

# **SOME RECENT DEVELOPMENTS AND TRENDS IN CLINICAL ENDOCRINOLOGY\***

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**T**HE purpose of this presentation is not to give you endless statistics or to recite details of endocrine therapy which readily can be gathered from any of half a dozen, good, recent, endocrinology textbooks. Rather, I wish to offer you a broad over-all view of developments in the laboratory as well as in the clinic—to gain, if we can, a perspective of the trends—to see where endocrinology seems to be going.

## **THE HYPOTHALAMUS**

For many years it has been clearly recognized that the pituitary function is greatly influenced not only by the function of the other endocrine glands and the over-all nutritional status of the body, but also by the nervous system—especially the hypothalamus. These facts have been pointed up particularly well by the work of Hume<sup>1</sup> in this country, and Harris<sup>2</sup> in England. Recently, a piece of information has been reported of new, and I think important, experimental work. Slusher and Roberts<sup>3</sup> have made extracts from the brain and from the hypothalamus that stimulate the anterior pituitary. One, a lipoid extract from the posterior hypothalamus, when injected produces an ACTH-like effect if the pituitary is intact, but if the animal tested has been hypophysectomized no such effect is seen, thus demonstrating a hormonal stimulation of the anterior pituitary.

## **THE PITUITARY**

### **Anterior Lobe**

The extensive investigations concerning hormones of the anterior lobe of the pituitary continue to be directed toward resolving questions such as: Does ACTH have two components, one which affects growth of the adrenal and the other function? What is the true nature of growth hormone? How does it correlate with other factors and, what is the mechanism by which it acts? What is its relation to growth? to healing? to cancer? The answers to such questions should become of great use to clinical practice.

For many years, in this country and abroad, a tremendous amount of effort has been exerted in an attempt to unravel the secrets of the growth hormone. It

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\* *From an Address presented at the Dallas Academy of Internal Medicine, Dallas, Texas, on October 12, 1954.*

has been reported to have various metabolic effects—such as those of fat mobilization, pancreatic stimulation, anti-insulin or glycostatic activities. Whether these metabolic effects are separate factors or are a part of a complex effect of one natural hormonal protein entity will become apparent only when pure-protein hormone products are available. One of the problems concerning growth hormone which has attracted the greatest attention is how it is related to diabetes. The work of Young<sup>4</sup> and Reid<sup>5</sup> supports the postulation that growth hormone itself may cause lasting diabetes. Raben and Westermeyer<sup>6</sup> reported evidence that the two factors are separable. This apparent discrepancy seems now to have been entirely clarified, however, since Reid showed that the Raben-and-Westermeyer product which produced growth without diabetes at a low pH level is diabetogenic if used at a pH of 10. In this respect it is interesting that at the recent conference on growth hormone in Detroit, Houssay<sup>7</sup> announced that prolactin had a diabetogenic action.

An accurate, expeditious method of assay for growth hormone is much needed. Kinsell, Michaels and Larsen<sup>8</sup> attempted to measure growth hormone in the blood of acromegalic patients by the method of rat epiphysal cartilage growth, but the correlation apparently was not good. Russell and Coppiello<sup>9</sup> demonstrated some years ago that the injection of growth hormone causes a fall in the levels of amino acid in the blood of nephrectomized rats, but we failed to measure quantities of this hormone in the body of man by this method. It is of interest in this regard that Carballeira and co-workers<sup>10</sup> demonstrated a fall in the amino-acid levels in the blood of man after injection of growth hormone. At the growth hormone conference previously mentioned, Segaloff<sup>11</sup> claimed the ability to measure differences in growth hormone levels at various clinical states. In our own laboratories, Westermeyer<sup>12</sup> recently has shown that as little as 5 micrograms of relatively pure growth hormone preparation can be measured by its ability to force radioactive sulfur into the epiphysis of the hypophysectomized rat.

