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MORPHOLOGIC CHANGES OF ADRENAL CORTEX IN DISEASE

Stimulation of the adrenal cortex by the "stress" of illness is now taken for granted. Numerous publications have described changes in adrenal cortical histology in particular diseases, and at least one author[1] has attempted a general study of the adrenal cortex in an autopsy population. Even so little attention is paid the adrenal cortex in the average autopsy performed by the average pathologist. This is partly because such attention is relatively unrewarding. In spite of the numerous publications devoted to adrenal cortical histology, few are sufficiently well defined with respect to age, sex, race, and types and duration of disease present. Few provide sufficiently detailed data to serve as a frame of reference for the pathologist. They do not tell how much hypertrophy is to be expected in a given clinical situation, or how much to be considered extraordinary, nor do they tell when lipid depletion is the "normal" response, and when it is noteworthy. This paper is an attempt to provide sufficient data to make such assessment possible.

MATERIALS AND METHODS

During a 20-month period (November 1959 to July 1961), adrenals from all autopsies were placed intact in 10 per cent formalin for later examination by the author. After fixation, the adrenals were carefully cleaned of adherent fat, blotted dry, weighed,** and sectioned at approximately two to three mm. intervals. Two to eight blocks from each adrenal pair were selected for microscopic examination. Routine sections were stained with haemotoxylin and eosin (H and E). Adrenals from cirrhotic patients with ascites and from 50 other randomly selected cases were also stained with Wilder's reticulum stain.

The 407 consecutive autopsies performed during this 20-month period provided 335 pairs of adrenals suitable for accurate weighing. Seventy-two pairs were excluded for the reasons shown in Table 1. However, material from some of these excluded cases

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** Fixed weight does not differ significantly from fresh weight.[1-6]

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was available for microscopic examination. Clinical data were obtained by a review of the patients' records and were supplemented by pathological observations.

Adrenal sections were examined by the author without knowledge of the clinical or other autopsy data. The cortices were measured with a millimeter ruler. The presence of the zona glomerulosa was noted, and its extent was graded on a scale of zero to three-plus. Both H and E, and reticulum-stained sections were used for this purpose. The extent of lipid depletion in the fasciculata-reticularis of the H and E stained sections was graded on a scale of zero to four-plus. A grade of zero was given to those

TABLE 1. GROUPS EXCLUDED FROM WEIGHT DATA

Total consecutive autopsies	407
Lost in processing	24
Excluded from weight data:	
Female patients	2
Medial hemorrhage	2
Amyloid	1
Metastatic cancer	38
Previous adrenalectomy	1
Autopsy limited to head	4
Total not weighed	72
Remainder	335

TABLE 2. ACCURATELY WEIGHED GROUPS

Total accurately weighed	335
Negro patients	16
Steroid-treated patients	27
Nodular hyperplasia	16
Nonsteroid-treated white males without nodular hyperplasia	276

glands without lipid depletion in any zone, one and two-plus grades constituted lipid depletion of zona reticularis and inner fasciculata, three-plus when depletion extended to the middle of the fasciculata, and four-plus when the entire thickness from reticularis to outer fasciculata was lipid depleted. These data were then correlated with independently obtained clinical data.

A control population (Table 2) was selected from the carefully weighed pairs by excluding adrenals from Negro patients, steroid-treated patients (all patients receiving steroids for more than one week) and adrenals containing large cortical nodules (nodular hyperplasia) (Fig. 3, adrenal 6). The remaining 276 adrenal pairs were considered the control population (*i.e.*, nonsteroid-treated white males without nodular hyperplasia).

Subgroups of the control population were selected to test associations between adrenal weight and a particular type of disease. Some of the subgroups were selected

because of previous reports that adrenal hyperplasia and hyperfunction were associated with carcinoma[4, 5] and particularly with bronchogenic carcinoma,[6–12] that adrenal hyperplasia was associated with hypertension[2, 3, 13–23] and arteriosclerosis,[24] and that adrenal hypofunction was found in liver disease.[25–29]

In analyzing the influence of disease on adrenal weight, patients were counted in only one group even though they might have qualified for more than one group by virtue of having more than one major disease. Thus all patients with cancer were selected first, then patients with hypertension, liver disease, chronic pulmonary disease, and severe arteriosclerosis (*e.g.*, myocardial infarction and cerebral infarction), in that

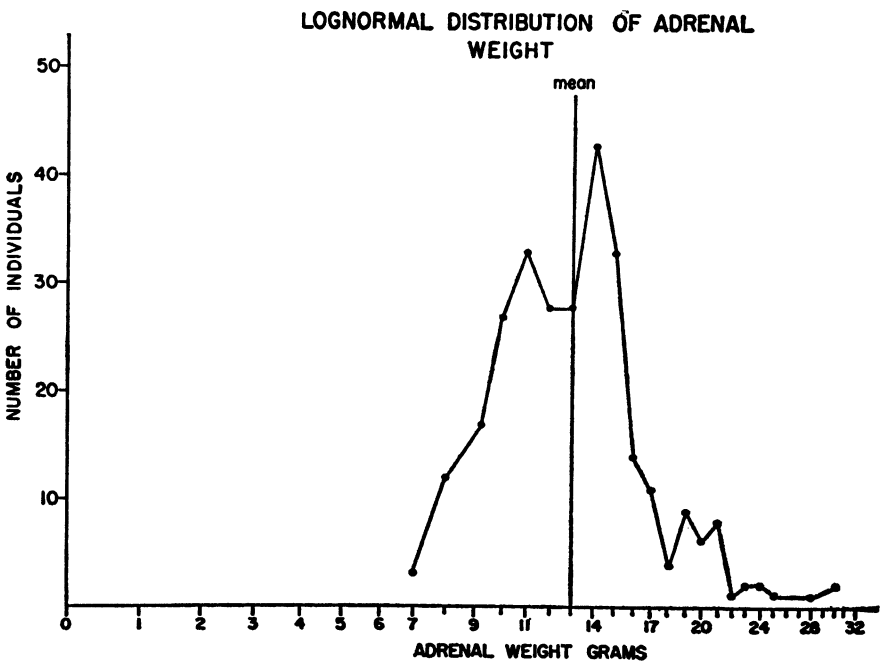

FIG. 1. Distribution of paired adrenal weights in grams plotted on semi-log paper.

order. This order was chosen after inspection of the data showed the larger glands occurring more frequently in the first two groups.

