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CUSHING'S SYNDROME

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CUSHING[1] recognized all the important clinical features of the disease that now bears his name, in the 16 patients on whom he based his original monograph in 1932. One observation stood out clearly: spontaneous remissions occurred. One patient received no treatment. The complete remission in another patient cannot be ascribed, as it was originally, to roentgentherapy to the pituitary. The records* indicate that the dose was probably approximately 400 r, which is not enough to produce a therapeutic effect. Remission occurred after roentgentherapy in another patient for whom the dosage is not known, but in view of recent developments is unlikely to have been in an effective range.

We have since learned that the features of Cushing's syndrome can be produced in animals and in man by injecting corticotropin (ACTH) or 17-hydroxycorticosteroids. Although the clinical picture in many patients having Cushing's syndrome is that of pure cortisone-like effects, curious mixtures of these and of other effects are observed, in which some features may be absent or may be greatly exaggerated. It is not infrequent that a mixture of effects of various steroids is seen: androgenic effects, for example, being slight in some patients and severe in others. In patients having carcinoma of the adrenal, especially, the pattern of steroid excretion may show striking alteration as the disease progresses.[2] In general, it is recognized today that most of the features of Cushing's syndrome are due to the chronic effects of an excess of hydrocortisone, or in other words hypercortisolemia. It seems likely, however, that in some patients there may be changes directly traceable to an excess of pituitary hormones, the effects of which are not mediated by the adrenals.

Pathogenesis

It is trite to say that little is known in regard to the fundamental cause of Cushing's syndrome. I shall, however, recapitulate briefly some of the outstanding points currently accepted in regard to adrenocortical control, which have a bearing on the output of adrenal steroids.

It is thoroughly established that ACTH is a major factor in stimulating the output of cortisone and corticosterone, and the administration of large doses of ACTH is accompanied by changes in the zona fasciculata and the zona reticularis.[3] One way in which ACTH produces its effects is by promoting biosynthetic

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hydroxylation reactions. These reactions are apparently due to an increase in the availability of a common cofactor, namely reduced triphosphopyridine nucleotide.[4,5]

The output of ACTH varies strikingly under the influence of a servo or feedback mechanism, depending on the amount of circulating cortisol (hydrocortisone). Normally, by this balance, deficiency of cortisol stimulates ACTH production, while excess of cortisol or other related steroids reduces ACTH and hence cortisol production to small amounts. In the absence of the anterior hypophysis, the secretion of cortisol is greatly reduced, but is not entirely suppressed.[6] Unless the adrenals are atrophied, injection of ACTH will almost immediately restore cortisol production.

In addition to a minimal activity, which appears to be autonomous, and an adrenal-pituitary feedback balance, the release of ACTH is under neural control. Harris,[7] in 1955, suggested that a neurohormone arising in or near the median eminence of the hypothalamus travels through the portal venous system[8] to the anterior pituitary, where it induces release of corticotropin. This neurohormone is termed "corticotropin-releasing factor" (C.R.F.). The mechanism may be excited by a great variety of stimuli. An extract of the median eminence which is free of ACTH has been shown by Royce and Sayers[9] to contain C.R.F. Other investigators[10-12] have also produced hypothalamic extracts that are capable of stimulating the production of ACTH both in vitro and in vivo. McCann and Haberland[12] demonstrated recently that lesions of the median eminence apparently prevent the production of C.R.F., as indicated by the fact that an operation blocks the ascorbic acid depletion of the remaining adrenal, which otherwise occurs after unilateral adrenalectomy.

The obvious question with regard to the pathogenesis of Cushing's syndrome with bilateral adrenal hypertrophy is: "What, if any part, of these mechanisms is at fault?" If the original concept is correct, an abnormally high concentration of circulating corticotropin should be demonstrable. Many attempts have been made to test this hypothesis and, until recently, almost no evidence has been found to support it. Sydnor, Sayers, Brown, and Tyler[13] found less ACTH in the blood of three patients with Cushing's syndrome, than in the blood of patients with untreated or treated Addison's disease. In 1954, Paris and associates[14] concluded from their own study and from examination of the results of others that in Cushing's syndrome with adrenal hyperplasia there was no increase in circulating ACTH.