Methods are being perfected for the bio-assay of several pituitary hormones so that they can be clinically applied. In our own laboratories we are accumulating data on the measurement of the interstitial cell stimulating hormone (ICSH) that, presumably, is identical with luteinizing hormone (L.H.). Hypophysectomized rats are used and the phosphatase content of the animals' prostates is measured and compared to the amount in the prostates of controls. The increase in phosphatase content is dependent upon the amount of androgen produced by the testes, the Leydig's cells of which are stimulated by the injected material.

Dobyns and Steelman<sup>13</sup> recently have found that pituitary extracts containing thyroid-stimulating hormone can be treated in such a way as to separate exophthalmos-producing substance almost entirely from thyroid-stimulating effect. At this time, neither this method of separation nor methods of assay for growth hormone or for ICSH effects have clear clinical applications.

The clinical use of ACTH assays will be spoken of in connection with the adrenal.

In the clinical diagnoses of pituitary failure, the findings of low levels of urinary gonadotrophins and of 17-ketosteroids are useful if interpreted from the standpoint of the whole clinical picture. It should not be forgotten that such tests as testicular biopsy (or the even simpler semen examination) or endometrial biopsy which are available to almost all clinicians make excellent qualitative assays if properly applied.

### Posterior Lobe

A recent development concerning the posterior pituitary which will have no *direct* effect on clinical medicine, will almost certainly have an extremely important indirect impact on it. I refer to the announcement that Du Vigneaud and his group<sup>14</sup> at Cornell have succeeded for the first time in synthesizing a protein hormone: pitressin and pitocin. If one protein hormone can be synthesized, then perhaps many hormones can be. It should be possible then to obtain protein hormones in perfect purity and, if desired, possibly in modified form and activity.

### Hypophysectomy

Another point, quite removed from the above but pertaining to the hypophy-sis, is the matter of hypophysectomy in the human being for hypertension, diabetic retinopathy, or as palliation in malignancy. It is a formidable procedure, and a complete hypophysectomy in the human being is difficult to perform. I have seen five patients in whom the procedure was attempted. Malignant exophthalmos was present in two, one of whom had diabetes mellitus and hypertension. One of these patients was operated upon before the days of cortisone; the anterior lobe was purposely damaged, but Simmonds' disease inadvertently was produced. The exophthalmos was greatly improved, but the patient eventually died of pituitary failure. The second patient died of repeated severe arterial thromboses, but she had shown much diminution in exophthalmos within two weeks postoperatively. The other three each had metastatic malignancy, from the breast in two, from the adrenal in the third. Although complete hypophysectomy was attempted, it was found later to be incomplete in all three. Pain seemed to have been relieved in one, but in the other two the disease appeared to have been unaffected. Other experience in this country at Memorial Center, New York Hospital and Sloan Kettering Institute,<sup>15,16</sup> Johns Hopkins, and in San Francisco<sup>17</sup> is still meager. Luft and Olivecrona in Sweden<sup>18</sup> have had the most experience. At the time of the Swedish report mentioned, it included 26 patients. Seven had advanced malignant hypertension; three of the seven died postoperatively, and two patients lived two months and five months, respectively. The mortality rate is high, both from unexplained post-operative cerebral edema and from uncontrollable hypotension with renal failure in patients who had hypertension or diabetes. Luft<sup>19</sup> subsequently re-

ported that Olivecrona had performed hypophysectomies on six patients with severe diabetic retinopathy. Two died; one was greatly relieved; and three were improved. Poulsen's<sup>20</sup> report of a patient having Simmonds' disease seems to prove that diabetic retinopathy may disappear after severe pituitary failure, but few physicians are willing to subject a reasonably well patient to the radical procedure of hypophysectomy and, for the seriously ill, the risk is great and in those with extremely advanced diabetic retinopathy the chance of much improvement in the eye seems remote.