While changes in adrenal weight reflect both duration of underlying disease and intensity of the stimulating or inhibiting effects, changes in cortical lipid content reflect morbid events during the few days preceding death. Therefore subgroups of the control population selected to compare lipid content are based mainly on pre-terminal events and differ from the weight groups.

Still a third grouping is necessary for consideration of the zona glomerulosa. Increased aldosterone is known to occur in some cases of hypertension and cirrhosis but not in cancer. Thus the presence of cancer in a patient with hypertension is assumed to have little effect on the cortical zonation and for the purposes of this analysis such an individual is grouped with the hypertensives.

TABLE 3. FOURFOLD TABLES USED IN CHI SQUARE TESTS

A. Comparison of adrenals weighing less than 7 gm. in steroid-treated and untreated groups.

	<7.0 gm.	>7.0 gm.	Totals
No steroids	1	275	276
Steroids	4	23	27
Totals	5	298	303

(Chi square = 23; $p > .01$)

B. Comparison of adrenal pairs exceeding 22.1 gm. in cancer and noncancer groups.

	<22.1 gm.	>22.1 gm.	Totals
Cancer	152*	7	159
No cancer	155	0	155
Totals	307	7	314

(Chi square = 5.1; $p = .05$)

C. Comparison of adrenal pairs exceeding 22.1 gm. in bronchogenic cancer and other cancer groups.

	<22.1 gm.	>22.1 gm.	Totals
Ca. lung	48*	4	52
Ca. other	105*	3	108
Totals	153	7	160

(Chi square = 1.1; not significant)

D. Comparison of incidence of arteriosclerotic heart disease (AHD) in patients over 60 with and without nodular hyperplasia of adrenal cortex.

	Nod. hyp.	No nod. hyp.	Totals
AHD	10	82	92
No AHD	5	114	119
Totals	15	196	211

(Chi square = 2.4; not significant)

E. Comparison of incidence of hypertension in patients over 60 with and without nodular hyperplasia.**

	Nod. hyp.	No nod. hyp.	Totals
Hypertension	5	29	34
No hypertension	9	167	176
Totals	14	196	210

(Chi square = 2.82; not significant)

F. Comparison of incidence of nodular hyperplasia in patients 60 yrs. and older with those younger than 60.

	Nod. hyp.	No nod. hyp.	Totals
60 yrs. & older	14	210	224
Under 60	2	93	95
Totals	16	303	319

(Chi square = 1.8; not significant)

TABLE 3 (Continued)

G. 1. Comparison of zona glomerulosa in patients with and without chronic pulmonary disease (CPD).

Grade	CPD	Other	Totals
2 to 3	5	50	55
0 to 1	22	246	268
Totals	27	296	323

(Chi square = <1; not significant)

2. Comparison of zona glomerulosa in patients with and without hypertension.**

Grade	Hypertension	Other	Totals
2 to 3	9	46	55
0 to 1	19	249	268
Totals	28	295	323

(Chi square = <1; not significant)

3. Comparison of zona glomerulosa in patients with and without cirrhosis.

Grade	Cirrhosis	Other	Totals
2 to 3	5	50	55
0 to 1	10	258	268
Totals	15	308	323

(Chi square = 1.8; not significant)

* Includes 38 adrenal pairs with gross metastases.
** All hypertensives were included whether or not cancer was present; thus more are counted than in the weight data.

Statistical methods

A lognormal distribution curve was obtained by plotting frequency on the ordinate against paired adrenal weights grouped to the nearest gram on the abscissa of semi-log paper (Fig. 1). Calculations of mean and standard deviations and statistical analyses were performed with the logarithms of the adrenal weights rather than with the weights themselves. The standard *t* test for comparison of means[30] was used to test separately the significance of the differences between the control group mean and the means of the steroid-treated and Negro groups. Heterogeneity within the control group was examined by an analysis of variance.[31] Subgroups were also compared by means of the chi-square test using the Yates correction.[32] The four-place tables used in making these comparisons are shown in Table 3.

RESULTS AND DISCUSSION

ADRENAL WEIGHT

Arithmetic distribution curves of weight are skewed; however, the logarithms of the weights are "normally" distributed and the usual statistical methods of determining the mean and standard deviation can be applied to the logarithms themselves.[33, 34] Such a distribution is called lognormal, and the antilog of the mean so obtained is the geometric mean. Figure 1 shows the lognormal distribution of the control population.

Table 4 shows the mean weights and the standard deviations of the various groups. The differences between the mean weights of the control group and the steroid-treated and Negro groups are significant ($p>.001$ in each instance). A significantly lighter mean weight is expected in the steroid-treated group since exogenous steroids suppress endogenous ACTH, thereby producing adrenal atrophy.[35] Support for this result comes from comparison of the number of adrenals weighing less than seven grams

TABLE 4. SUMMARY OF STATISTICAL DATA

Group	N*	$\bar{x}$**	*log* $\bar{x}$	SD†	*Range two* SD
Control	276	12.9	1.1109	0.1174	7.5 - 22.1
Ca excluding lung	95	13.2	1.1202	0.1256	7.4 - 23.5
Ca lung	27	14.1	1.1489	0.1479	7.3 - 27.8
Hypertension	21	14.5	1.1522	0.0910	9.6 - 22.4
Chronic PD‡	27	12.6	1.1011	0.1090	7.6 - 20.9
Liver disease	14	11.3	1.0513	0.0924	7.4 - 17.2
G A S ¶	28	12.8	1.1070	0.0864	8.6 - 19.0
Misc.	64	12.8	1.1069	0.1168	7.5 - 21.9
Negro	16	10.4	1.0174	0.0927	6.8 - 13.2
Steroid R_x	27	10.6	1.0230	0.1204	6.1 - 13.4

* N = number of adrenal pairs.
** $\bar{x}$ = mean weight.
† SD = standard deviation.
‡ Pulmonary disease.
¶ Generalized arteriosclerosis.

in the control and steroid-treated groups by means of the chi-square test (Table 3, A). The result $p>.01$ indicates more adrenal pairs weighing less than two standard deviations in the steroid group than would be expected by chance. Negro adrenals were originally excluded from the control group because a lower mean weight for this group has been reported.[36] The above results are consistant with this finding. These conclusions assume that the control group is large enough to provide valid values for the mean weight and standard deviation, and that the distribution of disease in the three main groups is random enough so that the differences noted are due to steroid therapy in one group and race in the other, and not to an increased frequency of a particular disease. Tables 5 and 6 give the appropriate data for the two groups.