Recent reports have made it seem much more likely than has been thought for many years that the ACTH-producing mechanism is at fault. Several reports[15,16] of pituitary tumors that were found after adrenalectomy in patients having Cushing's syndrome have been published. It is impressive that although such tumors occur after total and sometimes subtotal adrenalectomy for Cushing's syndrome due to adrenal hyperplasia, they have not been observed after adrenalectomy in patients with metastatic cancer nor in those with spontaneous Addison's disease. This, then, seems to imply strongly that the pituitary is being affected abnormally in patients having Cushing's syndrome, and the possibility of neural stimulation of the pituitary comes to mind. In some patients with Cushing's syndrome the titer of ACTH in the blood is much higher than that found in patients

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with Addison's disease.[17,18] It would seem likely that this propensity to excessive production of ACTH antedated the adrenalectomy and was exaggerated by it. The fact that suppression of corticoid production by administration of steroids occurs less readily, or less completely, in a patient with Cushing's syndrome associated with hyperplasia than in the normal person, may also be interpreted as meaning that there is increased force behind ACTH production in this condition.

In 1959, Liddle and associates[19] published data that seemed to favor strongly the idea of the presence of pituitary hyperactivity in Cushing's syndrome. Using as a test the drug SU-4885, which inhibits 11-hydroxylation, they showed that there is reduced production of cortisol, which is a good pituitary inhibitor, and that this reduction is associated with an abnormal rise in 11-desoxycorticosteroids such as compound S. This effect probably is the result of release of excessive ACTH. In this test, seven patients with Cushing's syndrome due to adrenal hyperplasia responded excessively as compared to normal persons and to patients having Cushing's syndrome who had been successfully treated by pituitary irradiation. In the latter patients the pituitary presumably was unable to muster sufficient vigor to produce an excessive amount of ACTH.

Nelson, Meakin, and Thorn[16] demonstrated the presence of excessive amounts of ACTH in 9 of 10 patients in whom pituitary tumors were found after adrenal surgery for Cushing's syndrome. The concentration of ACTH in these patients was higher than that found in patients with Addison's disease. By their method, however, excessive ACTH was not detectable in patients with untreated Cushing's syndrome.

The fact that some patients with Cushing's syndrome are hyperreactive to ACTH has not been explained. Jailer, Longson, and Christy[20] believe that this hyperreactivity may be due to some other associated neural or pituitary factor. The possibility that abnormalities inherent in the adrenal cortex cause its hyperreactivity must be considered. If these abnormalities are the cause, patients with severe pituitary deficiency should be capable of maintaining adrenal hyperfunction in Cushing's syndrome. Hamwi's[21] remarkable patient may be a case in point. The patient had severe florid Cushing's syndrome. At the first operation one adrenal and all but 2 gm. of the other were removed. The disease persisted. Treatment of the pituitary by roentgentherapy failed to produce improvement, and hypophysectomy was performed. At the time of operation, the sella turcica appeared to be completely emptied. The symptoms persisted and, several months later, the urinary hydroxycorticosteroids were at concentrations higher than 60 mg. per day. Another exploratory operation was performed and a 20-gm. mass of adrenal was removed, but the patient died because of an operative accident. Unfortunately, the completeness of the hypophysectomy was not proved by autopsy.

Possible mechanisms by which Cushing's syndrome may be brought about include: (1) stimulation from the hypothalamus via the pituitary to the adrenal cortex causing adrenal hyperplasia by ACTH or possibly some other similar factor,[22] (2) hypothalamic stimulation in addition to pituitary tumor, (3) autonomous pituitary tumor, (4) adrenal hyperactivity due to inherent adrenal abnormality as well as the known, (5) autonomous adrenocortical tumors.

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Pathologic Changes

Atrophy of the paraventricular nuclei in the hypothalamus has been described[23] as occurring in patients with Cushing's syndrome. It is thought that this atrophy does not represent a primary causative lesion but is secondary to the effects of corticoids, since similar changes after ACTH or cortisone treatment have been described.[24] So far as I am aware, gross hypothalamic lesions have not been found to be associated with the disease. This may or may not be relevant, since the same lack of association is true of other diseases in which pituitary hyperactivity is present, such as exophthalmos of Graves' disease, and acromegaly. A similar situation apparently exists with regard to the hyaline basophilic changes in the anterior pituitary described by Crooke,[25] since these too occur in cortisone-treated patients.[26]