## THE THYROID

With regard to the thyroid, one of the interesting recent developments is the recognition by radio-paper chromatography of a new thyroid substance, and its identification by Gross and Pitt-Rivers<sup>21</sup> as Tri-iodothyronine. These workers and others have investigated its effects. Blackburn and his associates,<sup>22</sup> for example, showed its effect in single injections to be about four times as strong as l-thyroxine, though this may not hold for larger doses and continued injections. With one dose, maximum effects are seen in about two days, as compared to nine days for thyroxine. Total decay occurs in about 15 as compared to 24 days for thyroxine.

Though these findings increase our knowledge of the thyroid, it is not clear how they will be very helpful in clinical practice. Werner and associates<sup>23</sup> have used Tri-iodothyronine in a test to compare thyroid function in a normal person with that in a patient having Graves' disease, and have produced evidence that Graves' disease is not of pituitary origin, as has been so generally hypothesized. In the tests, they used huge doses of 2.0 mg. per day, the equivalent of about 45 grains per day of thyroid. Such a dose markedly depressed radioactive-iodine uptake in normal persons in whom it was decreased from 53 to 15 per cent. On the other hand, in those having Graves' disease, the uptake decreased only from 71 to 63 per cent. In these hyperthyroid patients, sodium iodide reduced the protein-bound iodine (P.B.I.) content from 11.3 to 8.5 micrograms per cent, and after this reduction and during iodine therapy, thyroid-stimulating hormone (T.S.H.) quickly raised it again. Werner believes that this fluctuation of P.B.I. content indicates that the iodine acts directly on the thyroid cell and not on the T.S.H. As a test for hyperthyroidism, the procedure may prove very useful. Unfortunately, the diagnosis frequently is in doubt in patients with poor cardiac reserve, and the test has the disadvantage of adding stress to a weak heart; under such circumstances unless it is used with caution, the test may be dangerous.

Interesting supporting evidence of Werner's hypothesis concerning the action of iodine has been presented both by Halmi and associates<sup>24,25</sup> and by Vanderlaan.<sup>26</sup> They have shown that while the release of thyroid hormone is under the influence of T.S.H., the trapping mechanism for iodide is not. In hypophysectomized animals which have been injected with known quantities of T.S.H. and known quantities of iodide, it is the original iodide in the thyroid that regulates the further amount of iodine taken up by the gland. This appears to indicate that normally the iodine uptake for fabrication of hormone is gov-

erned by a mechanism inherent in the thyroid itself, and that quite possibly in Graves' disease the excess production of hormone primarily is a thyroid and not a pituitary abnormality.

Another test of clinical interest but still in the investigative phase is one based on the  $I^{131}$  thyroid uptake before and after the administration of 10 to 25 units of T.S.H. It was reported at the American Goiter Association meeting in 1950 by Querido and Stanbury<sup>27</sup> that such a test might be used to differentiate primary myxedema in which there was no response to T.S.H., from hypothyroidism of pituitary origin in which there was a response. Jefferies and associates<sup>28</sup> have investigated this test and believe that it is useful for the purpose mentioned and also to indicate whether persons with low metabolic rates have normal or low thyroid reserves. The test also can be used to assist in corroborating or in excluding the presence of hypothyroidism. In a child especially, it is a great advantage to obtain a prompt estimate. For example, if a child has been treated for a long time with desiccated thyroid under the assumption that hypothyroidism is present, normal function of the thyroid may have been markedly suppressed by the treatment. Theoretically, in such an instance, instead of waiting two or three months to test thyroid function, it may be tested at once. This promises to be a useful test. Dr. Penn G. Skillern of our group is analyzing the results of the test in 72 of our patients. So far our findings have been valid in all cases of primary myxedema. Four patients, each of whom has taken thyroid for a long time and who, we think, do not have myxedema, have not responded to one dose of T.S.H. However, in two patients each having myxedema and pituitary tumor, the increases in uptake were slight: 4 to 11 per cent in one, and 34 to 36 per cent in the other. Perhaps in these two patients the poor responses to T.S.H. are similar to the poor responses to ACTH in patients having pituitary failure, and a priming and second or third doses may be necessary. More time is necessary to evaluate our findings.

