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CUSHING'S SYNDROME*

ABBIE I. KNOWLTON

Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University

INTRODUCTION

FIRST of all, I want to say that I feel greatly honored to be one of the speakers participating in the Graduate Fortnight.

Cushing's syndrome, which is the subject under discussion, is a disease which has intrigued the neurosurgeons, endocrinologists and pathologists for years. Much of the interest in this entity has centered around the question as to whether the pituitary, the adrenal cortex or even the hypothalamus is the site of the initial lesion, though it is generally agreed that the end result is due to excess activity of the adrenal cortical hormones.

Recently the disease has attracted the attention of physicians in general due to the fact that this spontaneous form of hyperadrenalism invites comparison with the similar condition induced by long-term treatment with ACTH or cortisone. The earliest reports on the use of these substances drew attention to the Cushing-like features which the patients receiving them developed and as time has passed, each of the wide vari-

* Presented at the 25th Graduate Fortnight of The New York Academy of Medicine, October 13, 1952. From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York.

TABLE I—SYMPTOMS AND SIGNS FREQUENTLY ENCOUNTERED IN CUSHING'S SYNDROME

	Columbia Series (38 patients)	*Reports from literature (189 patients)*
	per cent	*per cent*
Obesity — truncal and facial	95	97
plethoric appearance	85	50
dermatological abnormalities	82	26
Hypertension	92	85
Disturbances in gonadal function, amenorrhea, oligomenorrhea, impotence	86	71
virilism	6	5
Hirsutism	76	69
Purple striae	69	71
Weakness and backache	68	50
Mental abnormalities	66	31
minor 40		
major 26		
Purpura, easy bruising	58	23
Poor wound healing or severe infections	42	30
Headache	40	34

ety of abnormalities seen in the spontaneous disease has been encountered in the group of steroid-treated patients. This similarity between the two conditions has stimulated interest in the natural history of Cushing's syndrome, and brought out the fact that although case reports abound, in no place has a large enough group of patients been collected to provide satisfactory data on the general course of the disease.

In order to provide such information, Dr. Charles Plotz, Dr. Charles Ragan and myself have reviewed the thirty-three patients with Cushing's syndrome who have been studied during the past twenty years at the Columbia-Presbyterian Medical Center. Since this number afforded a relatively small group from which to draw conclusions as to the overall picture of the disease, an additional 189 cases were collected from the literature. This combined group has recently been reported.[1] Since its completion, an additional five patients have come under our observation, and these have been added to the above series to form the basis

of the clinical material for this evening's discussion. In gathering this group of patients an effort was made to include only unequivocal examples of the syndrome and to obtain as long periods of observation as possible. In the Columbia patients, only one has been lost to follow-up; the remaining thirty-seven have been seen for periods ranging from a few months to twenty years.

Clinical Picture

There have been so many presentations of the clinical picture of Cushing's syndrome that to add yet another would be redundant, and indeed considering the excellence of the descriptions already available, it would be presumptuous. Hence I shall touch on this aspect only to compare the findings in the present series with those previously reported. As is well recognized, this disease is primarily one of young adults; the average age of onset in the Presbyterian Hospital group was twenty-nine, with the youngest patient being eleven and the oldest fifty-five. The fact that thirty of the thirty-eight patients were women is in keeping with the known preponderance in this sex. Only one instance of the occurrence of Cushing's disease in a Negro was found in the literature; however, three such patients were encountered in the present group. The more common symptoms and signs which have been seen in patients with Cushing's syndrome are summarized in Table I. The patients comprising the present series have been considered separately from the larger group gathered from the literature. In general the agreement between the two groups is excellent, but certain differences exist upon which I shall comment.

Obesity remains the hallmark of the syndrome, but the use of this term "obesity" requires amplification. It is true that the majority of patients gave a history of impressive weight gain; however, a certain proportion had no change in weight or sustained an actual loss. In each instance, whatever the overall change, there was a redistribution of tissue to give the characteristic facial and truncal obesity. Only one patient of the present series complained of discomfort in relation to the disposition of fat, hence the feature, "painful obesity," mentioned in Cushing's original paper,[2] would seem to be relatively uncommon. In conjunction with the rounding of the face, the great majority exhibited reddening or a dusky cyanosis about the head and neck. Dermatological abnormalities were seen very frequently in the present group; their much lower

incidence in the larger group gathered from the literature may well be due to the fact that, being a minor symptom, it was often not deemed worthy of recording. It is interesting to note, however, that one of the earliest and most completely described instances of Cushing's was reported in the dermatological literature in 1926. That is the case of Parkes-Weber which Cushing included in his original report. The type of skin lesions showed great variety, the most common being acne, fungal infections and patches of pigmentation.

High on the list of findings stands hypertension, and in general this was marked by impressively high diastolic levels. Considering the severity of the hypertension, it was remarkable to note its complete reversibility in patients in whom remissions occurred. This held true even though the blood pressure had been elevated for years. It is also surprising that fundoscopic abnormalities of note were described in only five of the thirty-four patients in whom the eye-grounds were examined.

Suppression of gonadal function was recorded routinely in these patients with Cushing's syndrome – impotence in men and amenorrhea or at least oligomenorrhea in women. However, gonadal function at times was surprisingly normal. An example of this among the present group was a patient, first seen in 1945 with symptoms suggestive of Cushing's syndrome, and readmitted four years later with evident progression of her disease. At this latter time she had severe hypertension, plethora, purple striae, diabetes, osteoporosis with wedging of one vertebra and amenorrhea. However, the amenorrhea proved to be secondary to a six months pregnancy! Dr. Ann Forbes has written us of another such instance where pregnancy became established while a patient was definitely hyperadrenal. Even where marked suppression of menstrual function existed, virilization was rarely seen and this distinguishes the Cushing group from patients with the adrenogenital syndrome. In the Columbia series of patients, enlargement of the clitoris was noted in only two of the women patients, and in none was the body configuration or voice masculine. It is true that hirsutism developed in the majority. Although this usually included the appearance in the women of facial hair over the moustache and beard areas, these sites were rarely the only ones involved. More commonly the entire face was covered with a fine lanugo-like hair including not only the upper lip and chin but also the cheeks and even the forehead. Similar hair frequently covered much of the body.