Adenomata, almost always too small to show evidence of sellar changes on roentgenograms, are present in about half the patients. They are usually stated to be basophilic,[27] though controversy still arises as to the type of cell.[28] Small adenomata of the anterior lobe occur in the absence of Cushing's syndrome[29,30] in roughly 5 per cent of pituitaries in which a search is made at autopsy. Such tumors are almost invariably benign. We have seen 1 patient with pituitary carcinoma among 85 patients with proved or suspected Cushing's syndrome. In some of these patients deep pigmentation develops.[31]

The adrenal glands are histologically abnormal in almost all patients with Cushing's syndrome. In most series, the clinical syndrome is associated with hyperplasia of the adrenals in approximately 75 per cent of the patients; adenoma is present in approximately 15 per cent, and carcinoma in 10 per cent.[27,32,33] Although adrenal adenomata are relatively common in association with Cushing's syndrome in women, it is a curious fact that they almost never occur in men.

In some of the adrenals that are free of tumor and are normal in size, signs of cellular hyperplasia are evident, but occasionally no abnormality is seen microscopically. In some glands of normal size, there may be an abnormal gross appearance though the microscopic appearance may not be distinctly abnormal. In such glands, a relatively thick, brownish-yellow zone may be present, bordering close to the outer rim of the cortex.[34] How frequently this may be due to preoperative steroid therapy is not known. Increase in the weight of the adrenals may vary in this disease from an almost normal weight to the tremendous amount of 86 gm.[35] for a total weight of both glands.

The zona fasciculata appears to be the most hyperplastic; the zona glomerulosa frequently is little, if at all, affected, or it may be atrophied. The medulla also may appear atrophied. Cohen, Chapman, and Castleman[36] summarized their observations of changes in the hyperplastic glands of 12 patients as follows:

> The development of hyperplasia was traced from apparently early stages to well developed nodulation. . . . In its initial phase the process was characterized by increased thickness of the zona fasciculata at the expense of the glomerulosa and medullary region. Initially this occurred without increase in total gland weight above normal levels. Lipid distribution was similar to that of the normal control, but depletion of sudanophilic material and particularly cholesterol was

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more marked. Cellular atypism noted in a number of the hyperplastic glands was considered an indication of unusual stimulation.

Although menstrual disturbances and amenorrhea are present in the majority of women with Cushing's syndrome, few pathologic ovarian changes have been described. Morris and Scully[37] studied the ovaries in four women and found neither polycystic changes nor abnormal luteinization. Iannaccone, Gabrilove, Sohval, and Soffer[38] reported findings in the ovaries of 10 women with Cushing's syndrome, four of whom were postmenopausal, and the ovaries were no different from normal postmenopausal glands. In the six patients in the fourth decade of life, the ovaries showed a sharp decrease in all follicular activity, and simulated changes due to aging.

A fascinating feature of Cushing's syndrome is related to its appearance in malignant disease primary in various organs. These include bronchogenic carcinoma.[35,41-45] In some of the patients with bronchogenic carcinoma a more profound electrolyte imbalance is present than usually occurs in Cushing's syndrome. The changes may mimic those seen in primary aldosteronism, but in at least two such patients aldosterone excretion was found to be slight.[42,46]

Cushing's syndrome has also been seen in patients with ovarian neoplasms of various types. Parsons and Rigby's[47] patient had an anaplastic carcinoma, and Deaton and Freedman's[48] patient had masculinovoblastoma. Some ovarian tumors associated with Cushing's syndrome produce more masculinization than is usually seen in this syndrome. The disorder has also been described as occurring in patients with thymic carcinoma.[49] Scholz and Bahn[50] reviewed 11 such cases briefly, and added one case. Cushing's syndrome has also appeared in association with pancreatic carcinoma, with metastatic carcinoma of the prostate, and recently in association with pheochromocytoma,[51] and with carcinoma of the thyroid.[52] It is interesting that the adrenal glands in patients with Cushing's syndrome associated with carcinoma elsewhere in the body are almost all enlarged and hyperplastic, but the weights vary widely.