So far as tests for hyperthyroidism are concerned, the over-all picture has changed little in recent years. Careful clinical evaluation still outshines all tests, and no combination of tests gives completely accurate results. Determining the basal metabolic rate remains a standard part of examination. In most medical centers  $I^{131}$  tracer uptake is used to great advantage in evaluating untreated patients having Graves' disease, and the use of a single tube seems as satisfactory from a practical standpoint as the use of multiple counters. Unfortunately, the test may be invalidated by the previous use of iodine in any of its many forms—sometimes for as long as years after its administration.

Many combinations of  $I^{131}$  have been studied as tests for hyperthyroidism. The fact that  $I^{131}$  is taken up faster in hyperthyroidism than in euthyroidism has led to the use of the "accumulation gradient." Urinary excretion rates or amounts per 24 hours may be determined. Faster answers to diagnostic questions may be had by the use of intravenous  $I^{131}$ . Turnover or clearance rates have been calculated by making repeated measurements over the gland and in the blood and urine.  $I^{131}$  precipitable with protein from the plasma may be used and the so-called conversion ratio, that is, the ratio of total plasma  $I^{131}$  to serum precipitable  $I^{131}$ , also is useful. Most of these methods are time consuming and

not well adapted to routine use in clinic or office practice but, what is more important, with none of them is it possible to escape the overlap of hyperthyroidism and euthyroidism.

Protein-bound iodine (P.B.I.), usually thought of as hormonal and as thyroid iodine, is useful, but the P.B.I. test is difficult to perform and there are unexplained false values usually high but also sometimes low. Perhaps further experience with butanol fractionation may explain some such discrepancies.

Until the cause of Graves' disease can be established,  $I^{131}$  therapy appears to be here to stay. It continues to gain in popularity after 14 years of use. We have now used  $I^{131}$  in the treatment of more than 1400 patients having hyperthyroidism, most of whom have had Graves' disease. Our rule is to use  $I^{131}$  only in patients more than 35 years of age, but our inclination to lower the minimum age limit continues.  $I^{131}$  is effective with our method of handling in almost 100 per cent of the patients. It is true that not all patients have been traced, so that some poor results may have escaped our attention, but I know of only one patient in whom the treatment had to be abandoned for surgery. Seventy-five per cent respond fully to one dose, and less than 1 per cent need four or more doses. Hypothyroidism occurs in patients treated with  $I^{131}$  about as frequently as it does in patients surgically treated. Transient tetany in one patient has been the only other complication of  $I^{131}$  treatment that we have seen.

In nodular goiter,  $I^{131}$  treatment is not nearly so satisfactory: larger doses, longer duration of treatment, incomplete disappearance of the goiter, and a slight risk of carcinoma are deterrents to its use. According to Crile and Dempsey,<sup>29</sup> the possibility of thyroid carcinoma's being present in multinodular glands in which there is no special reason to suspect cancer is less than 1 in 6000. When surgery is undesirable,  $I^{131}$  can be used. We recently have used from 30 to 50 millicuries of  $I^{131}$  in a single initial dose as treatment of nodular goiter. Of 10 patients having nodular goiters who each received 50 millicuries of  $I^{131}$ , in 9, complete or almost complete control of the disease was obtained within four months. Because it often is stated that one disadvantage of  $I^{131}$  in the treatment of nodular goiter is its inability to remove the mass, the impression is that the reduction in size that does occur is not useful. However, it frequently happens that a large nodular goiter may shrink to the point where it is scarcely noticeable. In selecting therapy for patients in whom the risk of surgery is prohibitive,  $I^{131}$  treatment should be kept clearly in mind as of value in relieving the pressure symptom from a large goiter in the neck or in the mediastinum.

