECTS

12.—General Remarks

When we come to study the hypophysis, or pituitary body, we have to do with two organs intimately bound together; the close association of the two lobes is such that an affection of one seldom leaves the other uninvolved. The inaccessibility of the gland makes experimental differentiation of the pathology of the two lobes a matter of difficulty.

Attention frequently has been called to an analogy between the lobes of the pituitary and the association of the thyroid and parathyroids, and with the corresponding adrenal apparatus (the cortex and medulla). Falta says that a certain physiological independence of the two organs (lobes) naturally might be expected from their morphological and embryological independence.

These differences have been studied extensively since Pierre Marie described acromegaly in 1886 and its etiological relationship to the hypophysis. The functions of the two lobes are now fairly well understood as they relate to certain important processes of growth and development.

The pituitary in man weighs only about half a gram and hidden away in the sella turcica at the base of the brain, is well protected from external injury. Certain characteristics of anatomy are aptly described by G. C. Johnston, of Pittsburgh: "Nature considers the pituitary of such importance in the animal economy that

she has located it in a most inaccessible and strongly fortified position, lying in a deep depression in the upper surface of the roof of the sphenoidal sinus in a bony pit roofed over with a strong projection of the dura and protected from pressure by the anterior and posterior clinoidal processes. The situation of the gland is unique, and arguing from analogy, its importance is commensurate to the care that has been exercised for its protection. . . . The pituitary with its stalk, the infundibulum, lies within the sella covered over by a prolongation of the dura, the diaphragma sellae, through an opening in which the infundibulum connects the gland with the brain. The anterior lobe is large and embraces on its median aspect the smaller posterior or cerebral lobe. The anterior lobe is of a glandular character, histologically, and is surrounded by a thick, loose, fibrous capsule. The posterior lobe is smaller and softer, and to it directly comes the infundibulum. This portion of the gland histologically is rather nervous than glandular tissue, especially during infancy and youth. . . . The anterior lobe resembles the thyroid and is rather kidney-shaped, receiving its blood vessels and the infundibular stalk in its hilus much as does the kidney. It is said to increase in size until about the 30th year. Its blood supply is rich and its function in connection with the growth of the body is now, thanks to the researches of Cushing and others, so well understood that we need not discuss it at this time. . . . It is thus seen that the pituitary, owing to its peculiar location, may be encroached upon to a degree by any hyperostosis of the posterior or middle clinoidal processes, since the tough dural roof completes its enclosure by bone."

13.—HYPERPITUITARISM

Acromegaly is the one definite manifestation of hyperpituitarism. Here is Falta's comprehensive definition: "By acromegaly we understand a disease that is characterized by the gradual enlargement of the peaked (acral) parts (nose, lips, tongue, lower jaw, hands and feet) and by hyperplastic alterations in the entire osseous system. There mostly develops an appreciable enlargement of the hypophysis, which leads to broadening of the sella turcica. Associated with this is localization of corresponding symptoms of brain pressure. To this are added very frequent alterations in the thyroid gland of a hyperplastic character; marked accentuation of the function of the interstitial glands; also very frequently loss of function of the genital glands after preliminary transitory increase of function, and apparently frequently, hyperplasia of the suprarenal cortex. Also the condition of excitability of the vegetative nerves is sometimes increased in manifold ways. Very frequently there occurs rapid withering away of the body and manifestations of degeneration of manifold nature. The pathological anatomical findings in the hypophysis is an adenoma or adenocarcinoma of the anterior lobe. To-day we refer acromegaly to an increase of function of the glandular hypophysis."

Apparently, there is some relation between epilepsy and hyperpituitarism, and it is a very interesting one. While the condition may not often be noted in cases of advanced acromegaly, if we reverse the tables we come across some very interesting material, for among epileptics a large number are found to have distinct pituitary involvement. G. C. Johnston made a study of the pituitary region of a number of persons who without apparent cause showed a development of epilepsy between the ages of 15 and 35. X-ray examinations of

this class of patients revealed certain pituitary changes with great regularity. "These changes consisted for the most part in an overgrowth of the anterior and especially of the posterior clinoidal processes, which in addition to an increase in area and length are slowly folded over and down upon the pituitary gland, enclosing it in a bony basket. In addition to this process, which is evidently one requiring considerable length of time for its accomplishment, there is very often noticeable a decided difference in the size of the pituitary fossa and, therefore, of the gland itself. The fossa is thus largely completely roofed over in some cases . . . illustrations of which will be shown in which the anterior and posterior clinoidal processes not only meet but overlap. The frequency with which this condition has been found is quite striking. At first we were inclined to look upon it as a mere anatomical deviation, but when it reached a point where we were almost able to prophesy from the history of the patient and a physical examination the practical degree of roofing to be expected in a given case, we were forced to attach some importance to this abnormality. . . . In addition to this overgrowth of the clinoidal processes, a large proportion of the cases showed a distinct increase in density of the bony tissues forming the roof of the orbits, the sphenoidal sinuses and the ethmoidal cells. In quite a number of cases the sphenoidal cells are blocked with newly formed bony tissues. This condition resembles to a marked degree the appearance of the skull in general acromegaly and has been interpreted by us in accordance with a theory advanced by McKennon and Henninger as a localized acromegaly."

We have here delineated the production of a vicious circle. Pituitary *hyperactivity*, through its specific effect upon the osseous tissues surrounding the gland, brings about pressure impairment of the gland itself. The interglandular relationship is therefore disturbed.

In the preceding definition of the acromegalic or hyperpituitaric state note is taken of associated hyperplastic changes in the thyroid, hyperplasia of the adrenal cortex, and marked accentuation of development of the interstitial glands. With the development of this condition, a *hypopituitaric* state obtains, due to pressure upon the gland, and as a result of this an abrupt change in these associated influences occurs, and in the instances given, the development of epilepsy was noted with a frequency that is more than coincidental.

14.—HYPOPITUITARISM

Enough has been said in the preceding paragraph to suggest the widespread disturbances which may follow pituitary impairment. The following from Cushing's book on "The Pituitary Body and Its Disorders" therefore is of interest:

"One may reassemble the data in regard to the possible relations of hypophyseal insufficiency to epilepsy as follows:

"1. Horsley, it will be recalled, in his first experimental hypophysectomies in the canine, observed no post-operative changes whatsoever in the condition of the animals. They were, however, used subsequently as subjects of cortical stimulation, and he noted that the motor cortex was unusually excitable.

"2. As already stated, we have observed a tendency to epileptiform convulsions in a number of our animals kept for long periods after partial hypophysectomy—animals that ultimately exhibited symptoms which we attribute to glandular insufficiency.

"3. The study of a series of cases of hypophyseal disease in man has shown that epilepsy—a symptom unobserved in states of hyperpituitarism—is a frequent accompaniment of clinical conditions in which an insuf-

ficiency of the gland is manifest. Moreover, that the brain under these circumstances is possibly over-excitable, is suggested by the number of individuals in whom gustatory attacks have occurred under the influence presumably of a direct local irritation of the adjacent uncinate cortex by the enlarged gland.

"4. As is well known, epilepsy is a frequent sequel of cranial injuries. In certain types of injury, as the common bursting fractures of the base, the pituitary body is prone to be damaged.

"5. If, as we believe to be the case, the posterior lobe secretion normally enters the cerebrospinal fluid and thus comes to be in solution in a fluid which subsequently bathes the cortex, it is possible that its diminution from hypophyseal disease or injury may unfavorably affect the activity of the cortical cells. On this basis it is conceivable that a local scar which involves, or a tumor which presses upon, a given area of the cortex, may prevent the access to the cells of a substance which is essential to their functional stability.

"6. Many individuals supposed to be suffering from so-called genuine or essential epilepsy, present manifestations of a nutritional disorder—a tendency to adiposity and a high sugar tolerance, coupled with a lowered temperature and pulse rate—closely akin to the constitutional state which characterizes hypophyseal deficiency. In some of these individuals the administration of hypophyseal extract has served to moderate the seizures from which they previously suffered."

A number of other writers have expressed a belief that the pituitary gland plays a rôle in the production of epilepsy. Clark and Caldwell, in an article published in the *Journal A. M. A.*, state that the circulatory disorders in some cases of epilepsy, shown frequently in slow pulse, vasomotor stasis in the extremities and an invariably low blood-pressure when arteriosclerosis is

not advanced, the tendency to obesity and a ravenous appetite, suggest a disturbance of the pituitary body.

Livon and Peron found that partial removal of the anterior lobe in a dog caused, among other things, epileptiform seizures. Beverley R. Tucker, of Richmond, in an article published in 1916, gives a number of case histories which bear out the belief that certain cases of epilepsy depend upon changes in the region of the pituitary. In a subsequent article published in the *Archives of Neurology and Psychiatry* other cases are reported. Tucker finds two types of pituitary dystrophy resulting in epilepsy. He designates them as the (1) *chronic or congenital* and (2) the *transitional* types. The chronic or congenital type exhibits certain features of marked pituitary deficiency of the Froehlich type, such as increased fat, lack of body hair, feminine distribution of pubic hair, scanty menstruation in the female, increased sugar tolerance, small genitalia, and frequently bradycardia and lowered blood-pressure. The transitional type of patient may show evidence of "normal pituitary secretion or hypersecretion in the past, which during adolescence became lessened. This is at times traceable to some illness or trauma. In these cases the patient begins to take on flesh, has an increased desire for sweets, becomes less energetic, eats voraciously, perspires less and may have a slow pulse and lowered blood-pressure. In either type occasional or periodic convulsions may occur, which usually make their appearance during adolescence. Convulsions may also occur in cases of tumor of the pituitary body, as pointed out by Cushing, but the discussion of tumor cases is not included in this paper."

Tucker described the x-ray picture of the chronic or congenital type as showing a small pituitary fossa with large clubbed posterior clinoidal processes and frequently elongated anterior processes which tend to bridge the fossa. The transitory type cases show nor-

mal sized or enlarged fossae, according to whether the symptoms pointed to normal or hypersecretion in the past. It will be seen, therefore, that the roentgenographic differences lie "chiefly in the size of the fossa, that of the chronic type being decreased, and that of the transitional being normal or enlarged in general contour even if encroached upon by bony growth."

The study was based upon 200 cases of epilepsy from various sources; of these, 63 cases showed evidence of pituitary disease. Because of possible extraneous causes, such as hydrocephalus, syphilis, nephritis, active foci of infection, etc., 35 of these 63 cases were ruled out, leaving 28 pure pituitary cases remaining. Of these, 17 were of the chronic type of hypopituitarism; 11 were transitional cases. A table giving detailed data will be included in a subsequent chapter on Clinical Experiences.

15.—Intracranial Hypertension

Every surgeon is familiar with the symptoms of increased intracranial tension. Cases of depressed fractures of the skull often show symptoms of this condition, such as unconsciousness, localized or general convulsions (Jacksonian epilepsy), slowed pulse, stertorous breathing, etc. Most of these symptoms and signs are present in nearly all grand mal attacks of epilepsy, and suggest very strongly the presence of an increased intracranial tension. In defining acromegaly, Falta describes the enlargement of the hypophysis and broadening of the sella turcica. "Associated with this is localization of corresponding symptoms of brain pressure." Cushing mentions the fact that a number of individuals having enlarged hypophyses experience gustatory attacks "under the influence presumably of a direct local irritation of the adjacent uncinate cortex by the enlarged gland."

In cases of tumor of the pituitary symptoms of intracranial hypertension are naturally expected. Falta refers to such symptoms: "To the symptoms called into existence by the growing tumor belong also headache, and eventually dizziness and vomiting." Enlargement of the osseous tissues may cause increased tension from localized pressure. Falta quotes the case of Schulte and Fischer: "Here the disease (acromegaly) began at the eleventh year of life. Since that time there had existed headache, vomitings and temporary salivations. The patient had never menstruated. In the course of three days she became blind and almost deaf (probably on account of narrowing of the inner ear on account of osseous thickening)."

S. Stephenson, in the *British Journal of Children's Diseases,* reports as a case of dyspituitarism the following: A girl of 15 had a simple bilateral optic atrophy, diminished power of vision of the left eye (5/36); the sella was much greater than normal in size. The girl had never menstruated, and there was a lack of hair on the pubis. Stephenson gave her thyroid therapy without results. The case is evidently one of intracranial hypertension (pituitary?) associated with gonad insufficiency.

Timme has discussed the interconvertibility of migraine and epilepsy. In so far as the production of periodic attacks of migraine are concerned he believes that there is an enlargement of the pituitary at periodic intervals due to increased demands upon it incident to disturbances in other glands, such as a drawing out of the available adrenin supply in fatigue, menstruation, intense cold, or intense mental occupation, all of which disturb the circulation and cause an engorgement of the highly vascular pituitary. Timme considers that increased adrenal action stimulates the pituitary to compensate for the purpose of maintaining a proper blood sugar supply and a proper blood-pressure. These

factors apply, of course, to the production of the migraine attack, but there are some suggestive features contained therein.

Bram, of Philadelphia, believes that essential epilepsy is to be attributed to nervous instability which is accompanied by and is probably the result of an abnormally high intracranial pressure. An attack or fit, according to his view, is probably consequent upon a sudden increase of blood pressure (general) above the patient's normal pressure, associated with a tremendously high intracranial pressure. For the relief of this he recommends venesection. Adrenal and vasomotor factors may have something to do with the production of increased tension in the cranium, inasmuch as the "wave" of cortical stimulation may take origin in a vasomotor relaxation—a "blushing" of the brain, such as one sees in similar vasomotor disturbances of the surface of the body. Such an engorgement would account for the sudden stimulation of the motor areas, the loss of consciousness, and the syndrome of intracranial hypertension. It would also account for the rather prompt recovery from the stupor and other symptoms of the fit, since the circulatory disturbance as a rule is of a temporary nature. The mode of origin is important to determine—whether it be due to an enlarged pituitary, a closed-in pituitary, or to periodical engorgement from associated disturbance of other glands. Attention already has been called (Chap. 7) to the probability that hypothyroidism causes an edema or infiltration of the brain itself which, according to Hertoghe and others, may prepare the cerebral motor cells for the condition which favors epilepsy. Undoubtedly this causes intracranial pressure from mechanical reasons. Incidentally, hypothyroidism is not infrequently connected with hypopituitarism, both as cause and effect, hence the pluriglandular aspect of this condition takes on added importance.

Pituitary dystrophy of whatever type ultimately represents a condition of hypofunction. This hypofunction in relation to the internal glandular balance is very important, since it is probably in the derangements of this balance or harmony that the circulatory disturbances, vasomotor or otherwise, doubtless take origin. The syndrome of intracranial hypertension is a most important feature of the epileptic fit and deserves much consideration. In cases due to pituitary hypofunction pituitary feeding does good; where two or three glands are involved pluriglandular therapy does better, evidently by building up an endocrine "reserve" against undue demands upon it incident to sudden or periodical fluctuations in other glands.

V

GONAD ASPECTS

16.—Dysovarism

That there is an ovarian form of epilepsy has long since ceased to be a surmise, and a number of references indicate that physicians believe that disturbed ovarian function may be the cause of epilepsy. With this I am inclined to agree, and yet not without some qualification.

We have seen thus far that endocrine imbalance may bring about certain changes in the detoxicating mechanism, in the circulation, or in the sympathetic balance, which either favor or actually cause epilepsy. It is quite certain that dyscrinism, or disturbed endocrine functioning, aggravates an epilepsy coming as a result of other causes.

Just how far ovarian hormone production is concerned in the cause or aggravation of epilepsy is very difficult to determine, but many clinical experiences indicate that epilepsy may be connected with ovarian manifestations, and many physicians have come to the conclusion that because a woman has an epilepsy initiated in connection with the menopause or aggravated in relation to her menstrual conditions, and especially when the latter is the case, they very naturally conclude that the ovaries are at fault.

Now, we have seen already that the thyroid and the pituitary gland are both of them likely to be involved in those cases of epilepsy in which the endocrine factor is prominent, and it happens that the thyroid gland

is very intimate functionally with the ovaries. Dysthroidism is a very common cause of dysovarism. It is also true that ovarian derangement is a veritable cause of thyroid insufficiency. It may be recalled that Oliver Osborne, of Yale, says that ninety per cent. of cases of myxedema occur in women, and of these no less than ninety-five per cent. occur in the decade between forty and fifty. In this connection Falta says: "The reason myxedema is commoner in women than in men should be sought in the fact that the normal sexual processes in women determine an important affection of the function of the thyroid, and that an exhaustion of this is produced the more easily by damages to the parenchyma, due to common infections or intoxications. For this assumption speaks the fact that the mitigated forms of hypothyroidism tend to become worse during pregnancy and that not rarely the myxedematous symptoms disappear at the sexual involution."

We are not concerned for the moment as to whether myxedema is commoner in women than in men, but we are interested in the probability that when there is an ovarian dysfunction there has been previously or will shortly follow it a thyroid dysfunction, and I confidently believe that thyroid disorders favor epilepsy.

Virtually the same thing is true about the pituitary gland. The pituitary is responsible for regulating ovarian activity. Hypopituitarism invariably spells hypo-ovarism, and the occurrence of the so-called "pituitary headaches" in connection with ovarian insufficiency (the pituitary having a large part in maintaining ovarian activity, when the latter is insufficient, naturally there ensues an increased circulation and functional activity in order to help out the lagging ovaries, and the limitations of the bony sella turcica prevent the enlargement of the gland and an intracranial pressure results) is further evidence of the

pituitary-ovarian relationship; and since pituitary dysfunction has been connected even more definitely with epilepsy, it is clear that there may be an ovarian cause for the pituitary trouble and thus an indirect ovarian cause for the epilepsy.

In other words, when the condition that has been called "ovarian epilepsy" is encountered, it is practically always the result of disturbed activity in the endocrine glands chiefly associated with the sex glands, notably the thyroid and the pituitary gland, and ovarian epilepsy therefore is really a pluriglandular difficulty. Clinical experience assuredly shows this to be the case, and there are a number of reports indicating that an epilepsy that is initiated or aggravated in connection with the menses can be benefited by ovarian therapy, and repeatedly where ovarian and corpus luteum extracts alone did not render the expected service, a pluriglandular formula containing thyroid, pituitary and ovary has turned the trick.

When an epilepsy is in any way associated with manifestations which indicate that ovarian function is not normal, it is perfectly rational to attempt to modify not merely the epilepsy itself but the associated dysovarism which, as we have seen, may be either the cause or part of the cause of the difficulty. In girls with an epilepsy which has originated in conjunction with the onset of puberty, the regulation of the usually associated dysovarism frequently has ended the epileptic seizures. In women at the change of life, where a "normal hypo-ovarism" is expected, the same manifestations have been noticed; and the same treatment directed at the *tout-ensemble* of the thyroid, pituitary, and ovarian functions many a time has succeeded in mitigating or ending entirely the epileptic seizures.

In individuals where epilepsy is associated with menstrual irregularity and especially amenorrhea, and particularly in those where there is a tendency for the

attacks to occur at or near the menstruation, Parker calls this trouble "menstrual insufficiency," and discussing a case which he treated successfully, says: "Why the human female menstruates no one seems to know. The function must have a purpose in the physical economy, and when it is depressed the body doubtless suffers in some way. Possibly if the flow (or its stimulus) is insufficient the interglandular harmony is upset . . .there may be formed some toxic metabolic products, or there may be some such product which fails to be eliminated by the flow. Witness the many obscure phenomena presented by many patients—spells of depression and excitation, headaches, nervousness, etc., as well as the more marked evidences of upset, such as the nausea of early pregnancy, the psychoses following parturition and the flushes of the climacterium.

"The significance of all this lies in the predilection of the convulsions to occur at the peak of the inter-menstrual period, if I may so designate it, a time when a failure to eliminate precipitated a crisis marked by convulsion. This significance is dramatically illustrated by the onset of a convulsion on the day a period was missed, eighteen months after she had been free from attacks."

In conclusion, I can say that in several instances coming to my notice in which epilepsy obviously had an ovarian aspect, and other glands—notably the pituitary —had been presumed to be chiefly at fault and treatment already had been directed at this fault with poor results or none at all, treatment directed at the ovarian aspect has been helpful in an occasional case, while pluriglandular therapy has increased the proportion and character of the results very much more. To me, the principal deduction is that when epilepsy is of endocrine origin, usually several of the related glands are at fault together.

17.—Eunuchoidism and Hypogonadism

While the above two conditions are not synonymous, both refer to endocrine defects of the sex glands. The former refers particularly to a condition found in the male, and the latter may include hypofunction of the testes or the ovaries. In this chapter, at least, hypogonadism refers particularly to deficient gonad function in the male.

It may be interesting to give here the definition of eunuchoidism and as quoted from Falta's book:

"Eunuchoids we term, according to Tandler and Grosz, individuals who, without being castrated, entirely simulate in their clinical manifestations the true eunuch type, or are at least extraordinarily similar to it. They are either tall, or if complications are absent, are at least not stunted in their growth; they show the typical fat distribution of eunuchs, and eventually pronounced obesity; the epiphysial junctures persist abnormally long, the skeletal dimensions are characterized by an especial length of the extremities, and furthermore, the individuals show a definite psychical habitus. Finally, there is found a more or less pronounced disturbance of development of the genitalia with faulty development of the secondary sexual characters. It is probable that in such cases we have to do with a developmental disturbance beginning primarily in the sexual glands, and indeed the interstitial glands, as functional disturbances of the generative glands alone do not lead to eunuchoidism."

This explicit definition indicates that eunuchoidism is a disturbed developmental condition originating in the young before the epiphyses in the long bones have joined, and the increased growth is due to this and not to the pituitary dysfunction in the sense that we find gigantism in hyperpituitarism.

Eunuchoidism may occur in later life, and is then

termed late eunuchoidism. Falta defines it thus: "I term 'late eunuchoidism' a clinical picture that comes about by the fact that in an already matured organism in which also the function of the sexual glands have attained their full development, there occurs atrophy of the accessory genital apparatus (in man retrogression of the penis, scrotum, prostate, etc.; in woman the labia majora and uterus), and retrogression of the secondary sexual characters (mustache, beard, hairiness of the axilla and pubis, the trunk and extremities). Moreover, there develop more or less distinct collections of fat on the breast, the mons Veneris and the hips, and often certain alterations of the psyche. The typical eunuchoidal alterations of the skeleton cannot go on developing, especially where the development of the skeleton has been already closed off; that is, where the epiphysial junctures have already united."

Without a question, the two conditions mentioned above involve more than the gonads themselves. The picture of late eunuchoidism painted above has many points in common with that of hypopituitarism, and the adiposogenital dystrophy of Froehlich may be very easily mistaken for eunuchoidism provided the bony dystrophy is ignored.

Not infrequently epilepsy is found in these gonad-pituitary cases. As to whether the condition is brought about by the gonad dysfunction in a manner similar to that which has been discussed in relation to ovarian functions and its relation to epilepsy, cannot be said. Personally, I believe that the chief factor at the bottom of the endocrine cause of epilepsy in individuals who have gonad dysfunction is related to the thyroid and the pituitary equally with the sex glands themselves.

Wilhelm Stekel, of Vienna, in his recent book on impotence, notes that among cases of impotence, the psychotherapeutist quite frequently comes across men who also are suffering from epilepsy. On the other

hand, not rarely one finds a gradually developing symptom-complex in which both impotence and epilepsy (petit mal more commonly than grand mal) are related. Here, I believe, we are justified in studying the endocrine causes of the hypogonadism, and treating them in the hope that the epilepsy may be modified simultaneously.

At all events, the point to bear in mind is that in epilepsy with a gonad disturbance the treatment should involve measures calculated to regulate this dyscrinism, and those measures will vary in relation to the clinical manifestations and the indication as to which glands are involved. Usually the glands to be given consideration in epilepsy in cases of this type are the thyroid, the pituitary and the interstitial cells of Leydig.

18.—Pubertial and Menopausal Epilepsy

It is not surprising that epilepsy should begin in youth, for it is at this time that there occurs those marked changes which constitute puberty. New glandular influences are becoming manifest and a new phase of interglandular harmony established. Should these changes take place smoothly the organism is healthy in that respect. Maladjustment naturally leads to perversion of important functions, such as that of menstruation. At this time are seen some of the results of the diseases of childhood. There may result from such prostrating infections impairment of ovarian function with amenorrhea; there may result a hyperthyroidism from foci of infection; secondary hypothyroidism is often noted at this time. Enough has been said in previous chapters to indicate the far-reaching results of endocrine impairment in the young. Subsequent case reports will elucidate this still better.

The relation of the monopause to epilepsy lies in those factors which have been discussed under Minor Hypothyroidism as an Aggravating Factor, and Gonad Aspects. The factors which influence the associated glands in earlier life bear a distinct relation to disturbances of the menopause, such as primary and secondary hyperovarian function, hypofunction, etc. The significance of the predilection of attacks to occur near the menstrual periods is to be remembered in menopausal epilepsy. The onset of epilepsy following the withdrawal of the ovarian hormone, especially if this be sudden or premature, indicates a lack of integrity in the internal glandular system. In this respect one may quote a line from Ehrenfest: "It is clear, therefore, that if one woman be better adjusted than another against the removal of all ovarian secretion, she will show less signs of menopause."