In patients in whom Cushing's syndrome is associated with carcinoma that is primary in other organs, the concentrations of urinary 17-ketosteroids and corticoids may be greatly increased, sometimes to the concentrations commonly seen when adrenal tumor is present. In a patient of ours with probable thymoma, the concentration of urinary 17-hydroxycorticoids increased to 73 mg. per 100 ml., and that of the plasma corticoids to 60 mg. per 100 ml. Under such circumstances, the question of whether or not these neoplasms in some way sensitize the adrenal cells or produce a corticotropin, is among the many questions that remain to be settled.

The demineralization in patients with Cushing's syndrome, although generalized, affects chiefly the spine, which leads to compression deformities or fractures of the vertebrae, kyphosis, and shortened stature. The central portions of the vertebrae on roentgenograms appear extremely pale, and the line of calcification beneath the chondral plates stands out more clearly than normally. The intervertebral discs bulge, causing wedging or hourglass deformities of the vertebrae. The ribs and pelvis are affected, and fractures, often of a painless type, occur.

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The skull takes on a patchy or mottled appearance, the laminae dura may disappear and the clinoid processes may become so pale as to simulate the appearance of a pituitary tumor. The osteoporosis apparently is due not to acute catabolism but to the antianabolic effect of cortisol. This explains the fact that negative calcium balance cannot be demonstrated in the disease.

It is interesting that many years after a so-called "cure" of Cushing's syndrome and complete disappearance of back pain, the central portions of the vertebrae may remain osteoporotic, remineralization being limited almost entirely to the regions adjacent to the chondral margins.[53] Skeletal destruction is almost certainly intimately connected to the tendency to renal calculous disease. Renal calculi were found in 5 per cent of 100 patients reported by Sprague and associates.[54]

Exophthalmos in this condition was described by Cushing.[1] It has been reported by Plotz, Knowlton, and Ragan[27] to be present in 7 per cent of patients. We have not observed exophthalmos of consequence in any of our patients. Malignant exophthalmos has been reported by Morgan and Mason[55] as occurring in a patient who had Cushing's syndrome and agitated depression. The concentration of urinary 17-oxyhydrocorticoids was 21.4 mg. per day (as determined by the Reddy method), and the blood pressure was 175/120 mm. of Hg. At autopsy, no signs of thyroid abnormality were noted except for one microfollicular cyst.

The available explanations for the hypertension are not adequate. Sodium retention is named as a factor,[56] but in view of work in recent years this does not seem acceptable. As has been mentioned, hypernatremia is not usually associated with the hypertension of Cushing's syndrome. It is true that under experimental conditions in rats, doses of 2.0 mg. of cortisol resulted in an elevation of the blood pressure[57] and larger doses caused nephrosclerosis.[58]

Sodium appears to be a sensitizing factor in causing the hypertension of desoxycorticosterone (DCA) but not that of cortisol.[59] This difference has been sharply emphasized by Guillemin[60] who showed that in rats on a sodium-restricted diet, severe hypertension developed during cortisol therapy, while in DCA-treated animals under the same conditions it did not. The addition of sodium to the cortisone treatment actually decreased the responsiveness of the test animals.

It has been suggested, but not proved for Cushing's syndrome, that cortisol may sensitize the cells to epinephrine, so that a normal amount of the latter may under some circumstances bring about hypertension. It is impressive that some patients have extremely severe Cushing's syndrome without hypertension; the absence of hypertension suggests that factors besides cortisol are at work. In Skanse, Gydell, Wulff, and Koch's[61] remarkable patient, the blood pressure was 250/140 mm. of Hg when the disease was mild, and fell to 140/95 mm. of Hg as the disease progressed; this was accompanied by a reduction in cardiac size.

In some patients, all measurable evidence of Cushing's syndrome may disappear except the hypertension. It is commonly assumed that the remaining hypertension under these circumstances may be due to irreversible vascular damage, since extensive vascular and renal changes are well known to occur. According to Glenn, Karl, and Horwith,[62] such changes range from minimal to marked ". . . arteriolar thickening, fibrosis and hyalinization of the glomeruli, tubular degeneration and

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focal infiltration of inflammatory cells." Such renal changes[63] would seem to furnish a reasonable explanation for the hypertension that may persist in patients in whom Cushing's syndrome has been controlled, because hypertension occurs not only after subtotal adrenalectomy but may occur after complete adrenalectomy.