Although the use of propylthiouracil or methylthiouracil is diminishing in popularity, I believe that they still have a place in treatment. In patients having Graves' disease and small-to-moderate-sized goiters who are treated with the thiouracils, complete control for one to two years is followed in about 77 per cent of the cases by lasting remissions. In patients having very large diffuse goiters or toxic nodular goiters who are operated upon, only 50 per cent have lasting remissions. In young people in the selected group mentioned, thiouracil treatment has the advantage of leaving the thyroid gland intact and presumably normal, and of causing no lasting complications.



There is little new to be said about the treatment of thyroiditis. In the sub-acute form, cortisone may relieve symptoms till the disease abates; or symptoms may subside rapidly under propylthiouracil. Struma lymphomatosa, when suspected and diagnosed by needle biopsy, may largely disappear when 3 grains of thyroid is administered daily. The mechanism by which struma lymphomatosa is thus controlled has been explained in a most illuminating study of the disease and I think the most important paper on the subject since the disease was first recognized. Gribetz, Talbot and Crawford<sup>30</sup> showed that in this disorder the P.B.I. may be high and yet there is no hyperthyroidism. This is explained by the fact that the butanol-extractable protein-bound iodine level is not elevated. It seems entirely reasonable to believe that the thyroid under these circumstances is producing an abnormal product incapable of the natural power of pituitary inhibition and that therefore high titers of T.S.H. cause excessive thyroid growth. This hypothesis seems to be corroborated by the finding that thyroxine fed to such patients does not cause a rise but a fall in the level of total protein-bound iodine.

## THE PARATHYROIDS

In regard to the parathyroid glands, two points come to mind: The first is that Grollman<sup>31</sup> has just reported that the administration of parathyroid hormone is effective in nephrectomized animals, a finding that seems to settle the long-standing controversy as to whether the hormone reacts solely on the renal tubule. The second point concerns hyperparathyroidism and the Howard-intravenous calcium test. Dr. Robert Schneider of our group—has used the test in 30 patients in whom hyperparathyroidism was suspected. The results in no case proved to be wrong, although several tests gave borderline results that were too difficult to interpret to be useful. In one of the 30 patients, the Howard test was positive and hypercalcemia persisted, but surgical exploration revealed no adenoma in the neck. Exploration of the mediastinum disclosed a tumor on the aortic arch. In our last patient operated upon recently, the outcome has not been so fortunate. Although the patient had a positive Howard test, persistent hypercalcemia, and hypercalciuria, exploratory surgery of the neck and mediastinum revealed no tumor.

## THE PANCREAS

With regard to the pancreas, there is only one point I wish to mention. You may not all be acquainted with the fact that the hormone glucagon—the hyperglycemic glycogenolytic factor (H.G.F.) of the pancreas—has been definitely isolated, crystallized, and its component amino acids have been defined. Intravenously, it causes a sharp rise in the level of blood sugar, which lasts about one hour. It apparently is the first normal line of defense against hypoglycemia.

Its physiology, its relation to diabetes, and its application to clinical use are being explored.

## THE ADRENALS

### Adrenal Medulla

With respect to the adrenal medulla and the diagnosis of pheochromocytoma, in addition to the standard tests based on inhibition of adrenalin and noradrenalin (regitine, benzodioxane) as well as provocative tests (histamine), the measurement of urinary products of adrenalin or noradrenalin is proving a very accurate guide. The estimate of catechol amines can be accomplished by chemical, chromatographic fluorometric, or by biologic means. A very accurate method is said to be that of Weil-Malherbe and Bone.<sup>32</sup> Von Euler's<sup>33</sup> method is biologic. Attention is directed to the very valuable paper by Goldenberg and associates<sup>34</sup> on chemical screening methods.