VI

CLINICAL EXPERIENCES

19.—Monoglandular Therapy

Given a case of idiopathic epilepsy, at once there is presented the problem as to what factors may be acting in the production of the disease. One must canvass the entire field of possible causes, noting any outstanding features which may offer a clue to the real situation. The sex of the patient offers a starting point. In the male one hardly looks for gonad causes since these have been mostly limited to the opposite sex. However, in marked cases of eunuchoidism or other symptoms which point to some defect in the genital system such cases should be thoroughly studied, especially as there may be some related trouble in other glands.

Pituitary. It is in pituitary dystrophies that many cases of epilepsy in the male have been found, and as these come more strictly under the head of monoglandular therapy they will be taken up clinically. Those who have noted these marked cases have become very strongly convinced of the rôle of this gland in the production of the disease. Thomas M. T. McKennan, of Pittsburgh, in an article published last year in the *Archives of Neurology and Psychiatry* said: "The question of pituitary feeding in epileptics, in my opinion, is an important one. I have found that the extract of the whole gland in 2-grain doses three times a day, and given four hours after eating, is the most

satisfactory. Bromides should always be used in conjunction with pituitary extract. I am in the habit of using 45 to 60 grains of bromide daily. After a year less bromide can be used, but the pituitary feeding must be kept up indefinitely, probably during the life of the patient.

"I am coming to the belief that essential epilepsy is largely due to a crippling of the pituitary gland in one way or another. I believe that the most frequent cause is recurring hyperemia of the gland; that second in importance is a gland that has not evoluted properly—a small, inefficient gland; and third in importance is pituitary tumor or struma, or in some cases probably simple hypertrophy. The question of abnormality of the pituitary gland in its relation to epilepsy is greatly illuminated by a consideration of cases originating in persons over 35 years of age."

J. F. Munson, of the Craig Colony for Epileptics at Sonyea, New York, in a paper on the conformation of the sella turcica in epilepsy, practically confirms the above remarks by McKennan.

Joughin, in the *New York Medical Journal,* cites the case of a girl 16 years of age presenting a syndrome which began with the first epileptic period. Eight to ten 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.

In a discussion in *Endocrinology,* I quoted the case of Spears, of Louisville, who likewise treated a sailor 28 years old for pituitary epilepsy. There had been three to four attacks a week; as many as eight in one week, the longest interval being 20 days. He had had no

seizures for eight months following the beginning of treatment.

Mention was made in a previous chapter of the different types of pituitary epilepsy, as noted by Beverley R. Tucker, and referred to previously. He divides them into the *chronic* or *congenital* and the *transitional* types and gives a table of case histories based on a study of 200 cases of epilepsy. For reasons set forth previously only 28 of these are included in this table, which is given herewith:

CHRONIC HYPOPITUITARY TYPE

Age at Onset	Type of Attack	Aver. Freq.	History of Head Inj.	Prep. Used	Result	Remarks
11	Gr. Mal.	1 a mo.	Injury to head at 7	Total	2 attacks in 18 mos.	Marked improvement
14	Pet. Mal.	1 a mo.	None	Total	None in 3 yrs.	Cured
18	Gr. Mal.	1 ev. 6 wks.	Head inj. as child	Total	None in 14 mos.	Attacks ceased
18	Gr. Mal.	1 ev. 2 mos.	None	Ant. lobe	1 ev. 2 mos.	Not improved
11	Gr. Mal.	1 a mo.	None	Total	3 in 18 mos.	Marked improvement
12	Gr. Mal.	2 to 3 a wk.	None	Total	None in 3 yrs.	Cured
10	Pet. Mal.	Daily	Head inj. as child	Total	None in 3 yrs.	Cured
13	Pet. Mal.	Many a day	None	Total	None in 3 yrs.	Cured
12	Gr. Mal.	3 a year	None	Total	None in a year	Prospects for cure
13	Gr. & P.	1 to 2 a wk.	Head inj. as child	Total	Once a mo.	Improvement
9	Gr. Mal.	3 or 4 a year	Head inj. age of 5	Ant. lobe	None in 2 yrs.	Prospects for cure
30	Gr. Mal.	1 ev. 6 wks.	None	Total	1 in 2 yrs.	Prospects for cure
17	Gr. Mal.	3 a year	Malaria	Total	Same as before	Took medicine irregularly
15	Gr. Mal.	1 a wk.	None	Total	1 in 2 mos.	Marked improvement
13	Gr. Mal.	1 ev. 6 wks.	Rheumatism	Total	1 ev. 3 mos.	Improvement
11	Gr. Mal.	1 a mo.	None	Total	None in 2 yrs.	Apparent cure
8	Gr. Mal.	1 ev. mo. or two	None	Total	None in 6 mos.	Marked improvement

All the above cases had definite clinical hypopituitarism, and roentgenographic signs of the chronic or congenital type. The general health improved upon the treatment.

TRANSITIONAL TYPE

Age at Onset	Type of Attack	Aver. Freq.	History of Head Inj.	Prep. Used	Result	Remarks
18	Gr. Mal.	1 ev. 2 mos.	None	Ant. lobe	1 attack in 18 mos.	Marked improvement
25	Gr. & P.	1 ev. 2 mos.	None	Total	Recent	Too recent to judge
13	Gr. Mal.	1 ev. 3 wks.	Head inj. as child	Total	2 in 9 mos.	Marked improvement
24	Gr. Mal.	1 ev. 2 mos.	None	Total	Same as before	No improvement
20	Gr. Mal.	1 ev. 6 mos.	None	Ant. lobe	None in 2 yrs.	Prospects for cure
12	Gr. Mal.	1 a wk.	None	Total	None in 18 mos.	Prospects for cure
17	Gr. Mal.	1 ev. 2 or 3 mos.	Head inj. as child	Total	1 series of several attks	Improved
17	Gr. Mal.	2 to 4 a wk.	None	Total	None in 8 mos.	Improved
22	Gr. Mal.	1 a mo.	None	Total	1 ev. 2 mos.	Improved
22	Gr. & P.	3 a wk.	Inj. to head few yrs. before	Total	None in 18 mos.	Prospects for cure
18	Gr. Mal.	1 a wk.	None	Ant. lobe	1 ev. 2 mos.	Much improved

It will be observed that in the above cases there was a frequent history of injury to the head in which there was probably some injury to the base of the cranium, such as a linear fracture, the scar involving the pituitary gland. The feeding of gland substance on the whole was more successful when the whole gland was administered. The anterior lobe was occasionally successful, but inasmuch as an affection of the anterior lobe usually involves the posterior lobe also, especially in enlargements of the gland, the administration of whole gland is to be advised.

G. C. Johnston, of Pittsburgh, details nine cases in which the results from pituitary treatment were fair.

His findings have been tabulated for convenience:

Age at Onset	Type of Attack	Aver. Freq.	History of Head Inj.	Prep. Used	Result	Remarks
13	Gr. M.	1 ev. 6 wks.	At 7 yrs.	Ant. lobe	Good for 1 yr.	Returned on disc. med.
19	Gr. M.	1 ev. 2-4 wks.	.....	Ant. lobe	1 att. in 2 yrs.	Excellent
11	Gr. M.	frequent.	At 4 yrs.	Ant. lobe		
13	Gr. & P. M.	1 a mo.	.....	Ant. lobe	3 att. in 2 yrs.	2 yrs. treat.
17	Gr. & P. M.	?	At 3 yrs.	Ant. lobe	Improving	
18	Gr. & P. M.	1 ev. 1-3 mos.	.....	Total	Some impr.	
31	Gr. & P. M.	6-8 a yr.	.....	Total	No impr.	
18	Gr. & P. M.	1 ev. 4-5 wks.	.....	Total	No att.	6 mos. free
49	Gr. & P. M.	1 ev. 3-4 mos.	.....	Total	No att.	2 yrs. free

An interesting point is that Johnston's systolic blood-pressure figures were all low.

Timme mentions the varied picture of endocrine dystrophy, pointing suggestively here and there to those evidences of damage to this system. Continuing, he says: "If our epileptic patient withstands to a great extent these inroads on his endocrine assets, then he is not of our present class. Those that fall well within our suspicions can be divided into two groups. The first is represented by the adipose, sluggish individual with smooth, velvety skin, hairless body, small genitals almost imbedded in the lower fatty abdominal folds, with a high sugar tolerance and a small closed-in sella turcica. This group represents the type of which Froehlich's dystrophy is the classic. There are many variations with a corresponding change in the physical signs. Those of this group that have epileptic seizures —and there are many—frequently have the uncinate fit with aurae of smell or taste. They are distinctly pituitaric. Feeding them with appropriate doses of pituitary gland, frequently the anterior lobe extract

only, produces marked improvement and even cures the disease. The epileptic fit is produced as a symptom of this state. . . . A periodic enlargement of the hypophysis . . . in a sella not roomy enough to accommodate it, causes the critical moment. At times in these cases a migrainous attack accompanies the seizure, or is the equivalent of a seizure and the uncinate features are presumably due to the extension of the pressure to the uncinate gyri of the temperosphenoidal lobe immediately surrounding the sella. This serves to explain the interconvertibility of migraine and epilepsy, cited 40 years ago by Gray, an observation which in the experience of each of us has had its examples."

Ovarian. As one goes through the accumulated literature on this subject, there are enough references to ovarian or corpus luteum therapy in epilepsy to make it a close second in importance to either pituitary or thyroid.

An interesting report given below showed how a presumably pituitary case evidently was really principally an ovarian type. [Incidentally, I feel justified in saying that had pluriglandular therapy been tried earlier the results might have been both earlier and better.—H. R. H.]

Landon D. Walker, of Charlotte, N. C., reports a case of endocrine epilepsy in *American Medicine.* Omitting preliminary remarks the history is as follows:

"E. H., 18½ years old, white, 97 pounds; normal baby; full term; breast fed. Menstruation began at 16 years of age, and was regular and normal up to the present illness. [Menstruation beginning as late as 16 shows a tendency to hypogonadism.—H. R. H.]

"Family History: No epilepsy, nervous disorders, tuberculosis or syphilis.

"Present Illness: In January, 1914, had mumps, with accompanying ovaritis. One week after onset had a convulsion which appeared to be epileptic in

character. There was complete loss of consciousness with facial contortions and general muscular contractions. Three weeks later she had a similar convulsion and thereafter about three a month. They came on usually just before awakening in the morning, and also in the day with slight warning. Menses became irregular, scanty and finally ceased entirely. At first the convulsions seemed to bear a relation to the menses, coming within a week before or after. Constipation was very marked, the breath foul and the tongue coated. In 1916 the convulsions became more frequent, to four a week, and resisted usual treatment where before there had been some response. No treatment had any effect upon the amenorrhea. The patient had bromism.

"Treatment: Two years of usual treatment with bromides, hyoscyamus, chloral hydrate and catharsis, a restricted diet, hygiene, etc. Spent several months in New York under the care of a neurologist.

"X-ray examination of the skull was made by a Richmond man who made a diagnosis of 'dyspituitarism' and administered anterior pituitary extract and sedatives. The patient was better for one week and then developed convulsions which were more frequent than ever. The pituitary treatment was kept up 60 days with no result except lessening of the headache and depression. [Note: Attention is called to an apparent antagonism of the anterior pituitary to the menstrual function. This will be discussed later.] Dr. Walker states that it was very apparent to him that the patient was suffering from a disturbance of glandular function, but so far the deficiency had not been supplied. He tried out thyroid and pituitary, and then gave corpus luteum extract, grains 2, beginning September 15, and increasing the dosage up to ten tablets a day just before the menstrual time. All other medication was dropped. The convulsions ceased as if by

magic and the menstrual flow came on normally, both as to color and amount. The tablets were kept up but were reduced to three a day. The patient gained three pounds, color improved, tongue cleared and bowels became more regular. On November 15, two months later, no return of convulsions and patient in splendid physical condition.

"Conclusions: A marvelous result. It seems strange that the ovary was not given earlier. Parotitis and ovaritis produced injury to the glandular substance which was manifested by epileptic seizures."

Perrin and Richard, in the *Rev. de Neurol.*, Paris (1919), report two cases of epilepsy with a pluriglandular dystrophy in which the predominating difficulty was hypo-ovarian. The result of ovarian therapy was good.

A Dublin physician, J. S. Ashe, reports some recent clinical experiences with ovarian therapy in epilepsy. The first was completely cured by hypodermic injections of an ovarian solution. The second complained of dysmenorrhea and inward pains since an attack of mumps some months ago. Both ovaries were enlarged and painful. She had five well-marked epileptic seizures, bit her tongue, etc., which she never had done until she had the mumps. Dysovarism was presumed to be indirectly the cause of the epilepsy. Since giving ovarian extract, "she has not had an attack since."

In the third case, a girl was given a pluriglandular formula and the results have been satisfactory in three respects: (1) The length of time between attacks has greatly increased; (2) they are always at night now; (3) she can tell when they are coming on.

Quoting from Ashe's concluding remarks: "The deduction I have tried to evolve is that the toxin which acts as the predisposing factor in some cases of epilepsy is produced by (a) absence, diminution or change in the ovarian ferment, leading to (b) some multiple func-

tional deficiency of the endocrine organs which upsets the hormone balance, producing further toxins which act upon the cerebral cortex, causing epilepsy in some cases. This theory may appear far-fetched, but if we accept Osler's definition of 'epilepsy' as 'an affection of the nervous system characterized by attacks of unconsciousness with or without convulsions,' I think those of us who have had experience in gynecology cannot deny the association between ovarian insufficiency and epilepsy."

Thyroid. Judging from the number of articles on epilepsy in which thyroid therapy is more or less casually recommended, it seems that a great many neurologists are leaning toward the probabilities of an endocrine aspect to this. Pershing, of Denver, states that of late years he has used small doses of thyroid with advantage. Sicard, of Paris, emphasizes the value of this treatment and states that the tendency to bromism from the associate use of bromides may be combatted by the use of thyroid gland. In other words, the combination of bromides and thyroid is far superior to bromides alone. His usual does is 1½ grains of thyroid gland a day, while he gives 30-45 grains of potassium bromide a day.

F. X. Dercum, of Philadelphia, in emphasizing the necessity for placing as little strain as possible upon the liver, thyroid and other defensive glands, says: "In some cases the administration of small doses of thyroid (⅛ to ¼ grain three times a day for long periods) often seems to raise the epileptic patient's physiological level with marked benefit; and it may be that this is another reason for considering the thyroid in the solution of the epilepsy problem. Again, H. H. Drysdale, of Columbus, Ohio, believes that thyroid therapy "has true therapeutic worth" in epilepsy since a considerable number of these cases show endocrine disturbances which stand out more or less prominently, and he be-

lieves that "it is quite probable that the internal secretions have some relationship to this disease."

20.—Pluriglandular Therapy

My interest in the consideration of epilepsy from the endocrine standpoint has been developed largely from the standpoint of the possible results of pluriglandular therapy. Undoubtedly pluriglandular therapy is indicated in cases which show not only a dystrophy of some individual gland, but an accompanying deficiency in an associated gland. Naturally, these cases depend chiefly upon functional rather than organic changes in these glands and unfortunately, their consideration embraces a wide range of endocrine disturbances.

My first interest in the subject came about as a result of the coincidental betterment of several cases of epilepsy in children who were being treated with pluriglandular therapy for developmental dystrophies which obviously were of endocrine origin.

It is known that the class of children that require special attention, those who are backward in their studies, in whom there is some developmental defect, or who may be in the well defined endocrine class such as cretins or mongols, not infrequently have as a part of their symptom complex a tendency to *petit mal* or even full blown epilepsy. Many of these children have been treated with thyroid extract and in some instances there was considerable betterment, but I have been in the habit of giving a combination of anterior pituitary, thyroid and thymus known as Antero-Pituitary Co. to these developmentally deficient children and the aggregate of results have certainly been very encouraging. It happens that a number of these children in whom epilepsy was present seemed to gain benefit in regard to the number and character of their epileptic attacks and I have records in my office of a number of cases of

epilepsy in children that seem to have been cured entirely.

Of course this is empirical therapy because I confess that not always is there a clear-cut demand for each one of the three endocrine products which I have been routinely recommending, but we have some solace in the fact that when an endocrine product is given without any particular need for it, provided the dosage is within reason, no harm can come from it. It is merely oxidized like any other food, while, on the other hand, if we treat an endocrine dystrophy with the corresponding product and we have overlooked one or more associated glandular troubles, the very best indicated treatment directed at the single or monoglandular aspect cannot reach the associated aspect and consequently monoglandular therapy has failed many times where pluriglandular therapy has made a remarkable change for the better. This happens to be the case in epilepsy and despite the criticism which naturally comes to those who are not afraid to lean toward empiricism, we are making progress and many a parent is rejoicing to-day as a result of the "accidental results" which have been secured in this way.

It was very natural for some physicians who had secured good results with the Antero-Pituitary Co. in children to extend its use to older persons and while the results have not been so good, there have been results and many of my correspondents are encouraged to make a trial of this form of treatment when confronted with this clinical problem.

As we have already seen, there is quite a well defined ovarian aspect to epilepsy in young girls at puberty, in young women with dysovarism and in older women at the menopause. In all of these the regulation of the presumed ovarian dysfunction is a rational procedure and if this is accompanied by an attempt to modify a presumably associated endocrine trouble, the deranged

hormone balance may be so steadied that an accompanying epilepsy may be quite considerably benefited or even cured. I have seen cases in my own practice where epileptic attacks connected with the menstruation have been cured as by a miracle by the regulation of the associated menstrual difficulty. In the reports in my laboratory there are references to numerous cases of this type and all of them were treated by pluriglandular therapy directed at the dysovarism and the accompanying endocrine trouble.

The following case reported last year in the *Illinois Medical Journal* by W. G. Parker illustrates the pluriglandular aspect of this form of epilepsy very well:

Miss ———, was born prematurely at the eighth month. During childhood she suffered from a severe attack of whooping cough; she had two attacks of chorea at 7 and 13. Menstruation was always rather scant and painful. The patient was chronically constipated and had an acne. She was of somewhat slight physique as compared with other children in the same family.

When 17 years old she had a general convulsion. Her menses continued scant and painful, and she exhibited temperamental tendencies similar to those mentioned by Clark. In 1916 when she was 26 years old she had a second convulsion of great severity, which was attributed to overwork. She gave up her studies in a musical conservatory. At the next menstrual period she had another seizure, and seizures thereafter which corresponded closely to the menses, although they were at times more frequent. During the past five or six years the menstrual flow gradually lessened in amount. The thyroid became enlarged; she had a bad color; constipation was very marked. There were no symptoms of hyperthyroidism.

She entered a university hospital and underwent a curettement on the advice of a gynecologist. A neurol-

ogist made a diagnosis of idiopathic epilepsy, prescribed bromide, rest and a limited diet. No improvement except a slight effect from the bromide was apparent from this treatment. Following the curettement the menses became further depressed and finally ceased altogether. The attacks continued, and because of bromism and increased constipation and acne the patient declined to take bromide further.

An acute mental disturbance came on suddenly, characterized by hallucinations, periods of excitement, attempts at self-destruction, grimacing and posturing, insomnia and great physical depression. The breath was foul, the tongue heavily coated and the bowels constipated. The patient refused to eat, and because of inability to care for her at home she was placed in a State hospital. She remained there for six months, during which time she was in an unimproved condition for several weeks, following which she began to improve very markedly, being released later in a normal condition. The thyroid enlargement disappeared, she became well nourished and had a good color; the constipation was relieved for the first time in years. The acne was also cured.

The treatment she received from the beginning consisted of bromide before her mental derangement. When Parker treated her later he recognized a pluriglandular element, and to remedy the amenorrhea gave her corpus luteum for several months, but without apparent effect at the time. No bromide was given at any time after this. He attributes her recovery to a delayed readjustment of gonad secretion. An interesting phase of the case was the fact that she continued amenorrheic for several months after her release from the hospital, the menses gradually returning. She discontinued treatment, although advised at this time to take a pluriglandular treatment. A year and a half later she showed signs of glandular failure and toxemia

characterized by headache, a feeling of depression and irritability. On the day a menstrual period was due a convulsion occurred, the menstruation being missed. Pluriglandular treatment was at once started with the result that the menses were reëstablished and convulsions ceased.

The treatment consisted of ovarian extract (whole gland), thyroid extract and posterior pituitary extract. The basis of this combination was Bandler's classification of the endocrines with respect to their effect upon the generative organs. He divides them into two groups, the stimulators and the depressors, thus:

Stimulators: Ovary, thyroid, adrenals, posterior pituitary.

Depressors: Thymus, mammary, anterior pituitary and placenta.

Parker considers that this patient exhibits several "cross sections" as follows: (1) Prematurity of birth with its depressing effects; (2) the depressing effects of the diseases of childhood; (3) ovarian insufficiency with amenorrhea and consequent "toxemia" or hormone upset; (4) secondary thyroid failure with effort hypertrophy (goitre), development of epilepsy; (5) acute psychoneurosis from accompanying toxemia; (6) abatement of epilepsy and readjustment of hormone balance by endocrine treatment, with coincident betterment of depressed bodily functions.

21.—Possibilities of Failure

The pitfalls which lie in the way of one who cares for the patient with an idiopathic epilepsy are many. The complexities of the endocrine system are manifold and to be able to recognize clinical types requires careful study of this branch of medicine.

With the foregoing chapters in mind there should be no doubt that endocrine disorders are capable of excit-

ing the condition we know as epilepsy, which itself seemingly is a variable condition depending upon different factors. Certain cases show histological changes in the cortex, but whether these are the cause or the result of the disease is unsettled. Failure in the treatment of *endocrine* epilepsy lies chiefly in the following:

1. *Incomplete Examination.* Where there are no suggestive features to guide one a complete survey of the patient is necessary. Thyroid function should be tested out by means of the thyroid function test, the Goetsch test, metabolimetry, the search for evidences of dysthyroidism (goitre, maldevelopment, etc.), history of early menstrual irregularities of the subthyroid type, etc. Most goitres are of the hypothyroid type, and are often associated with derangement in other glands. Engelbach has pointed out the following characteristics of the subthyroid type of girls: Often overlarge at birth—every baby over ten pounds at birth should be suspected of having been influenced by parental thyroid deficiency; tendency to late healing of the cord; frequency of intestinal upsets in childhood; the tendency to late eruption of the teeth (the opposite in pituitary infants); tendency to rickets; late walking and talking; retarded progress in school life, often due to blunting of sound or sight perception (not to lesions of these special sense organs); early menstrual history; early maturity with copious flow and freedom from dysmenorrhea, later followed by a gradual tendency to amenorrhea.

It should be the rule to have a competent X-ray examination of the sella turcica, especially in cases giving a history of head injury and those in whom the attacks come in young adult life. Routine X-ray examination is advisable always when it can be had.

Further points relating to pituitary dystrophy are signs of growth disturbances (the subpituitary type, it has been observed, are often of diminutive build;

these are *not* of the acromegalic type), a tendency to amenorrhea (decreased pituitary action predisposes to sex retrogression), the upper body measurements being greater than the lower (symphysis to vertex; symphysis to soles of feet). Types of pituitary disease of later onset show a tendency toward the Froehlich syndrome —increased fat, with fat pads characteristically grouped about the breasts, mons, etc., as described previously; a voracious appetite; general hairlessness of the body (not head), low blood-pressure, and other signs which have been described. There may be acromegalic signs.

The characteristics of gonad deficiency and other abnormalities have been mentioned. One must contrast the pituitary, thyroid and eunuchoid types to determine the significance of such disturbances as amenorrhea, enlarged thyroid, etc. The peculiarities of eunuchoid build have been described: they embrace a lengthening of the long bones, resulting in a greater measurement of the lower part of the body (symphysis to soles of feet) and span equal to height. Menstruation is late, scant and painful as a rule; the patient is often thin. It is to be remembered that all cases of hypogonadism are not of the eunuchoid type physically, since these physical changes occur while the osseous tissues are growing and before closure of the epiphysial junctures have closed. These points are noted merely to recall some of the essential considerations of a complete examination.

2. *Insufficient Treatment.* Failure may also arise from insufficient treatment. It is to be remembered that there are no sure criteria of the intensity of the required therapy. These cases have as a rule been developing over long periods of time, and it is to be expected that time will be required to bring about an adjustment of the hormones, and maintain it. A case that has physiologically run so low as to terminate in

a convulsive state must be treated a long time. It is probable that most cases will require treatment throughout life. Exception may possibly be made in cases of thymic epilepsy, in which X-ray therapy causes retrogression of a persistent thymus. A return of symptoms means that the required hormones are not being supplied, or that they are not being supplied in sufficient quantity.

3. *Incomplete Treatment.* The pluriglandular idea must be mentioned again in this connection because cases of disturbed endocrine function in whom a certain endocrine aspect is prominent, have been treated with the presumably obviously indicated extract with little or no benefit, whereas, when an associated organotherapy has been instituted the results have been quite phenomenal. This is not the place to go into the philosophy of pluriglandular therapy but it must be said that the most satisfactory method of treating endocrine epilepsy is with pluriglandular therapy rather than with single extracts alone; and I confidently believe that where an administered preparation is not really needed by the organism it is oxidized without further concern, while, on the other hand, a treatment of this kind directed at several of the factors that are related in a given case, just as in many other conditions, accomplishes a much more satisfactory outcome.