TABLE 5. STEROID-TREATED WHITE MALES

Autopsy no.	*Disease*	*Age*	*Body weight*	*Type steroid*	*Total amount received (mg.)*	*Number days given*	*Adrenal weight*	*Date last dose*	*Date death*
A59-249	subacute myelogenous leukemia	31	–*	prednisone	2063	21	13.7	12/28	12/28
A60-73	acute bronchial asthma, status	51	117	prednisone	635	20	6.6	4/21	4/21
A60-111	bronchogenic Ca, hypercalcemia, emphysema	66	109	prednisone	900	15	13.5	7/7	7/7
A60-131	decompensated Laennec's cirrhosis	36	160	prednisone decadron	450 18	30 3	10.0	8/11	8/11
A60-138	chronic lymphatic leukemia	61	–	decadron	116	27	12.2	8/22	8/23
A60-147	subacute hepatic necrosis	71	–	prednisone	2075	49	9.0	9/4	9/5
A60-173	subacute glomerular nephritis with nephrotic syndrome	37	170	decadron prednisone	84 630	7 14	16.5	9/11	10/16
A60-189	scleroderma	47	125	metacortin	1600	40	11.5	2/9	11/15
A60-197	multiple myeloma	64	162	decadron	21	28	13.0	12/1	12/1
A60-199	Hodgkin's disease	65	155	cortisone	1800	18	11.1	12/1	12/1
A60-207	bronchogenic Ca hypercalcemia	41	–	prednisone	705	19	11.5	12/9	12/16
A61-5	regional ileitis, staphylococcal septicemia	29	–	metacortin	3340	82	9.0	10/20 1960	1/5 1961
A61-8	staphylococcal pneumonitis, hypertension, diabetes	66	150	prednisone	43	10	14.0	1/10	1/10
A61-11	Ca prostate with osteoblastic metastases	68	–	metacortin	1270	57	16.5	1/14	1/14
A61-28	rheumatoid arthritis aspiration pneumonitis abscess	65	–	prednisone	7300	365	6.6	1/19	2/4
A61-72	myelofibrosis, acute blastic leukemia	57	155	prednisone	1260	29	13.5	3/29	3/29
A61-74	pemphigus, arteriosclerotic heart disease	74	105	prednisone ACTH (40 u)	3700 160	37 4	8.9	3/14 3/18 –	3/29 3/19
A61-97	chronic myelogenous leukemia	29	180	prednisone	260	10	8.7	4/27	4/27

* Not recorded.

TABLE 5. (Continued)

Autopsy no.	*Disease*	*Age*	*Body weight*	*Type steroid*	*Total amount received (mg.)*	*Number days given*	*Adrenal weight*	*Date last dose*	*Date death*
A61-113	sarcoidosis, renal lithiasis pyelonephritis	45	95	decadron	6837	477	6.0	12/1 1960	5/18 1961
A61-126	hemolytic anemia, staphylococcal pneumonitis diabetes	65	180	prednisone	1750	20	8.0	6/2	6/2
A61-128	tuberculosis, vasculitis amputation, pulmonary emboli	42	110	metacortin	1600	16	10.0	6/2	6/4
A61-136	idiopathic cardiomegaly	50	140	prednisone	500	13	10.5	6/5	6/19
A60-143	subacute hepatic necrosis	64	-	prednisone	1500	37	6.5	7/1	7/2
A59-246	Ca bladder, pyelonephritis	54	182	prednisone	720	13	13.7	12/19	12/19
A60-53	mitral stenosis	51	C**	prednisone	1580	50	9.0	3/25	3/27
A60-61	rheumatoid arthritis necrosis femoral heads bacteroides septicemia pulmonary asbestosis	68	C	prednisone	16000	1095	12.8	8/4 1957	4/8 1960
A61-64	tuberculosis Hodgkin's disease	69	C	metacortin	360	9	12.3	3/17	3/17

** Cachectic.

A similar comparison between the subgroups means (Table 4) and the control mean is not valid. The subgroup means could be compared one with another or their total variance analyzed to determine the likelihood of their being drawn by chance from a single population. The latter analyses yielded $p = .05$, suggesting that some of the differences noted are not simply chance.

Adrenal pairs exceeding a weight of plus two standard deviations from the mean (22.1 grams) occurred only in patients with carcinoma. This distribution was tested with the chi-square technique (Table 3, B) and found significant ($p = .05$). The incidence of heavy adrenals in patients with bronchogenic carcinoma was compared to that in patients with other types of malignancy (Table 3, C.). A significant difference was not found.

The preceding statistical comparisons also assume a random distribution of age and body weight. In fact, age and body weight show little correlation with adrenal weight. Table 7 shows no correlation of adrenal weight and age, with the possible exception of the oldest age group where a tendency toward lighter adrenals is noted. A recent study[37] has demonstrated decreased cortisol metabolism by liver and impaired renal excretion of

TABLE 6. NEGRO PATIENTS

Autopsy no.	*Age*	*Body weight*	*Blood pressure*	*Adrenal weight*	*Disease*
A59-241	63	133	180/100	13.0	Ca pancreas
A60-21	58	136	160/85	9.0	Ca lung
A60-81	41	130	210/120	8.3	Hypertension
A60-89	37	163	300/140	14.6	Hypertension
A60-92	65	116	120/80	10.5	Tuberculosis
A60-116	41	C*	140/70	14.0	Multiple sclerosis, osteomyelitis
A60-169	64	150	210/110	11.3	Hypertension
A60-195	67	-**	150/80	7.0	Bronchitis, emphysema
A60-210	65	C	110/70	8.2	Ca prostate
A61-20	73	-	110/70	10.2	Reticulum cell sarcoma
A61-22	60	185	140/80	9.8	Tuberculosis
A61-26	69	C	120/80	8.7	Ca lung
A61-75	73	160	170/90	12.0	Acute pulmonary embolism
A61-89	27	190	220/110	10.5	Glomerulonephritis
A61-96	66	180	180/90	9.5	Ca bile duct
A61-139	76	139	110/70	13.5	Emphysema

* Cachectic.
** Not recorded.

cortisol with advancing age. Endogenous ACTH secretion would be reduced and some adrenal atrophy would be expected.