The negative nitrogen balance of Cushing's syndrome is thought to represent increased gluconeogenesis, and to contribute to the progress toward diabetes mellitus but, as Ingle[64] has shown, it in no way explains it fully. Some degree of diabetes can be demonstrated by glucose tolerance tests in about 75 per cent of the patients having Cushing's syndrome, and this appears to be due, at least in part, to an interference with the action of insulin. Usually such diabetes is relatively mild, and for patients in whom insulin is required, dosages similar to those for the average diabetic patient are effective. In such diabetes there is little tendency to ketosis, greater than usual evidence of protein loss, and increased hepatic glycogen deposition, as well as a greater concentration of pyruvate and a lower concentration of phosphate than is found in the average patient with diabetes mellitus.[65]

Pronounced brownish hyperpigmentation of the skin and mucous membranes which occurs in some patients with Cushing's syndrome is of interest. Sulman[66,67] demonstrated, by testing human blood extracts in the tree frog, that there was an excess of chromatophorotropic hormone in three patients after adrenalectomy, in 25 of 30 patients with Addison's disease, in 15 of 45 patients with Cushing's syndrome, and in all three patients with Cushing's disease (pituitary tumor). He considered the test of value in designating which patients with Cushing's syndrome had pituitary tumor.

Few histologic studies have been made of the skin in Cushing's syndrome. My colleague, Dr. George H. Curtis[68] in the Department of Dermatology, has permitted me to quote some of his preliminary observations. "In general, the flattening of the epidermis with absence of rete pegs and papillae, edema of the upper corium, apparently increased but fragmented and frayed elastic fibers, and an apparent decrease of collagen and fibrous tissue, are distinctive features of the histologic changes in the skin from the forearm."

In some patients, there is a peculiar and unexplained disparity between some of the clinical and laboratory findings. Edema is a striking feature in some patients, but not in the majority, though electrolyte patterns and serum protein concentration may not differ, and urinary aldosterone may not be increased.[52]

Many of the symptoms can be accounted for on the basis of the protein antianabolic effect of corticoids. These effects include weakness and atrophy of muscles, thinning of the skin, osteoporosis and, probably, also a decrease in the power of wound healing.

I agree with Ragan,[69] and Frawley, Kistler, and Shelley[65] that there appear to be fairly constant differences between the spontaneous and the iatrogenic types of Cushing's syndrome. In most series of patients having the spontaneous type, arterial hypertension occurs in nearly 90 per cent, and some disturbance of carbohydrate metabolism is present in perhaps 75 per cent. In the therapeutically imposed type these features are rarely present.

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In the presence of some diseases, such as lupus erythematosus, large amounts of cortisone or an equivalent drug may be administered over a period of months or years without producing the symptoms of Cushing's syndrome. As an example, one of our patients with lupus erythematosus was given treatment with corticoids from October, 1954, to the time of her death in May, 1960. Cortisone, in a dose of 100 mg. daily, or an equivalent of some other steroid, was used almost steadily from November, 1957, with no suggestion of the appearance of Cushing's syndrome, of hyperglycemia, or of hypertension.

Laboratory Tests

Tests most commonly employed in Cushing's syndrome have been those relating to the effects of: (1) stimulation with ACTH, and (2) inhibition of ACTH by administered steroids. These tests are of some value, not only in differentiating patients with Cushing's syndrome from those with other diseases, but also in differentiating Cushing's syndrome due to hyperplasia and that due to neoplasm.

Among the many laboratory tests the results of which may be abnormal in Cushing's syndrome are those indicating erythrocytosis, lymphopenia, and eosinopenia. Hypernatremia is rare, but often alkalosis of the hypochloremic and hypokalemic types is present. The hypokalemia may be severe in the absence of a measurable increase in aldosterone.[52,70] In Hökfelt, Sjögren, and Falkheden's[52] patient, for example, there were spells of muscular weakness, polyuria, hyposthenuria, serum potassium concentrations of 2.2 mEq. per liter, and hypochloremia alkalosis; yet only traces of aldosterone were found in the urine, and none was detected in the adrenals.