Another aspect which may be considered under this head is mentioned with some diffidence. I have met physicians who have become interested in the endocrine treatment of epilepsy, who have failed to continue the dietetic, hygienic, and other treatment of the patient thinking that organotherapy was a miraculous means of curing the patient in a few weeks or months. Pluriglandular therapy is but an incident in the treatment of this disease. It extends our control of the combination of circumstances which bring about the epileptic condition. It should be accompanied by the removal of

toxemia by every possible means, the reduction of sympathetic irritability, and the tendency to motor irritability by suitable sedatives, and the removal from the diet of easily putrefiable proteins and other toxins or toxin-producing substances. I have found that epileptics not infrequently have a tendency to protein sensitization and attacks have been brought on by the use of foods to which the patient was particularly sensitive. The only way to treat this condition is to discover these allergies and prevent the use of such foods.

Epilepsy is a very large problem and just as other problems have been solved by concerted action, so in the treatment of this disease we must combine every useful measure simultaneously and push these measures to what we hope may be a satisfactory conclusion, and organotherapy has merely extended our facility and broadened the possibility of results.

The matter of management of the psychic state of certain epileptics may be such as to tax one's judgment. If such patients could be given some outlet for their interests and ambitions it would remove a certain amount of psychic stress. Many persons with epilepsy feel humiliated, and are yet compelled for various reasons to remain in the home and be dependent against their wills upon family or friends.

The use of bromides or other sedatives in connection with glandular therapy is a matter to be decided in each individual case. Grimberg thinks that the disadvantages of the bromide treatment so far outweigh its advantages that its use is rarely justified. Luminal was used by Grimberg in a number of cases with good results, which seemed limited to grand mal cases. There was no mental effect or stomach disturbance, and no tendency to habit formation. I have recommended luminal in 12 or 15 cases with benefit. It is far superior to the bromides. I believe that should experience show some form of sedative to be necessary to control the

convulsive state temporarily while specific treatment is being started, that luminal is to be selected in preference to bromide, inasmuch as it has not the evil effects of bromide upon the mind and upon body processes in general.

Brodsky lays down the principle that sedative treatment should be interrupted to reach the best results. This is contrary to the advice of some authorities who believe in keeping up the effect continuously.

My idea is to get away from the use of sedatives as soon as consistent. It is to be remembered that the use of bromid, especially in the young, is most deleterious to the organism. The use of such remedies is in no real sense curative, nor do they even supply any need of the body of a temporary nature. On the other hand, the application of endocrine therapeutics represents the only logical advance in the treatment of so-called idiopathic epilepsy that has been made in the history of the disease.

In going over the finished copy a feeling of despair is felt because so many writers have expressed themselves as favorable to so many organotherapeutic methods in the treatment of this disease. Undoubtedly, the importance of the thyroid and the frequency of satisfactory results from its use predominate, but it is clear that we must not ignore those who emphasize the relation of the parathyroid gland and the possibilities of using parathyroid extract, the adrenal glands and especially the pituitary gland.

The general practitioner who reads through this collection of opinions may find himself at a loss to know what to do and I feel justified in making some conclusions which for several years have been the basis for my own actions when confronted with epilepsy.

Epilepsy in children, especially in developmentally defective children, is more likely to be of endocrine origin. Organotherapy, directed at the developmental dystrophies, sometimes has entirely controlled the epilepsy, no matter whether it was petit mal or grand mal. I could report many cases mentioned to me in correspondence in whom the use of the combination of my pluriglandular formula containing anterior pituitary substance, thymus and a suited small dose of thyroid (Antero-Pituitary Compound) was given with benefit to the developmental dystrophies and also to the epilepsy.

In adults, on the other hand, this treatment is not so prospectively helpful although it has been spectacularly valuable in occasional cases. A number of reports have been printed in various issues of *The Organotherapeutic Review.*

In women, epilepsy is more likely to be connected with the ovaries than any of the other ductless glands, though the two endocrine organs which are most intimately related to ovarian activity—the thyroid and the pituitary—very frequently are equally concerned. Many cases of menstrual epilepsy or menopausal epilepsy, or epilepsy which seems to manifest a wave-like change in its frequency or intensity related to the periodical menstrual wave, are benefited by an organotherapy directed at the underlying dysovarism. Numerous cases of this type of epilepsy have been cured entirely by a three or four months' course of Thyro-Ovarian Compound—a combination of the above-mentioned trinity of endocrine products.

In all epilepsies detoxication is of paramount importance. It should not be necessary to emphasize how serious are the influences of the alimentary toxins upon the sensitiveness of these unusually important cells. Protein foods should be limited as far as possible and the easily putrefiable meats discarded entirely. An attempt should be made to discover whether epileptics

are especially sensitive to certain proteins—food anaphylaxis—and sometimes it will be discovered to the surprise of all that the patient's attacks are initiated by the use of foods to which he is unduly sensitive but which sensitiveness had not been considered before. The greatest advance in the treatment of epilepsy has been the broadening of our appreciation of the influence of the glands of internal secretion upon the underlying factors of epilepsy, both general and cerebral, and whenever there is any sort of an excuse to treat a well-defined or probable dyscrinism, this most certainly should be attempted in conjunction with all other indicated measures; and in this connection it must be remembered that several months of pluriglandular organotherapy directed to the most likely endocrine disorders will serve as a diagnostic agent and vindicate its use or indicate its uselessness.

VII

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TABLE OF CONTENTS

ENDOCRINOLOGY IN PEDIATRICS.

INTRODUCTION.

1.—Preliminary Remarks.

THE FREQUENCY of endocrine disorders in children; the rapid growth of our clinical knowledge of the subject; the increasing interest in the study of the disorders of the ductless glands and the vast amount of elaboration on the scientific research work upon this subject by eminent physiologists, pathologists and practical clinicians, I believe, make the need of a manuscript on "Endocrinology in Pediatrics" peculiarly felt by the medical profession.

There is perhaps no field in which the study of organotherapy is of such fundamental importance as in that of pediatrics. This Monograph aims to give a practical description of the ductless gland disorders as they occur during infancy, childhood and early youth, which will include fairly comprehensive details of anatomy, physiology, general and pathological desiderata and clinical studies.

It is necessary in disorders of one endocrine organ to consider the others, as all these organs have a mutual influence on each other. The effects produced through hypofunction or hyperfunction of these glands or of both, cause a great deal of metabolic and growth disturbances early in life. In order to get the best

and most lasting results it is indeed important to recognize these changes early, if possible at or before puberty, before the pathological changes in the organism become fixed and difficult to treat. Although in many instances in which endocrine symptoms and signs are manifest the syndrome presented may permit us to localize the primary and predominant pathological process in which one or more of the glands of internal secretion would seem to be involved, not infrequently we find cases in which almost all these glands are simultaneously disturbed in function. It must be obvious that in such pluriglandular syndromes the clinical analysis is a far more difficult matter than in the syndromes of predominantly uniglandular origin. A thorough acquaintance with the latter will greatly facilitate the analysis when the clinician is confronted with a patient who suffers from the former and more common variety of disorder.

We also may note symptoms due to a particular gland that have been produced by a disturbance compensatory to the original imbalance. Every clinical case, every abnormal child requires individual study. In other words, we must generalize the disease and individualize the patient. The careless practitioner, who, after examination of the patient, and the finding of certain symptoms and physical signs, concludes the case to be one of a type belonging to a general class of diseases—that is, a practitioner who individualizes the disease instead of the patient—ultimately will fail in his purpose. Undoubtedly this explains the cause of so many failures among those who oppose organotherapy, or who become very critical and skeptical as to its usefulness, for instead of practising it judiciously, too often they abuse its administration. Their science consists mostly of speculation, chance and random.

Of course, we must be careful not to label every abnormal state an endocrine disturbance and thus

convert the whole subject into a present day fad. Naturally, such practices in time would condemn themselves. There are other abnormal pathological states independent of endocrine involvement, as the contagious and infectious diseases, various parasitic diseases, etc. These require other therapy. Ordinary cases of malnutrition and those more recently called vitamine deficiencies, should also be mentioned. Often, in such cases, the ductless gland products can be employed to great advantage together with the vitamines or indicated drugs in certain conditions to which reference will be made later.

The administration of ductless gland products should not be construed as the cure for all ills. And, as stated above, neither is every complaint, pathological state, mental aberration and every functional or organic deviation from the normal, an internal secretory disturbance. The misunderstanding, misuse, or abuse of these fundamental principles by the general practitioner may prove detrimental to the laity and the profession. It belittles a rational form of therapy that is by no means of little importance but is of specific value when indicated in certain conditions.

Historical Data. Craterus, the brother of King Antigonus, wrote, "The subject was an infant, a young man, a mature man, an old man, was married and begat children and all in a space of seven years." Others described dwarfs, giants, cases of individuals now known as pubertus praecox, etc., and though Paracelsus in the fifteenth century described his observations of cases of cretinism and goitre, yet the entire subject has been dormant until Johannes Müller and Ruysch in 1844, showed that the blood received secretions from ductless glands. The term "internal secretions" was first used by Claude Bérnard, in 1855, when he described the glycogenic function of the liver. But our clinical knowledge and the real beginning of ductless

gland research dates back to 1855 when Thomas Addison described the syndrome caused by the changes in the adrenal glands.

In 1849, Berthold of Göttingen experimented on animals to ascertain the true nature of the ductless glands. Leydig, in 1850, described his work with the gonads; the intertubular connective tissue cells of the testes bear his name. The thyroid was first studied by Schiff in 1856, yet Parry in 1825, Graves in 1835 and Basedow in 1850, contributed greatly to our knowledge of exophthalmos, goitre and hyperthyroidism.

In 1865 Pflueger explained that menstruation was the result of pelvic hyperemia induced reflexly by the pressure of a growing Graafian follicle on the ovarian nerve terminations. This theory was universally accepted until it was disproved by the experimental work of Knauer, Marshall and others. These investigators showed that removal of the ovaries, thereby severing all their nerve connections, does not cause cessation of menstruation, provided that the ovaries be transplanted elsewhere into the body, which shows it is of endocrine nature.

Sir Wm. Gull, in 1873, was first to describe the idiopathic form of myxedema as a cretinoid state supervening in adult life in women. To this condition, William Ord and Charcot, two years later, applied the term myxedema. Hadden, in 1882, laid emphasis upon the small thyroid gland in this disease. Kocher, in 1882, first called attention to the cachexia strumipriva that follows goitre operations in which the whole thyroid is removed. Reverdin, in 1883, proved this was due to the absence of the functional activity of the thyroid. From the studies of the myxedema commission of the clinical society of London in 1888, it was made clear that the functions of the thyroid gland are necessary to normal growth and for the normal functions of cer-

tain organs. Later on, Murray and McKenzie and others demonstrated the possibility of preventing post-operative myxedema by the administration of thyroid extract subcutaneously or by mouth. Later, Kocher called our attention to certain atypical and latent forms of hypothyroidism, *myxedème fruste.* In 1886, Moebius first spoke of hyperthyroidism as the cause of Basedow's disease and in 1889, Brown-Séquard spoke of the effect of testicular extracts on distant organs.

Some of the clinical phenomena of tetany were recognized by Clarke in 1815 and Lellie in 1816. The clinical knowledge of this syndrome developed rapidly through the efforts of Dance, Steinheim, Tonnelle, Trosseau, Chvostek, Gley, Pineles, Jeandelize, Erdheim, Vassale, Generale and MacCallum, from whom we have periodical and scientific reports from 1864 to the present.

As to the thymus gland, Kopp, in 1855, called attention to the occurrence of sudden death in childhood following cyanosis and stridor. The later work of Basch, Klose, Matti, Paultauf, in 1889, Bartel in 1912 and Wiesel in 1913 have thrown much light upon status thymolymphaticus and other functions of the thymus.

Acromegaly was described by P. M. Marie of Paris in 1886, and Mainesco, Bendar and Erdheim demonstrated certain pathological conditions of the hypophysis. Froehlich in 1901 and Franckle-Hochwart soon afterward described the syndrome of dystrophy adiposo-genitalis.

Experimental work on the pituitary body was carried on in this country by Harvey Cushing, in 1912, Wm. Engelbach and Atwell, in 1920, and in Italy by Ascoli and Legnani. Howell, in 1898, demonstrated the direct effect of pituitrin on the vessels. Rogowitsch, in 1886, found that the pituitary, chiefly the pars anteria and intermedia, enlarges after removal of the thyroid; also seen in myxedema. Oliver and Shäfer

called attention to the important therapeutic value of the posterior lobe extract.

Foa, working on fowls; Sarteschi, on rabbits, wrote clearly on the pineal gland. Dandy got no bad effects from total extirpation and Timme holds this gland responsible for some of the myopathies and reported extensive clinical data. Bailey and Jelliffe in 1911, Horrax in 1916, and McCord in 1917 wrote comprehensively on this subject.

Oliver Shäfer in 1895 showed that the extract of the adrenal medulla has potency. The chromaphilic substances were isolated by Frankel and prepared by Von Furth, Abel and Takamine. Cannon, Stewart, Rogoff, Elliot, Sajous and others wrote and experimented a great deal with this subject. Herter and Wakeman found that swabbing the pancreas with adrenalin produced glycosuria. E. P. Joslin and F. M. Allen wrote considerably on the pancreas and diabetes mellitus.

The Skoptsy, a religious sect in Russia and in the Balkans, practise castration as a mutilating religious rite. Tandler and Grosz fully describe two types of eunuchs—the tall, long-boned, lean type and the short, fat individuals with broad hips. In 1895, Griffiths described cases with hypoplastic sex organs whose bodily configurations resembled those of eunuchs. Lydston, of Chicago, tried transplantation of sex glands from one person to another in these conditions; and, too, the experiments by Steinach in Europe are interesting. The work of Erdheim abroad and MacCallum and Voegtlin in this country have added much to our knowledge of the parathyroids, and they showed that parathyroidectomized animals lose their calcium rapidly. E. A. Schäfer distinguishes hormones which promote activities of another ductless gland from chalones, which have an inhibitory influence. Starling applied the term "hormone" to the active principles of the internal secretions.

Bayliss and Bradford, in 1885, reported an investigation of the electrical changes attending glandular activity. Cannon, Cattel and later Gesell, have recorded the secretory action of the salivary and thyroid glands. Brown, in 1921, reported his observations of estimating the activity of one lobe of the thyroid as compared with that of the opposite side by the use of the electrocardiograph. Goetsch, Ascoli, Fagiuolo and myself have instituted various diagnostic endocrinological tests.

Many theories have been advanced to explain the individual functions of the ductless glands. It can be realized today how wide the field of activity is regarding ductless gland work when the literature upon the subject is consulted. Barker, Cushing, Tilney, Sajous, Harrower, Timme, Goetsch, Pottenger, Borchardt, Atwell and others have written extensively on this subject describing histological, anatomical, physiological, clinical and syndromal data.

2.—Anatomical and Physiological Data.

The Thyroid

It is a ductless structure built upon the general principle of a compound alveolar gland, and originates as a diverticulum from the entoderm of the primitive pharynx. The thyroid is an extremely vascular body, situated at the front and sides of the neck and extending upwards upon each side of the larynx. It is larger relatively in children, particularly in females (a point to be noticed), and consists of two lobes and an isthmus; occasionally we find a middle lobe. The embryological thyro-glossal duct disappears entirely or is represented in the adult by such rudimentary structures as the so-called prehyoid, suprahyoid accessory thyroid glands.

Gley showed that while removal of the thyroid alone does not necessarily cause death, it was the removal of the parathyroids which caused the nervous phenomena and the fatal ending. Removal of the thyroid alone produces morbid phenomena more severe in the younger animal. The animal fails to grow, the bones and epiphyseal cartilages fail to develop, the skull alone escaping, the abdomen projects and becomes larger. Sterility, due to non-formation of semen, has been noted.

That the organ is a secreting one is shown by the fact that it can be transplanted or grafted from its normal site to other parts of the body. (Schiff, Eiselberg and Christiana.) We should lay stress upon the correlation of the thyroid functions and general nutrition. It increases nitrogen excretion and other tissue wastes, respiratory and tissue respiration and metabolic processes both in the cutaneous tissues and in the organism at large.

The Pituitary Body

The pituitary gland is a pinkish gray, vascular mass thoroughly protected by nature in being centrally located at the base of the skull and surrounded by a bony encasement called the sella-turcica, where it is retained by a process of dura mater (diaphragma sella) which covers the sella turcica and has an opening in its center through which the infundibulum passes. It consists of the anterior, or glandular portion, which is considerably larger than the posterior, or nervous part. The anterior, epithelial part is further divided into the large pars-anterior proper, which constitutes about three fourths of the gland (pinkish gray), and the posterior narrow zone, of whitish appearance, called pars intermedia. The latter constitutes the epithelial lining or encasement of the posterior lobe and extends upward along the infundibulum frequently up to the

floor of the third ventricle. Between these two divisions of the epithelial or glandular portion lies the cleft, the embryonic remains of the original cavity of Rathkes' pocket.

Tilney described a distinct third epithelial lobe that extends nasalwards from the junction of the pars intermedia and the anterior lobe proper, to surround the infundibulum and to spread out for a variable distance under the brain floor. Because of its close relation to the tuber cinereum in many animals, he named this part the pars tuberalis. He also showed that the pars tuberalis is distinct histologically and embryologically and does not contain the eosinophile cells which are so characteristic of the anterior lobe, and is more vascular than the pars intermedia. It arises from a pair of thickened ridges which are situated at the nasal side of Rathkes' pocket.

The anterior lobe is of ectodermic origin, developing as a diverticulum from the primitive oral cavity. It is a compound tubular gland. The posterior lobe is developed as an outgrowth from the embryonic brain of ectodermic origin. It consists mainly of neuroglia with a few scattered cells, which probably represent rudimentary ganglia cells and a few nerve fibres. The pars intermedia develops with the pars anterior and like it consists of a connective tissue framework and epithelial cells. Characteristic of the pars intermedia are small cyst-like structures which contain colloid, presenting an appearance not wholly unlike thyroid, although chemically the colloid of the two glands is not identical. The alveoli of the pars anterior sometimes is found to contain colloid material.

Physiological Data. The secretion derived from the posterior lobe is considered by many to find its source in the pars intermedia. It causes a marked rise of blood-pressure, increased flow of urine and of milk, a general contraction of involuntary muscle, especially

that of the uterus. The secretion from the anterior lobe does not have much if any influence upon the blood-pressure on introduction into the circulation, but exerts its influence on body growth, particularly of the bones. Perhaps between no two ductless glands is there a closer interrelationship in function demonstrable than between the pituitary and the sex glands. Overfunction of the pituitary anterior lobe cells is associated with overactivity of the sex glands. Deficiency of this secretion in the individual is followed by genital hypoplasia in the young and by sexual inactivity and retrogression in the adult. Primary alterations in the function of the sex glands, as in pregnancy, and after castration, are followed by pituitary hypertrophy and hyperplasia.

The secretion of the anterior lobe seems to be intimately connected with calcium metabolism. Ascoli and Legmani retarded dentition of puppies by removing their pituitaries, while Franchini reports that calcium metabolism is much reduced and that there is an increase of calcium salts in the circulating blood. The posterior lobe increases calcium excretion; while on the contrary, hyperactivity of the anterior lobe, as in acromegaly, causes lessened excretion with the typical bone changes of that disease; and its removal, defective growth and infantilism.

The Adrenal Glands

These glands are situated on the upper and anterior surface of the kidney. Each is surrounded by a capsule and consists of a cortex, or outer zone, and medulla, or central portion. The cortex and medulla are sharply differentiated both in general appearance and in their histological structure. The former is of rather firm consistency, its cells are arranged in rows, with blood-vessels between them, giving the zone a striated appearance. Its cells also contain fat droplets

and peculiar granules known as lipoid granules which give the cortex a yellowish tint.

In contrast, the medulla is soft and vascular and has a dark reddish color. Its cells contain granules known as chromaffin.

Physiologically we may divide the adrenal glands into two great systems, i. e., the cortex or interrenal system and the medulla or chromaffin system. The latter is a part of the larger chromaffin system, which tissue is spread over various parts of the body.

Cortex. The cortex is subdivided into three layers, (1) a narrow, superficial layer, the glomerular zone, (2) broad, middle or fascicular layer, and (3) a narrow, deep or reticular layer. The epithelial cells of the first zone are columnar, containing fat droplets with nuclei rich in chromatin. In the middle zone the polyhedral cells contain less chromatin but many large fat droplets, and because of this they are called spongioblasts. The third series of cells sometimes contain fat droplets and they form a coarse reticulum of irregular anastomosing cords.

The adrenal cortex seems to have a peculiar influence over the functions of the gonads and is intimately connected with the developmental secondary sex characters. In vitro the cortical lipoids have been found capable of fixing and neutralizing toxins, and Bonamour has advanced the theory that the cortex has for its purpose to absorb and neutralize toxic metabolic products. Biedl, on the other hand, believes there is sufficient evidence to warrant consideration of the interrenal system as a true internally secreting organ, to be included in the group of organs which, like the thyroid, thymus, pituitary and sexual glands, produce assimilatory hormones exerting an influence, directly or indirectly, upon somatic and psychic development. This evidence consists of the observations pointing to the influence of the adrenal cortex on the development

of the brain and sexual glands, upon body growth, and upon the changes taking place in the period of puberty. Voegtlin and Macht have detected in the cortex a body having a digitalis-like action, and Iscovesco also demonstrated in it a lipoid exerting a tonic effect on the heart. Langlois has advanced the theory that the cortex chemically transforms the poisonous wastes arising in the metabolism of contracting muscular tissue and thereby prepares a substance from which the medulla elaborates adrenalin.

As to the functional significance of the cortical tissue, it does not contain epinephrin and it is probable that its functions are different. Biedl finds that extirpation of the cortical organ (interrenal) of fishes was followed by a condition of progressive muscular weakness ending in death. This result would indicate that the cortical tissue has some specific and essential internal secretion. Chemical examination of the cortex shows the presence of much lipoid material particularly of the cholesterin esters, and it may be that through this material the tissue influences the metabolism in other parts of the body. It also has some relation to the activity of the sexual glands.

Medulla. The medulla consists of spherical and oval groups of cells with cords of polygonal cells. These contain the chromaffin content. The secretions of this medullary part of the adrenals is known as adrenalin, apparently the mature condition of the intracellular chromaffin granules. Associated with the plexuses of the medulla, less commonly of the cortex, are numerous conspicuous groups of sympathetic ganglion cells. The cortex develops from the mesoderm. The medulla has an entirely independent origin, being derived from ectoderm as part of the peripheral sympathetic nervous system. Small accessory adrenals are often found in the connective tissue around the adrenals proper. The numerous arteries which enter the adrenal bodies pene-

trate the cortical part of the gland, where they break up into capillaries in the fibrous septa, and these converge to the very numerous veins of the medullary portion, which are collected together into the adrenal vein, and emerge as a single vessel from the center of the gland.

THE PARATHYROIDS

These are small ductless glands, usually about four in number, the size of orange seeds, that lie upon the posterior surface of the lateral lobes of the thyroid. They are constant in man and more distinct in infants than in adults. The number of the parathyroid glands is subject to variation but there are usually a superior or external, and inferior or internal pair. Small groups of cells having the structure of the parathyroids have been found below the thyroid, within the thyroid and thymus or embedded upon the trachea or upon the surface of the lateral lobe of the gland between the terminal branches of the inferior thyroid artery. They are composed of solid masses of epithelial cells arranged in a more or less columnar fashion with numerous intervening capillaries. These columns anastomose and are connected with much lymphoid tissue. They are surrounded by a connective tissue capsule, from which septa divide the glands into lobules. The stroma consists largely of reticular tissue and is very vascular. Some lobules have a distinctly alveolar structure and contain colloid in their lumen. The cells are spheroidal, cuboidal and pyramidal with basal nuclei and often we find colloid between them and colloid material with glycogen within the cells. The cells are of two types: (1) chief, clear, or resting, which are numerous; and (2) granular or oxyphilic cells that are larger, granular and take strong eosin stain. Intermediate types have been described. The granular are the active or secreting cells. These little glands originate as epithelial evagi-

nations from the third and fourth branchial grooves and develop wholly independently of the thyroid.

Physiological Data. The parathyroid secretion serves to neutralize the toxic wastes which give rise to tetany. It also plays an important part in calcium metabolism. Broderick shows that complete parathyroidectomy causes death from tetany which he believes to be due to a lack of floating calcium in the blood.

The experimental evidence in the case of the parathyroids tends to support the view that their function consists in neutralizing toxic substances in the blood and through their calcium metabolic influence prevent calcium insufficiency, which also helps to precipitate and make inert the toxic guanidin principle.

