STRUCTURE OF THE ADRENAL CORTEX IN RHEUMATOID DISEASES, INCLUDING SOME OBSERVATIONS ON THE ADENOHYPOPHYSIS

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ABSTRACT

The adrenal cortex of rheumatoid patients not treated with steroids shows a characteristic, dystrophic change consisting of swelling and lipid depletion. The adrenals of patients treated with steroids showed an apparent improvement of the histological structure of the gland, but sharp reduction in volume.

The adrenal cortex shows the greatest degree of structural variability of all organs in healthy human beings. Eight distinct structural types, several of which may occur concurrently in the adrenal cortex of a single, normal person, were described by Elias & Pauly (1956).

In patients who died with a variety of systemic diseases, 16 additional structural types were found. Some differed markedly from the basic types, but most of them represented adaptive or degenerative modifications (Elias & Pauly 1960 a, b). In all the clinical conditions hitherto studied (alcoholism, primary hepatocellular carcinoma, diabetes mellitus, eclampsia, leukaemia, malaria (Plasmodium vivax and falciparum), narcotics addiction, narcotics poisoning, nephrosis, pulmonary tuberculosis, gastric and duodenal ulcers and starvation) primary adrenocortical pathology could be excluded; and the specific modifications of the histological picture could be interpreted as a response or reaction to the altered physiology of the sick organism.

Diseases, the symptomatology of which can be influenced by administration

Sponsored by the Arthritis and Rheumatism Foundation of Illinois.
of adrenocortical steroids, belong in a completely different category. In such diseases a functional disturbance of the gland, however minute, might be a contributing factor in the development or maintenance of the condition. Such functional disturbance or imbalance may well express itself in microscopic structural changes. To determine whether such changes existed, the morphology of the adrenal cortex was studied in 26 persons who died of rheumatoid diseases. Fifteen of these cases have been presented in a preliminary report (Elias & Rothstein 1962).

MATERIALS AND METHODS

These studies were carried out on autopsy material from the Seattle Veterans Administration Hospital, the Massachusetts General Hospital, and the Clinical Center of the National Institutes of Health, made available through the courtesy of Drs. D. V. Brown, Benjamin Castleman, Louis B. Thomas and Harold L. Stewart, to whom we express our gratitude. The material consisted of slides of the adrenal glands, and in a few cases of the pituitary gland, from 26 patients who died with (not necessarily from) rheumatoid arthritis, rheumatic fever, rheumatic heart disease or disseminated lupus erythematosus, or a combination of some of these conditions. Some of these patients had received steroid hormone treatment. For purposes of description and discussion, the cases were divided into three groups: patients who had never received steroid treatment (7 cases), patients who received intermittent or discontinued steroid therapy (8 cases) and patients who received uninterrupted steroid treatment until shortly before death (11 cases).

The duration of continuous hormone therapy (cortisone, prednisone, dexamethasone and decadron) ranged from one month to seven years. Corticotrophin was used in one case. In every case observation and detailed description of the histological picture preceded the reading of the case history to avoid biased interpretation of the slides.

A relationship was found to exist between the duration of steroid treatment and the histological structure of the gland, as well as between duration of treatment and size of the gland. At first this size factor was expressed by such qualitative phrases as 'swelling', 'thick cortex', 'thin cortex' and 'extremely thin cortex'. Not satisfied with such a superficial notation, we attempted to describe these observations in a more quantitative manner. For more significant than the increase in thickness is the increase in volume.

The tire glands were, of course, not available for direct volume determination. Only sections could be evaluated. When complete transverse sections through adrenal glands were available, their area was measured by means of a polar planimeter. If the adrenal glands were cubic in shape, and if only sections parallel to one of the facets of a cube were used, the volume would be: \( V = (\sqrt[3]{A})^3 = A^{\frac{3}{2}} \). Adrenal glands, however, resemble in shape oblong, folded sheets.