It is equally fascinating that there are cases of Cushing's syndrome in which there are elevated values not only of urinary 17-hydroxycorticoids, but also of urinary aldosterone in amounts as great as 232 mg. per day.[71]

The most characteristic laboratory finding in Cushing's syndrome is an increase in the concentration of urinary 17-hydroxycorticoids. However, the amounts may decrease to within normal range when renal damage is severe.[72] The concentrations of urinary 17-ketosteroids in patients with hyperplasia may be normal or moderately elevated; frequently they are higher in patients with adenoma, and sometimes rise to extreme heights amounting to nearly 2.0 gm. per day in patients with carcinoma.[73]

In the presence of bilateral adrenal hyperplasia the response to ACTH is frequently greater, sometimes much greater, than normal. It is unfortunate for the diagnostic value of the test, that responses to ACTH much greater than the average normal response occur in a number of other conditions, including obesity, hyperthyroidism, hypothyroidism, hirsutism without other evidence of Cushing's syndrome in women, the last trimester of pregnancy, and the normal.[74] Even in Cushing's syndrome the results reported by various investigators appear to be at unexplained variance. The findings of Grumbach and associates,[75] of Christy, Wallace, and Jailer,[76] of Laidlaw and associates,[77] of Lindsay, Migeon, Nugent, and Brown,[78] and of Jailer, Longson, and Christy[20] seem to show a rather consistent hyperresponse to ACTH in patients having Cushing's syndrome;

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Bayliss and Steinbeck,[79] and Christy, Longson, and Jailer[80] found that prolonged administration of ACTH to normal persons did not cause an adrenal hyperresponse similar to that seen in patients with adrenal hyperplasia. Birke, Diczfalusy, and Plantin[81] found an exaggerated adrenal response in six of eight patients with Cushing's syndrome and hyperplasia.

Others[82,83] have found the response to be inconsistent. Jagiello[84] reported an increase of 25 mg. in urinary corticoids after intravenous injections of ACTH for two days in one patient having Cushing's syndrome, and a decrease in this value after two days of intramuscular administration of ACTH in another. Even more striking is the recent report of Dyrenfurth, Blair, Beck, and Venning[85] that there was a much greater percentage response to ACTH in the specimens of urine from 21 normal subjects than in those from 14 patients with Cushing's syndrome. In their tests, four men with Cushing's syndrome showed an average increase of urinary corticoids of 38.9 mg. per day as compared to an average of 23.8-mg. daily concentration in the normal men, which is a considerable difference. In their series of 10 women with Cushing's syndrome, however, the increase in urinary corticoid output after stimulation averaged 18.9 mg. daily, as compared to an average of 17.7 mg. in the normal women. It is to be hoped that an adequate explanation of these apparent discrepancies will soon be forthcoming.

In persons having adenoma of the adrenal, the ACTH-urinary corticoid response is unpredictable: it may be slight, normal, or great.[77,78,86,87] In those having carcinoma of the adrenal this response usually is absent.

Among the most promising new diagnostic aids when uncertainty exists as to the presence of Cushing's syndrome are the suppression tests. A number of variations of this type of test have been reported by several groups over the past few years.[77,78,82,86-88] It seems reasonably certain that the adrenal is suppressed through inhibition of the pituitary ACTH-production, and therefore it is not surprising that adenomata and carcinomata usually behave autonomously and show little or no suppression as compared to the normal gland and to the hyperplastic gland.

The new and interesting test embodying partial adrenal suppression by SU-4885, has been mentioned.[19] Gold, Kent, and Forsham[89] have recently reported the use of the SU-4885 test in 10 patients with Cushing's syndrome. In six of these, proved to have adrenocortical hyperplasia, an abnormally high concentration of urinary 17-ketogenic steroids existed before the test. It was raised further by the administration of SU-4885 in all of them, and rose to even higher concentrations following intravenous administration of ACTH, and was suppressed by dexamethasone though not to low concentrations after doses of 8 mg. per day for three days. In two patients with benign adenomata and Cushing's syndrome there was no response to SU-4885, but a response to ACTH; while in two with carcinoma and Cushing's syndrome there was no response to either agent. In suppression tests, steroids commonly employed are Δ^1-9α-fluorohydrocortisol or its 16α methyl analog (dexamethasone). Jenkins and Spence,[90] and also Liddle[91] reported that the administration of these steroids in divided doses totaling 2.0 mg. per day produces almost complete suppression, measured as concentrations of

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urinary corticoids, in normal persons, and mild suppression in patients with Cushing's syndrome. In doses of 8.0 mg. per day the concentration of urinary corticoids in 35 patients with Cushing's syndrome and adrenal hyperplasia decreased to nearly zero; whereas, in 8 patients with adrenal tumor no such decrease in urinary corticoids appeared.