The Pineal Gland

This small body of reddish gray color is placed immediately above and behind the posterior commissure and between the anterior corpora quadrigemina on which it rests. It is covered by the velum interpositum, which intervenes between it and the splenium of the corpus collosum. Embryologically, it develops as an outgrowth from the second cerebral vesicle. In early life it has a glandular structure which seems to reach its greatest development about the seventh year. After this period, particularly after puberty, it undergoes a process of involution during which the glandular structure gradually disappears and its place is taken up by fibrous tissue. Its follicles contain a transparent viscid fluid and a quantity of sabulous matter named brain sand, composed of phosphate and carbonate of lime, phosphate of magnesium and ammonia and a little animal matter. These concretions are almost constant and are present at all periods of life. They are found upon the surface of the pineal body and occasionally upon its peduncles.

Physiological Data. Intravenous injection of its

glandular extract gives rise to a distinct fall in blood-pressure, indicating the presence of depressor substance. It has to do also with muscular development. Timme has shown by X-ray examination of the skull, that cases showing pineal shadows indicating an early evolution of the pineal gland, were suffering from muscular asthenia, from mild muscular fatigability, to the extreme types of muscular dystrophy. This may show even early in life, and puberty may be ushered in prematurely. The genitals develop early in these cases.

THE THYMUS

The thymus originates in the entoderm in the region of the third branchial groove. It is an organ of foetal and extrauterine life, reaching in man its greatest development at the end of the second year. After this age it undergoes a slow retrogressive change into fat and connective tissue, until by the twentieth year scarcely a vestige of glandular tissue remains. The entire gland is surrounded by a loose connective tissue capsule which attaches it to the surrounding tissues. It is divided into lobes and lobules and each lobule into a number of chambers. The lobule consists of a cortical and a medullary portion. In the cortex we find lymphoid cells and reticular tissue similar to those found in a lymph node. In the medulla are found a number of spherical or oval bodies composed of concentrically arranged epithelial cells (Hassal's corpuscles) which represent the only remains of the original glandular epithelium. Nucleated red cells occur in the thymus which may indicate that the organ is a source of red blood cells.

Physiological Data. The physiology of the thymus is rather obscure. It is in some way concerned with the processes of growth and in early life its secretion influences body metabolism. Formerly, it was thought that the gland reaches its maximum size at birth and

afterwards undergoes a process of atrophy or involution so that it is entirely absent in adult life. More careful observations indicate to the contrary, that the gland retains its size and presumably its full activity until the period of puberty. Thenceforward it does undergo a gradual atrophy, but apparently throughout life some remnants of the gland tissue persist embedded in fat. It appears that under pathological conditions there may be a persistence of more of this tissue than is normal, or there may be a real hypertrophy, together with hyperactivity, a condition which might be designated hyperthymism. The anatomical facts in regard to the involution of this gland after puberty indicate that the function it exercises is of especial importance in the period preceding the maturation of the sexual glands but that in post pubertal life it plays some subordinate rôle.

THE GONADS

The organs of reproduction have a remarkable influence upon general metabolism, muscular tone, stimulation of the spinal centers, nervous system and mental activities, improving physical vigor. Poehl prepared a substance he named spermin (C^5 H^{14} N^2) which he found to have a beneficial effect upon body metabolism. Zoth and Pregel found by means of orgographic records that injections of testicular extracts in man cause not only a diminution in the muscular and nervous fatigue, resulting from muscular work, but also lessen the subjective fatigue sensations. Most of the recent works indicate that the testicular internal secretion influences sexual characteristics and sexual appetite. This secretion is formed in the interstitial cells of Leydig. The interstitial cells of the ovary have their internal secretion, which has a specific influence upon the female sexual characteristics, and also stimulate general body metabolism. They have a

functional relationship with other ductless glands, mainly the thymus, pituitary, pineal and the adrenal cortex.

The ovaries form a specific substance, which is capable of increasing the oxidations of the body. While these effects may be referred to the internal secretion of the interstitial cells of the ovaries, other facts indicate that other elements in the gland may also furnish a specific secretion. Thus, the implantation of the fertilized ovum in the uterine mucosa and the development of the placenta have been supposed to be effected through the agency of some chemical stimulus arising in the cells of the corpus luteum. The gonads are calcium excretors and in this way play a rôle in calcium metabolism. They really become active at the time of puberty, also taking part in fat metabolism.

Paraganglia Glands

Under this head are grouped certain small ductless glands and small groups of cells which are closely associated both anatomically and embryologically with the sympathetic system. They include the carotid, which are two small ductless glands each about the size of a grain of rice, which lie on either side of the bifurcation of the carotid artery. They are composed of a vascular connective tissue supporting large polyhedral epithelial cells. The gland cells contain chromaffin granules, and the secretion acts similarly to the adrenal medulla. The coccygeal body, or Luschka's gland, lies in front of the apex of the coccyx. Its structure and secretion is similar to the former. The tympanic gland and the parasympathetic organ of Zuckerkandl, are small collections of chromaffin cells—the former lying on Jacobson's nerve in the tympanic canal; the latter lying in the retroperitoneal tissue at about the level of the bifurcation of the abdominal aorta; and the adrenal

medulla which has already been described.

One characteristic of these organs is that their cells take a yellowish brown stain when placed in a solution of chromic acid or its salts. For this reason the cells are called chromaffin cells and the organs, chromaffin organs, and act similarly to adrenal medulla. We must also consider among the appendages of the ductless glands, so to speak, other organs that in all probability have their own internal secretion, as the liver in glycogenic function, the pancreas in sugar metabolism, the spleen a hemopoetic organ, lymph glands assisting the thymus, etc.

II

THE ETIOLOGY.

3.—HEREDITY.

THE PAST few years considerable interest has been aroused in the subject of endocrinology by the study of defective children, and it is surprising how many of the stigmata which cause us to place children in this category are connected with abnormal endocrine function and, also, how frequently on investigating their antecedents we uncover a more or less well marked endocrine disorder in the parents or grandparents which properly may be regarded as a part of the cause of these unfortunate conditions in their offspring.

Sajous brings sufficient evidence to show that glandular insufficiencies of a minor character in mothers are likely to be impressed upon their unborn offspring and the obvious thing to do in cases of this character is to be sure that these insufficiencies are minimized at the time when this treatment will offer the greatest prospects of results. In other words, if a mother is suffering from thyroid insufficiency it is likely that her child will have leanings in the same direction and thyroid feeding is in order during pregnancy. I have personally discovered in scores of cases a very clear relation between ductless glandular disturbances in the mother and her offspring. In fact, it is almost the rule to find that the woman with a goitre transmits a tendency to goitre to her daughter and when patients come for treatment the history will show almost always

a hereditary basis for troubles of this character.

By reprinting a few weighty sentences from Sajous' address, perhaps a greater appreciation of this subject may be stimulated:

"Any disease capable of injuring the ductless glands sufficiently to inhibit their functional activity impairs correspondingly the development and functional activity of the brain, by reducing the supply of secretions this organ requires to carry on these physiological processes.

"The main underlying cause of defective mentality in both parent and offspring is inherited deficient activity of the ductless glands.

"We should start a campaign having in view the salvation of these unfortunate infants by supplying, through the intermediary of their defective mothers, and, after birth, through their food, the secretions they lack to complete their development.

"In the majority of functional cases of feeble-minded and backward children met in current practice, the predominating pathogenic factor is hypothyroidism, though deficiency of other internal secretions is also discernible in most instances.

"On the whole, the intimate relationship between the ductless glands and everything that concerns reproduction, the greater relative size of these organs in the product of conception, and the teachings of practical experience in organotherapy, all tend to indicate that whenever the father or mother is a mental defective, or both parents show any sign of deficient activity of one or more ductless glands, or are mental defectives, organotherapy should be instituted as soon as pregnancy is recognized.

"The mental and physical status of all pregnant women as regards the functional efficiency of their ductless glands, which may be determined by the stigmata of deficiency of these organs, should invariably

be established. If found deficient, organotherapy should be used to protect them against renal disorders and convulsions through toxemia, and also their offspring against imperfect development and mental deficiency."

The great law of heredity is that like produces like. But the law is modified by many external causes, which produce continually new effects and results. To trace the facts of heredity, the original germinal cell must be considered. In discussing the Mendelian laws of heredity it is assumed that both the female and male sexual cells transmit unit characters to the offspring produced by their union. The heredity may be direct, or a transmission of paternal and maternal qualities to the child; reversional or atavismal, in which the qualities, physical and moral, of some remote ancestor may reappear in the child; collateral or indirect, when the child resembles a member of an indirect line, as an uncle or aunt (rare); and heredity of influence, in which a woman may bear to a second husband children showing the characteristics of the first husband.

Each sexual cell of either type, male or female, is known as a gamete, while the union of a male and female cell is known as a zygote. This zygote, therefore, embraces the unit characters of the two gametes fused. When the zygote in its turn produces gametes, this combination is broken up and the reverse process of disintegration of the combination of unit characters takes place. Again, a unit character is either absent in the gamete or it is present. In each case, the absence is quite as important as the presence, and must be indicated. The unit character is transmitted as such in the gamete unmodified in degree or intensity. In these character transmissions the heredity may be of growth variations or metabolic disturbances or different proportions of both; and this also explains the different forms of hereditary traits that are met with

clinically. There are phases, however, that are difficult to understand.

The importance of investigating such inheritance is that it may enable us to forecast, within some limits of probability, the characteristics of the offspring of certain marriages, and to advise the prospective parents of such probability. It forces on us the necessity of closer study and investigation into the nature and treatment of the endocrine disturbances.

Timme observed in a family showing hereditary endocrine disturbances that the abnormal growth zygotes were male while the abnormal metabolic ones were female. It would, therefore, seem that abnormal growth is dominant in the male and recessive in the female; while abnormal metabolism may be dominant in the female and recessive in the male. This subject, however, requires further investigation.

The interesting family reported by Timme began with a moderate giant 74 inches in height who married a woman of diabetic tendencies who later developed diabetes, from which she died. This marriage gave rise to a family of three apparently normal daughters, of whom one still lives. One died at the age of 62 of cancer and the third died of pneumonia, following the puerperium. Not one of the three showed during her lifetime any tendency, as far as we can now recognize, toward internal glandular disturbance. All three of them married. The oldest had a family consisting of six children, of whom one had exophthalmic goitre; the second, harelip; the third, chalky degeneration of the teeth, with a tendency to diabetes; the fourth was born blind and puny and developed a sarcoma of the face and died in his first year of life. The third child mentioned married and had two children, of whom one is distinctly hyperpituitaric in character, while the other is normal. The second child, who had a harelip, married and had three children, of whom the

firstborn has osteomalacia resulting in a deformity of dwarf-like character, while the other two are seemingly normal. The first child married and has a family and two children apparently normal, of whom the first is now beginning to show an exophthalmos.

I had many such experiences of instances that clearly showed inherited direct and indirect endocrinopathies, in the offspring. In one case the father shows dyspituitaric evidences; the mother suffers persistent headaches (occipital and vertical) for which she has been treated by a number of specialists for her eyes, nervous system, stomach, etc., as well as gynecologically, with no results and for the past few months is getting wonderful relief from her headaches taking ovarian extract combined with small doses of thyroid and pituitary whole gland. She has five children. Three sons—16, 14 and 12 years of age respectively—are all over six feet in height. The eldest has glycosuria. One daughter, 11 years of age, is developed similar to one 16 years, with fully matured breasts, libido-sexualis and has menstruated since the age of 10. She is 70 inches in height and weighs 167 pounds—all of which show distinct endocrine earmarks that are inherited.

In hyperthyroidism, for example, it will surprise one how frequently there is a hereditary disturbance of that subtle thing which might be called the "physiological substratum" which permits a given exciting cause to initiate a hyperthyroidism in one individual, whereas, the same circumstances, or perhaps even worse ones, make no impression whatever upon another individual.

Heredity certainly plays a predisposing part, and there are numerous reports of familial exophthalmic goitre, including that of Harvier, of Paris, who reports a case in a young man whose mother, grandmother, maternal aunt and also a paternal aunt all were "Basedowians." In his paper this author goes into the neu-

ropathic and hereditary aspects of this disease quite fully.

Bumsted states that the direct inheritance of hyperthyroidism itself is not so uncommon as is generally supposed. He cites a case reported by Rosenburg, in which the patient's grandmother, father, two aunts and two sisters had suffered from exophthalmic goitre, and also Oesterreicher's statement that in a family of ten children, eight of them suffered from this condition. Bumsted himself has had four sisters under his observation during the last five years. Two of them have severe exophthalmic goitre, the third, early symptoms, while the fourth manifested symptoms when she had been for some time at home with her sisters after leaving school. One often finds an overlooked simple goitre in a mother who brings her hyperthyroid daughter for consultation.

Joshua H. Lioner, drawing certain conclusions from the study of pubertas precox, says: "Pubertas precox arises in certain individuals whose progenitors show a particular type of endocrine imbalance. The condition may arise in utero, or as a result of functionating rests, i. e., tumors, later in childhood, previous to puberty. The entire internal glandular system is involved, but primarily the gonads, pineal and adrenal cortex."

E. Bosworth McCready, a well-known authority on pediatrics, makes the following pertinent remarks on this subject: "Conditions having a vitiating influence upon cell development, as tuberculosis, syphilis, cancer, chemical poisons, malaria, alcoholism, drug habits, insanity, goitre, malnutrition, and environmental influences of various kinds occurring in the progenitors, result in imperfect growth of the developing embryo. In the first few weeks of fetal life, when the ductless glands begin to appear, the cells of which they are composed also grow imperfectly; and unable to secrete to the extent to which they were destined, further de-

fective development ensues and we have as a result infantilism, hypoplasia, degeneracy, call it what you will, in varying degree."

The general preliminary remarks as to the anatomical, physiological, experimental data and heredity in relation to the ductless glands in children, of necessity plant their footprints and importance in this particular monograph, and for this reason I have dwelt somewhat at length on the fundamental principles.

4.—Diet and Vitamines.

After the heredity of an infant, the second important etiologic factor in endocrine derangement is the diet; and the only really natural infant food is human milk. J. Wallace Beveridge and William E. Fitch, of New York, in writing on the evil effects of artificial feeding, say: "Cow's milk can be so modified that on analysis it seems to be in most respects identical with human milk and yet it does not nourish the young child in a like satisfactory manner. It is lacking in some elusive constituents which render it less nutritive. These are probably the vitamines although up to the present this is more or less conjecture."

To sterilize milk by boiling does not solve the problem, for while this process may free it of dangerous germs and filth, certain nutritive properties have been taken from it and scurvy, rickets and such diseases often follow the feeding of sterilized milk. Pasteurized milk, which is perhaps the best of artificial foods, is not to be compared to breast-feeding.

These authors state that "The puny man or woman, improperly developed in body, with an unstable nervous system is more often than not the result of artificial feeding when an infant. . . . The diseases, affections and conditions which are mainly owing to errors of diet when young manifest themselves in many ways. Perhaps the most conspicuous of these is

rickets. . . . The descriptions of the physiological causation of rickets are so many and various as to be almost confusing. Stoeltzner has connected rickets with diseases of the adrenal bodies. He is authority for the statement that not only are the adrenals small in rickets, but also that they are deficient in adrenin. . . . Rickets is referred to as, although the most obvious, only one of the diseases which may be laid at the door of malnutrition of the young; there are many others which exert a profound influence on the after life of an individual and in which the internal secretions are largely concerned. It must be borne in mind that the digestion of food within the bowel requires for efficient action not only the special ferments secreted by the intestinal mucous membrane, but the coöperation of the other secretions provided by the liver and pancreas as well as of the other ductless glands. There exists an intimate relationship between all the ductless organs. For example, if the stomach does not furnish an adequate amount of acid the supply of 'secretin' will be curtailed in proportion to the lowered acid supply, and owing to this diminished secretion the activity of the pancreas itself will be injuriously affected. Again disordered metabolism due to improper feeding reacts in a sinister way on the thyroid gland and perhaps most cases of goitre could be traced to malnutrition in infancy and childhood.

"Thus, if by reason of errors of diet in the young, bringing about lack of acid secretion, 'secretin' fails to exert its stimulating effect on the pancreas, disordered metabolism will ensue, the entire machinery of the digestive and intestinal organs and functions will be thrown out of gear and the human engine will be damaged sometimes beyond hope of repair. The ductless glands of the body, even those remote from the immediate scene of action, will suffer to a greater or less degree and unless a rational mode of restoring

the functions to the internal secretions directly concerned be instituted these glands may never regain their normal state. The proper development then of the digestive functions of the stomach and intestines is a matter of such supreme importance and upon this development hinges so greatly the future well-being of the individual and race, that the feeding of infants should be regarded as the paramount duty of the physician and of those in whom the care of the infant has been placed. . . .

"The effects of bottle feeding are shown in various ways and on the whole, the method may be stigmatized as being often irrational and unnecessary. *The damage that it does to the ductless glands is frequently of so serious a nature as to render these glands less serviceable than they should be and sometimes impotent for good to a very large extent.* [Italics are ours.] As we have stated on many occasions, it is our firm belief that the adequate and smooth working of the internal secretions is a *sine qua non* of good health. when, therefore, by improper feeding, overfeeding or underfeeding in infancy and childhood, these secretions are injured, sometimes beyond repair, the future life of the man or woman is largely spoiled."

I cannot resist quoting further from these authorities, for while their statements are strong, yet I believe that they are absolutely true:

"Race deterioration, which is in evidence in all countries, is owing, in a degree not realized and which appears to be sounding the knell of some nations, to a lack of appreciation of the malign after consequences of faulty feeding of infants. To how great an extent the internal secretions are involved in this question cannot be explicitly stated. . . . Enough knowledge has been gathered on the subject to permit of the statement that the well-being and welfare of the infant and the adult is inextricably bound up in the internal

secretions. If one of these glands fails in its function, all suffer with it and the organs of the body will not work in the harmonious way which is a first requisite of good health. In order to keep the internal secretions at the proper rhythmical working pressure they must not be hindered or foiled in any respect. This end can be reached by so feeding the body and especially the body of the infant that it allows the ductless glands free action. . . .

"Exactly to what extent the internal secretions are involved in the question of the artificial feeding of infants is not known, but enough is known to state with a considerable amount of assurance that these secretions are injured and robbed of much of their powers for good by improper feeding in early childhood, and that their future functions are damaged to such an extent that the future of the artificially fed child is handicapped both from the physical and mental standpoints."

The Vitamines. On this subject of malnutrition McCready, of Pittsburgh, says: "In the great majority of backward children it is impossible to lay the blame upon any single gland. It is a question in the writer's mind whether most cases of so-called malnutrition in school children are not cases of general glandular insufficiency. Malnutrition in childhood is more than a question of insufficient food. We find it among the children of the well-to-do as well as among the poor. It is not rare to find an excellent state of nutrition where the food supply is scanty. The malnutrition which is severe enough to be reckoned with as a factor in faulty development is usually hypoplasia plus malnutrition, sometimes entirely dependent upon the hypoplasia, often further complicated by insufficient or faulty diet."

The present-day vogue in vitamines is of special interest to the pediatrist, who is interested in endo-

crinology, for the lack of vitamines fails to encourage a normal endocrine function, and we have as a result, the malnutrition and developmental dystrophies in children. Vitamines are endocrine stimulators and, whereas we now know the vitamine question comes up for consideration, equally does the endocrine aspect come up for consideration.

These vitamines, so vital for the sustenance of life, known as the fat-soluble A, and water-soluble B, and C, are present in the animal fats, tomato, potato, yeast, milk, polishings of rice, maize and in other vegetables and foods. These vitamines are essentially stimulants and restoratives to the metabolic processes. Here we can see the close proximity that exists between the action of these and the ductless glands.

McCarrison considers that a decrease in the water-soluble B vitamine brings about an alteration in the endocrine glands giving rise to a faulty carbohydrate metabolism, and, if a large amount of carbohydrate is consumed, acidosis. Funk has shown that hyperglycemia results from a lack of this vitamine. Emmett and Allen reported that a lack of this type of vitamine produced definite changes in the thymus, adrenals and liver and that there was more or less passive congestion in the pancreas, spleen, ileum, colon, kidneys and lungs.

It is my opinion that most individuals who eat a variety of foods, cooked and non-cooked, get plenty of all of the necessary vitamines yet they may suffer from one or more varieties of vitamine deficiency. Why? Because the tissues will not take up and utilize the vitamine substances.

We know that oxygenation has a certain effect upon the vitamines. We also know that oxygenation, or pulmonary and tissue respiration so-called, is a very important process in the body to carry on normal metabolic changes. Sajous has shown that the adrenal

secretion when reaching the air cells absorbs oxygen and becomes a constituent of the hemoglobin and of the red blood corpuscles; that the oxygen-laden adrenal secretion is a constituent of the albuminous hemoglobin in the blood-plasma, which is estimated to be over 90 per cent. The red corpuscles after absorbing this, yield it to the blood plasma in the form of droplets, the so-called "blood platelets." The albuminous constituent of the hemoglobin is then distributed by the red cells to all parts of the body as an oxidizing agent.

It is, therefore, the adrenal secretion which, after absorbing oxygen from the pulmonary air and being taken up by the red corpuscles, supplies the whole organism, including the blood, with its oxygen. It is as such, the oxidizing constituent of the hemoglobin, which in turn, sustains tissue oxidation and metabolism. Hence, it is called adrenoxidase. The thyroid apparatus acts similarly by virtue of its own hormones and by its stimulating action upon the adrenals.

In enhancing metabolic activity through oxygenation, the body tissues are thus prepared to utilize the food and vitamines by building up their own tissues and ridding themselves of their waste products through anabolic and catabolic chemical and physical changes. Even in mild thyroid and adrenal deficiency the oxidation processes of the body are lessened, metabolism slowed, and waste products accumulate, giving rise to various clinical manifestations of nutritional disturbances. In rickets we find that thyroid improves and often cures the most obstinate cases when the ordinary means fail.

It seems that the hormones prepare the tissue, giving it receptive power to receive and properly utilize the vitamines. Our laboratory and clinical findings indicate that the all-important vitamines and internal secretions are interdependent. This is seen in rickets, scurvy, various degrees of malnutrition and in growth

disturbances, with evident vitamine deficiencies, where organotherapy in conjunction with proper diet or vitamines was very helpful in bringing about a cure.

5.—Infection and the Exanthemata.

Infection plays no small part in the etiology of endocrine disturbances in childhood. Many a glandular disorder can be traced to some focal infection. The most common single cause of hyperthyroidism, for example, undoubtedly is focal infection, especially of the structures near the thyroid gland. Bergh, of Christiania, reports that in his own opinion the primary source of infection, which most often causes the thyroid derangement responsible for the exophthalmic goitre, is in the tonsils, nose, or throat. All of his own cases had this as a large measure of the etiology. He cites Solling's report on ninety-seven cases, no less than sixty of which displayed a tendency toward infectious sore throat. In sixty-two of these ninety-seven cases, the hyperthyroidism began evidently as a local process in the thyroid. This sustains Bergh's assertions that chronic catarrh of the nasal mucosa is not a superficial harmless thing, but may spread along the lymphatics to the thyroid.

Tonsillitis is among the commonest of the causes of thyroid disorders in children and, in no case of dysthyroidism, no matter how serious or insignificant it may seem to be, should careful study of the tonsils be omitted, not even if the history is negative and the parents assure us the tonsils have been removed or that nothing is wrong with them in this respect.

Harvey G. Beck, of Baltimore, believes that acute or chronic infectious processes are etiological factors in either hypo- or hyperthyroidism, and that this fact has been demonstrated clinically. In fact, the removal of

chronically inflamed tonsils, gall-gladders and appendices has been advocated as the first procedure in the treatment of Graves' disease.

Sajous states that syphilis, tuberculosis and other infections so weaken the thyroparathyroid apparatus and the adrenals, which are so closely linked to it functionally, that hypothyroidism results. And he gives as hereditary causes of this condition, chronic intoxications such as syphilis, alcohol and gout.

"All the infectious diseases of early age and of later on," as Hertoghe states, "fall heavily on the vitality of the thyroid gland. Acute rheumatism of the joints has a most nefarious influence and causes even after years the outbreak of severe myxedema."

Fifty cases of thyroid enlargement of children under twelve years of age have been observed by Reede coincident with chronic gingivitis. He also cites a case in which goitre symptoms were relieved after removal of two abscessed teeth; and another case in which goitre, arthritis and pyorrhea followed tonsillectomy, from which the patient recovered after treating the pyorrhea and extracting an abscessed incisor.

Regarding the effect of infection upon the adrenal glands, Beck states: "It has been observed by Gley that the suprarenal glands are more or less severely attacked by various microbic toxins, and the extract of glands coming from infected animals appears much less active than that from normal glands. Other glands of internal secretion may be similarly affected by these toxins. Both parenchymatous and interstitial changes occur in the thyroid in chronic toxemias, with the result that there is not only a quantitative disturbance of the secreting function, but a qualitative as well."

In the study of a certain series of cases, Doctor Beck says that no special attention was given at the time to the matter of infections. It was only after an examina-

tion of the tabulated records that the importance of the matter manifested itself. The results obtained, therefore, can not be attributed to over-enthusiasm or prejudice.