A pathologist or technician, when preparing an adrenal gland for sectioning usually cuts a slice close to the widest place which will yield sections perpendicular to the capsule. But buckling is often greatest at the widest place. Due to these irregularities, as we have determined in ten test cases, the above value must be multiplied by an approximate factor of 2.5. Thus the formula

\[
V = 2.5 \cdot A^{\frac{3}{2}}
\]
yields a value which roughly approximates the volume of the gland. However, when the glands are enlarged by hypertrophy, hyperplasia, or swelling (dystrophic and oedematous), a section near the middle of the gland would not find space on a slide. As a consequence, as our experience showed, in cases of such enlarged glands the volume estimated by the above formula is much smaller than the true volume, because a technician will select a slice from near an extremity of the gland small enough to be accommodated on a slide.

**OBSERVATIONS**

Considerable variation was found in the sizes of normal adult adrenal glands (from accident cases). The planimetrically estimated volume of the smallest gland in this group was 325 mm³, that of the largest 2727 mm³, with an average (arithmetic mean) of 1225 mm³. If one uses the value \( V_s = 1200 \text{ mm}^3 \), \( i.e. \) a round number near our average, as the standard volume of a human adrenal gland, one can refer the estimated volume of each individual gland to this standard volume by expressing it as a multiple or fraction of \( V_s \). According to this notation, the estimated smallest volume among healthy glands was 0.288 \( V_s \), and that of the largest, 2.33 \( V_s \).

Fig. 1 shows outline drawings of entire sections of some of adrenal glands used in this study. Wherever, in the text, the volume estimate is omitted, the histology of the case was examined before the introduction of the method of volume estimation.

1. *Cases Not Treated with Hormones*

Slides from patients who had never been treated with hormones were necessarily from the period before 1949, the year in which Hench, Kendall, Slocumb and Polley discovered the now so frequently used treatment (*Hench et al.* 1949). Since that time, most patients who suffer from rheumatoid disorders have, at some time during their illnesses, received adrenocortical steroids.

Six of the seven glands in this group show identical changes. The one divergent case was complicated by severe kidney disease associated with hypertension, a condition which in our previous study is marked by adrenocortical hypertrophy. In the other six cases, the parenchymal cells of the adrenal cortex are depleted of lipid. The cells are swollen and show a tendency to dissociate and to undergo liquefaction.

Because of the tendency to dissociate and eventually liquefy, these cells and cell groups have a certain similarity to the atrophic types as encountered in severe cancer cases, diabetes mellitus, and in hunger cachexia. On close examination, however, it is seen that they differ markedly because, in these rheumatoid patients, the parenchymal cells are enlarged rather than atrophic. As Fig. 2 shows, this is evident if one compares the atrophic condition from a
hepatoma case (A) with the swollen condition of the adrenocortical cells in a typical case of rheumatic fever (B and C). All three pictures on that plate are photographed at the same magnification. The term »dystrophy« is proposed for this typical change. There is lipid depletion throughout the cytoplasm, dissociation of cells and liquefaction, and in addition to these changes there is also vacuolization (Fig. 7). Large spaces between cell groups are filled with a delicate interstitial material which perhaps is debris of liquefied cells (Figs. 2, B and C; 3, 4, 5, 6, 7).

In some cases of »untreated« rheumatoid arthritis and rheumatic fever, the adrenal gland is enlarged. Volume estimates in three of these cases were: 2300 mm$^3 = 1.83 V_s$; 2850 mm$^3 = 2.4 V_s$ and 3844 mm$^3 = 3.2 V_s$. The enlargement may be ascribed to the presence of the interstitial material and to the swelling of cells.

2. Cases Treated with Steroid to the End of Life

Information on dosage is not always available. In fact, in no case was there
identity of medication throughout the course. This is expressed in slight inconsistencies of the histological picture. Volume estimates are given with each case, if the section was complete and permitted planimetric measurement.
Figures 3-7:
Adrenal cortices from three cases of rheumatoid arthritis not treated with hormones
Case a. After cortisone treatment of one month, there was no change in the appearance and structure of the gland (Fig. 8). Dystrophy, liquefaction, abundance of interstitial material were noticed, as in the untreated cases.