Of the various signs associated with the syndrome, certainly the occurrence of purple striae is the most useful diagnostically. While striae may develop under any situation in which the skin is rapidly stretched, the bright red or purple type are peculiar to this syndrome. Although such striae were found in the majority of the patients, a significant proportion remained in which this helpful diagnostic sign was lacking. Weakness and backache were noted as frequently as was the occurrence of striae, but their non-specificity of character rendered these symptoms far less useful diagnostically. In a few instances weakness dominated the clinical picture, suggesting a primary muscle-wasting disease. It is interesting that backache, although at times in association with compression fractures of the spine, was never incapacitating.

Up to this point the agreement between the cases of the present series and those gathered from the literature has been fairly good. In the incidence of mental abnormalities, however, there is considerable discrepancy. The reason for this is not clear unless it be related to the generally longer follow-up available in the present series, during which there was more time for these abnormalities to become manifest. In the present group, abnormal reactions have occurred with disturbing frequency. In the milder forms, the disturbance might be no more than that the patient was emotionally labile, uncooperative and presented a difficult problem in ward management. However, nine patients, or 26 per cent, had major mental disturbances. The types of abnormality varied widely and included depressions, paranoid reactions and confused states. One attempted suicide; six became so acutely disturbed that it was necessary to transfer them to institutions for specific psychiatric treatment. The uniform clearing of the mental picture in the event of a remission in the other aspects of the disease was strong evidence for an intimate relationship between the psychic abnormality and the metabolic disturbance. However, when the metabolic abnormality persisted, no prediction could be made as to the appearance, intensity or persistence of the mental abnormality. For example: in one patient the disease progressed to death with no evidence of abnormal mental response during the entire course; in another, the onset of abnormal behavior paralleled the progression of other signs of hyperadrenalism; in a third, a sudden psychotic episode appeared after the physiological stigma of the syndrome had been present but not progressive for more than a year; while in still a fourth, an acute paranoid psychosis, which had

necessitated psychiatric hospitalization, cleared sufficiently to permit the patient to resume her life at home despite the fact that the other features of hyperadrenalism progressed relentlessly until her death in cardiac failure a year later.

Purpura and easy bruisability were remarked upon in the majority of patients in the Presbyterian Hospital series. Why the spontaneous type of hyperadrenalism is accompanied by a bleeding tendency, while ACTH and cortisone have proved of some value in the treatment of such conditions, is wholly unknown.

The incidence of poor wound healing or of unusual infections was alarmingly high in both groups of cases reviewed.

A significant number of patients complained of severe and protracted headaches. In the present series, no correlation existed between this symptom and other evidence of neurological disease. It so happened that the three patients subsequently proven to have adenomata of the pituitary – one had a basophilic adenoma and the other two each had a chromophobe adenoma–were not troubled with severe headaches, while this symptom was particularly severe in three patients with benign adrenal tumors and in one suffering from an adrenal carcinoma.

Of this group of symptoms and signs, the almost universal hypertension, the frequently abnormal mental reactions and the likelihood of poor wound healing or of unusual infections stand out as the three most serious and as real threats to the life of the patient with Cushing's syndrome. Their high incidence in the spontaneously occurring form of the disease suggests that similar difficulties might be anticipated in patients under prolonged treatment with ACTH or cortisone. It is fortunate that, during such therapy, hypertension has developed with much less frequency than in Cushing's syndrome, and has been limited chiefly to patients with underlying renal disease, as pointed out in a recent article by Dr. George Perera.[3] On the other hand, the appearance of abnormal mental reactions and the insidious development and serious nature of intercurrent infections, although less common than in Cushing's syndrome, have been among the chief concerns in patient management on ACTH or cortisone.

Laboratory Data and X-ray Findings

An analysis of the laboratory data from the cases reported from the literature proved to be difficult, due to the fact that the amount of data

TABLE II—FREQUENTLY ABNORMAL LABORATORY AND X-RAY FINDINGS IN CUSHING'S SYNDROME

(Columbia series — 38 patients)

	Per Cent Abnormal	*Average*	*Range*
Diminished carbohydrate tolerance (31)	94		
overt diabetes	24		
fasting blood sugar mg.%		116	C1-300
X-ray evidence of demineralization			
spine (35)	74		
skull (36)	50		
compression fractures of spine (35)	34		
rib fractures	11		
Increased 24-hr. excretion of "corticoids" (10)	70		
Formaldehydrogenic method (7)		3.0	0.9-7.7
(normal 1-2 mg/24 hr.)			
Phosphomolybdic acid method (3)		7.0	4.1-9.9
(normal 2-4 mg/24 hr.)			

varied greatly from case to case and the laboratory techniques employed were often not comparable. For this reason the review of laboratory data and of the x-ray findings were limited to the thirty-eight patients observed at Presbyterian Hospital. The impressive feature of this review was that no one test was uniformly abnormal; indeed very few were abnormal consistently enough to be of help diagnostically. These few are set forth in Table II, along with an indication of the percentage of instances in which the abnormal results were observed. In this table the figures in parentheses which follow a specific test indicate the number of patients in the series in whom that particular determination was made. Where no parentheses occur, data were available on all thirty-eight patients.