The Exanthemata. The exanthemata are definite causes of glandular disturbances. Sajous mentions as causes of hypothyroidism acute infectious diseases such as measles, mumps, smallpox and typhoid, which cause interstitial and parenchymatous lesions, with sclerosis and atrophy.

Some authors question the relation between parotitis and prostatic atrophy, but Dr. Wm. J. Robinson, of New York, reports seven cases of "partial or complete (so complete that not a vestige of prostatic tissue could be made out) atrophy of the prostate in which an antecedent parotitis seemed to be the sole etiologic factor; in some of these cases (five) the atrophy was accompanied by atrophy of the testicles; in two, the testicles seemed to be unaffected." Then Doctor Robinson calls the attention of the profession to the connection between the parotid and the prostate and says, "The relationship existing between far distant glands, organs and tissues and the genital organs forms a fascinating field of study and research."

That the adrenal glands play no small part in typhoid fever, has been emphasized by Sergent for a long time. They are severely affected by the toxin in the early stages of the disease, and this depletion of the adrenals is responsible for the dangerously low blood-pressure and prostration of the typhoid syndrome, which often is the direct cause of death. Sergent combats this cardiovascular derangement by supplying systematically the active principle of the adrenals, and forestalls the development of untoward symptoms by giving adrenal extract early in the disease. He advises giving it twice a day in small doses.

III

CLINICAL DATA.

6.—Types of Mental Defectives.

RETARDED MENTAL Development in a child may be functional, dependent upon some impediment of the special senses such as defective eyesight, myopia, astigmatism, far-sightedness, adenoids, diseased tonsils, malnutrition, defective hearing, and trauma —which may cause an injury to the brain and give rise to mental deficiency. Defective cerebral development, or the congenital type, which leads on to the more severe forms of mental deficiency and moronity —also called the formative type—is frequently met with. Schlapp described a functional type in which there is a disturbance in the proportion of the different chemical factors in the surrounding medium from which the cells draw their necessary potential energy and activiating substances, and, therefore, the cells do not react normally to stimulation. In all of these cases, and also in the traumatic type from indirect cause, the ductless glands in one way or another are intimately involved.

From the etiologic point of view, however, mental deficiency is only a symptom seen in a variety of cerebral lesions, and the clinical manifestations may be the same whether the origin of the lesion be a congenital developmental anomaly or some lesion acquired in extra-uterine life. We must also think of hereditary influence, consanguinous marriage, endocrine disturbances, history of alcoholism, syphilis, cerebrospinal

lesions, tuberculosis (rare), rheumatism (rare), and other neurotic and physical stigmata in the parents which may be strongly suggestive of intra-uterine influence as the chief factor in the production of the defective development of the brain.

"Backwardness" and "Hypoplasia." The great number of the more or less mentally weak children is fortunately beginning to attract serious attention. The Russel Sage Foundation found in thirty-one American cities that over 20 per cent. of the school children belonged to the retarded class. Dr. Ira S. Wile stands out prominently, advocating mental hygiene and cultural education during childhood for these mental defectives and unruly children. Doctors S. Josephine Baker and S. Sobel are also pioneers in this work. Barr has well said, "the backward child is not a mental defective but a mental invalid, so to speak, possessed of all his powers, and has the same chance of attaining mental vigor that any sickly child has of being brought to normal health when given the proper treatment."

We are now able to grade the various degrees of backward and mentally defective children in our schools by means of the Binet and Simon method. These cases are now being identified and properly classed and cared for, and saved the brutalities which formerly were meted out to them when their defective work and slow progress at school were attributed to laziness, arbitrariness or stupidity. The medical diagnosis of these cases requires a careful scrutiny of the many factors which may prevent development of the mind. We must exclude adenoids, diseased tonsils, excessive myopia and errors of refraction of all kinds, astigmatism, defective hearing, malnutrition etc., which must be treated before we can expect any results from organotherapy.

McCready, in discussing the subject of the backward

child says. "The majority of backward children in whom the backwardness is not due to accidental causes, such as illness, lack of training, and other purely environmental influences, present evidence of ductless gland irregularity, emphasized often in some particular gland."

References to the syndrome "hypoplasia" are now being seen in the literature upon the retarded, backward or deficient child, and according to Noble, the hypoplastic individual is one whose nutrition and development is below par, the condition being congenital or acquired during infancy or early childhood. There are varying degrees of hypoplasia reaching from backwardness, which is often not observed until the child has been in school for some time, to the serious organic dyscrinism which is sometimes called infantilism and sometimes mal-development.

It is difficult to say how much of the symptomatology of this condition of hypoplasia may be referred to the thyroid gland. Much of it at least is of thyroid origin and Hertoghe refers to it frequently in his writings and uses the term "thyroid inanition" as indicating a condition of slow starvation and inactivity without particularly obvious changes in contour or weight.

McCready, who is a close and intelligent student of this subject, states that malnutrition and a lack of bodily tone is practically the rule in mentally deficient children. He says of hypoplasia,

"The hypoplastic backward child is distinguishable from his normally constituted fellow through anatomical, physiologic, and psychic characteristics, the interpretation of which serves to implicate the glands of internal secretion as a factor of etiological significance. The clinical picture most often seen is the undersized, undernourished child whose unstable nervous system is still further handicapped by the effects of reflex disturbances arising from nasal obstruction,

defective vision, or perhaps phimosis. These conditions are often erroneously looked upon as direct causes of backwardness. They should be considered as evidences of evolutional hypoplasia. Other symptoms are delayed epiphyseal union (as revealed by the X-ray), tardy dentition and abnormalities in the growth of the hair. Deficiency of the eyebrows in the outer third, the *signe du sourcil,* is considered a symptom of thyroid insufficiency. Delayed sexual development is common, though sexual precocity may be found, suggesting hypophyseal involvement. Premature eroticism leading to masturbation and perversions of the sexual instinct are of frequent occurrence in hypoplastic children. In some cases early development of libido seems to be due to hyperthyroidism, as I have found an over-acting thyroid in practically every girl I have examined in Juvenile Court accused of offenses to sexual morality."

Feeble-mindedness. In the scale of the mentally deficient, the feeble-minded are one step below the "backward" children. Clark states that the percentage of feeble-minded persons in the general population is not known. It has been placed as high as four per cent by some observers.

Raeder, of Boston, studied one hundred cases of feeble-mindedness that came to necropsy. The necropsies were performed by Doctors M. M. Canavan and D. A. Thom. The cases were taken in chronological order from the pathologic service of the Massachusetts Commission on Mental Diseases. Twenty-one per cent of the cases showed decided changes in the glands of internal secretion. Fifty-three per cent additional showed a lesser degree of glandular involvement, making a total of seventy-four per cent in which there were evidences of gland change. There were signs of syphilis in eleven of these, but since Wassermann tests were not made in all cases, it may be argued that

others of those cases considered glandular were possibly syphilitic. On the other hand, some of the cases which were designated as syphilitic, because of vascular or chronic inflammatory or exudative changes, may not have been. To quote Raeder on this point: "Furthermore, the dysfunction of the endocrine system itself may be due in these cases to syphilitic influence on the secreting cells of the glands."

All of which merely establishes still further the fact that the endocrines are almost invariably involved in feeble-mindedness.

The feeble-minded baby may be extremely quiet, with prolonged periods of slumber, lying passively in any position in which it is laid down, scarcely ever moving its hands, feet or eyes. Such a baby is in special danger of neglect regarding its mental condition for it is pretty certain to be called a good baby by its mother, who is enabled to get so much done each day because of its abnormal quietness. Later on, when walking time is approached, the unfounded complacence of the parents will turn to dismay as they see months, and sometimes even years, come and go without their child making any attempt to take his first step.

The very opposite to the apathetic baby is the excitable. Here all is agitated, constant activity of the child in incoordinated, purposeless and jerky motions. This makes the typical cross baby—fretful, peevish and nervous to an unexplainable degree, always irritable, crying and refusing to be pacified.

Idiocy. There are all grades of mental deficiency. Idiocy is applied to a condition in which the mental development is never beyond that of the normal child of two years. Imbecility is a slightly higher grade of mentality which at its height is never beyond that of a normal child of seven years. In a moron the degree of mentality is never beyond the normal child of 12

years. There are still milder grades of mental deficiency or backwardness, which, however, are difficult to detect in children ordinarily except with the aid of the Binet and Simon tests, but which are recognized by certain peculiarities of psychic development which manifest themselves in young adult life. These cases are usually spoken of as high grade imbeciles.

We are now able to place the entire field of idiocy upon a more rational plane than heretofore. In hypothyroidism and myxedematous infantilism we find types of mental deficiency in which the thyroid apparatus is at fault. It seldom shows itself within the first year, especially breast-fed babies, because they receive, through the maternal milk, enough thyroid secretion to compensate for any deficiency that their own gland may have acquired in utero or in the course of labor. These babies show the usual evidences of hypothyroidism: the delay in walking and speech, characteristic skin, small-appearing eyes, pudgy stature, irregular, delayed and defective dentition, subnormal temperature and cold extremities, and husky voice, with defective eyesight. When these cases are detected early thyroid extract in small and graduated doses kept up for a long period gives remarkable results.

Very often cases of this sort will present evidences of disturbed pituitary secretion, particularly deficiency of the pars anterior, with consequent stigmata of metabolic and growth disturbances. This is found in dystrophia adiposo-genitalis or Froehlich's disease, which is a manifestation of diminished activity of the pituitary, characterized by a marked tendency to obesity, moon face, arrest of development of the genitals and the feminine type of male body. When caused by a tumor, we will observe local pressure symptoms, severe headaches, lapses of memory and contraction of the visual field and color blindness,

small stature and weak pulse. Anterior pituitary extract and thyroid help materially. At times I combine this with thymus gland.

In such conditions we get a mental condition showing a high grade of imbecility, in which mental apathy, dullness, childishness and delusions are merged in with active mental symptoms and irresponsibility.

The symptoms of idiocy vary according as the individual represents a high or low grade of this condition. There may be a condition of hydrocephalus or its opposite, microcephalus. Again, idiots may have normally developed crania, both as to size and shape. In the lower grades there is usually some physical malformation in connection with the mental impairment, as already described. The temperament may be violent or good-natured, the mood often alternating. The sense of morality is wholly lost and they are very cruel to animals and even to children. They show an early indication of perversion. In the severer forms their muscular movements are incoordinate, irregular and awkward, and their speech is almost unintelligible. The idiot does not take notice of surrounding objects even if his sight and hearing should be perfect. Epileptiform convulsions are common occurrences and spastic paraplegia may occur. The characteristic symptoms are strabismus occasionally, drooping head, drooling, lack of cleanliness, falling, limpness and unsteadiness of limbs, and often the child cannot sit up alone, stand or walk unsupported. The muscles of the neck are very weak and the head just bends over on the chest or to the side from lack of support. The vertebral column fails to support the trunk and bends to a marked degree, giving rise to all sorts of orthopedic deformities and all the muscles are feeble and comparatively useless. We frequently encounter premature ossification of the skull and microcephalus. There is a lack of power of concentration, attention

and memory in all cases. All these symptoms indicate that the interdependent functionating of the ductless glandular system is at fault.

Each individual patient requires prolonged observation and study to distinguish between the simple backwardness, the mild and the severe forms of mental deficiency, in order to institute the proper treatment and give the prognosis. The degree of mental development which can be obtained in these cases and the possibility of the child leading a future life which is at least partially useful, depend not only upon the extent of the lesion, but also upon the skill with which the treatment is employed. We must treat the physical defects and correct the faulty endocrines; improve the home surroundings and environment and give the child every advantage of expert mental training and education.

Amaurotic Family Idiocy. This is an obscure congenital defect, familial and always fatal, first described by Warren Tay in 1881. The infant may be normal up to about the fifth or tenth month when it will more or less cease to grow physically and mentally. It becomes increasingly weak, pale and blind. The macula lutea becomes a cherry red. They may also suffer from periodic convulsions. Some claim that a strong toxic element is at work which it is believed is caused by an extreme adrenal insufficiency permitting accumulation of certain probable (myogenic) waste in the blood. However, all forms of treatment are of little avail.

Mongolian Idiocy. This condition is characterized by the striking resemblance of the little patient, even at birth, to a Mongolian, particularly a Chinese. These cases show the slanting eye-slits and the epicanthal folds, flattened skull and short thumbs and little fingers of the eastern Asiatic. They resemble the hypothyroid and hypothymic types. They often suffer from middle-ear disease, adenoids, and diseased tonsils. Most striking is the frequency of cardiac atony, due to

deficient adrenal secretion. They are subject to infections. The lack of the thymus, thyroid and the adrenal secretions that are probably the cause of this condition is the etiological factor of the faulty tissue metabolism and immunity. The mental status of these children may be materially improved, but at the cost of much patience and perseverance. The prognosis is as a rule very unsatisfactory. We get the best results by feeding the mother with thymus substance during the nursing period, and the child later on with thymus, thyroid and adrenal gland products. The tonsils and adenoids, if troublesome, must be removed. Any disease in the parents, if detected in the parental period, should receive proper attention.

In a study of a series of cases of Mongolian idiocy, Timme found roentgenologically an excavation under the anterior portion of the fossa pituitoria. He suggests that further investigation and postmortem study of the pituitary body is essential. In all likelihood, dyspituitarism is in a measure responsible for this condition.

Cretinism. The rôle of the thyroid in idiocy and other types of mental defectives has been discussed, but mention should be made here also of the cretin. While cretinism is also a developmental anomaly and will be given some consideration under Growth Dystrophies, it is essentially a condition definitely traceable to deficient thyroid activity and, fortunately, being decidedly benefited by substitution therapy or the administration of the missing chemical substances.

Starkey has given a concise picture of the cretin which we quote here: "The symptom complex of thyroid insufficiency when occurring in infancy and early childhood is called cretinism. It is a congenital atrophy or dystrophy of the thyroid. The same struma in adult life is termed myxedema. Cretinism may develop immediately after birth, or any time be-

fore puberty. The gland may be congenitally absent or deficient in development. However, the child may appear perfectly normal up to the sixth month, during which time the thymus is actively functionating and may possibly compensate for the lack of thyroid secretion. The picture of the cretin child is one of the most striking and pathetic that we have in the whole realm of medicine, and the results of treatment are perhaps the most brilliant. The cretin is defective in development both mentally and physically. The fontanells remain open, the hair upon the scalp is thin, dry and brittle, the skin is of a lardy color, the head, as a rule is small and round, with prominent forehead, and the face pudgy and swollen in appearance, which causes the eyes to appear as mere slits. The lips and mouth are large and conspicuous. The tongue is large and protruding, seeming to be too big for the mouth to properly contain. There is usually dribbling of saliva from the mouth. The conformation of the body is pot-bellied; the knees are wobbly and the extremities very much underdeveloped. The teeth are few and widely spaced; they decay early. Walking is delayed. The mentality of the patient is always very much impaired. Idiocy is the rule."

Hoag reports the case of a girl who came under his care at the age of 3½ months. Her appearance was that of a typical cretin. He began thyroid treatment at once and at the time the report was made (when the child was 5½ years old) she was 40 inches in height and weighed 43 pounds. She talks and plays like any other child and the mother states that she does not show any abnormality. The child was at first given one quarter of a grain of thyroid extract twice daily. This was gradually increased, until for a time, when she was four years old, she showed signs of excessive dose when getting five grains a day. She now receives three grains a day.

This case is an example of what excellent results can be obtained in cases of cretinism if medication is begun early enough.

The Adrenal Type. Apert, Morgagni and others found atrophy of the adrenal cortex in anencephaly in a few cases of congenital hydrocephalus and microcephalus. It seems that this part of the adrenal gland is necessary for the proper development of the brain or organ of the mind. The lack of its secretion and also that of the medulla has been shown to correspondingly restrain the growth of the neurons, thus leaving the brain in a state of partial development, which in turn entails a correspondingly marked degree of idiocy. We have found in just such cases a diminution of the number of lymphocytes in the blood, and a hypoplasia of the thymus; hence, a lack of phosphorus and nuclein supply of the nerves. The stigmata of hypoadrenia these patients show, are muscular weakness, cold extremities and sensitiveness to cold, weak cardiac action, low blood-pressure and poor pulse, anorexia, constipation, mental torpor, slow intellect even to the degree of idiocy, pallor and localized alopecia, deficient oxidations resulting in acidosis and accumulation of waste products. Here adrenal extract, gr. 2 t. i. d. with thymus gland, gr. 5 t. i. d., gives encouraging results. Small doses of thyroid and anterior pituitary gland extracts in some cases are synergistic.

It has been noticed in the study of incorrigible boys that there is slight pigmentation of the skin in conjunction with lowered blood-pressure. This would invite still further study and investigation into the function of the adrenals. (McCready.)

The Thymus Type. This gland has an important relationship with the body metabolism as regards the rôle of phosphorus in the process. Klose and Vogt, Morel and others have shown mental disorders in puppies the fifth and sixth month after removal of the

thymus. Supplied through the agency of the lymphocytes which develop in the thymus there is a wealth of nucleates and phosphorus. The delay in the development of the brain, illustrated by idiocy of children with a small thymus or none at all, indicates the constructive influence of this organ. The thymus, as indicated above, supplies through its agency, the leucocytes, an excess of phosphorus in organic combination and nuclein, which the nervous system and brain requires for its development and growth in infancy, childhood and even after puberty. The mental defectives of this endocrinopathic condition show the following stigmata: deficiency of bony development, osteomalacia, bone deformities, rickets, defective growth or small stature—due to defective assimilation of calcium, owing to a deficiency of the thymic nucleins which take part in the building up of calcium phosphate—a low lymphocyte count, because of the inadequate formation of thymocytes, and deficient mental development, including various grades of idiocy. These conditions are all due to the insufficient production of thymic nucleins which should supply the neurons of the central nervous system during its development.

Sajous states that in 28 mentally weak and epileptic children examined by Bourneville the thymus was absent in 25 and that in another series of 292 cases it was absent in 74 per cent. Quoting McCready on this point: "That defective development of the thymus must be seriously considered as a factor in some cases of defective mental development is shown by the statement of Morel, that '75 per cent. of idiotic children with normal thyroids, meninges, and nerve-centers, possess no thymus. Thus, at Bicêtre, from 1890 to 1903, autopsies of 408 non-myxedematous idiots ranging in age mostly from 1 to 5 years—none being above 15 years—showed the thymus present in 104 instances.' He believes that in view of the occurrence

of idiocy in dogs in which the thymus has been extirpated shortly after birth, congenital absence of the thymus is actually the cause of the idiocy. Hyperthymism, in which the toxic action would seem to occur by reason of either quantitative or qualitative abnormality of the secretion, presents the following characteristic features: (1) Pale skin, scanty hair covering, exaggerated panniculus adiposus, and poor development of the genital glands and adnexa; (2) hyperplasia of the various groups of lymph-nodes (neck, axillae and mesentery); (3) hyperplasia of the tonsils; (4) hyperplasia of the lymphoid follicles of the nasopharynx, base of the tongue, and intestinal wall; (5) hyperplasia of the spleen; (6) hyperplasia of the thymus; (7) cardioaortic aplasia; (8) lymphocytosis, etc. These stigmata are seldom all present at once. (Paltauf.)"

7.—Growth Dystrophies.

The conditions of abnormal growth and development, especially in "children requiring special attention," constitute a very serious and difficult problem in medicine.

Laboratory investigations and clinical experience have shown that disturbances of the internal secretions are responsible for the anomalies of growth and morphogenesis. The difficulty in diagnosis, as well as treatment, lies in one's ability to recognize these abnormalities early, when one's efforts are more likely to be effective. If, when making the physical examination of the child, we will note the normal anthropometric data, the normal mental status, the tonicity of the muscles, the condition of the skin, the size and integrity of the sex organs, the condition of the special sense organs and the physical signs dependent upon sympathetic, parasympathetic and vasculomotor control, we will discern much valuable information re-

garding the early stages of pluriglandular dysfunction. Many cases of stunted growth and mentality, if recognized in infancy as due to hypothyroidism, and treated with thyroid extract for a long time, will grow up normally.

In the class of cases under discussion, many of the "stigmata" obviously are manifestations of an organic nature and should not be expected to be remedied; but since the underlying element is a disturbed function of some of the endocrine glands, their remarkable responsiveness to hormone stimuli may enable us to bring about some noteworthy organic changes, so that even in these cases organotherapy may assert a definite influence upon structural, as well as functional, defects.

The differentiation between those defective children that are likely to respond to organotherapy and those in whom there is no likelihood of benefit is very difficult, and it is a serious thing to doom a child to lifelong disability by saying that this method of prospectice merit, or that, need not be used because it is useless.

The importance of giving early attention to the defective child cannot be too strongly emphasized. Kerley said on this point: "At the age of seven years the boy is seven-tenths the man and the girl seven-tenths the woman. If errors in development from whatever cause exist at this age they will never be entirely eradicated."

It might facilitate reference value if this subject were considered under the heads of the various glands that are involved, but since I contend that they are never involved alone, the matter immediately becomes complex and, therefore, for convenience the different growth dystrophies will be considered under their clinical names rather than under the names of the glands which seem to be most obviously involved.

Dwarfism. Dwarfs have been classified by Bassoe as follows:

I. Proportionate dwarfs:
   A. Primordial dwarfs (essential microsomia).
   B. Hypophyseal dwarfs.

II. Disproportionate dwarfs:
   A. Achondroplasia (chondrodystrophia fetalis).
   B. Stunting of growth from rickets or Pott's disease.
   C. Cretinism.
   D. Congenital syphilis.

In the case of primordial dwarfism, heredity is given as the cause as it is usually present at birth. No endocrine or other abnormality has so far been demonstrated. These individuals are well-proportioned though diminutive. Bassoe states that they might be called "normal" dwarfs.

Of the proportionate ones, the "hypophyseal dwarfs" are the most interesting to us. They have been called the "adults in small mould," the antithesis of the acromegalic giants. They are plain cases of pituitary deficiency. Dunn reports a case under his observation whose sella turcica measured 7 x 9 mm. Her hands and features were delicate, and although she was thirty-two years of age, her expression was girlish and her body had the contour of a maiden just passing into womanhood. These dwarfs do not acquire normal sexual or osseous development.

Under the disproportionate dwarfs Bassoe calls attention particularly to the victims of achondroplasia, or the "short-limbed dwarfs." These cases are all remarkably alike—have relatively large and broad heads, short limbs, and are unusually strong and agile. Most of the dwarf acrobats of circuses belong to this class. Of this type Bassoe says: "In nearly all the descriptions of these dwarfs the large size and excellent functional conditions of the genitalia are dwelt

upon, and logically the theory that perhaps the dwarfing of these individuals is due to premature inhibition of cartilaginous growth by excessive gonad hormones. . . . Be this as it may, the mere theory helps in impressing on you the rôle of the endocrines in growth disturbances which I have tried to bring home to you."

While there are examples of rachitic dwarfism, and the disease produces this anomaly of growth, it is nevertheless a nutritional disturbance and will be discussed more fully under diseases of nutrition. However, a statement on this subject by Dunn may be quoted here:

"If perverted thymus function is the determining cause of rickets, and the recent experimental evidence points that way, we have another manifestation of a ductless gland exerting a profound influence on growth. Its intimate relation to the chromaffin system, to the other ductless glands, and to the sexual organs, although poorly understood, is manifested in the status thymico-lymphaticus. Sexual activity is not dulled in rachitic dwarfs to any great extent, as in cretinism or hypophysis disease, but pelvic deformity puts a check to perpetuation of this type of physical undesirables. It is interesting to note how much more certain and relentless is the check to reproduction by interglandular correlations when both defective cerebral and physical development is concerned."

Cretinism has been given attention under Types of Mental Defectives, but mention should also be made here of the cretinoid types of dwarfs. "It is obvious," says Hertoghe, "that myxedematous dwarfism and infantile cretinism cannot escape detection by a physician of even moderate attainments." And Hertoghe reports several cases of cretinism who developed remarkably under thyroid medication. One case in particular came to his notice when the child was fourteen

years of age. His height at that time was 29 inches—the height of a baby of eighteen months. "The infiltration of the entire body, the gaping mouth from which the over-large tongue protrudes, the bent tibias, the enormous protrusion of the abdomen, the umbilical hernia, the scanty hair, all these signs point to but one diagnostic conclusion, namely, subthyroidic cretinism in its most extreme form. The intelligence is nil; the expression of his emotions by a few grunts is as much as he is able to accomplish. He is invincibly constipated, and is unable to control his urine either by day or night."

This case was under thyroid treatment for twelve years. His height increased by 27½ inches, the expression of the face is intelligent, sexual organs perfectly developed. There is, however, an exaggerated lumbar curve due to relaxation of the dorsal ligaments. This is a sign observed after prolonged treatment with thyroid extract.

To quote Hertoghe further on the influence of thyroid on growth: "The thyroid governs the building-up of the cells, that is to say, the formation and growth of the tissues; and it regulates the destruction of the albumen molecule, and governs the processes by which waste material, resulting from the incessant regeneration of the organs, is eliminated."