Table 8 shows no correlation between adrenal weight and body weight, with the possible exception of the largest individuals. This comparison is not too reliable because of the rapid weight loss induced by disease. Atrophic adrenals, not steroid-induced, were usually associated with extreme cachexia.

Table 9 relates adrenal weight to cortical thickness. Cortical thickness has been used as the criterion of hyperplasia in two recent studies.[10, 25]

CORTICAL ZONATION AND LIPID CONTENT

The adrenal cortex is described as having three zones: an outer zona glomerulosa, a middle zona fasciculata, and an inner zona reticularis. Recently, Symington[88] convincingly showed that under the stimulus of

TABLE 7. VARIATION OF ADRENAL WEIGHT WITH AGE

		Adrenal weight (grams)											
Total individuals	*Average weight*	*>26*	*24-25.9*	*22-23.9*	*20-21.9*	*18-19.9*	*16-17.9*	*14-15.9*	*12-13.9*	*10-11.9*	*8-9.9*	*6-7.9*	*Age in years*
3	17.0				1		1		1				20-29
18	13.2					1	1	6	3	5	2		30-39
42	14.7	1			2	4	3	11	11	8	2		40-49
28	13.9				2	3	4	7	2	7	1	2	50-59
126	13.5	1	2	3	5	5	5	27	27	30	17	4	60-69
58	12.7	1			1	1	3	11	11	16	13	1	>70

TABLE 8. VARIATIONS OF ADRENAL WEIGHT WITH BODY WEIGHT

		Adrenal weight (grams)											
Total individuals	*Average weight*	*>26*	*24-25.9*	*22-23.9*	*20-21.9*	*18-19.9*	*16-17.9*	*14-15.9*	*12-13.9*	*10-11.9*	*8-9.9*	*6-7.9*	*Body weight (lbs)*
56	12.6	1			1	2	4	9	10	16	10	3	Cachectic*
8	13.0						1	2	3		2		80-99
25	11.8				1		1	2	8	3	9	1	100-119
37	15.0	1		1	4	2	4	6	9	8	2		120-139
35	13.0		1		2	1	2	5	8	8	6	2	140-159
30	14.2			1		3	3	11	3	6	2	1	160-179
18	14.2				2	1	1	6	2	4	2		180-199
17	15.1			1	1	2		6	4	3			>200

* Only description available.

ACTH, the lipid-laden cells of the fasciculata become transformed into lipid-poor, RNA-rich cells identical with those in the zona reticularis. Thus, the middle and inner zones represent the same cells in different degrees of activity. The subcapsular zone, zona glomerulosa, has been shown to produce aldosterone in the ox,[89] and to vary in thickness in response to body electrolyte changes in the rat.[40] In the ox, rat, and dog the zona glomerulosa is well defined, but in man it is a poorly defined zone which varies from place to place and from individual to individual, merging imperceptibly with the outer fasciculata.[41-43] Even so, in man,

histologic changes in this zone have been correlated with serum electrolyte imbalance and hypertension.[19, 44-46] One author has attempted to correlate the outer fasciculata rather than the glomerulosa with aldosterone production.[46] Reticulum stain has been suggested as a valuable method of identifying the zona glomerulosa.[45, 46]

In the present study precise measurements were not attempted because of the large series and inherent variability of the zona glomerulosa. Instead, the subcapsular zone was appraised for distinctness and extent, and graded on a scale of zero to three-plus. Repeat appraisal of 40 randomly selected cases after a lapse of three years showed agreement in 31 cases (77%). Reticulum stain did not facilitate grading.

TABLE 9. CORRESPONDENCE OF ADRENAL WEIGHT AND CORTICAL THICKNESS

	Adrenal weight (grams)											
Cortical thickness mm.	*6–8*	*8.1–10*	*10.1–12*	*12.1–14*	*14.1–16*	*16.1–18*	*18.1–20*	*20.1–22*	*22.1–24*	*24.1–26*	*26.1–30*	*Totals*
2.0–3.0				3	1	2	5	5	4	1	3	24
1.6–1.9		1		2	1	3	4	1				12
1.3–1.5		8	11	19	24	6	3	2				71
1.0–1.2	5	21	38	41	23	2	3	1		1		133
0.8–0.9	7	9	15	5	3	1						39
0.6–0.7	6	14	5	1								26
Totals	18	53	69	71	52	14	15	9	4	2	3	310

The majority of glands (268 of 323) were graded zero to one-plus. Six pairs were graded three-plus and 49 were two-plus. Electrolyte data was available for two patients in the three-plus group. One of these, a cirrhotic, had hyponatremia during the week preceding death. The other, with cor pulmonale and emphysema, had normal electrolytes five days prior to death. Of the remaining four cases graded three-plus, one had cirrhosis, one septicemia, and two carcinoma (lung and sinus). Electrolytes were available for 17 of the 49 cases graded two-plus. Only two of these had hyponatremia.

The grade two-plus and three-plus groups were combined for statistical analysis. Among these 55 cases were nine hypertensives and five cirrhotics. Chi-square analysis (Table 3G) does not show a statistically significant incidence for any group tested.

The work of Symington[88] provides the pathologist with a guide to the evaluation of ACTH function based on the extent of cortical lipid

depletion. Figure 2 shows the extent of lipid depletion in various subgroups of the control population. The total number of individuals in these subgroups differs from the total used to establish mean weight. In choosing these categories, the preterminal events were considered of

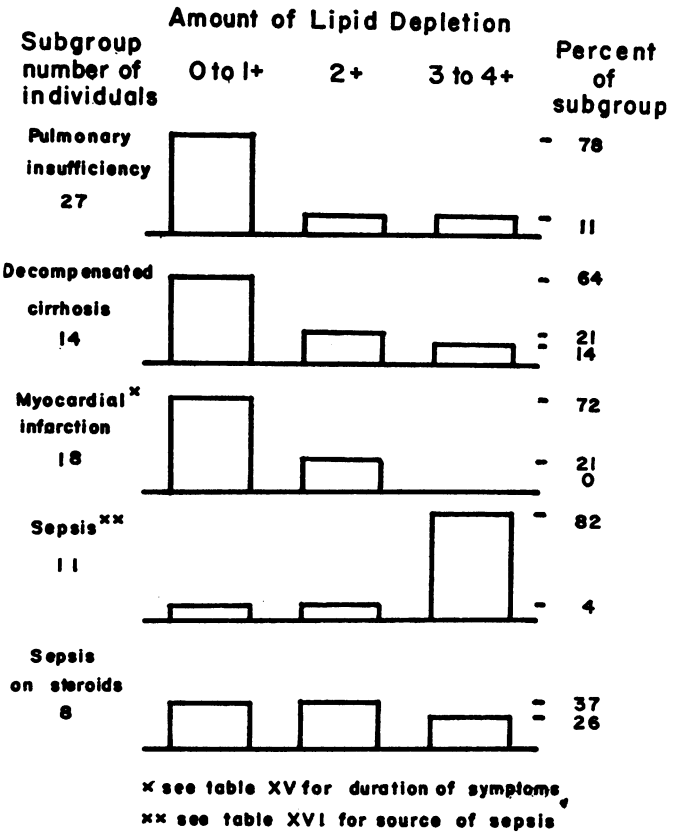

FIG. 2. Patterns of lipid depletion associated with the various disease categories.