### Adrenal Cortex

The clinical status of Addison's disease is not changing rapidly. The best test is the intravenous ACTH test with estimation of urinary 17-hydroxysteroids as well as 17-ketosteroids. The Power-Kepler water-excretion test is simple and, if intelligently interpreted, usually accurate. If doubt exists, the 24-hour excretion of 17-hydroxycorticoids may be measured after intravenous administration of ACTH. In women, the presence of normal neutral 17-ketosteroids in the urine usually excludes the possibility of Addison's disease, though it should be remembered that some normal women have very low levels of 17-ketosteroids. Nowadays, the treatment of Addison's disease with cortisone or hydrocortisone usually is extremely simple, and desoxycorticosterone acetate (D.O.C.A.) or extra salt seldom is needed. Overtreatment with cortisone is to be avoided for fear of suppressing remaining adrenal function. The great disadvantage of the use of cortisone or hydrocortisone in Addison's disease lies in the fact that withdrawal of therapy may be disastrous. Some patients who have lived for many years in poor health because of undertreatment may blossom into apparently excellent health under the effects of small doses of cortisone and suddenly die as a result of the drug's having been carelessly omitted for two or three days.

In mentioning new developments relating to the adrenal cortex, one cannot omit electrocortin, more recently called "aldosterone," discovered in 1952 by Tait, Simpson and Grundy.<sup>35</sup> It is the sodium-retaining factor long known to be a very active constituent of the amorphous fraction of adrenal extracts. It has a sodium-retaining power said to be 120 times as great as desoxycorticosterone<sup>36</sup> and an action at least as great as cortisone in so far as cold stress is concerned.<sup>37</sup> It apparently has little effect on carbohydrate metabolism.

Aldosterone almost certainly is the substance that during the phase of water retention has been shown to be greatly increased in the urine of patients with



cardiac decompensation, cirrhosis of the liver, and nephrosis. It has been identified with certainty in one patient who had episodes of paralysis and high loss of urinary potassium without retention of excess sodium,<sup>38</sup> and more recently has been identified in normal urine.<sup>39,40</sup> In doses of 100 micrograms per day, the hormone has already been shown to have a marked effect on electrolyte balance and a slight effect on carbohydrate metabolism in Addison's disease. It also has the remarkable power of causing rapid fading of the pigmentation present.<sup>41,42</sup>

In a recent issue of *SCIENCE* (Nov. 5, 1954) in a report of the September Laurentian Hormone Conference, a paper by Tait<sup>43</sup> was mentioned. Tait outlined the methods used for the isolation and identification of aldosterone (electrocortin). He pointed out that aldosterone differs from most of the other adrenal steroids in that it possesses an aldehyde group at C<sup>13</sup>, has an extremely high sodium-retention potency, has a very small concentration in normal adrenal venous blood, and strangely enough appears to be little, if at all, under ACTH control.

Recently the discovery of a new, interesting, and clinically promising adrenal steroid has been announced.<sup>44,45,46</sup> It is a modification of hydrocortisone in which a halogen is attached in the 9, alpha position. The sodium-retaining and potassium-excreting effects of very small doses (25 to 100 micrograms) of the chloro- and fluoro-derivatives in adrenalectomized dogs are like those of D.O.C.A. Early trials in treating Addison's disease suggest that fluorohydrocortisone is considerably more effective than equimolar quantities either of D.O.C.A. or hydrocortisone itself.<sup>47</sup> Unpublished findings from early trials suggest that suitable dosages of fluorohydrocortisone may range from 0.5 to 2.0 mg. per day. Fluorohydrocortisone recently has become available for local use. It has not been found to be as useful as cortisone for treatment of connective-tissue diseases.

## ACTH

The assay of ACTH in the blood of man can be made by several methods. A highly sensitive method is that of Sayers and associates.<sup>48</sup> The results of various workers employing Sayers' method have been reviewed by Paris, Upson, and associates.<sup>49</sup> Two outstanding facts appear; namely, that this hormone may be measured in the blood of patients having untreated Addison's disease, but usually not in those having untreated Cushing's syndrome. It has been established that the production of ACTH can be suppressed by cortisone, and the correlation of this fact with certain new developments regarding virilism is important.

One of the most intriguing of recent developments in clinical endocrinology is a clarification of our understanding of virilizing syndromes. We cannot go into the differential diagnosis in any detail now, but let me recall some outstanding points to mind. The clinical manifestations of the virilizing syndrome vary according to age and sex.