The endocrine organs are so closely related that rarely is it possible to place the blame for any disturbance on one gland alone. Some authors emphasize especially the influence of the thyroid on growth, others the pituitary, but the genital organs are also at fault in certain dystrophies of growth. "Not only the hypophysis, but the thyroid and the gonads are important factors in the product of infantilism. To realize the importance of the thyroid in connection with growth it is only necessary to recall to you the stunted growth of the typical cretin and the startling growth

stimulated in cretins by thyroid opotherapy. The influence of the gonads on growth and development is demonstrated by the profound changes brought about when these structures become functionally active, a stage which we designate puberty." (Bassoe.)

Progeria, although a very rare condition, can properly be classed under dwarfism, for the pitiful victims of this malady never attain normal stature. This disease, as defined by Gilford, does not affect normal children. It develops only in those who are subject to a form of delayed or arrested growth, or a type of infantilism, and he says of it, "We may describe the condition as one of infantilism upon which has descended the blight of premature senile decay."

Rand reports several cases of progeria and says regarding this condition: "True progeria always occurs in youth. The body arrested in its growth becomes prematurely the subject of senile changes. Infantilism and senilism are both present in the same body at the same time. Progerians pass from delayed childhood directly into a premature old age."

Variot and Pironneau believe that the cause of progeria is to be found in the adrenal glands. Gilford believes, however, that the pituitary body may be a possible factor.

The results of but one autopsy which was performed by Gilford are reported. As to the condition of the endocrine organs it is stated that the adrenals were degenerated and the thymus was persistent and degenerated. The thyroid, pituitary and pineal bodies appeared to be normal.

Of this autopsy and the probable pluriglandular cause for the disease, Rand says:

"Unfortunately the pituitary gland in Gilford's case was not examined histologically. He considered it possible that this gland, constituting the 'growth center,' might prove the key to the situation. Indeed, he seri-

ously considered terming the disorder 'micromegaly,' as contrasted with acromegaly. In the case of Elizabeth G. the Roentgen ray examination does not help us. The sella turcica is of normal configuration and its size is well within physiological limits. Its influence upon body growth and general development has been pointed out by Cushing and others on animals. It has been found diseased many times in certain conditions of gigantism, dwarfism, etc. In progeria it is conceivable that one may be dealing with a polyglandular syndrome."

Gigantism, Acromegaly and Eunuchoid Gigantism. It is impossible to consider either one of these conditions from the standpoint of the involvement of one gland. The influence of the pituitary, thyroid and gonads on giantism, no matter of what type, has been unquestionably demonstrated, and there is considerable reference in the literature to the influence of these glands on growth. The pancreas should also be mentioned, for there is almost invariably a glycosuria present in cases of acromegaly.

According to Bassoe, there are no "normal" giants. He places all cases of gigantism in the following groups:

"(a) Gigantism with infantilism, (b) gigantism with acromegaly, (c) gigantism with infantilism and acromegaly.

"When gigantism and acromegaly are combined the former condition appears first. About half of all reported giants have had acromegaly.

"Both gigantism and acromegaly are due to hyperfunction of the hypophysis. In a general way it may be said that when the gland disorder begins in childhood or early youth a giant is produced, while if the disease commences after the epiphyseal lines have closed, growth can only take place at the tips of the segments ('acrons'), and acromegaly results. . . .

"We have also subordinate glandular symptoms due to secondary or associated disorders of the other endocrine glands, such as amenorrhea and other genital symptoms, and abnormal pigmentation, growth of hair, and other skin changes attributable to the adrenals and thyroid. Then the enlargement of the hypophysis *per se* gives rise to two sets of symptoms: (1) local pressure symptoms chiefly affecting the optic chiasm and nerves, causing changes in the visual fields, and frequently optic atrophy and blindness; (2) in the later stages, if the hypophyseal tumor grows to a large size, the usual general symptoms of brain tumors."

Gigantism results from overfunction of the hypophysis during the developmental period, before the epiphyseal lines of the long bones have closed. If this occurs later in life acromegaly develops.

That hypersecretion of the anterior lobe of the pituitary body is responsible for gigantism appears to be well established, and in writing on this subject Packard and Barrie state: "One should recognize, however, that the disease, in its general deviation from normal processes, is perhaps the result of pluriglandular disturbances, with still other factors participating that are not yet understood, rather than the result of a pathologic condition of the hypophysis alone. . . . According to Horrax, the course of the disease termed gigantism, which is apparently brought about in large degree by hyperfunction of the anterior lobe of the pituitary body, tends eventually to a hypofunction of the gland, such change expressing itself in weakness, hypotrichosis, impotence, adiposity and low body temperature."

These authors report a case of gigantism in a boy 16 years of age, who is over six feet tall, or a case of so-called "preadolescent hyperpituitarism, presenting all the stigmas of gigantism . . . widened space be-

tween malars and spread nostrils, absence of hair on chest and abdomen, large genitalia, disproportion between size of hands and feet, prominence of ears, round back and backward displacement of os calcis." A slight glycosuria was sometimes manifest—this latter symptom suggesting an involvement of the pancreas, as previously mentioned.

It seems that a hypersecretion of the anterior lobe of the pituitary accelerates the growth of the gonads, while the posterior lobe retards their development. Bohenroth experimented on young rats and found that injections of pituitrin produced premature and extensive development of the genital system of both male and female. Anterior lobe feeding was tried by Dr. E. Goetsch (*Johns Hopkins Hosp. Bull.*) on dogs. After seven months the ovaries of the one receiving the injections were examined and they showed numerous corpora lutea and albicantia, while those of the control contained simply unripe Graafian follicles. The same results were obtained with young rats by administering extract of the whole gland and, "The ovaries, tubes and uterus of animals fed with extract of the whole gland were larger and more vascular than in controls and the ovaries reached sexual maturity from one to two months before normal."

On the other hand, feeding with the posterior lobe did not stimulate growth or sexual development; rather, it retarded. To quote from a *Lancet* editorial: "These results explain why in acromegaly, now believed to be due to overactivity of the anterior lobe consequent on adenomatous hyperplasia, there is in the early stage increased sexual activity and in the late stage, with pituitary involution, disappearance of the sexual function and atrophy and degeneration of the sexual glands."

The close relationship between the pituitary and the gonads is further demonstrated by the fact that cases

of pituitary diseases presenting symptoms of sexual failure, such as amenorrhea and impotence, have been benefited by the administration of pituitary extract.

The syndrome of acromegaly develops slowly over a period of years. In some patients, cerebral and genital symptoms appear years before the skeletal changes are noted. Headache, sleepiness, apathy or disturbances of vision may be the first signs. Menstrual irregularities or amenorrhea may be the first symptom in the female, or a diminution in libido and potentia in the male. The characteristic spacing between the upper incisors due to enlargement of the superior maxilla is to be noted. The lower mandible enlarges much more but is not noticeable so early. In some cases we may notice also enlargement of the viscera such as the liver, heart, spleen, pancreas, kidneys. Later, the symptom complex consists of skeletal overgrowth, a highly sensitive sympathetic system, excessive sexual development—often to precocity in children, excessive hair growth and distribution, and reduced carbohydrate tolerance. Hyperpituitaric individuals are irritable, bright but distrustful, petulant, indecisive, abusive and unreliable. This condition is often associated with syphilis, and, therefore, a Wassermann test should be made in every case. The Froehlich, Burnier and Cushing types include most of all the possible dyspituitary changes. Several special forms have been described such as an amytrophic form, a painful form associated with gigantism, trophodema, myxedema and one accompanied by severe nervous and mental symptoms. Some acromegalics become obese in the latter stages due to hypophyseal hyperfunction followed by hypofunction. Some maintain that acromegaly is a perversion and not hyperfunction of the hypophysis. If treated early, pluriglandular therapy helps these cases a great deal.

As stated in an editorial in the *Lancet,* acromegaly

"has its primary origin in hyperfunction of the pituitary gland, is often complicated by contemporary or successive phenomena dependent on functional or organic change in other glands with internal secretion. . . . In fact, the case might be taken as an example of a thyro-genito-pituitary syndrome to which various authors, chiefly French, have drawn attention in recent years. The implication of the other glands except the pituitary, whether it represents an independent and accidental occurrence or one subordinate and necessary, is not, however, equivalent to saying that acromegaly is a pluriglandular syndrome. Changes in these glands do not signify their participation in the pathological process of acromegaly, but, according to these observers, are capable of an entirely different explanation, which is that the endocrine system constitutes an organofunctional whole, whose constituent elements are physiologically in such intimate connection that one of them cannot undergo any change without a reaction taking place in the others."

Acromegalic giants are of more symmetric build than the ordinary types of gigantism or eunuchoidism because of the usual development of the disease after the ossification of the epiphyseal junctures.

Cases of eunuchoid gigantism usually present the dystrophy of long limbs, small head, broad pelvis —heavily cushioned with fat, scantiness of pubic hair, and infantile genitalia. Dr. Bassoe says of the relation of the gonads to growth: "The influence of the gonads on growth and development is demonstrated by the profound changes brought about when these structures become functionally active, a stage which we designate puberty. As eunuchoidism, first described by Griffith, we designate a developmental disorder from which a defect of the testicular interstitial glands, in which the character described in eunuchs also are present. When there is an additional tendency

to excessive deposits of fat we have reason to suspect hypophyseal disorder as well, while carious teeth and marked skin changes implicate the thyroid."

Boyd Kay reports a case of hypopituitarism, Froehlich type, in a child nine months old. This child was born healthy, weighing seven pounds, showing no abnormality until the third month, when its weight began to increase rapidly. The mother also noticed that it became more and more stupid and slept almost continuously. The waking moments were devoted almost entirely to feeding periods. His abdomen was rather obese with most of the fat distributed below the level of the umbilicus. The external genitals were very small and hips ponderous. The extremities, especially the thighs, were very fat and short. The eyes, outside of a slightly pale disc, were normal, as also the urine and blood. He showed a marked increased carbohydrate tolerance. I have had many such cases but none so young. The glandular involvement here is one of dyspituitarism and hypothyroidism. This patient reported by Kay is showing marked improvement with thyroid and pituitary extracts as to its growth and intelligence.

8.—Nutritional Disturbances.

The ductless gland disturbances giving rise to the various nutritional disorders so common during infancy and childhood should be detected in their incipiency so that remedial aid can be effective. Various types of malnutrition have been met with, i. e., the marasmic baby, the rachitic child, the hypo- and hyperadrenal form, dyspituitaric type, hypo- and hyperthyroid child, the lymphatic, hemopoietic and the pluriglandular type.

In the marasmic baby, the thymus is usually abnormally small. Some of these cases resist all forms of treatment. In my hands organotherapy gives the best

results. Thymus gland substance, combined with thyroid, improves the infant's ability to absorb and assimilate its food. At times I include lymphatic gland which, with the improved metabolism and cellular oxidation, favors the lymphatic circulation.

The hypoadrenal type of the pale, emaciated and tired child, gives evidences of low blood-pressure, capricious appetite, cold extremities, marked asthenia and sluggish mentality, often associated with nephritis because of the accumulated waste products. These cases are helped by the administration of thyroid and adrenal extracts with special care for the emunctories, good food and enforced rest. The hyperadrenal individual is usually tall, dark, thin and delicate, with long and silky hair, and very active. They suffer from indigestion and anemia. Preparations containing pancreas, which opposes the adrenals, give excellent results.

The lymphatic type of malnutrition includes such cases in which the liver, spleen and lymphatic glands are definitely involved. These children appear to be undernourished, underfed and phlegmatic. They breathe like asthmatics and are subject to various blood and lymphatic dyscrasias. The lymphatic glands may be enlarged and large tonsils and adenoids are frequent. They are predisposed to tetany and convulsive seizures. Here we have a pluriglandular disturbance involving the pineal, parathyroid, thyroid, pituitary, adrenal cortex, thymus and the hemopoietic organs. They improve on a pluriglandular formula directed at the most obvious phases of their symptomatology. The interstitial cells of Leydig, lymphatic gland substance and thymus gland give satisfactory results.

Thyroid insufficiency also produces a certain type of malnutrition in children—the lazy, obese, constipated type. These are benefited by long-continued use of thyroid extract in gradually increasing doses. Hyper-

thyroidism produces a type of malnutrition also—the thin, high-strung child.

Anemia. A good deal might be said about anemia, for undoubtedly the hemopoietic system is related to the endocrines and the disturbances in nutrition resulting from thyroid or pituitary diseases or, for that matter, any disturbed function of the endocrines necessarily would reflect upon the body as a whole, including the hemopoietic organs and their blood-producing capacity. Serious anemias are common in cretins, for the blood-forming organs are just as infiltrated and puffed up with their own wastes as the rest of the body. The same thing is true in all forms of hypothyroidism, but merely varies in degree.

Again, when conditions in the nature of marasmus, rickets, etc., have been permitted to develop, it is clear that the nutritional aspects are not limited to the most obviously involved organs—the ones we see—but involve also the endocrine glands, thereby modifying their influence upon blood-making and other functions, and upon the blood-forming organs themselves, so that really in such instances there is a double reason for the anemias so commonly encountered. Certain conditions involving the bones themselves and the bone marrow, osteomalacia and scurvy—all of them serious nutritional disturbances with serious endocrine aspects—naturally invariably are associated with anemia, and the treatment directed at the anemia is bound to fail unless these fundamental underlying elements are regulated simultaneously.

All stages of anemia in some way involve the ductless glands. In most instances, and especially in pediatrics, the involvement is one of a general nutritional character, whereas in certain rarer conditions there seems to be a specific difficulty of a toxic nature which is really at the bottom of the trouble.

Acidosis and Diabetes. The problem of diabetes and

its treatment by organotherapy has caused the publication of a large number of articles both here and abroad. Without a doubt, the capacity of the body to burn up sugar is related to the glands of internal secretion. Disturbed thyroid function may cause glycosuria. We know that hypopituitarism causes a very marked increase in the tolerance to sugar, and that the adrenal glands are very definitely related to glycosuria. It has been found, for example, that the use of adrenalin for nose and throat surgery or other reasons, in persons with a glycosuria, causes a very marked increase in the amount of sugar during the time that the adrenalin is acting.

It has also been found that the pancreas is a principal factor in diabetes mellitus and that the hormone from the islands of Langerhans is as von Noorden has it, "the brake to the sugar mechanism." In other words, diabetes mellitus really often is a condition of pancreatic hormone insufficiency and essentially a deficiency of the tail of the pancreas, because 90 per cent. of the islets which were named by Langerhans are found in the posterior portion of this gland.

Acidosis is frequently the cause of death in diabetes and every individual with diabetes mellitus has a tendency toward a deficiency of the alkaline reserve and consequently to an excess of acid substances of the disturbed metabolism. As Dr. F. H. Smith says, "the child dies of acidosis, if it dies of diabetes." For that reason we are considering these two conditions together.

Acidosis has been ascribed to poor combustion of fats, due to carbohydrate deficiency. Often, however, in these cases the child eats voraciously to within the hour of the onset. There can be no carbohydrate lack. To quote Smith again: "The explanation is probably this: In recurrent vomiting the child's metabolism is more than usually vulnerable, is handicapped, perhaps

by some fundamental fault; any dietary or other indiscretion succeeds in overwhelming metabolism; and for the time being, carbohydrate metabolism is in abeyance; and the result is the same as if carbohydrates are withheld if they can't be utilized by the tissues.

"Whether or not this be the true explanation, it appears indisputable that most of these children are acetonuric, and are to be handled successfully on that basis. Just as Allen contends that feeding fat while withholding carbohydrate is the surest way to induce acidosis in diabetes, so it has seemed to me that these cases of cyclic vomiting in children are oftenest initiated by a diet too rich in fats.

"But while it is certain that some dietetic error is oftenest responsible for the immediate break, I have been struck with the further fact that the victims of these recurrent attacks often have some source of infection somewhere within the body, oftenest bowel disorders, diseased tonsils, or adenoids, or appendicitis. It has been my experience more than once to see these patients recover after removal of the focus of infection. Such infection should be searched for in all such cases."

An infection in the adenoids or tonsils is also a part of the etiology of diabetes. Blodgett in writing on the subject of diabetes in children states that on careful inquiry it will frequently be learned that the child had some infection affecting the tonsil within at least a month (usually within a week) of the commencement of the thirst. He states further: "It is very important to have the throat, and especially the tonsils, examined by a competent man, and where any abnormality is found, to have the tonsils removed (not cut off). If this is not done, it may happen that after the urine has been sugar-free and the patient seems to be progressing favorably, some day an infection shows in the tonsils and the blood sugar increases, likewise the

urine sugar, although the patient may be taking much less carbohydrate than before the tonsil infection occurred."

Mohler throws a different light on this aspect of diabetes in the following words: "Just as in pneumonia, organs other than the lungs may suffer more severely and be permanently damaged by the products of the pneumococcus, so in a similar manner the pancreas (whose internal secretion has to do with sugar mobilization) may be the seat of an acute pancreatitis as part of a general infection. Thus may be explained the relation between diabetes and an acute infection."

Langdon Brown regards diabetes as a product of an exaggerated metabolism evoked through the sympathetic. The thyroid, adrenals and pituitary are all overstimulated, but the pancreas is underactive. It may be due to a functional disturbance or to structural changes in the glands affected, and this increased metabolism asserts itself first in relation to the most abundant food material (carbohydrate), but later expresses itself in relation to all.

Dermatoses. The important influence of the thyroid on metabolism and the nutrition of the skin has been emphasized again and again, so it would not be out of place to look for a thyroid involvement in inflammatory skin diseases. Many stubborn cases of eczema have been cured by the administration of suitable doses of thyroid extract. A. Z. Hall reports the cases of two brothers, aged six and three, who were literally covered with a sticky eczema, the eruption being worse at the elbows, knees and neck. Sleep was almost impossible for the children and their parents. At times asthma complicated the eczema, the one increasing in severity as the other decreased. Various local applications such as ointments, washes, dusting-powders were tried but invariably failed in the long run. Internal remedies, from arsenious acid to lobelia, were tried in

vain. Cleanliness, plain living, fresh air and general sanitary measures had always been the rule in their home and no blood dyscrasia could be discovered. At last one eighth of a grain of thyroid extract was administered every second morning, as well as a tried local application. Two months of such treatment was sufficient to restore these boys to robust health, with an entire disappearance of the asthmatic attacks and the eczema.

On the other hand, Ravitch and Steinberg think that the type of infantile eczema which is due to disturbed thyroid secretion is always a dry eczema. The skin in such cases as they report is harsh and rough; there may be sweating, but no fatty or oily secretion present. The treatment of these cases, however, consists in the administration of iodin, iodid or thyroid gland.

A case of scaly weeping eruption, involving cheeks, forehead, chin, scalp, neck, shoulders, chest and upper and lower extremities in a boy of three and one half years of age, is reported by Edelman. The child was of Hebrew parentage and the only point of any significance in the family history was the fact that the mother and a sister became gray at the age of twenty years. In spite of constant treatment and well regulated diet, the condition persisted—from the age of four months. At the time of his admission into the hospital he showed the typical characteristics of cretinism. His tonsils were small and adenoids were present. In fact, there was a general glandular enlargement. The child was given one half grain of thyroid extract daily, no change was made in the diet, but bran baths were ordered every night. A month later he returned greatly improved. The eczema of the scalp, face and neck had almost disappeared and that of the legs had improved slightly. For the first time in three years the child slept through the night.

Owing to a loss in weight the thyroid was discontinued soon afterward, sugar and fats were eliminated from the diet, and unguentum ointment was used for local applications. The patient then became worse and thyroid extract was again administered, one quarter of a grain being given daily. Improvement was again marked.

In commenting on Edelman's paper, the editor says: "In considering the treatment of hypothyroidism it must be borne in mind that a child with deficient thyroid secretion has lessened metabolic powers. Talbot had found that the metabolism of a cretin three and one half years of age was about equal to that of a normal child eight months of age. This meant that one must give less food to these children at the beginning and increase the amount as they improved. Fairly large doses of thyroid extract should be administered at first in order to remove the results that might have been produced by privation of thyroid secretion; later smaller doses were administered in order to maintain a normal equilibrium and prevent recurrence."

Another interesting angle to this subject was presented by the late Doctor Harris in 1916, in his presidential address before the Chicago Dermatological Society. He stated that the sensation of itching, which is a marked symptom of eczema, can be prevented and counteracted by epinephrin. It is possible to prevent the inflammation of the conjunctiva and skin, which usually results from the use of strong irritants, by paralyzing the reflex arc in different ways, one of which is the local or subcutaneous use of epinephrin. But since the vasomotor changes in eczema are so closely connected with the itching, and it has been so clearly demonstrated that epinephrin prevents them both and is a normal constituent of the blood, it naturally follows that a deficiency of the active principle of the adrenals in the blood could account for the increased

sensitiveness of the skin and the itching as well. It is suggestive too that eczema, low blood-pressure and asthma, each condition counteracted by epinephrin, are frequently associated. Harris also gave as possible causative factors of eczema, diet, influence of the gastro-intestinal tract, the action and formation of histamin, indican and anti-trypsin.

Rickets. Rickets is a nutritional disorder of children, a form of starvation, hence before it can be treated effectively we must know what factors are prominent in the production of the disturbed metabolism and what elements can be given acceptably to replace those that are deficient. From an experimental standpoint, rickets is now understood to be a result of endocrine disorder. It has been produced more easily and quickly by the removal or destruction of certain of the glands of internal secretion than by dietetic restriction. In fact, the dietetic element in the etiology of rickets seems to be losing a good share of the importance that was until recently attributed to it.

Comby states that 76 per cent. of a series of 1,262 cases occurred between one and two years of age.

The thymus is blamed as the cause of rickets by Basch, Klose and Voght; the opinion of Stoeltzner and Salge is that the adrenals are at fault; while Hertoghe and Ausset, Claude and Rouillard blame the thyroid.

According to Howland and Kramer, the finding of a low content of inorganic phosphorus in the serum of young children is practically conclusive evidence of rickets. They state that children under two and one half years of age, in whom the inorganic phosphorus content of the serum has been found to be 3 mg. or less per hundred cubic centimeters, have been suffering from active rickets.

Guiseppe Carpani, whose researches were published in *Il Morgagni*, believes that this is a disease of bony development due, in large measure, to the derangement

of four glands—thyroid, thymus, pituitary and adrenal. Any one of these glands, failing to function properly, will cause this dystrophy, because when one is affected the others are invariably deranged, and so rickets becomes at once a disease, the etiology of which is a pluriglandular disturbance. Carpani found that giving dried gland substance in toto in doses suitable to age, in the milk, daily for fifty days, with the omission of one week after the first month, produces rapid and striking improvement during the first four weeks of treatment. The progress was slower during the following weeks, the benefits being noticed chiefly in the blood and osseous system.

The treatment of rickets will be discussed more fully, however, in the chapter devoted to that aspect of the subject.

Dental Aspects. The function of the teeth in children is so important for the act of chewing and preparing the food bolus for deglutition, that proper digestion and normal metabolism of foods are entirely dependent upon it. Hence body and mental growth and function is closely related or subordinate to a healthy set of temporary teeth, later followed by a permanent set in the child.

The destruction of the enamel and of the dentin are microbic in origin; that is to say, the acid solvent of both the hard structures under consideration originates from the fermentative action of bacteria in carbohydrate medium by which the acid solvents are generated in each instance. It is, therefore, essential to have the ductless glands functionating normally, especially during childhood, for to this a normal alkaline saliva rich in mineral salts, particularly calcium, is dependent.

Caries starts usually as a minute destruction of the enamel over a small area, gradually deepening, until the dentin is reached. This is then destroyed by a

process of liquefaction and digestion, undercutting the enamel in all directions until a large hole is formed, then the unsupported brittle enamel cracks away, leaving a cavity. Therefore, little enamel and much dentin is destroyed. In the tooth, however, in which we eventually find arrested decay, there has evidently been first of all, a large amount of destruction of enamel, and practically none of dentin, which contrary to expectation, becomes hypercalcified and instead of being liable to almost immediate destruction becomes almost immune to caries.

Broderick's theory is that an infection, such as an acute attack of measles in a child, gives first of all, greatly increased work to the ductless glands as a whole group, which act as toxin eliminators. This increased activity of the glands will doubtless be followed by a period of reaction, causing the correct balance between intake and output of calcium salts to be upset; and this balance, when upset in children—where normally the intake is greatly in excess of the output—will suffer. And when the teeth, together with the other tissues, lose their abundance of lime salts, with their alkalinity, there results a complete destruction of the enamel. Then the patient begins to improve, perhaps goes away to the seashore, the pendulum swings to the other extreme, and the body is flooded with calcium salts. It is now manifestly impossible to recalcify the enamel, as the scaffolding is gone, but the dentin takes up the superfluity of lime and becomes hypercalcified and hence an arrested carious tooth is the result. This hypercalcification must be rapid, more rapid, that is, than the destruction of unprotected dentin, otherwise the disintegration would reach the pulp and any chance for spontaneous cure be lost. It is, therefore, correct that the calcium content of the saliva and the blood can be increased by suitable pluriglandular therapy, and that this calcium can be laid down as fixed lime in

the teeth. It would seem feasible to believe that arrested caries can be produced artificially. Increasing calcium absorption floods the tissues with ionizable lime; then not only will it be laid down in the dentin but damaged or even undamaged enamel will be built up and strengthened and the teeth protected against another period of calcium starvation. Similar to Broderick's experience, I have also observed this in many cases. Therefore, it is possible to produce artificially a condition very similar to, if not identical with, arrested caries and probably also convert malacotic into sclerotic teeth.