greater significance than the underlying disease. Thus most patients with hypertension died from myocardial infarction or cerebrovascular accidents and were so classified. Sections were available from some adrenals not suitable for weighing and *vice versa*. Categories with the least depletion were cirrhosis, pulmonary insufficiency, and myocardial infarction. Patients with severe sepsis showed the most marked lipid depletion. Pseudotubule formation was frequently observed in completely depleted

glands, and a few showed focal infarction and necrosis. The two cases excluded because of massive intramedullary hemorrhage were also cases of severe sepsis. The significance of these observations is discussed in subsequent sections.

LIPID DEPLETION IN RESPONSE TO INFECTION

Lipid depletion in response to severe acute bacterial infection was an early and frequent observation.[1, 52-55] Occasionally, in addition to lipid depletion, degenerative changes (focal necrosis and pseudotubule formation) are seen. Hemorrhagic cortical necrosis is an extreme form of degeneration associated with gram-negative septicemia and particularly meningococcemia.[54, 56] Berry and Smythe[57] suggest that small amounts of endotoxin stimulate the adrenal cortex, but large amounts are toxic to it. More recently, attempts have been made to characterize this response to sepsis. Nadel, *et al*,[58] compared the effects of ACTH and endotoxin, and found that both increased excretion of three polar corticosteroids, (6 (B)-hydroxycortisol, 2(a)hydroxycortisol, and cortisol) *in vivo*. However, Glenchur and Doe[59] measured plasma and urine 17-hydroxycorticosteroids in seven patients with bacterial pneumonia and found elevated plasma levels but decreased urine levels. The half-life of exogenous cortisol was increased. The authors suggest four possible mechanisms to explain their findings: abnormal hepatic conjugation, renal retention of conjugates, increased plasma protein binding, and increased conversion of cortisol to 20-hydroxy forms.

The foregoing suggests that chronic sepsis would lead to adrenal hypertrophy, and this may be one of the stimuli to adrenal hyperplasia in some cancer patients whose long illnesses are complicated by repeated or persistent sepsis.

EFFECT OF STEROID TREATMENT

The earliest and most consistent effect of steroid treatment is decreased lipid depletion.[60] While prolonged steroid administration leads to cortical atrophy, this is presumably a reflection of endogenous ACTH suppression by the exogenous steroid. Extreme atrophy (less than 7.0 grams) occurred in four steroid-treated individuals. Two of these (cases A60-73 and A61-28, see Table 5) received steroids continuously for at least one year. Case A60-143, subacute hepatic necrosis, received 1,500 mg. of prednisone over a 37-day interval. The severe liver damage may have potentiated the steroid effect. Case A60-73 received only 635 mg. of prednisone over

a 20-day interval, and died in *status asthmaticus* during the first night of reduced dosage. The combined adrenal weight of 6.6 grams would seem to be an inordinate amount of atrophy for a relatively short period of treatment. This patient's adrenal atrophy may have preceded treatment and may have been related to the late and sudden onset of severe asthma.[61]

TABLE 10. CANCER ASSOCIATED WITH ADRENAL HYPERPLASIA

Type cancer	*Adrenal weight*	*Clinical Cushing's syndrome*
Oat cell Ca lung	29.0	Yes
Oat cell Ca lung*	39.0	Yes
Epidermoid Ca mouth	25.0	No
Adeno Ca rectum	29.0	No
Epidermoid Ca lung	27.5	No
Epidermoid Ca lung	22.9	No
Undifferentiated, probably pancreas	23.0	No
Adeno Ca lung	24.0	No

* These adrenals were examined after completion of data collection for this paper and are not included in other weight calculations.

ADRENAL RESPONSE TO CARCINOMA

Fulminant Cushing's syndrome in association with "non-endocrine" carcinoma is a well-established clinical entity. These cases are summarized in several recent reviews.[62-64] The adrenal hyperplasia and hyperfunction is stimulated by ACTH-like peptides produced by the cancer.[65] The general or specific nature of this phenomenon is still in question. Several recent studies of blood and urine steroid levels in patients with bronchogenic carcinoma have shown elevated baseline steroid levels and hyperresponsiveness to ACTH when compared to a variety of control groups.[8, 11, 12] Other authors have attempted to demonstrate anatomic evidence of adrenal hyperplasia in patients dying of bronchogenic[10] and other types of carcinoma.[4] It can be seen from Table 4 that the mean adrenal weight for patients with bronchogenic carcinoma was slightly higher than other nonhypertensive groups. Both carcinoma groups show greater deviation from the mean than other groups. All of the adrenals exceeding plus-two standard deviations from the control mean were associated with carcinoma (Table 10). These data support the suggestion that cancer is occasionally associated with adrenal hyperplasia. However, the frequency