The diminished tolerance for carbohydrates is well known, and was encountered with a high degree of consistency. A much smaller percentage exhibited frank diabetes, and the overall average fasting blood sugar on the entire group was normal. The mildness of the carbohydrate disturbance seen here is compatible with the fact that no instance of diabetic acidosis was met with in this group, and in the 189 reports of

Cushing's syndrome which we reviewed only one such occurrence was recorded.[4]

Although x-ray evidence of demineralization was present in a smaller percentage of the patients than was the abnormal glucose tolerance curve, it was a finding of greater value diagnostically, since the disease involves chiefly those in the younger age group where other causes of demineralization are relatively rare. The most frequent site in which the lack of calcium was demonstrated was the spine, in 74 per cent of the patients, while the skull was involved somewhat less commonly. In a little over half of the patients with demineralization of the spine, compression fractures were present and a small number had spontaneous rib fractures. Unfortunately these bony changes are not confined to the spontaneously occurring forms of hyperadrenalism, as was initially thought. Demartini, Grokoest and Ragan[5] have recently reported the appearance of such fractures in a group of patients on long-term cortisone therapy. Some comfort may be derived from the fact that such lesions have not been seen in patients receiving cortisone in the doses commonly employed for rheumatoid arthritis unless the patient was post-menopausal or bedridden.

An increase in the excretion of so-called "corticoid" material in the urine was anticipated since cortisone and related steroids, the precursors of such urinary products, are thought to be present in excess in Cushing's syndrome. These determinations have been made on ten patients in the present series at a time when they were hyperadrenal. Two different methods have been employed, both based on chemical techniques. In the majority of instances these substances were found to be present in greater than the normal amounts, but I should like to emphasize that this was not true in every case. Among the three patients who excreted normal amounts of these "corticoids" was one with a proven benign adenoma of the adrenal cortex accompanied by all other evidences of the syndrome. Why the excretion of these substances is normal in some cases is not known. However, the current methods of determining these "corticoids" are relatively crude and the values so obtained represent only a fraction of the total excretion. Hence it may be naive to expect the universal finding of an increased urinary excretion of these substances with the present techniques.

The excretion of 17-ketosteroids was normal on the average in this group of patients with Cushing's syndrome. The results are set forth in

TABLE III—17-KETOSTEROID EXCRETION IN CUSHING'S SYNDROME
(mg/24 hr.)

	Average	Range	*Average*
Adrenal cortical hyperplasia			16.4
females (9)	15.5	(7.2-20.9)	
males (5)	18.1	(16.0-27.6)	
Benign adrenal cortical adenoma			5.0
females (7)		(0-8.5)	
Adrenal cortical carcinoma			**35.5**
male (1)			35.5

Table III, where the patients are grouped according to their underlying adrenal pathology. Our findings are in keeping with the recent report of Forbes and Albright.[6] These authors pointed out that the output of these substances was significantly higher in patients with hyperplastic adrenals than in those in which the adrenal was the site of a benign adenoma. In the latter group it is presumed that the tumor suppresses endogenous ACTH production with atrophy of all adrenal tissue apart from the tumor itself, and if the chief products of the tumor are cortisone-like in character these should contribute but little to the total amount of 17-ketosteroids excreted. As an aside I should like to comment on the fact that all seven of our patients with a benign adenoma were women, a point which Dr. Forbes remarked upon in her report. This, I believe, was due to chance since two reports of a benign adrenal cortical adenoma occurring in males with the features of Cushing's syndrome were encountered in the literature, Lightwood's[7] case of an 18-week-old infant, and Josephson's[8] account of a 17-year-old boy. Dr. Forbes has reported that the values met with in adrenal carcinoma where the excreted steroids may vary widely in character may range from extremely low to extraordinarily high figures, and levels from 1.1 to 649 mg. in twenty-four hours have been recorded. In our one patient with carcinoma in whom this assay was made the values were definitely, but not greatly, elevated.

Although the higher values in patients with hyperplasia than in those with benign tumors is statistically impressive, the level in a given case

TABLE IV—THE EFFECT OF CORTISONE ON URINARY 17-KETOSTEROID EXCRETION IN PATIENTS WITH CUSHING'S SYNDROME

	A.G.† F	*J.J.*† M	*C.C.*† F	*S.K.*† M	*C.R.*‡ M
Control	23.8		14.3	22.1	51.6
	15.1	29.9			40.8
	22.9	25.9	9.0	16.6	39.3
Cortisone 100-200 mg. o.d.	11.2		6.3	13.8	53.1
	8.0		5.8	14.2	56.1
	11.0	22.9	3.6	12.6	63.0
	13.5	23.6		13.1	59.3
		19.2			

† Bilateral adrenal hyperplasia
‡ Adrenal carcinoma

cannot be relied upon to differentiate conclusively between the two conditions because of the known instances in which the values have overlapped. In the last few months, Dr. Jailer has introduced a new diagnostic approach based upon the 17-ketosteroid excretion which shows real promise as a physiological means of distinguishing the patient with a tumor from the one with hyperplasia. He has been kind enough to let me present to you his preliminary results. In his lecture last Friday evening Dr. Jailer pointed out that cortisone, in addition to its real therapeutic benefit in the adrenogenital syndrome, had proven most useful in distinguishing those patients with adrenal tumors from those with hyperplasia. The tumor, being autonomous, was unaffected by the suppression of ACTH induced by the administered cortisone, whereas hyperplastic glands which remained under pituitary influence, showed a diminished output of 17-ketosteroids in response to the cortisone injections. It is also well known that the normal individual like the adrenogenital patient with hyperplastic adrenal cortices, will respond to large doses of cortisone with a reduction in 17-ketosteroid excretion.[9] It was reasoned that the patient with Cushing's syndrome with hyperplastic adrenals might respond similarly, whereas if an adrenal tumor were present providing a constant output of androgenic material, or if a pituitary tumor were present providing a constant supply of ACTH no change in the urinary excretion of the 17-ketosteroids would be expected. To date five patients have been available to assay the validity

TABLE V—ADDITIONAL LABORATORY DATA ON PATIENTS WITH CUSHING'S SYNDROME
(Columbia series, 38 cases)