In the causation of dental caries the ductless glandular balance is upset in the direction of calcium hunger. Mild endocrine derangements, early stages of disease, acute infections, overwork, mental strain, worry, starvation, lack of sleep, malnutrition, autointoxication, strong emotions, gastro-intestinal disturbances and bad hygienic surroundings, etc., frequent or transitory, may be blamed for dental caries.

The internal secretions have a certain favorable influence upon the dental tissues in bringing about eruption; cause sufficient calcification previous to eruption; increase calcification after eruption, which is concerned in the prevention of caries through the alkalinity of the saliva; arrest decay should caries supervene; and possibly by means of a trophic action keep the tooth tissue in such a healthy state as to resist caries. It accounts for good teeth in the dirty mouth and bad teeth in the clean.

If we bear in mind the position of the parotid duct and the fact that the parotid saliva is usually the least alkaline and, therefore, the first to lose that alkalinity in calcium hunger, it accounts also for excessive caries in the young and its absence in the aged. Pyorrhea probably is due to the opposite, or calcium saturation. Here we get an excess of lime salts deposited during

the paroxysms of saturation around the necks of teeth as tartar. This irritates the gingival margins and opens up the gum pockets normally found there; or possibly as some suggest, this tartar is laid down, not as a deposit from the saliva but directly from the blood. This is most probable, for it would seem that it is rather the tartar under the gum edge than the large chunks about the necks of teeth that causes the damage, and these pockets of damaged inflamed gum are laid open to any pyogenic organism present in the mouth. Pyorrhea becomes, then, not a disease at all but a symptom of a general constitutional condition due to disordered metabolism.

Experimental removal of the thymus causes delay in the development of the teeth. Cases are reported where thyroid feeding hastened eruption of teeth, and thyroidectomy caused retention of deciduous teeth. Kravitz has shown that regeneration of the teeth of rabbits are much retarded after the operation. Pond considers that the thyroid affects the growth of bones and governs the organs of reproduction; and Matthews believes that the thyroid, together with the parathyroids and pituitary, are responsible for calcium retention. Fleishman says that the teeth of all persons that he examined who had a history of infantile tetany, showed hypoplasia of the enamel. One can see from the above what an important rôle calcium salt metabolism and the ductless glands, that govern this, play upon the body economy.

9.—Endocrine Diseases.

Thyroid. Various degrees of thyroid insufficiency give rise to malnutrition in children of a sluggish type. They tend to be constipated, lazy, obese, easily fatigued, have poor appetite, feel sleepy most of the time and their mentality is slow and sluggish. They often suffer from arthritic and muscular pains with frontal

and occipital headaches. The secondary sex characters may be undeveloped and sexual appetite below normal. Long-continued use of thyroid extract in gradually increasing doses, watching for untoward symptoms, gives remarkable improvement.

Gordon classifies the manifestations of hypothyroidism in children under two heads: Mental defects and physical defects. "The mental defects may range from a slight dullness to a marked aberration resembling that present in cretinism. . . . The physical defects observed are backwardness in development of the power of holding up the head, sitting, standing, walking, talking, and teething. To this may be added certain changes in the bony system, in the skin and appendages and various other deviations from the normal, due to a disturbed metabolism. These abnormalities may be present either singly or in groups, with or without an accompanying mental deficiency. The most frequent delinquency noted among children of the hypothyroid type is in the function of speech. The next most frequent is probably in the power of voluntary muscular coördination as exemplified in holding the head erect, sitting up, and in walking—the latter being generally associated. Disturbances in the teeth are very common. Delay in the time of eruption of both the first and second set is noted, or else a child may have early dentition at the age of five or six months, acquiring all its teeth in the normal time and then gradually losing the majority of them in a few months as a result of caries."

Cretinism, a disease due to a lack of thyroid secretion, has been considered previously.

The opposite class of cases, or hyperthyroidism in children, occurs usually in older children or at puberty. Exophthalmos may be associated with this condition but is infrequent. They are tall, thin and highstrung, in a way similar to the hyperadrenal child. In these

children is noticed evidences of sympathetic irritation, such as palpitation of the heart, bounding arterial pulsations; they blush easily and perspire freely. Urticaria and other dermatoses are frequent. The prominent large eyes, sometimes associated with nystagmus, may be mistaken for multiple sclerosis. Migraine, neuritis and active mental disorders are common. Pancreas, adrenal, pituitary and ovarian substance given combined and long-continued have helped to stabilize the hyperthyroid state. Lymphatic substance, thyroidectine, bromides—particularly the quinin hydrobromate —are also synergistic. In few cases surgical intervention may be necessary, but where possible it should be avoided or held as a last resort.

Of the relation of hyperthyroidism to toxemia, Mackenzie says: "It has long been recognized that toxemias, acute infectious diseases, so-called 'rheumatism,' and even carious teeth; in fact, any condition capable of producing systemic poisoning, were associated or in some way intimately connected with hyperthyroidism in its various forms."

Thymus. While it is granted that our knowledge of the thymus gland is none too definite as yet, we are safe in assuming it to be an important factor in defective children. It has been suggested that the principal function of the thymus is to produce lymphocytes, and Sajous, of Philadelphia, believes that any effects that it may exert upon metabolism, positive or negative, are due to these cells or their contents. Of course, it is quite possible that these blood cells carry within themselves certain chemical substances which are very closely allied to hormones, if not actually such. Most authorities consider the thymus a temporary organ, reaching its height of development about the age of two, and retrograding slowly until puberty, at which time it is supposed to disappear.

It is generally conceded that the thymus inhibits the sex glands.

Proof that it is not a lymphoid organ alone is found in the fact that there is an intimate relation between the thymus and the metabolism of the mineral salts, especially calcium phosphorus.

"The thymus is susceptible to infections and conditions affecting the general nutrition of the body. Pathological involution often results. In acute diseases like starvation, pneumonia, acute nephritis and acute infectious diseases, this change is usually followed by a return of the organ to normal. In chronic disorders, however, a return to the normal does not take place, the gland itself undergoing a permanent sclerosis with resultant permanent involution. Heredity, syphilis, tuberculosis and diphtheria produce atrophy and degeneration." (Gordon.)

Klose and Matti found that disturbance of growth, a condition resembling rickets, and changes in the adrenals and thyroid followed the removal of the thymus in animals. Thymectomy in puppies resulted in adiposity, which lasted two or three months. This condition was followed by cachexia and a form of idiocy. Death resulted in four months.

It is not improper to presume that thymectomy in children will produce dwarfism.

Marasmus is quite commonly associated with thymus insufficiency and when children manifest disturbances in growth and development the thymus aspect should be considered until it is definitely proved that they are not suffering from hypothymism. This condition is often associated with anemia and another incidental defect mentioned by Browning is stammering. But while all cases with an enlarged thymus do not stutter, all stutterers will be found to have an enlarged gland, although some deny this. Sajous suggests that progeria in children is really due to thymus disease.

Hyperthymism is not a common or easily diagnosed condition. Other glands are usually involved, particularly the thyroid.

The following paragraphs are taken from the chapter on the diseases of the thymus in "Practical Organotherapy":

"It seems to be a somewhat different clinical entity not uncommonly found in infants and children and, unfortunately, too often only at the autopsy table. Many times this hyperplasia causes no well-defined symptoms and is altogether latent until sudden death—the so-called *'mors thymica,'* is the first indication that something is wrong.

"In infants, where an enlarged thymus is present, the initiation of breathing may be a prolonged and difficult matter. The cyanosis present at birth may persist and the breathing may be difficult and stridorous. In such cases the outcome is often fatal after a few hours or days.

"Dyspnea in children is probably the most marked symptom of thymus hyperplasia, and its presence should always cause a careful search for other associated findings. It may vary in degree, depending upon the pressure, from an insignificant stridor, worse on stretching the neck or drawing back the head, to a serious and alarming air hunger.

"In such cases the general health is poor. The skin has a pasty, badly nourished appearance, not unlike that of cretinism. There may be vague respiratory symptoms due to tracheostenosis, which later may develop into a peculiar harsh and intermittent cough which is sometimes erroneously called a 'tooth' cough, a 'stomach' cough or, for lack of a better name, a 'nervous cough.' This cough occasionally may be short and dry during the day and considerably worse at night. It is possible that the cough may not be due to pressure on the air passages, but no irritation of

either the recurrent laryngeal or vagus nerve, although tracheal stenosis is the most usual cause."

Status thymolymphaticus is evidently an acquired condition and is usually found in older children and young adults. It is a complex condition, the hypertrophic changes in the thymus being accompanied by a general enlargement of the bronchial, mesenteric and other lymphatic glands. According to Hart, the existence of a true status lymphaticus has not yet been proved with absolute certainty. Adenoids and enlarged tonsils are usual, hence cases with a well-marked adenoid facies and other evidences of lymphatic enlargement should be studied, as likely cases of status lymphaticus and the thymus should be sought for, and if possible, measured.

Warthin, writing on status lymphaticus in Osler's "Modern Medicine," says: "The sudden death in status lymphaticus is dependent primarily and wholly upon the thymus enlargement, and the latter condition becomes therefore the most important feature clinically. Moreover, thymic enlargement, leading to thymic death, may exist without any of the other clinical features ascribed to status lymphaticus. Nevertheless, the latter term serves a good purpose by designating the cachectic complex of thymic enlargement associated with adenoids, enlarged tonsils, enlargement of the superficial lymph glands, rachitis, etc."

Pituitary. Under diseases of childhood attributable to the influence of the pituitary gland particularly, are infantilism and gigantism. Aside from the well-known manifestation of pituitary dysfunction known as the Froehlich type, is the Lorain type of infantilism, which condition is unquestionably due to pituitary insufficiency. The more marked cases are those in which the disturbance is initiated before adolescence, "though a state of hypopituitarism which is inaugurated very late in the second decade will doubtless

dwarf the stature. This is true, likewise, of deficiency in other members of the ductless gland series—in the thyroid, the adrenal and the thymus, as is known both from clinical and experimental observations. . . . Lorain, some years ago, characterized as 'infantilism' an 'arrest of development' resulting in 'delicacy and smallness of the body,' and a genital dystrophy such as may result when tuberculosis or the cardiopathies affect young adolescents. . . . Brissaud objects to calling this condition infantilism and agrees with Meige that the term should be restricted to an anomaly of development in which the general morphological characteristics pertaining to infancy persist in a subject who has passed the age of puberty." (Cushing)

The relation between the pituitary and the sex glands has been well-established. To quote Goetsch on this subject: "One of the most striking examples of this distant change in function and structure of one gland produced by changes in another is to be seen in the alterations in the genital system consequent upon functional disturbances of the pituitary body. These alterations apply not only to primary changes in genital function, but also to the anomalies in the secondary qualities of sex. . . . If the pituitary insufficiency antedates puberty, we find the genitals hypoplastic, one of the most striking features in the condition now known as infantilism. The secondary sex characteristics fail to develop. In the main the body configuration is of the female type," and vice versa in the female.

Then there is the obese child, whose condition is due undoubtedly to pituitary dysfunction, which is particularly common in youth. It is often accompanied with a genital dystrophy and skeletal underdevelopment. The adipose tissue is fairly well distributed, save perhaps an excess about the abdomen and thighs. Cushing believes that in some of these cases of pituitary

obesity that "an internal hydrocephalus is equally capable of producing an insufficiency of the posterior lobe secretion, and, at the same time, may apparently either stimulate or inhibit anterior lobe activity. Hence, coupled with the obesity we may have the combination of overgrowth with sexual precocity."

Tucker, Cushing and others are of the opinion that a hyposecretion of the pituitary results oftentimes in epilepsy, and it may be functionally disordered by injury, illness, tumor, adolescence, or pregnancy. A hyposecretion of the posterior lobe produces lowered blood-pressure, increased sugar tolerance and adiposity. Slow pulse and voracious appetite result from an insufficiency of the secretion of the anterior lobe.

Hyperpituitarism. If a hypersecretion of the gland occurs before puberty, there is precocious mental and sexual development, excessive body hair, long bones, and early puberty, producing gigantism and acromegaly—conditions which have been quite fully discussed under Growth Dystrophies, so this aspect of pituitary disease will be but slightly considered.

Tucker says on this point: "One of my patients has menstruated regularly since her second year and had fully developed pubic hair at the age of six years. If the anterior lobe is especially affected by hypersecretion the sex characteristics are prominent and an increased libido is often present. Hyperactivity of the posterior lobe will account for increased carbohydrate tolerance and at times increased blood-pressure."

He divides cases of preadolescent pituitary dysfunction as follows:

"In studying this subject, I divided my cases into the following groups.

"Group 1. Those cases which gave evidence of preadolescent hypersecretion, with an apparent increased hypersecretion during adolescence.

"Group 2. Those cases which gave evidence of pre-

adolescent hypersecretion with an apparent marked decrease in the secretion occurring during adolescence.

"Group 3. (a) Those cases with a preadolescent approximately normal history, in which during adolescence the secretion was increased.

"Group 3. (b) Those cases with apparently normal preadolescent secretion, which during adolescence seemed to have a decided decrease in the pituitary secretion.

"Group 4. Those cases in which there had been preadolescent hyposecretion and in which during adolescence the secretion appeared to be still further decreased.

"It was thought that our present clinical knowledge was too indefinite to attempt to separate into groups the cases in which symptoms of the anterior or posterior lobe seemed to predominate, although at times such predomination was noted. Also, for the reason that in all cases both lobes appeared to be more or less affected, the secretion of the gland was considered as a whole."

Pineal. There is a lack of unanimity in the literature on the subject of the pineal gland in pediatrics. The conclusions, therefore, "must be flexible rather than dogmatic." Pineal feeding has produced opposite results; but that the gland does have some influence upon the sex glands is unquestionable, therefore, it is practically impossible to consider the subject without giving attention to other glands in the endocrine chain—as is the case in the consideration of any one of them.

It is generally conceded that the pineal undergoes involution at puberty and that its influence upon mentality, sexual development and growth is confined to prepubertal years.

Some investigators believe that the pineal is a gland of internal secretion and that this secretion arrests

body growth and inhibits sexual and mental development until the natural time for such development. This inference has been drawn because of sexual precocity following a tumor of the gland, it being assumed that the tissue is destroyed and that the disturbance in the sex glands results from an insufficient secretion of the pineal gland.

"These disturbances can be grouped under two classes of symptoms: neurological and metabolic, the clinical manifestations of both arising from the encroachment of the neoplasm on the intracranial contents and are indicative of disturbance in pressure, in placement, and in destruction of tissue. When occurring in children before puberty, they give rise to metabolic symptoms and are referable to disturbances of the secretory function of the gland. They may have neurological signs associated. Lesions occurring in adult life produce neurological manifestations and never any metabolic as the gland does not functionate after puberty. . . . The metabolic symptoms are: (a) adiposity; (b) sexual changes, and (c) cachexia. This is the syndrome of hypopinealism found in children suffering from a lack or a diminution of pineal secretion, according to one set of investigators." (Gordon.)

Symptoms that are referred by many to a hyposecretion of the pineal have been produced by Dana and Berkeley following pineal gland feeding.

"Recent work by McCord strengthens their findings and tends to show that the feeding of pineal extract to young animals produces changes which are similar to those which were thought to be due to deficiency of the gland, and are contrary to the belief that the pineal secretion holds in abeyance too rapid somatic, sexual and mental development in early life." (Gordon)

Of the effects of pineal feeding upon delinquent children, Gordon states:

"Cornell and Goddard reported the effects of pineal feeding in delinquent children. They found that the gland was beneficial in cases of simple mental retardation without any organic changes but useless in Mongolians, congenital idiots or in defectives over fifteen years of age. The beneficial results were in inverse proportion to the degree of physical defect present, in other words, the greater the number of stigmata in the patient, the less the effect of the feeding, and vice versa. There was an increase in mentality and physical development in the subjects up to a certain point, except in the weight, in which there was a slight reduction below the control, but not below the normal. The investigators felt that they could not be certain of any mental defect in the children which might be ascribed to either deficiency or entire lack of the pineal secretion."

Such contradictory opinions and results of investigators preclude any definite conclusions as to the function of the pineal and its effects upon the organism. That it is an important link in the chain, however, cannot be denied, and though the results of feeding are opposite, its influence is apparent and just as in the case of the thyroid, either a hypo- or a hypersecretion can produce a hypertrophied condition of the organ, so the years will probably reveal the reasons for the contradictions that we now see in the influence of this gland upon mentality, growth and sexual development.

Sex Glands. Puberty is considered in its physiology and pathology as an endocrine event in which the secretions of the genital glands, the hypophysis, thyroid and suprarenal cortex take part as excitants of the sexual development, while the thymus and the pineal glands act as inhibitors. The harmonious action, reaction and interaction of the endocrine system determine the successful pubertal development. A dis-

turbance in the balance results in the evolution of a pathological condition.

In hypogonadism the children increase in weight, the skeletal bones are large, and the head is small. There is a tendency to glycosuria and adiposity. Again, in others we may see an essential infantilism with defective development of the genitals and secondary sex characters. In the male the development of the genital organs is controlled by the interstitial cells of Leydig, but are secondarily affected by the thymus, pituitary, thyroid, pineal and the adrenal cortex. The treatment of these cases depends upon the presence of the other physical signs associated with the hypogonadism.

Eunuchoidism is an acquired disorder of the interstitial cells of Leydig. Those cases manifesting this disturbance are quite similar in functional capacity to a castrate, but without the absence of the testicles. This condition is usually associated with dyspituitarism, hypothyroidism, and hypoadrenia. Undescended testicle is not due to adhesions, as formerly thought, but to some pathological condition or abnormal lining of the Leydig cells. When organotherapy alone is insufficient, early operation is indicated in order to avoid untoward complications.

In hypergonadism there is an enormous overdevelopment of the body, excessive growth of hair and distribution and the libido-sexualis is developed as in adults. Van Haller reports a case in a girl of this type, who was impregnated at 8 years of age, shortly after this abnormal growth showed itself, and who died at the age of 75 years. The intelligence is well-developed but childish, the voice is prematurely changed and erections and ejaculations have been noted even in infancy. In these cases the excessive development of the genitals precedes the over-development of the body. As a result of this, premature

closure of the epiphyses is brought about, and these children, although too big for their age, cannot become giants. They are as a rule sexual perverts. Malignant disease of the ovaries or testicles may give rise to this condition. In females, we get over-development of the breasts, uterus, and vulvae, menstruata praecox, excessive body growth with premature ossification of bone centers, dentition and epiphyseal closure.

In these cases we have an abnormally early atrophy of the thymus and parathyroids with hypersecretion of the pituitary, thyroid and adrenals. An early involution of the pineal gland may also give rise to this condition. It is interesting to note that in older children the symptoms of hypernephroma also manifest themselves by overdevelopment of the sexual sphere. They approach the masculine type and often grow beards and mustaches. In pseudohermaphroditism of the feminine type there is found a bilateral hypertrophy of the adrenal cortex. The enlargement of the adrenal cortex has been noticed in animals during breeding, pregnancy and after castration. This, and the fact that the cortex is of small size in deficient sexual development, are additional evidences of the association of the adrenal cortex with sex characteristics.

In those suffering from ovarian and testicular disturbances we get sexual perversions, mental disorders, erotomania and active or depressed mania. The menstrual periods have special bearing upon the metabolism and mental forces. In these disorders they improve on organotherapy, such treatment being instituted according to the predominating symptoms in the individual case. Much can be done along these lines for children before puberty, which will help to prevent these psychic disorders later on. Sajous has found that sixty-five per cent of all idiots are deprived of their thymus before six years of age.

Many children regarded as wayward, incorrigible,

uncontrollable, irritable, precocious, masturbators, sexual perverts and those who manifest congenital psychoses, psychopathic personalities and show signs of mild or severe forms of mental derangement, belong to the great group of endocrinopathies or pluriglandular dyscrinisms. We should group them according to their physical signs, whether they are of thyroid, pineal, pituitary, adrenal, thymic or gonad types, or a combination of these, and treat them accordingly. We must also study the physical, psychological, educational and social factors that enter into the reactions of childhood and include in the therapy the proper environment, diet, good habits, sex hygiene and—when indicated—drug adjuvants.

10.—Nervous and Muscular Disturbances.

The rôle played by the endocrine disorders in the production of highly nervous and excitable, or backward and diffident children, has been considered elsewhere. There are some nervous phases, however, to be taken into account in this chapter.

McCready reports Falta's opinion: "The ductless glands themselves are vegetative organs. They are supplied by vegetative nerves—it is assumed that the function of the ductless glands is in a great measure regulated by the nervous system," and conversely, "The ductless glandular system influences the excitability of the vegetative nervous system by the hormones that it gives off to the nervous system."

More specifically Dana and Berkeley, of the Rocke feller Institute, believe that the pineal gland promotes the development of the nervous system and supplies a minute amount of intracellular ferment accelerating the growth of the gray matter of the brain.

A very common complaint is of headache. This symptom is troublesome to the patient and is a source

of much concern on the part of the physician who attempts to trace its origin. In the absence of gastro-intestinal disorder, gynecological abnormality, accumulated toxic wastes, focal infections, sinusitis, middle ear inflammation and eye abnormalities, and also eliminating caries and infected teeth as a possible source of bacterial infection, there are cases in which the headache will still persist. Close study of the latter has proved to me that certain endocrinopathies are responsible for this suffering. Proper diagnosis of the endocrine gland or glands at fault, and the institution of corrective ductless gland therapy, have given remarkable relief to most patients, in many instances effecting a cure with no return of the headache after stopping treatment for many months. An equilibrium among the ductless glands has thus been established. In several cases of thyroid insufficiency, thyroid treatment relieved them. Other cases suffering from menstrual disturbances were relieved with ovarian therapy. Many of my young patients, mostly girls about the age of puberty, showed signs of hypoadrenia. In these cases adrenal extract, together with thyroid, gave relief.

Along the line of muscular difficulties, the endocrine system may be at fault.

Hyperparathyroidism is believed to be a cause of myasthenia paralytica (Chvostek) and of the rarer condition known as myotonia periodica. Thyroid and parathyroid therapy help in these maladies. Abnormalities of the pineal gland, due either to pressure from a tumor upon it, or disturbed function, give rise to various muscular dystrophies and genital defects. Parathyroid insufficiency induces trophic disturbances of the skin, nails and hair; myotonia; myoclonia; tetany; myoclonic convulsive movements and epileptic seizures. These cases do exceptionally well on anterior

pituitary extract with or without parathyroid. Thyroid is synergistic.

A large thymus is said to be responsible for the condition known as myasthenia gravis, undeveloped genitals and hypogonadism. This gland is often small or absent in mentally deficient and marasmic children.

Chorea is a distressing symptom complex frequently met with in children. It is characterized by irregular involuntary contractions of the muscles, a considerable physical upset, and a noteworthy susceptibility to acute endocarditis. As to the etiology, there is certainly a familial tendency, and some attention must be paid to the various foci of infection.

This subject is given some consideration in "Practical Organotherapy," from which the following paragraphs are quoted:

"Quite a number of children with this motor difficulty have been found to show simultaneously, evidences of glandular dysfunction—notably of the thyroid and parathyroid glands. Some Italian investigators have emphasized the relationship between tetany and the convulsive manifestations that are connected with hypoparathyroidism and chorea. From the standpoint of the thyroid gland, the French have been most active in their study and several writers emphasize the importance of considering the thyroid aspect of every child with chorea, and, if there is evidence of dysthyroidism, these writers naturally urge the control of this condition as well as the treatment of the chorea.

"Personally, I do not think that chorea is essentially an endocrine disease. When it is found in conjunction with dyscrinism or disturbed function of one or more of the glands of internal secretion, naturally the treatment should include measures directed at the endocrine trouble, or organotherapy."

Some of the convulsive disorders of children are of endocrine origin. In the *Rivista di Clinica Pediatrica*

(Florence), Pincherle and Maggesi report the autopsy findings in seven children, six having died of laryngospasm and the other from tetany. "Necropsy revealed evident anatomic changes in the endocrine organs in every case, sometimes of the whole endocrine system and sometimes of only a few. The thymus was never found normal in any of the seven, and the parathyroids in all but one showed more or less anatomic changes."

One of *Harrower's Monographs* has recently been devoted at some length to a consideration of epilepsy, so a brief resumé of the etiology here will be sufficient.

L. Pierce Clark, made a study of thousands of seizures in epileptics and concludes that the principle of the pathogenesis of the condition is an initial toxin or autointoxication, i. e., an accumulation of waste products. The literature and clinical experience shows plainly that the dominant note in the initiation of the convulsions is impairment of metabolism, and that the spasmogenic agent is some toxic element in the blood stream.