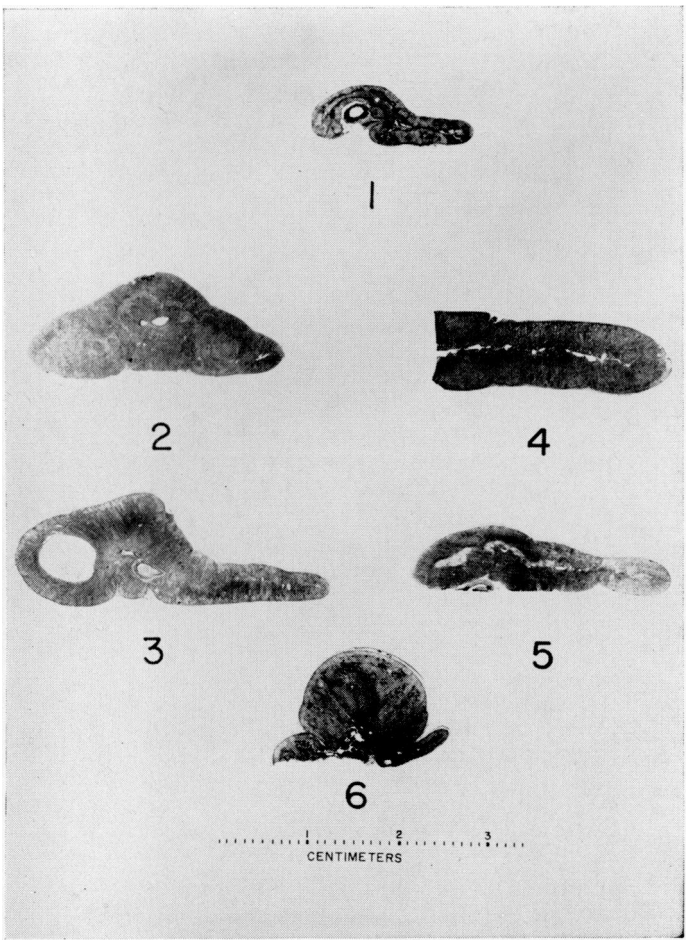

FIG. 3. Types of adrenal hyperplasia:

1. S62-1958, 12.4 gms., normal.
2. A61-30, 29.0 gms., diffuse hyperplasia, carcinoma of the rectum.
3. A61-66, 27.5 gms., diffuse hyperplasia, epidermoid carcinoma lung.
4. S61-354, 39.0 gms., diffuse hyperplasia, oat cell carcinoma lung, Cushing's syndrome.
5. A60-22, 29.0 gms., diffuse hyperplasia, oat cell carcinoma lung, Cushing's syndrome.
6. A61-19, 21.3 gms., nodular hyperplasia.

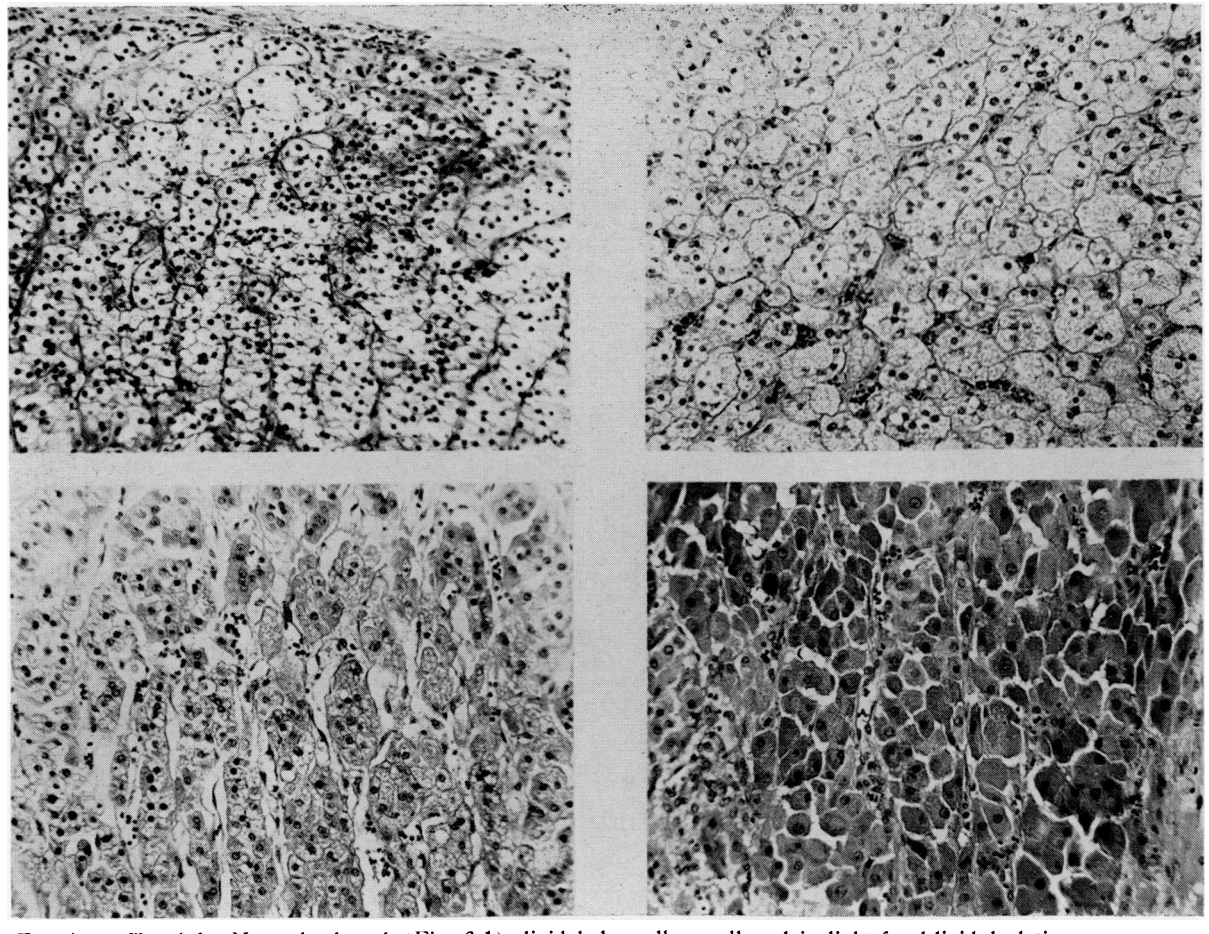

FIG. 4. a) Top left: Normal adrenal (Fig. 3-1), lipid laden cells, small nuclei, slight focal lipid depletion.
b) Top right: Nodular hyperplasia (Fig. 3-6) lipid laden cells, small nuclei.
c) Bottom left: Diffuse hyperplasia *without* Cushing's syndrome, (Fig. 3-2), moderate hypertrophy of cells and nuclei, moderate lipid depletion.
d) Bottom right: Diffuse hyperplasia *with* Cushing's syndrome: (Fig. 3-5) marked hypertrophy of cells and nuclei, uniform lipid depletion.