	Average	*Range*
Red blood cell count million/mm³ (36)	4.62	(3.4-6.9)
White blood cell count /mm³	10,200	(5,800-15,000)
Eosinophiles /mm³	53	
Serum sodium mEq/L (19)	142.6	(136.0-147.0)
Serum potassium mEq/L (16)	3.9	(2.1-5.3)
Serum carbon dioxide content mEq/L (32)	29.6	(21.2-46.2)
Serum chlorides mEq/L (32)	100.3	(78.1-110.2)
Serum calcium mg% (31)	10.0	(9.0-11.3)
Serum phosphorus mg% (27)	3.0	(2.2-4.4)
Basal metabolic rate per cent (34)	—6	(—37 to +32)
Serum cholesterol mg% (32)	263	(138-460)
Radioactive iodine uptake % in 24 hr. (6)	23	(8-51)

of this assumption, and the results are shown in Table IV. The first four patients all have had adrenal cortical hyperplasia established at operation. C.C. and S.K. had each had a course of pituitary radiation totalling 3350 R and 4500 R tumor doses respectively, given twelve and seven months prior to the administration of cortisone. In the first three patients significant falls in the 17-ketosteroid excretion occurred during the four to five days of cortisone administration; in the fourth the fall was less impressive. However, in the patient with an adrenal carcinoma with metastases it is evident that no fall whatever ensued. This patient subsequently underwent total hypophysectomy which had no effect upon the level of androgen excretion, offering further evidence of the autonomous nature of the neoplastic tissue in this instance. Unfortunately, no patients with benign tumors have been available for this type of study as yet. If subsequent experience is as definitive as these few cases would suggest, this approach may provide a useful diagnostic tool in determining the basis of the Cushing's syndrome.

Apart from the studies already mentioned considerable additional laboratory data were available from the present series. For the most part these values approximated normal and they are summarized in Table V. The polycythemia which has long been associated with the syndrome was present in only an occasional patient in our series, the overall average erythrocyte count being high normal. Similarly the white blood

count was at the upper limits of normal on the average, although a few patients showed a significant leukocytosis. Eosinophils were consistently reduced, but as this may be seen in so wide a variety of conditions its diagnostic value is limited. With respect to electrolytes, the present group of patients had normal serum values on the average, and only a rare individual demonstrated the low potassium and low chlorides associated with an elevated carbon dioxide content and sodium which has been associated in the literature with the syndrome. The consistently normal levels of calcium and of phosphorus in the face of marked demineralization is a well recognized feature of the syndrome. Measurements of thyroid function afford a wide range of figures, with little consistent correlation demonstrable in individual patients between the basal metabolic rate, serum cholesterol and radioactive iodine uptake values.

I have already mentioned the help derived from x-ray in establishing the diagnosis of Cushing's syndrome. In addition to providing evidence of osteoporosis, specific data have been obtained from x-ray as to the presence or absence of adrenal tumors. The larger tumors may occasionally be suspected from distortion of the renal outlines on a simple flat plate; one such case was encountered in the present group. Of the nine patients proven to have tumors, six had intravenous pyelograms; in only half of these was the presence of tumor indicated. This is not surprising since the majority of the benign adenomas of the adrenal are relatively small, and would not be expected to disturb the normal spacial relationships in the adrenal area. For this reason, the technique of peri-renal air insufflation was introduced to aid in delineation of the retroperitoneal space. In all, twenty-nine patients in the present group had such airograms performed, and as Cahill[10] mentioned several years ago, the interpretation of these films in patients with Cushing's syndrome is rendered particularly difficult by virtue of the "edema in the perirenal tissue" in this condition. The record bears this out. In twenty-three of the twenty-nine patients the airogram was considered suspiciously abnormal; of the sixteen who were subsequently explored and an additional two from whom autopsy data were available, a tumor was found in only eight. However, it should be added that no falsely negative results were encountered. It is possible that the newer technique of introducing air presacrally may offer better delineation, but we have not had sufficient experience with this to be certain at the present time.

Treatment

The treatment of Cushing's syndrome should logically be directed at reducing the output of adrenal hormones. The method selected will vary with whether the physician directing the therapy belongs to the school which believes the pathology lies primarily in the pituitary, or in the adrenal or even in the hypothalamus. The available evidence as to the site of origin of this condition is confusing. In briefest summary it is as follows: Cushing in his original paper[2] attributed the disease to the presence of a basophilic adenoma in the pituitary. However, the many cases now on record in which serial sections of the anterior hypophysis have failed to reveal such a lesion make this hypothesis untenable. Others have thought that the disease arises in the adrenals. Cases secondary to adrenal carcinoma would be compatible with this theory but what explanation can be offered for cases in which no abnormality in the size or histological structure of the adrenal has been demonstrated? In 1935 Crooke[11] described a characteristic hyaline change in the pituitary basophile cells in cases with Cushing's syndrome. Extensive study, among which should be mentioned the work of Thompson and Eisenhardt,[12] has confirmed the almost universal finding of this abnormality in such patients. It has, however, been seen in patients with virilism as well as in the classical Cushing's syndrome,[13] and recent work of Laqueur[14] suggests that the hyaline change may be secondary to excess circulating adrenal hormones, rather than the primary cause of adrenal secretion. Her evidence rests on the demonstration of similar changes in the pituitaries of patients who at the time of death were under treatment with exogenous ACTH or cortisone. In 1944 Heinbecker[15] proposed the theory that the initial lesion in the syndrome lay in the hypothalamus where he consistently found abnormalities. However, it seems likely that these hypothalamic lesions, in turn, are secondary rather than of primary importance since Castor et al.[16] have reported the experimental production of lesions in similar areas with ACTH and cortisone. Considering these many conflicting findings, Dr. Plotz, Dr. Ragan and I thought it would be of interest to summarize the present clinical material with respect to the frequency and variety of pathology encountered in the adrenal and pituitary glands in Cushing's syndrome. In ninety-eight patients there were sufficient data available on the condition of both of these glands. It was somewhat difficult to analyze the material