Prognosis and Therapy

It is well recognized that natural remissions in Cushing's syndrome do occur, but they are not common. Plotz, Knowlton, and Ragan,[27] in studying the natural history of the disease, found that about half the patients died within five years after the diagnosis was made. In their experience, one of the leading causes of death was infection due to bacteria. This is not true today; now the chief cause of death is cardiovascular-renal disease. In our experience death has frequently been due to coronary artery thrombosis. Cerebrovascular accidents are also common. Unfortunately, myocardial infarction remains a likely cause of death when the disease, although apparently cured, has existed in severe form for some time. In our series, two men less than 40 years of age died from myocardial infarction after all major evidences of the disease were eliminated, and another young man had severe myocardial infarction but recovered.

When adenoma or carcinoma of the gland exists, removal of the mass is the only treatment that holds hope of effectiveness. Removal of a benign adenoma from a patient who has Cushing's syndrome of short duration produces a swift change toward normality and highly satisfactory results. In many, if not most, instances in which carcinoma of the adrenal exists, the carcinoma cells have already spread from the gland into the adjacent veins at the time the diagnosis is made.

There are two approaches to treatment of Cushing's syndrome with bilateral hyperplasia of the adrenals: (1) attack upon the pituitary, and (2) attack upon the adrenal. The pituitary may be treated by: irradiation; section of the pituitary stalk; partial or total removal of the pituitary; implantation of radon, gold, or more recently yttrium^{90} seeds, into the anterior lobe.

The first pituitary surgery for Cushing's disease was performed by Naffziger in 1933.[92] In his patient, remission lasted a year; subsequently the condition recurred and the patient died of Cushing's syndrome seven years after the operation. No autopsy was performed.

Luft, Olivecrona, Ikkos, and Hernberg[82] reported two patients operated on for Cushing's disease: in one patient, electrocoagulation of the pituitary was performed, and in the other, hypophysectomy. In both patients, the signs of the disease disappeared.

In 1938, Pattison and Swan[93] reported improvement after implantation of radon seeds in patients with Cushing's disease. Radon implantation was used by Northfield[94] in four patients: one patient improved dramatically; one improved slightly; one was not benefited; and one patient died. Successful treatment of Cushing's syndrome has followed the implantation of yttrium^{90} into the pituitary gland. This radioisotope would seem to be a particularly promising type since its beta rays extend such a short distance from the site of implantation. Complete regression of signs and symptoms after implantation of yttrium^{90} in two patients

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has been reported by Molinatti, Camanni, and Tedeschi,[95] and by Brooks, McSwiney, Mattingly, and Prunty.[96] In both of these patients the blood pressure reverted completely to normal, and in Molinatti, Camanni, and Tedeschi's patient, the daily concentration of urinary corticoids decreased from 30 mg. before treatment to between 0.2 and 0.5 mg. two months after treatment, indicating that a rather severe pituitary insufficiency had ensued.

Roentgentherapy, and more recently cobalt[60] teletherapy, to the pituitary has been tried; good results have been reported in a number of patients, but the cure rate is not high.[97] Johnsen,[97] in 1952, reported the treatment of 12 patients with roentgen doses ranging from 6,000 to 16,000 r. Good results were obtained in 50 per cent of the patients. Three were considered definitely cured; the others had remissions, two of which lasted for three or more years. The experience of Dohan, Raventos, Boucot, and Rose[98] was approximately the same. Twelve patients were treated; results were excellent in five. The patients who showed the best results received doses ranging from about 4,000 to 5,000 r, over a relatively short period. Soffer and Gabrilove[99] also found that unsatisfactory results follow "extensive pituitary irradiation or pituitary irradiation and unilateral adrenalectomy" in more than half the patients thus treated. In the remainder, removal of most of the opposite adrenal is prescribed.