of hyperplasia was similar in bronchogenic and nonbronchogenic carcinoma. Only one patient with large adrenals had clinical evidence of Cushing's syndrome. The adrenals of this patient with oat cell carcinoma showed a distinctive morphology.[64] A second patient with oat cell carcinoma and Cushing's syndrome (Table 10) was studied after completion of data

TABLE 11. HYPERTENSIVE PATIENTS

Autopsy no.	*Blood pressure*	*Terminal event*
A59-219	190/110	MI*
A59-233	210/110	MI
A59-247	Cardiomegaly (>700 gms)	MI
A60-12	200/90	Uremia
A60-35	210/140	MI
A60-55	200/150	MI
A60-58	175/120	MI
A60-64	200/120	MI
A60-78	210/95	CVA**
A60-104	180/100	CVA
A60-106	230/110	Peritonitis
A60-113	240/120	MI
A60-122	160/110	MI
A60-170	180/120	CHF†
A60-190	210/120	CHF
A60-203	Cardiomegaly (>700 gms)	MI
A61-60	240/160	CVA
A61-79	250/150	CVA
A61-114	230/125	CVA
A61-135	220/120	CVA
A61-138	220/120	MI

* MI = myocardial infarction.
** CVA = cerebrovascular accident.
† CHF = congestive heart failure.

collection. Both cases showed a uniform hypertrophy of the adrenal cortex which was composed of large polygonal eosinophilic cells, presumably an exaggerated ACTH response. The hyperplastic adrenal cortices from patients with carcinoma but without Cushing's syndrome were composed of smaller cells often containing abundant lipid (Figs. 3 and 4).

Marks, *et al,*[9] studied a patient with carcinoma, large adrenals, and ACTH hyper-responsiveness but without Cushing's syndrome. He postulated production of an adrenal weight-maintaining factor distinct from ACTH. If this is so, tumors secreting such a factor, though uncommon,

are less rare than those producing an ACTH-like material. In fact, only four types of tumors have shown *multiple* instances of associated Cushing's syndrome. These are oat cell carcinoma,[63-64] islet cell carcinoma (with and without insulin hypersecretion, but all occurring in women),[64,65] bronchial adenoma of the carcinoid type with and without serotonin pro-

TABLE 12. PATIENTS WITH NODULAR HYPERPLASIA

Autopsy no.	*Age*	*Blood pressure*	*Adrenal weight*	*Heart weight*	*Degree of arteriosclerosis†*	*Other*
A59-228	71	140/80	20.0	400	MI	Tbc. renal adenoma
A59-250	56*	100/70	21.0	300	Mild	Epidermoid Ca Esophagus
A59-251	67	100/60	8.2	450	Severe	Ca pancreas
A60-7	61	140/80	24.5	370	None	Glioblastoma
A60-44	70	140/80	19.2	650	MI	
A60-51	64	160/80	13.5	350	None	On steroids Multiple myeloma
A60-215	65	"high"	21.2	600	MI	Hypokalemic alkalosis attributed to diuretics
A60-216	82	190/90	10.8	600	MI	Acute pancreatitis
A61-19	62	220/110	21.3	400	Mild	Ca prostate
A61-32	68	160/80	17.5	350	MI, CVA	
A61-34	61	110/70	25.0	350	MI	Paget's Disease Ca cecum
A61-46	71	200/100	19.2	550	Infarct of the bowel	
A61-56	67	130/90			AHD, MI	
A61-81	69	180/70	28.5	600	MI	
A61-112	72	120/70	15.0	370	MI	
A61-118	48*	120/70	23.0	200	None	Ca lung

* Under 55 not included in chi square statistics.
† Abbreviations used follow:
MI = Myocardial infarction.
CVA = Cerebrovascular accident.
AHD = Arteriosclerotic heart disease.

duction,[66,67] (a recent report notes this association with an abdominal carcinoid),[68] and thymoma. The latter have shown an atypical histology, having an organoid appearance somewhat like that of the bronchial adenomas.[66] ACTH-like material has so far only been extracted from oat cell and islet cell carcinoma.[69] Therefore, while adrenal hyperplasia is occasionally present in patients with a variety of carcinomas, Cushing's syn-

drome is probably a specific association with only a few rare and possibly related types of tumor.

HYPERTENSION

Without nodular adrenals

The numerous studies of adrenal morphology in patients with hypertension have produced conflicting results. Hyperplasia has been found by

TABLE 13. PATIENTS WITH PULMONARY INSUFFICIENCY*

Autopsy no.	*Age*	*Adrenal weight*	*Disease*	*100 per cent MBC*	*100 per cent VC*	*97-99 per cent arterial O_2*	*38-42 mm Hg arterial PCO_2*
A60-2	61	7.2	PE, old, multiple	37	53		
A59-212	62	14.5	tbc, E, CP	21	40		
A59-230	61	9.8	E, CP				
A59-229	62	13.5	E, CP				
A60-9	62	10.0	PE, old, multiple				
A60-18	69	7.5	E, CP				
A60-19	67	13.0	E, CP				
A60-119	81	10.5	E, CP				
A60-129	62	10.9	E, CP	26	64		
A60-140	46	10.5	E, CP	19	38		
A60-146	63	10.0	E, CP	18	38	44	81
A60-191	74	9.0	E, CP	31	37		
A60-214	59	14.7	E, CP	29	78		
A60-217	50	15.0	E, CP	28	48		
A61-2	59	11.0	E, CP	25	56		
A61-9	66	13.0	tbc, E, CP				
A61-21	..	18.7	E, CP	17	46		
A61-38	59	16.5	E, CP				
A61-49	65	8.0	E, CP	15	33		
A61-76	59	15.0	tbc, E, CP				
A61-83	75	11.7	E, CP				
A61-105	64	11.5	E, CP				
A61-120	63	10.5	E, CP				
A60-8	59	10.5	E, CP, bleeding ulcer				
A60-162	70	13.7	tbc, PE				
A60-165	73	10.6	tbc, MI				
A60-196	46	14.0	tbc, E, CP, MI				

* Abbreviations follow:
MBC = Maximum breathing capacity.
VC = Vital capacity.
PE = Pulmonary emboli.
tbc = tuberculosis.
E = Emphysema.
CP = Cor pulmonale.
MI = Myocardial infarction.

some[8, 14, 24] and not by others.[15, 16] Micronodules were associated with hypertension by some[8, 17, 20] but not by others.[12, 15, 16] Several authors[14, 24, 46] have observed glands from hypertension to be lipid-laden, and two authors[8, 17] thought that cortical lipid actually increased.