TABLE VI—RELATION BETWEEN PITUITARY AND ADRENAL LESIONS
(97 Autopsied Cases — Cushing's Syndrome)

Pituitary Findings	*Adrenal Findings*						*Total*
	Hyperplasia of adrenals	*Carcinoma of adrenals*	*Unilateral* benign tumor with atrophy of opposite gland*	*Hemorrhage or infarcts in one or both adrenals*	*Hypoplasia of adrenals*	*Normal adrenals*	
Crooke's hyalinization without other pituitary abnormality	17	11	5			1	34
Basophilic adenoma	24		1	2	1	3	31
Increased number basophils or basophilic invasion of posterior lobe	4	1	1			2	8
Mixed basophilic-chromophobe adenoma	3						3
Chromophobe adenoma	5	1				1	7
Mixed chromophobe-eosinophilic adenoma	1						1
Eosinophilic adenoma	1	1					2
Increased number eosinophils		1					1
Unspecified adenoma	1		1			1	3
Atrophy and fibrosis	1						1
Scar destroying neurohypophysis and pars intermedia						1	1
Normal	1	2	3				6
Total	58	17	11	2	1	9	98

* Includes two cases with unilateral hypertrophy of one adrenal without actual tumor.

since it represented the work of many different pathologists who used descriptive terminology which varied considerably. Also the data perforce included cases recorded prior to the publication of Crooke's paper, hence the percentage in which the Crooke's change was reported is undoubtedly falsely low. Its high incidence can only be guessed at from the fact that in all the cases where this hyaline change was searched for, only four authors specifically denied its presence. The results of the analysis are set forth in Table VI. The several categories of adrenal findings are listed horizontally, and the various pituitary lesions are set forth vertically. "Hyperplasia" of the adrenals was arbitrarily defined

as a combined adrenal weight of greater than 15 grams and/or histological evidence of overactivity. The truly impressive feature about this chart is the extraordinary variety of adrenal and pituitary pathology which has been reported in the Cushing's syndrome. We encountered twenty-nine different possible combinations of lesions, all of which have been associated with the same clinical picture. The combination most commonly met with was hyperplasia of the adrenals with a basophilic adenoma of the pituitary. The second most frequent was hyperplasia of the adrenals, with no pituitary abnormality apart from the ubiquitous change in the basophils and, due to the inevitable omission from this group of cases antedating the description of Crooke's change, this particular category may well be the one most commonly encountered. Third most common was a malignant tumor of the adrenal with hyaline changes in the pituitary basophils. Two additional points should be emphasized. Of the various adrenal abnormalities hyperplasia is the one most often encountered while the benign adrenal adenoma occurs in only a small percentage of the cases. Of the pituitary lesions, basophilic adenomas were found in only one-third of the patients; however, pituitary tumors of one sort or another occurred in half of the patients.

From these data it is evident that no blanket outline for treatment can be made but that the approach to therapy must vary with the underlying pathology present in the individual patient. In every work-up there should be investigation to rule in or out the presence of a pituitary tumor. It is extremely rare for the basophilic adenoma to give local symptoms or signs, i.e., restriction of the visual fields or enlargement of the sella, but since a significant percentage of the pituitary tumors in this group of patients may be mixed cell type, chromophobic, or even eosinophilic, signs of local expansion should be searched for and, if found, treatment would logically be directed initially to the pituitary.

In the absence of symptoms suggesting a pituitary neoplasm an effort should be made to rule out an adrenal tumor. When more patients have been studied this may be satisfactorily settled physiologically by the administration of cortisone as described above. However, at the present, direct visualization affords the only decisive means of arriving at this knowledge. Because the removal of such a tumor may be followed by complete remission of the syndrome early exploration of the adrenal area has seemed justified despite the small percentage of those with Cushing's disease showing such tumors. In our group, twenty-two patients

TABLE VII—ADRENAL OPERATIONS IN CUSHING'S SYNDROME

	Total	*Unchanged*	*Sl. imp.*	*Cured*	*Died*
Removal benign adrenal adenoma	6			3	3
Exploration of one adrenal	2	1			1
Biopsy and/or partial resection of one or both adrenals for hyperplasia	10	10			
Subtotal adrenalectomy for hyperplasia	2		2		
Removal adrenal carcinoma	2		1*		2

* Improvement 11 months

were subjected to exploration of one or both adrenals (Table VII). Of the six patients with benign cortical adenoma, three died in the immediate postoperative period and three went on to complete remission of their disease. The three who died were all operated on prior to the availability of ACTH or cortisone. The three who survived all had somewhat stormy postoperative courses. It is interesting that one of these patients, as the evidences of hyperadrenalism cleared, developed disabling arthralgias which persisted for several months. The fatal outcome in one patient who died after exploration without removal of any adrenal tissue was due to the development of a hemolytic streptococcal wound infection with necrosis and gangrene of the abdominal wall, and ultimately generalized peritonitis. This progressed despite wide incision and drainage and the use of sulfadiazine. In the ten patients with hyperplasia of the adrenals in whom biopsy or partial resection of one or both glands was performed, the operation produced no significant change in their course. One of these patients, we have heard, subsequently underwent a subtotal adrenalectomy at the Mayo Clinic with marked improvement. In the two patients in the Presbyterian Hospital series subjected to bilateral subtotal adrenalectomy, the initial results have been somewhat encouraging, though not dramatic. In one patient there has been some improvement in carbohydrate tolerance and in the severe facial acne, decrease in edema and some clearing of his paranoid psychosis. Of the two individuals with adrenal carcinoma, one was unimproved and died four months after his initial operation with widespread metastases; the other enjoyed a remission of eleven months before return of her symptoms and subsequent death from metastases.