Today, adrenal surgery is the preferred method of treatment for most patients. Until a few years ago, the commonest form of surgical therapy was complete removal of one adrenal gland and removal of approximately 80 per cent of the opposite gland. Bilateral total adrenalectomy has frequently been advocated.[100,101] It has the advantage of producing an almost certain remission of the disease, but the disadvantage of imposing Addison's disease in place of Cushing's syndrome. Although severe adrenal deficiency can be treated effectively nowadays, there is still the undependable human element; and some patients with Addison's disease have died as the result of careless omission of treatment. There is also a risk because of the chance that sufficiently large doses of corticoids may not be quickly available in an emergency. In addition, the recent appearance of a number of postoperative pituitary tumors must be reckoned with, and these have occurred much more frequently in patients who have undergone bilateral adrenalectomy than in those who have undergone partial adrenalectomy.

When adrenal surgery is to be performed, the patient should be supplied with thoroughly adequate cortisone therapy: we usually prescribe 150 mg. per day intramuscularly for one or two days preoperatively; approximately 300 mg. intramuscularly in the early morning on the day of operation, and for one or two days postoperatively, diminishing to 50 to 25 mg. per day orally within a week, provided that the patient's condition appears to warrant it.

Mason, Richardson, and King[102] in discussing the matter of choice of partial or total adrenalectomy, state that in patients more than 45 years of age with slowly advancing disease, subtotal adrenalectomy is safer than total ablation and is adequate. They advocate a two-stage operation in these older patients, and recommend bilateral adrenalectomy in young patients and in those with rapidly progressing severe disease.

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Postoperatively, it is well to supply each patient who has undergone adrenal surgery with a card to be carried in his wallet, to certify in the event of an emergency that he has the approximate equivalent of Addison's disease. In addition to identification cards, our patients are supplied with two 100-mg. ampuls of hydrocortisone together with printed instructions to be kept near them at home or when traveling, for their use in case of emergency.

More long-term, careful, follow-up studies are needed after surgical treatment of Cushing's disease. The report of Cope and Raker[32] is interesting. Of 11 patients operated on for adenoma, one patient died after relief of the disease, and 10 patients were well at the time of the report. Of 27 patients with hyperplasia, operation was not performed in two, and they died of Cushing's syndrome. Two patients underwent partial resection and died of Cushing's syndrome. The 23 remaining patients underwent subtotal resection: four died of the effects of hypercortisolism; two died after a period of some relief; two were alive at the time of the report and still had Cushing's syndrome; and 19 were well.

Glenn, Karl, and Horwith[62] reported the results of surgical treatment in 30 patients. In their experience, unless the unilateral operation relieved the patient, bilateral adrenalectomy was performed. Thirty patients were operated upon; there were no operative deaths. In one patient with a small fragment of adrenal remaining, ophthalmoplegia developed from a pituitary tumor. Two patients subsequently went through normal pregnancy. One nine-year-old boy had no surgical treatment except a bilateral biopsy of the adrenal, and was in a complete remission at the time of the report. The remaining patients, seven years after operation, appeared to be doing well.

Estrogen therapy has been advocated but apparently is not effective.[103] Androgens have been highly recommended for their anabolic effect.[104] It appears that most physicians dealing with Cushing's syndrome do not depend on androgens as the sole method of treatment, but their value should not be overlooked as an adjunct to other forms of treatment in assisting with the repair of protein tissues and in the hope of repairing osteoporosis. The value of such therapy is not established.

Inhibition of corticoid secretion by amphenone has been reported by Hertz, Pittman, and Graff,[105] by Thorn and associates,[106] and by McCullagh and Tretbar.[107] Amphenone interferes with enzyme activity, blocking steroid synthesis, removing pituitary inhibition, and leading to adrenal hyperplasia.

Ortho p'D.D.D.[108] also is a drug that suppresses adrenocortical function. It appears to act as a rather specific cytotoxin to adrenocortical cells. This effect may be highly beneficial in some otherwise hopeless cases of adrenal cancer. Unfortunately, both amphenone and ortho p'D.D.D. are relatively toxic; they cause nausea, dizziness, and weakness suggesting a neurotoxic effect. They do, however, offer great hope that more practical effective compounds of a chemical nature may be found.[108]

It is hoped that in the future we may have not only agents that can be used safely and efficiently to suppress adrenal function by direct action, but possibly also hormonal or chemical substances by which we may control adrenocortical

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steroid production by direct effects upon the anterior pituitary gland, or even upon the hypothalamus.

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