In an infant boy having the congenital form of the disease, the penis may be very large; there may be evidence of excess androgen and yet he may be a sodium waster; he may vomit and mistakenly be considered to have pyloric stenosis, and therefore he may die of cortisone deficiency. A similar situation sometimes exists in prepuberal boys. Boys having this condition can be maintained in good health by cortisone.

In infant girls, a congenital defect may produce pseudohermaphroditism; in prepuberal girls, it may produce *pubertas praecox* with markedly advanced skeletal maturity, and tendency to masculinization; and in women, adrenogenital syndrome. Sydnor and associates<sup>50</sup> have shown that children having this condition have high levels of ACTH in the blood, which is consistent with poor production of cortisone. Many patients with this condition have abnormally high levels of urinary 17-ketosteroids which quickly will fall to normal with cortisone therapy and may be maintained at normal with dosages as small as 25 mg. per day orally.

The subject of virilization has been nicely reviewed by Jailer<sup>51</sup> who with Wilkins and associates<sup>52,53,54</sup> has done outstanding work in clarifying this issue. Jailer points out that in these individuals, ACTH produces an abnormal response: The levels of urinary 17-ketosteroids and pregnanediol go up. There is, however, no increase in 11-oxysteroids as there should be normally, no fall in the number of eosinophils, and no sodium retention. These effects occur normally if compound F is present. What then is the explanation? Hechter and others<sup>55</sup> showed that the normal adrenal can hydroxylate 17-hydroxyprogesterone to compound F; and it had been shown before<sup>56</sup> that 17-hydroxyprogesterone is masculinizing. It thus appears that the enzyme system concerned fails to produce the full metabolic shift that is needed to change 17-hydroxyprogesterone to compound F. Because of the tendency toward underproduction of cortisone and like materials, pituitary ACTH is overproduced. In response to excess ACTH, the adrenal in its attempt to produce enough cortisone-like materials, produces a continued excess of a masculinizing product. (There is still some difficulty with this theory at the moment, because although it was originally reported that 17-hydroxyprogesterone was androgenic, there is now doubt about this.<sup>57</sup>) If this explanation is correct adrenogenital syndrome, excluding that due to tumor, must be classed as an enzyme disease. Cortisone under these circumstances is a highly effective hormone for treatment. For similar reasons such a response may be studied and used in differentiating adrenal hyperplasia from adrenal tumor. In patients with tumor, the typical marked reduction in the level of urinary 17-ketosteroids is less likely to occur.

### Adrenalectomy

One last word about the adrenals, and that is concerning the status of bilateral adrenalectomy. Firstly, for control of hypertension: In the Philadelphia series, Jeffers and associates<sup>58</sup> last year reported their findings in 82 patients who had undergone bilateral adrenalectomies and most of whom had had

sympathectomies as well. The adrenalectomies had been performed 1 to 33 months before the report was published. The results were called excellent in 23 per cent; poor in 32 per cent. In the Boston series of Thorn and associates,<sup>59</sup> 15 patients (12 having malignant hypertension and 3 having chronic glomerulonephritis) underwent bilateral adrenalectomies. Five survived more than one year. In only one of these five patients was there definite improvement that lasted more than one year. One patient had improved greatly and returned to work, but 11 months after the operation died of coronary occlusion. Five patients with malignant hypertension resistant to other modes of treatment have been under study by the Research Division before and after bilateral adrenalectomy. Four of these, who were in renal failure, showed no benefit from the operation, which only complicated the rapid and inexorable progress of their disease. The other survived four months, manifesting only slight decreases of average arterial pressure during episodes of adrenal insufficiency and maintaining at other times the severe hypertension from which eventually he died. Secondly, let me mention bilateral adrenalectomy used in an attempt to control metastatic malignancy: This form of treatment largely has been discarded because the administration of cortisone is capable of producing such complete suppression of adrenal function that, usually, adrenal surgery could not improve the results.

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