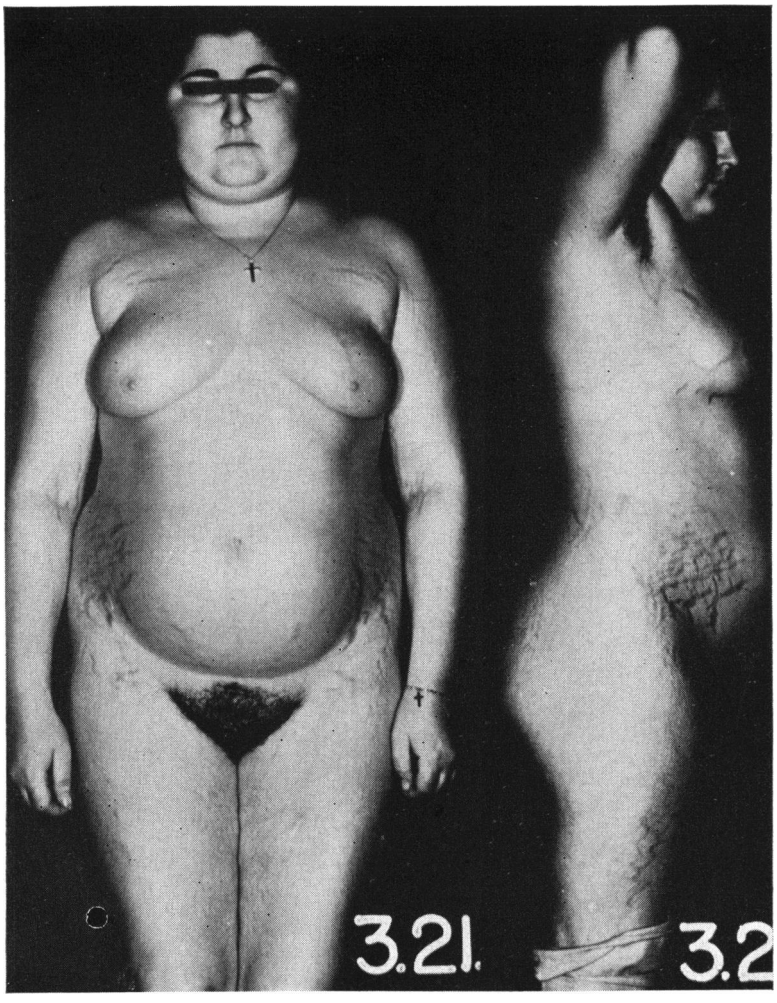

*Figure 1—M.F. Cushing's syndrome, prior to therapy, 3/21/39.

The number of patients in the present group who have had pituitary irradiation now totals twenty. The results obtained by us have paralleled those recently reported by Sosman.[17] Ten of the present twenty patients enjoyed some degree of remission following x-ray, although in only half this number has the improvement been maintained to date. The dosages employed and the duration of time over which therapy was given have varied widely, and no correlation was evident between these

* Figures 1-4, photographs reproduced with the permission of Presbyterian Hospital, New York, N. Y.

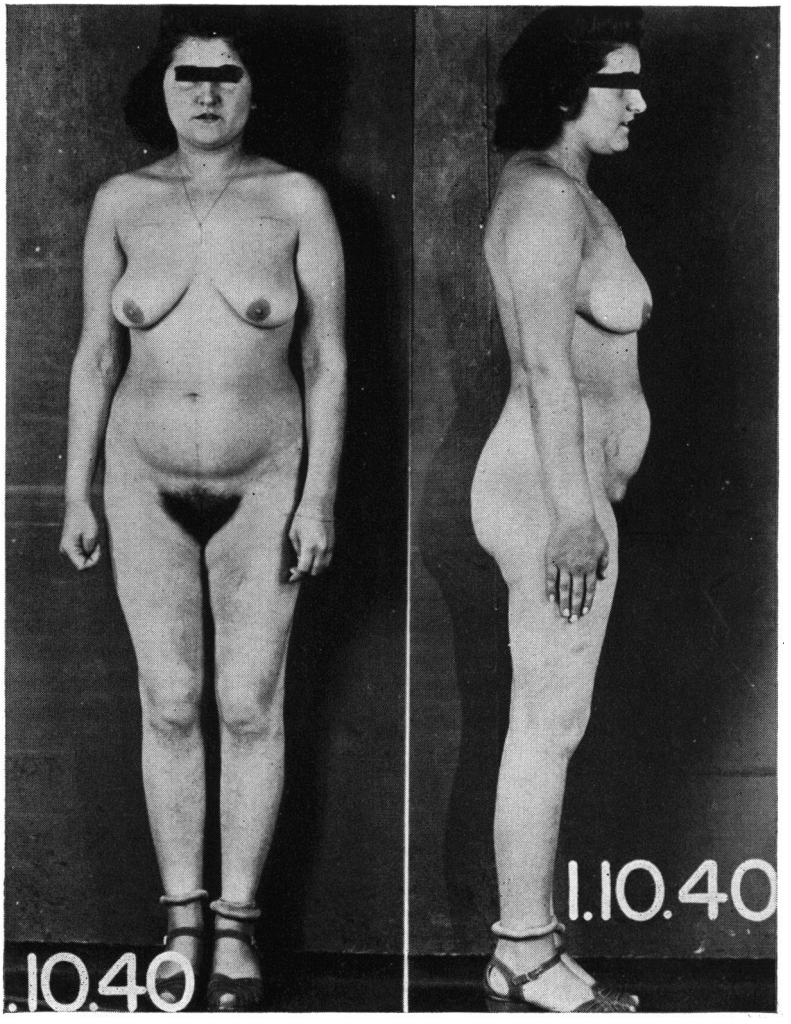

Figure 2—M.F. Cushing's syndrome, 9 months after pituitary irradiation.

factors and the degree of improvement. The accompanying figures show how dramatic this improvement can be. The first photograph shows the patient M.F. as she appeared in 1939 at the age of seventeen, at which time she was suffering from the classical symptoms and signs of Cushing's syndrome, of which the obesity, facial fullness and striae are visible here. In March of 1939 she received a tumor dose totalling only 800 R over a twenty-eight-day period. No other treatment was given. The