In the present study hypertensives were selected on the basis of a well-documented hypertensive history with diastolic blood pressures of 90 mm. of Hg. or higher. Twenty-one patients met these criteria (Table 11). Patients with hypertension secondary to primary renal disease were ex-

TABLE 14. ORIGIN OF GROSSLY VISIBLE METASTASES

Lung	25
Prostate	4
Lymphoma	2
Melanoma	1
Pancreas	1
Stomach	1
Testes	1
Esophagus	1
Hepatoma	1
Bladder	1
Total	38

cluded. Patients with nodular adrenals and hypertension are considered in the next section. The mean weight for this group was slightly higher than other groups (Table 4) and all but one had lipid-laden glands. Lack of lipid depletion may be related to terminal events, since most died suddenly from myocardial infarctions or cerebral accidents (Table 11).

Since most of the nodules removed from patients with primary aldosteronism have had a lipid-laden fascicular pattern, one author[46] has suggested that lipid-rich adrenals from hypertensives may also be producing excessive aldosterone. However, this same author and others[14, 70] have also suggested that this lipid-laden appearance of the adrenal cortex simply reflects arteriolar disease in the adrenal capsule. Certainly a lipid-rich cortex does not suggest excessive ACTH stimulation.

Nodular hyperplasia

Several authors have correlated nodular adrenals with hypertension and arteriosclerosis.[8, 14, 17, 20, 24, 46, 71] Common features in these observations were lipid-laden glands and elderly patients. While some authors have suggested that nodular adrenals are related causally to hypertension[71] and

arteriosclerosis,[24] others have considered the adrenal changes degenerative secondary to arterial disease.[14, 46]

Clinical data from patients with nodular adrenals segregated in this study are presented in Table 12. Of the 16 cases, only two were under 60. Five had documented hypertension and ten had severe manifestations of arteriosclerosis. None of these incidences is statistically significant when tested by the chi-square technique (Table 3 D,E,F).

TABLE 15. ACUTE MYOCARDIAL INFARCTION

Autopsy no.	*Duration of symptoms*	*Shock*
A59-219	36 hours	no
A59-226	24 hours	no
A59-220	6 hours	yes
A59-225	<1 hour	no
A59-222	10 hours	yes
A59-247	12 hours	yes
A60-39	1 week	no
A60-58	1 week	no
A60-64	72 hours	no
A60-72	48 hours	no
A60-122	6 hours	no
A60-151	96 hours	no
A60-167	24 hours	no
A60-188	10 hours	no
A60-203	12 hours	yes
A60-208	72 hours	yes
A61-15	No data available	
A61-141	24 hours	no

CIRRHOSIS

Recent studies have shown impaired metabolism of hydrocortisone in cirrhotic patients. The half-life of infused exogenous cortisol is doubled.[26, 27] Since the miscible pool of cortisol is normal in these individuals, suppression of endogenous ACTH and decreased cortical stimulation is probable.[26] Both the weight and lipid depletion data obtained in this study are consistent with ACTH suppression. The mean weight is less than other nonsteroid-treated groups (Table 4) and relatively little lipid depletion is noted (Fig. 2).

PULMONARY INSUFFICIENCY

Patients were placed in this group on the basis of clinical and autopsy evidence of severe lung damage (*e.g.*, emphysema, fibrosis, advanced tuber-

culosis, and cor pulmonale). Available information on the extent of pulmonary impairment during life is recorded in Table 13. The striking feature in this group is lack of lipid depletion (Fig. 2). This is interpreted as lack of or diminished pituitary response to the stress of chronic dyspnea. Normal plasma and urine levels of 17OHCS and normal responsiveness to ACTH have been recorded in patients with chronic pulmonary disease and dyspnea.[73]

TABLE 16. PATIENTS DYING WITH MAJOR SEPSIS

Autopsy no.	*Source*	*Other*
A59-213	Pelvic abscess	12 days post operative, subtotal resection of bladder
A59-224	Aspiration pneumonia	Ca lung metastatic to brain
A60-14	Pneumonia	Parkinson's disease
A60-28	Pneumonia	Multiple sclerosis
A60-37	Pneumonia	
A60-80	Pyelonephritis Pneumonia	Focal pancreatitis
A60-82	Septicemia	Chronic brain syndrome
A60-107	Septicemia	Aplastic anemia
A60-200	Peritonitis	Diverticulitis
A61-109	Peritonitis	
A61-110	Pyelonephritis Pneumonia Septicemia	Neurogenic bladder secondary to syphilis

MISCELLANEOUS

Three cases of myelolipomata were encountered in this series. This is higher than a previously reported incidence.[78] One unusual microscopic metastasis was noted. This was metastatic Kaposi sarcoma in a patient with Kaposi's sarcoma of limbs and bowel and adenocarcinoma of the stomach. None of the adrenals containing metastases were completely replaced, nor did any of the patients manifest adrenal insufficiency. A breakdown of gross adrenal metastases is presented in Table 14.

SUMMARY

Morphologic observations made on 335 intact pairs of adrenal glands obtained from 407 autopsies are correlated with clinical data.

Adrenal weight follows a lognormal distribution (geometric mean 12.9 gms., plus or minus 2 S.D., 7.5 gms. to 22.1 gms.). The geometric means

obtained from Negro patients and steroid-treated white patients were significantly lower than the mean for white males not on steroids.

Comparison of adrenal weight with body weight and patient's age showed little correlation except at the extremes of age and weight. Adrenal weight correlated well with cortical thickness.

Adrenal pairs exceeding a weight of 22.1 gms. occurred only in patients with carcinoma. Hyperplastic glands occurred with equal frequency in bronchogenic and other types of malignancy. Two cases of Cushing's syndrome occurred in patients with oat cell carcinoma. Glands from these individuals showed a quantitatively distinctive type of hypertrophy.

Cases with nodular hyperplasia were not included in weight data but were analyzed separately. Nodular hyperplasia did not correlate with age or disease.

Sections were graded with respect to the thickness of zona glomerulosa and extent of lipid depletion in the fasciculata-reticularis. Variations in the zona glomerulosa did not correlate with cirrhosis, hypertension, or renal disease. Lipid depletion of the fasciculata-reticularis was most striking in severe sepsis. Little cortical lipid depletion was seen in cases of decompensated cirrhosis and pulmonary insufficiency. This may represent diminished ACTH release in these "stressful" states.

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