In some cases, the causative factor or toxemia is primarily due to toxins derived from intestinal stasis, carious teeth, sinusitis, adenoids, tonsillitis and other focal infective points of bacterial origin. Other sources may be from reflex origin, such as intestinal worms, indigestible foods, dentition, nervous shock, masturbation, syphilitic lesions, urea retention, hereditary diathesis or idiopathic forms of alcoholic and lead poisoning. The treatment will be considered in a following chapter.

Enuresis is a most deplorable condition of childhood. Omitting organic causes, it has been referred to as "neurosis of the bladder," by the editor of the *Journal of the American Medical Association.*

According to E. B. McCready, the condition is a result of the hypoplasia or underdevelopment of some

children due to thyroid deficiency. To quote: "Symptoms may show themselves soon after birth or may not appear until development reaches a stage at which the glands are unable to meet demands made upon them by increased growth. Among the early symptoms to be noticed are delay in the power of walking and talking, late closing of the fontanels, etc. Progress in these respects may, however, be entirely normal, even more rapid than normal; the precocious child is often an hypoplastic one. Among the most prominent early signs are enuresis, nocturnal or diurnal, and adenoids. Adenoid vegetations have for a long time been a textbook cause of enuresis. The removal of adenoids, however, will often bring about no amelioration in the incontinence. In a very valuable paper appearing in the *Lancet* a little over a year ago, Leonard Williams describes a case in which the enuresis became worse after the removal of adenoids and tonsils. Reasoning that the economy of this child had been deprived of a corrective internal secretion, Williams began the administration of small doses of thyroid extract, with the result that the incontinence almost immediately ceased, followed by a marked increase in height and weight. Williams reported the results of thyroid medication in a series of twenty-five cases, with but one failure which was in a girl of seven who, on her fifth day in the hospital, vomited a round-worm. He attributes the enuresis in these cases, except the one mentioned, to thyroid insufficiency. All had symptoms of hypoplasia and a number had adenoids and enlarged tonsils.

Williams believes that adenoids and hypertrophied tonsils are compensatory in their action, correcting, as it were, the thyroid insufficiency.

IV

THE DIAGNOSIS.

IF THE fundamental principles of endocrinology are appreciated and the foregoing information has been absorbed, the diagnosis of disturbed endocrine function in children offers no serious difficulties.

The history, and especially the history of the parents, opens the way to an opinion which should be made and, if possible, maintained by the various diagnostic procedures that are possible. It is good policy to presume that under certain suitable circumstances an endocrine difficulty will be developed, for just as effect follows cause, so when causes are present the effects are probably there also, and as will be seen later, the procedures involved in the treatment of these individuals help us to establish more fully the more or less indefinite suspicions.

A good deal of information comes with the general impression of the child. In fact, the pediatrist depends more upon his eyes than the clinical measures of scientific medicine. The child with dyscrinism usually does not look right and this is the more obvious in those serious disturbances of ductless glandular function which have modified growth, development and mentality and to which attention has already been called.

In some of the more subtle endocrine difficulties the actual endocrine findings are not so easily uncovered, and here my plan always is to develop a case from the standpoint of the history of the condition confronting us, as well as the family history, especially of the

mother, and then try to find a point here or there which would add weight to the impressions that you may have had at the beginning of the interview.

These impressions sometimes can be materialized into some definite information by certain laboratory tests; the differential blood count is sometimes valuable; lymphocytosis being a hint of a thymus condition; an increase in the polymorphonuclears hinting at a possible hidden infective cause, and so on. The accepted laboratory measure for the determination of thyroid insufficiency or excess—the estimation of the basal metabolism—is well worth while, but in small children it is impossible to take it. The same applies to Harrower's Thyroid Function Test which can be given to children beyond a certain age, but not, at least, to infants. The sugar tolerance test is sometimes advantageous in emphasizing a presumed pituitary aspect; but taking it all in all, the most important diagnostic measure in endocrine pediatrics is organotherapy.

The principle of homostimulation as enunciated by Hallion and other French writers, and proved many thousands of times by a large number of the profession, assures us that, all things being equal, certain endocrine glands will respond to hormone stimuli from the administration of animal remedies containing the hormone in question. Hence, thyroid extract can be given for diagnostic purposes to determine a thyroid insufficiency, and if in a given case thyroid is administered and there is improvement, we are justified in agreeing with Léopold Lévi that "when the results are immediate, continued, constant and pronounced, they may be regarded as a diagnostic factor. In the case of pluriglandular syndromes, the results of thyroid treatment serve to distinguish between symptoms of thyroid origin and those provoked by derangement of other endocrinic glands. Even in cases where thyroid insufficiency is proved, the endocrine balance must be

maintained and the coexistence of other endocrine insufficiencies and instabilities (testicular, ovarian, parathyroid, suprarenal, pituitary) must be allowed for."

The same thing applies to any other glandular extract, and while some criticize this attitude, it is the most successfully applied and entirely the most satisfying of all the diagnostic procedure in pediatrics. In other words, if you have a presumed endocrine insufficiency and you proceed to replace the missing substances and as a result of this replacement certain manifestations or symptoms are obviously changed, it is very reasonable to presume that the benefit has been the result of the treatment even though some of our friends usually find an opportunity to hint that "it might have happened anyway," or that "one cannot be certain in such cases as these unless very carefully checked up with controls," etc.

Organotherapy is the best diagnostic measure in the investigation of pediatric endocrinopathies, and in view of the limitations of our knowledge of the subject and especially the limitations in the diagnostics of the subtle and early endocrine disturbance, I can cordially recommend it in the manner to be outlined in the next section.

V

TREATMENT.

12.—General Measures.

IN A GENERAL WAY, the treatment has been referred to frequently in connection with the different conditions observed. It will perhaps be found convenient, however, to correlate the findings here.

There is a great deal that can be done for children along the lines of ordinary living. To go back to the beginning: A birthright of sound body and brain should be a child's normal heritage. When the mites of humanity come into this world defective, then to the task for proper care must be added that of attempting to correct the faults and physical failings of the progenitors.

Many children and infants suffer from malnutrition. Dearborn, in a public health lecture, explains how children suffer more than adults, for three reasons: "(1) Their greater metabolism, (2) their less resistance because (3) of their less power of storage of fat and muscle. These children are cold and weak and sad. Also they are more susceptible to disease.

"If the thoughtless, even when very indigent, realized how much adequate food during childhood has to do with growth and right adult vigor, the child would get enough to eat at any cost as a matter of family and political economy, as well as of human mercy."

Then the question of general hygiene and proper clothing is worthy of more consideration in connection with children than of adults. Their inability to realize their own needs and, further, to supply them, makes

it imperative that the parents and medical profession provide for the health of the children.

Organotherapy. This monograph being concerned chiefly with the endocrine aspect of pediatrics, the treatment of the various disorders will be considered from the organotherapeutic angle.

In the third edition of "Practical Organotherapy," I have listed the forms of organotherapy and commented on them as follows:

1. Substitutive
2. Homostimulative
3. Empirical
4. Specific

"SUBSTITUTIVE: Properly prepared extracts of various glands supply a deficient physiological secretion of organs that correspond to those from which the extracts are made."

Example: Thyroid Extract and myxedema.

"HOMOSTIMULATIVE: The active principles of the internal secretory organs have a definite stimulative and restorative action upon the glands which correspond to those from which the extracts are made."

Example: Bile and hepato-biliary insufficiency.

"EMPIRICAL: Certain animal extracts seem to influence certain clinical manifestations, and as a result, have come to be used without a definite and acceptable scientific basis."

Example: Parathyroid and paralysis agitans.

"SPECIFIC: Finally, it has been found that extracts of certain organs exert a definite physiological influence."

Example: Liquor Hypophysis and uterine muscle during labor.

But the ductless glands are so closely interrelated that one cannot be deranged without damaging the complex. It has been said that "Pluriglandular disorder is much more frequent than disorders involving a single gland of internal secretion; hence, the reinforce-

ment of an indicated organotherapeutic extract with one or more synergists many times radically alters the results for the better." It is not sufficient to treat one gland—when each one is dependent on a host of others.

13.—Infectious Diseases.

The communicable diseases are infectious in origin and not etiologically responsible for a distinct endocrine disorder, but collectively, they leave a broad train of dyscrinism in their wake.

Since the adrenals are so extremely susceptible to external influence, they are easily "worn out." And the effect that such diseases have upon the adrenal glands is considered in "Practical Organotherapy," previously referred to, from which I quote the following: "Hypoadrenia is a complication of all the serious acute infectious fevers, since the adrenals are so intimately connected with the 'driving' of the body and are so susceptible to toxemia that the ultimate reduction of the accustomed adrenal stimuli is responsible for a slowing down of many of the sympathetic-controlled functions of the organism. Too often this sympathetic asthenia is the actual cause of death from disease of this character." However, if the case does not come to post-mortem, we are apt to find the typical hypoadrenal syndrome of "asthenia, sensitiveness to cold and cold extremities, hypotension, weak cardiac action and pulse, anorexia, anemia, slow metabolism, constipation and psychasthenia." If the fire is out, the only way to get warm is to replenish it. If the adrenal supply is low, replenish it.

Many of the acute infectious diseases also affect the thyroid, that synergist of the adrenals, and a condition of hypothyroidism results. Quoting Hertoghe, "All the infectious diseases of early age and of later on, fall heavily on the irritability of the thyroid gland."

This depletion must be similarly supported by organotherapy.

14.—Mentally Deficient Children.

The defective or backward children, the feeble-minded and idiots are many of them defective pluriglandular victims. The pineal, pituitary, thyroid, thymus and adrenals may be one or all at fault. Sajous states that "any disease capable of injuring the ductless glands sufficiently to inhibit their functional activity, impairs correspondingly the development and functional activity of the brain, by reducing the supply of secretions this organ requires to carry on these physiological processes.

"In the majority of functional cases of feeble-minded and backward children, met in current practice, the predominating pathogenic factor is hypothyroidism, though deficiency of other internal secretions is also discernible in most instances. Whenever the father or mother is a mental defective or both parents show signs of defective activity of one or more ductless glands, or are mental defectives, organotherapy should be instituted as soon as pregnancy is recognized."

Dana and Berkeley have reported good results in the administration of pineal extracts at certain homes for the feeble-minded. As a rule, however, pluriglandular therapy is more effective. I wish to quote here a few sentences from an article I wrote on this subject in 1920. "At all events, the pluriglandular feeding of defective children has been a good deal more successful in my hands, as well as those of a good many of my friends, than thyroid or pituitary or thymus alone, all of which have been recommended in the literature as of use in these cases. . . . The miraculous change in the thyroid cretin, made possible by the use of thyroid

extract, has been one of the most magnificent advances in medicine, and it is well known that children that have the typical manifestations of hypothyroidism, can be made to grow and develop in a wonderful manner by supplying the missing hormone." Chas. Herrman reports three cases of sporadic cretinism in one family who showed marked improvement when administered a combination of the extracts of thyroid, pituitrin and suprarenal glands.

Glandular therapy must be used persistently. Watch results carefully and modify according to progress and symptoms. Use every associated effort that will favor improvement, being particularly attentive to proper elimination, and mineral salt metabolism.

15.—The Dystrophies of Growth.

It has been recognized for sometime that normal growth is dependent upon the proper functioning of the thyroid, pituitary and gonads. Infantilism may be caused by a number of glandular dysfunctions. Deficient thyroid or ovarian secretion and hypopituitarism have distinct symptom complexes.

The stimulating action of the thyroid on the ovaries has been used to good advantage in the treatment of ovarian insufficiency with the various manifestations —one of which is infantilism.

The hypophysis, or pituitary, has much to do with the chemical control of development, and while it may not be so important as the thyroid it is more important than some have thought. So far, I have used the desiccated anterior lobe of the pituitary with advantageous results in enough cases to establish my confidence in this form of treatment. Suffice it to say that many deficiencies in children have a pronounced pituitary origin and it is a routine in my work to study all such children from a pituitary standpoint. Many

cases could be cited in which pituitary substance, combined with thyroid, gave splendid results.

It remains for us to refer to the use of pituitary extracts in the treatment of these conditions. Pituitary medication does not cure hypopituitarism. There can be no doubt, however, about the value of substitution therapy with pituitary extract. The whole gland sometimes effects a cure, but often there is a recurrence of the symptoms unless the necessary dosage is kept up.

With dwarfism proper there is not so much chance for benefit from organotherapy, for many cases are due to heredity, showing no dyscrinism as an etiological background. Treatment of the cretin dwarf, where there is a well-organized thyroidism, has already been mentioned. There is one noticeable fact about the disproportionate dwarfs, however (Bassoe), and that is the large size and excellent functional conditions of the genitalia. This would suggest the production of an excess of the gonad hormones. This genital theory actually has been advocated, most recently by a German writer—G. A. Wagner. As far as I am informed, there have been no results recorded with this form of dwarfs from organotherapeutic treatment.

Gigantism is the hyperpituitary syndrome most peculiar to children, as acromegaly is really the post-adolescent manifestation. According to Horrax, the hyperfunction of the anterior lobe of the pituitary, which causes gigantism, will finally lead to a hypofunction. In "Practical Hormone Therapy," there is a chapter devoted to the consideration of the pituitary body, from which the following quotation is taken:

"In acromegaly the usual condition of hyperpituitarism may eventually become what is termed 'dyspituitarism,' and in such cases, moderately good results have followed pituitary medication while pluriglandular therapy has also been recommended."

Engelbach and Tierney, besides recommending the

treatment of any intercurrent infection as a lues, together with X-ray, radium and surgery, make a case report in which the patient "for a number of months at a time received considerable benefit from simple substitution of anterior lobe products. These were given in the form of anterior lobe extract and anterior lobe substance. During one interval this case was also markedly benefited by pituitrin (post lobe) treatment." Cushing also advises organotherapy.

16.—Diseases of Nutrition.

In the treatment of children suffering from malnutrition, mention has previously been made of a number of organotherapeutic measures which vary with the symptoms. Thymus, thyroid, lymphatic, adrenal and pancreas have all given good results.

In malnutrition associated with anemia, blood dyscrasias such as purpura, hemophilia and scurvy have been found clinically and experimentally to be due to faulty mineral metabolism, reduced alkalinity of the blood, changes in the viscosity of the blood and disturbances of the hemopoietic organs and lymphatics. Thyroid extract and the gonads increase the hemoglobin content. Thymus gland substance and calcium salts help to favor coagulation time. Iron compounds, hemoglobin, lymphatic substance and arsenic compounds give satisfactory results.

Cacodylate of iron, hypodermically, may be a better hematinic in what might be called "acute anemias"—those rapidly developing conditions of anemia due to toxic and nutritional derangements. However, in such cases it may be advantageously supplemented by hemoglobin, which is a much more satisfactory remedy in conditions where hypodermics are not acceptable. According to several French observers, hemoglobin exerts a homostimulative effect comparable to the effects of

other organotherapeutic producers, i. e., it definitely stimulates the hemopoietic organs, just as thyroid extract stimulates the thyroid gland or adrenal substance stimulates the adrenals.

Certainly in simple anemias, as well as in chlorosis and secondary anemias in lesser degree, the Hgb.—index is remarkably raised following a course of hemoglobin by mouth. Hemoglobin may be very properly combined with other remedies which reinforce its hematinic and reconstructant value.

Diabetes, with its associated acidosis, has been treated with good results with pituitary substance.

P. Lereboullet emphasizes the importance of the use of what is called in the United States Pharmacopoeia "Liquor Hypophysis," in the treatment of diabetes insipidus. In regard to the use of preparations of the posterior lobe of the pituitary gland, he states that "they have proved their certain symptomatic action. Both from the standpoint of diagnosis, therapeutics and pathogenesis, the results achieved form one of the most interesting chapters of modern organotherapy."

Many other practitioners have had the same good results.

Experimental work has been done along the line of the administration of pancreatic substance, and the stimulation of its secretion by the use of secretin. It may be said that the removal of the pancreas brings on immediate glycosuria, which may be mitigated or controlled by the successful implantation of pancreatic tissue and, quite often, by the administration of a pancreatic preparation rich in its internal secretory product. This is backed by much experimental evidence. The treatment of diabetes, therefore, resolves itself into adopting measures to counteract the excessive metabolism, and to increase the internal secretion of the pancreas.

The dermatoses in children which are amenable to

organotherapy, are the eczemas. Usually these are thyroid deficiencies, and are benefited by administration of this gland.

Eisenstaedt states in reference to the treatment of eczema: "I have repeatedly seen patients materially aided by small doses of thyroid substance, and several neurotic and underdeveloped young women I am sure were markedly benefited by the use of corpus luteum extract."

Attention has been called by Haines to the fact that the intense itching can be nicely controlled by adrenin.

In the rachitic children, I have frequently found the stigma and *disturbances of calcium metabolism* and lymphatic circulation. The disturbance has been frequently overcome by administering a pluriglandular formula including thyroid, a twentieth of a grain of parathyroid, with lymphatic gland substance and sometimes small doses of the other gland substances in cases showing marked evidences of one or another of the above glands mentioned to be at fault.

Gordon has obtained excellent results in the treatment of rickets by administering thyroid extract. One eighth of a grain, given twice a day, starts the treatment. This is gradually increased till as much as one grain three times a day can be given. In order to avoid untoward symptoms, the child is carefully watched and the medication is administered for ten days and then stopped for the same time. He recommends in the interim, elixir of the glycerophosphates of lime and soda in half dram doses two or three times a day and changes this at times to the compound syrup of hypophosphites. To those cases that are associated with convulsions, however, he gives one eighth grain of thyroid extract with calcium lactate, two grains two or three times a day, gradually increasing the thyroid to one grain three times a day.

In direct medication, I wish to mention five things that need to be accomplished (quoting from a previous discussion of the subject):

"1. Replace the missing mineral element in the blood and bones—calcium.

"2. Replace the missing vitamines. In therapeutics this is accomplished by suitable dietetic regulation and by organotherapy.

"3. Antagonize a tendency to acidosis.

"4. Enhance the mineral content of the blood. In addition to the calcium salts, we can advantageously give the salts secured from fresh vegetables.

"5. Favor the restoration of the conditions which cause or aggravate the disturbed mineral metabolism. This is best accomplished by suitable organotherapy. Many times small doses of thyroid extract will influence the nutrition of the rachitic child in a most decided manner. Thymus extract has been recommended upon the theoretical ground that the thymus controls calcium metabolism. . . . pituitary is occasionally recommended, while total adrenal substance has facilitated recovery."

The treatment and prevention of dental caries in children is important. This diseased state is due to insufficient calcium supply. In conditions where the alkalinity of the saliva is lessened, which in itself is an indication of calcium starvation, parathyroid, adrenal extract and anterior pituitary extract at times associated with thyroid and calcium lactate, have wonderful effect in preventing defects of the enamel or dentin. The rational treatment would be to eliminate lime salts and this is indeed a difficult task. Here also pluriglandular therapy will help. Extract of the posterior pituitary lobe and gonads are indicated. In the prophylaxis of caries in children, we therefore find three essential requisites, i. e., the saliva should be alkaline, and a cor-

rect balance of the metabolism of calcium which is necessary for health should be maintained.

17.—Glandular Disturbances.

Hypothyroidism is responsible for a variety of symptoms. No case of myxedema or cretinism, or even of the less marked but more important minor forms of thyroid insufficiency, shows the manifestations of thyroid dysfunction alone. Metabolism as a whole is reduced—and the thyroid is not the only endocrine gland concerned in the regulation of metabolism. Minor hypothyroidism is among the commonest of disorders. It complicates pediatric problems more often than almost any other single condition except, of course, disorders of infective origin. Suboxidation is the rule in these cases, and the special form that it manifests is a condition of cellular infiltration which varies in degree and in the number and location of the organs attacked. In the treatment of these cases the addition of the mineral salts to thyroid extract is based on sound reasoning, and clinical experience emphasizes its value. Thyroid extract is practically always given in the hope of increasing cell chemistry, for any degree of hypothyroidism from the least to the most serious, always entails reduced metabolism.

In the hyperthyroid cases, on the other hand, we have an increased cell chemistry and a decided plus metabolism as a result of the excessive thyroid stimulation. This condition has been exhaustively treated in a previous monograph, so the consideration here will be brief. No organotherapeutic measures will avail, if other etiological factors, as sources of infection or unbalanced emotional status, etc., be overlooked. The endocrine treatment resolves itself into antagonistic therapy. The adrenals are, of course, irritated and the

normal antagonist to adrenal action is the pancreas, which experimentally has a definite sedative action. Pituitary substance may be added for its supportive action on the heart.

Consideration of the thymus gland is distinctly within the scope of pediatrics for the gland is supposed to atrophy before puberty. In cases of thymus insufficiency with stunted growth and nutritional disorders, enlarged adenoids and other symptoms of lymphatic disturbance, thymus combined with anterior pituitary and lymphatic glands give good results.

Suitable gland feeding has been claimed to reduce the size of such abnormal hypertrophy and thereby modify mouth breathing, snoring and the nutritional disorders of this class. In these cases, especially where the stature is small and development is slow, this combination may be given with hope of better results than the lymphatic feeding alone.

Conditions of hyperfunction and hyperplasia of the thymus are of serious import and not very amenable to treatment. X-ray and surgery are practically the only recommendations of the medical profession.

The pituitary disturbances have been discussed under growth dystrophies, so will not have to be referred to here.

Investigations on the pineal gland have given such conflicting results that nothing definite can as yet be promised along the lines of therapy. Quoting from Gordon, "Rational and scientific treatment by means of pineal gland substance or extract is at the present impossible, in the light of our meagre knowledge of the functions of the gland. Any organotherapy with this gland must remain experimental until this uncertainty is removed by future investigations.

"The use of pineal extract in doses of one twentieth of a grain two or three times a day is being advocated by some for delinquent children who do not show any

deficiency in the thyroid or pituitary hormones, and without any organic changes, to be administered alone or in conjunction with the other gland extracts."

Dysfunction of the sex glands in early life has presented many phases. Cryptorchidism or the condition popularly known as "undescended testicle" is not always a permanent condition. I have reported a case in which organotherapy consisting of pituitary, thymus and thyroid substance corrected the disorder. In fact, in most of the cases of sex gland dystrophies, our attention is of necessity turned to these other glands. Many forms of organotherapy are known to effect genital function. Thyroid extract has been used time and again to control menstrual disorders. Its use has been equally efficacious in reestablishing a more nearly normal sexual development and activity in individuals suffering from both major and minor thyroid insufficiencies. The orthodox treatment of the Froehlich syndrome (dystrophia adiposo-genitalis) is pituitary feeding, and one of the therapeutic results is a favorable modification of sexual development and function.

Quite the most important phase of organotherapy in dysgenitalism is the use of extracts of organs corresponding to those affected—the ovaries or testes, as the case may be.

18.—Chorea, Epilepsy and Enuresis.

In the treatment of chorea, many clinicians and investigators are having success with thyroid, parathyroid and pituitary preparations.

A properly dosed pluriglandular preparation containing anterior pituitary, thyroid and thymus is also being used with considerable success.

Briefly, the object of the treatment of epilepsy should be to activate catabolism of spasmogenic wastes; to enhance oxidation processes and thus keep the blood

free from abnormal accumulation of toxic wastes or vasomotor irritants; dietetic measures to reduce the quantity of such wastes formed, and finally to cause rapid elimination of these wastes through increased urination, perspiration and through proper bowel function. The adrenals and thyroid must be functionating normally for proper tissue oxidation. In certain cases the faulty element may be a diminution or absence of ovarian hormones; in the male, of testicular hormones.

In these cases, ovarian extracts and testicular extracts respectively are helpful. When bromides and chloral are pushed we are doing the very opposite to that which we desire to accomplish—depressing endocrine functions and accumulating more wastes—and while we place the patient in a delusive calm, by depressing or sedating his nerves, we are aggravating the condition and sacrificing whatever chance one may have of being cured from his terrible affliction. I have had wonderful results in many cases from administering thyroid extract in small doses, only one half grain, three times daily. In cases showing pituitary stigmata I have employed anterior pituitary extract, one grain, together with the thyroid. At times ovarian extract and testicular substance, as mentioned heretofore, served well.

We must not lose sight of the fact that the parathyroids control the destruction of toxic substances which seem to have a special predilection for attacking the nervous system. In many of my cases I have combined parathyroid, thyroid, thymus gland substance (the latter controls phosphorus metabolism) with the anterior pituitary lobe extract, which seemed to have a favorable influence. Iodides and salicylates or salicin stimulate the adrenal center and are synergistic.

The treatment of enuresis, which is one of the symptoms of hypoplasia, is considered by McCready.

"Whether the secretion of the thyroid gland is the

particular element in cell nutrition which is lacking or whether the administration of thyroid extract acts, by its stimulating effect, upon other glands is a question that further investigation is necessary to settle. The administration of thyroid extract will, however, in suitable cases, accomplish a great deal. It may be found that the extracts of other glands will do better. I have had as yet but little experience with any but that of the thyroid. The thyroid extract should be given in small doses. It is my custom to give from half a grain to two grains twice daily. If enuresis be present it will usually cease about the end of the first or during the second week. The administration of thyroid extract will not only relieve the enuresis but will also cause a very marked improvement in the general physical and mental condition."

VI

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