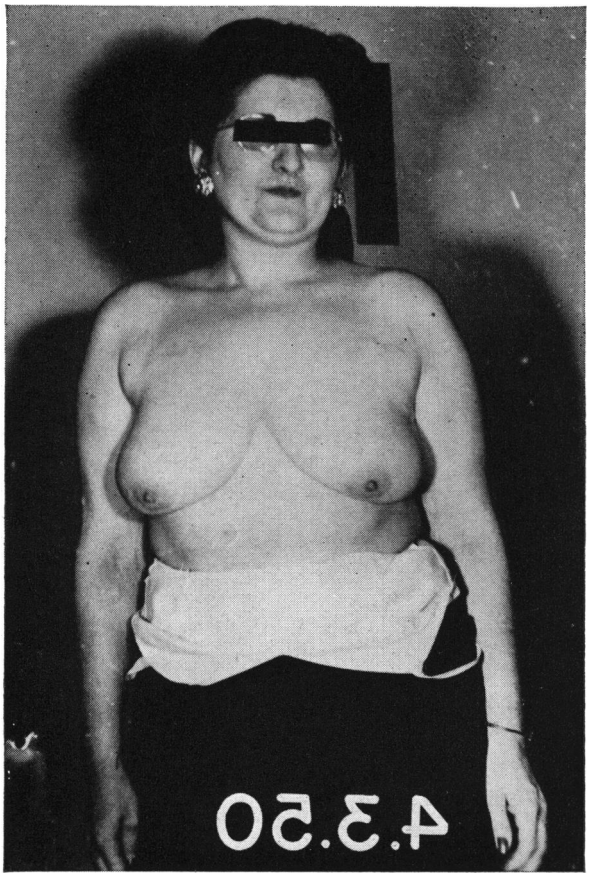

Figure 3—M.F. Cushing's syndrome, 11 years after pituitary irradiation.

next photograph shows her as she appeared in 1940, nine months later, by which time there has been a striking change in her appearance, and the third picture, taken in 1950, twelve years after the onset of her disease, indicates that the remission still persisted.

In the group of patients treated at Presbyterian Hospital only two were treated with androgens in large doses over a prolonged period of time. The results are difficult to interpret because both patients received pituitary and/or adrenal irradiation shortly before or after androgen therapy. Hence our experience with this type of therapy does not permit any conclusions.

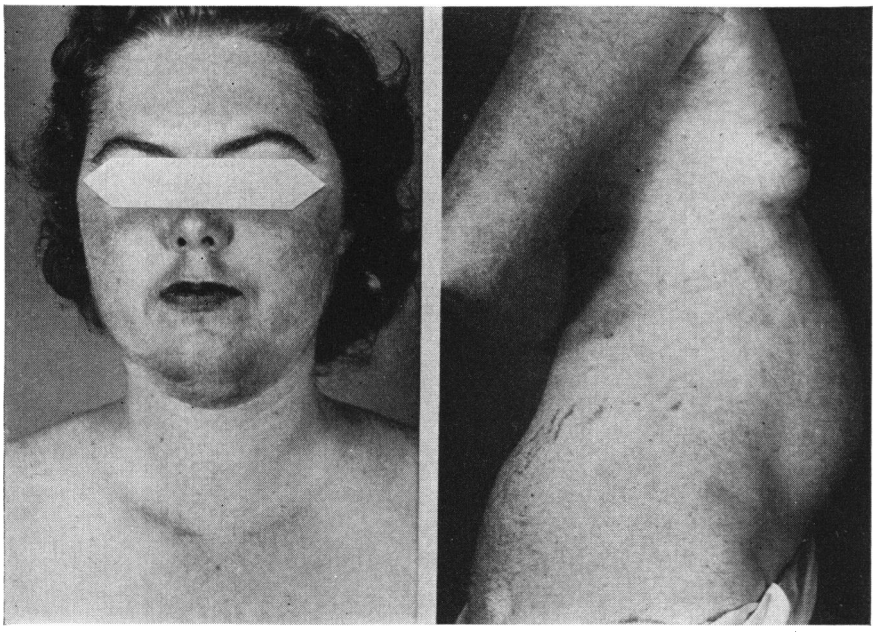

Figure 4—R.C. Cushing's syndrome, 1949.

Before leaving the discussion of treatment, I should like to show one additional figure. The fourth photograph was taken in 1949 when the patient was twenty-nine, having had evidences of the disease for two years. The abnormal features are striking. Bilateral partial resection of both adrenals was performed in June and July of that year. In August she developed an acute psychosis and was admitted to the hospital during which time pituitary irradiation totalling a tumor dose of 1400 R was administered in the course of sixteen days. Her symptoms and her psychosis persisted unabated for the next year during which time she was hospitalized in a state psychiatric hospital, given a course of electric shock therapy with "improvement at first, then later relapse." Beginning in the Fall of 1950 with no further therapy there occurred a gradual spontaneous improvement in her condition—clearing of her hirsutism and skin rash, resumption of menses, clearing of her mental picture and disappearance of her severe hypertension, such that multiple faded striae are at present the only reminder of the previous existence of her Cushing's disease. I mention this case only to emphasize that spontaneous re-

TABLE VIII—CAUSES OF DEATH IN CUSHING'S SYNDROME BASED ON 115 AUTOPSIED REPORTS

(Multiple causes listed in 37 cases)

Infection	54	(6 due to tbc.)
Cardiac failure	31	
Cerebrovascular accident	8	
Uremia	6	
Postoperative death	23	(8 adrenal insufficiency)
Carcinoma of adrenal	7	(present in 11 others)
Tumor of thymus	6	
Carcinoma of pancreas	4	
Sympathicoblastoma	1	
Pulmonary infarction	4	
Asthenia	2	
Acute gastrointestinal hemorrhage	2	
Suicide	2	
Renal colic	1	
Not listed	4	

missions can occur in this syndrome and that interpretation of the results of treatment must take this into consideration.

This happy occurrence is unfortunately all too rare, and one of the most impressive features of this survey was the overall mortality figure. Eighteen of the thirty-eight patients comprising the present series were dead at the end of five years. There are instances in which the disease runs a more benign course, of which the most famous example, probably, was Cushing's first patient, Minnie G. This woman, at the time she was originally reported, had had symptoms of her disease for twenty-nine years. However, the severity of Cushing's syndrome is worth emphasizing as a matter to be taken into serious consideration before undertaking long-term treatment with ACTH or cortisone in patients suffering from non-fatal diseases. From the eight autopsied cases in the present series and from an additional 107 autopsy reports available from the literature, Table VIII has been compiled, listing the more frequent causes of death among patients with Cushing's syndrome. The results are those that might have been predicted from a consideration of the symptoms of the disease. The leading cause of death was infection. Since many of the cases antedated the introduction of antibiotics this is less impressive a figure than it initially appears. However, it does serve to emphasize that the

decreased resistance of hyperadrenal individuals to infection and among these tuberculosis, as well as the pyogenic organisms, must be kept in mind. In confirmation of this there stands recent experimental work indicating the increased susceptibility of hyperadrenal animals to tuberculosis and to a variety of organisms.

The second major cause of death in these predominantly young individuals was cardiovascular disease—cardiac failure, cerebrovascular accidents and uremia. This undoubtedly was related to the severe degree of hypertension so consistently present, and possibly to the widespread presence of arteriosclerosis in these patients. Arteriosclerosis was noted as present in the autopsy reports of fifty-one of the fifty-eight cases in which data on this point were available. Since arteriosclerosis is so common a finding in adult autopsy material, too much emphasis cannot be placed on this finding. However, conclusive evidence of the increased incidence of such lesions under cortisone therapy has appeared recently in a report by Etheridge and Hoch-Ligeti[18] based on autopsy material from children, where arteriosclerosis normally is at a minimum. Comparing the aortas of cortisone-treated patients under eleven years of age with those of a control group, these authors found an increased deposition of lipid in the steroid injected group.

Postoperative deaths accounted for exitus in a distressingly large number of patients. A certain fraction of these could be ascribed to adrenal insufficiency following the removal of a functioning tumor; the rest were due to unexpected postoperative infections such as in the patient I described above. Carcinoma of the adrenal was listed as the cause of death in only a small percentage, the majority of patients with adrenal carcinoma dying of immediate causes other than the neoplasm.

In the Presbyterian Hospital series there were no patients in whom neoplasms were found in areas other than the pituitary or adrenal. In this respect, the present group is at variance with data available in the literature, from which the patients comprising the ensuing three groups are drawn.

In six patients thymic tumors were reported; in four of these the tumors were of malignant nature. Another four patients had carcinoma of the pancreas, while still another died with a sympathicoblastoma. These patients raise the question as to whether these neoplasms in some fashion acted as initiating agents for the hyperadrenalism, or vice versa, or whether the presence of over-activity of the adrenals was in some

manner carcinogenic. It is interesting to note that both the thymus and pancreas are tissues which may be affected in the course of Cushing's syndrome. The thymus commonly shows marked atrophy; the pancreas, though histological changes are less common, may be under physiological stress from the disturbed carbohydrate function. In addition to tumors there were several reports of abscesses and fatty necrosis involving the pancreas. From the reported cases it is impossible to answer the question as to whether the neoplasms ante- or post-dated the appearance of Cushing's syndrome. In only one instance was an attempt made to remove the neoplasm, in the patient reported by Hubble.[19] In this instance the operation was followed by death within twenty-four hours, far too soon to state the effect of the removal of the tumor upon the hyperadrenalism.

Four patients died of pulmonary infarctions. In addition, pulmonary or myocardial infarctions were noted in seventeen of twenty-seven cases in which these data are available. In one case death was listed as due to renal colic. In connection with this it is of interest to note that four patients in the present series have had renal calculi, which may well be related to the disturbed calcium metabolism. It is tempting to speculate that the two deaths ascribed to asthenia might have been due to low potassium levels; however, there was not sufficient information to draw this conclusion. Finally, the two suicides are not surprising in view of the frequency with which severe emotional disturbances have been encountered.

Summary

In summary, this review of the natural history of Cushing's syndrome has confirmed many well recognized features of the disease and has served to emphasize the following:

1. The impressively high incidence of hypertension (92 per cent), abnormal mental reactions (66 per cent) and of unusual infections or poor wound healing (42 per cent).

2. The frequency with which diminished carbohydrate tolerance (94 per cent), demineralization of the spine (74 per cent) and increased urinary excretion of the so-called corticoids (70 per cent) were met with, while the remainder of laboratory studies were but rarely abnormal.

3. The grave prognosis of the disease, with a mortality of 50 per cent by the end of five years and the frequency of the occurrence of

infections and cardiovascular complications among the listed causes of death.

4. The extraordinary variety of adrenal and pituitary pathology which has been associated with the clinical picture of Cushing's syndrome. In ninety-eight patients, basophilic adenomata were reported in 31 per cent although in a total of 50 per cent some type of pituitary tumor was present. Benign adrenal tumors were noted in 11 per cent, malignant tumors in 17 per cent.

Among the thirty-eight patients studied at the Columbia-Presbyterian Medical Center treatment has included:

a) Removal of a benign adrenal adenoma with a complete remission in the three patients who survived the stormy immediate postoperative period;

b) Removal of an adrenal carcinoma which was followed by death from metastases in two patients, one of whom enjoyed a year's remission;

c) Subtotal bilateral adrenalectomy with resultant slight improvement in two patients;

d) Pituitary irradiation which has been followed by temporary improvement in ten of twenty patients. This improvement was maintained in five instances.

A spontaneous and complete remission was seen in one patient.

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