Case b. Cortisone treatment for three weeks. The cell outlines were more distinct and there was no evidence of liquefaction, the cells were depleted of lipid and the interstitial spaces large (Fig. 9).

Case c. After cortisone treatment for 9 weeks, the zona glomerulosa showed predominantly typus apertofolicularis, depleted of lipid. Interstitial spaces were almost normal in width. The zona fasciculata was practically normal in appearance (Fig. 10).

Case d. Treatment with cortisone for 126 days. Because of a three-year interruption, the earlier treatment was disregarded. The adrenal gland was very small. There was very slight dystrophy. Swelling of cells (Fig. 11 A) and liquefaction (Fig. 11 B) occurred only at a few places in this small but structurally almost normal gland (Fig. 11).

Case e. Treatment with cortisone for 1 year. Estimated volume: \( V = 450 \text{ mm}^3 = 0.37 \text{ V}_s \).

In this case, the cortex was extremely thin (Fig. 12). It consisted of small, but lipid rich cells, except for the deepest portion of the zona reticularis, where swelling of cells and liquefaction were observed.

Case f. Treatment with cortisone for 6 months and prednisone, 6 months.

The adrenals were of normal structure. One of them was of normal size, the other small. This case was complicated by hypertension (in excess of 250 systolic). Thus the histological picture is not very significant, since hypertension is often associated with adrenocortical hypertrophy.

Case g. Steroid treatment for 2 years, mainly prednisolone. As in case f, there was a complication of hypertension. The one preserved adrenal was of normal structure and size. The anterior lobe of the hypophysis showed severe atrophy. The latter condition may be ascribed to the steroid treatment, since the product of a target organ of the hypophysis had been supplied artificially.

Case h. Treatment for 2 years with prednisone. This patient suffered from psoriasis for 8 years and during the last 2 years from severe, widespread rheumatoid arthritis. After the abrupt onset of the latter condition, prednisone treatment was instituted. The adrenal cortex was in good histological condition (Fig. 13).

The anterior lobe of the pituitary gland (Fig. 14) showed cellular atrophy with complete dissociation of the cells. The three cell types could be distinguished by their staining qualities.

Case i. Treatment for 2 years with multiple steroids; the last 4 months dexamethasone. Both adrenals were very small: \( V = 500 \text{ mm}^3 = 0.42 \text{ V}_s \). The left adrenal was structurally normal and the right had an extremely thin cortex. The entire thickness of this cortex is shown in Fig. 15. The zona
glomerulosa consisted of lipid-depleted, crenated, open follicles, while the zona fasciculata was made up of very short cords of cells containing some lipoidal vacuoles. The interstitial spaces were large.

Case j. Treatment for 3 years with prednisone. Both adrenals had a very thin cortex consisting of rather small, but lipid rich cells (Fig. 16). The an-
terior lobe of the pituitary gland showed severe atrophy and foci of hyalinization (Fig. 17). $V = 690 \text{ mm}^3 = 0.58 \ V_5$. 

Figs. 13-16.
Case k. Treatment for 5 years with cortisone, changed »shortly« before death to prednisone. The adrenal cortex was very thin, consisting of small, lipid rich cells. There was crenation and some dissociation of cells. Interstitial spaces were conspicuous.

3. Cases with Intermittent and Discontinued Steroid Treatment

It is impossible to arrange cases with intermittent or interrupted steroid treatment in a logical sequence. Usually, according to the case histories, steroid therapy was discontinued because of severe side effects. After resumption of treatment, it was usually discontinued again for the same reasons.

The three cases previously presented (Elias & Rothstein 1962), showed some of the degenerative changes seen in »untreated« patients, i. e. dystrophy consisting of swelling, and liquefaction of cells. Such areas of degeneration alternated with areas suggesting histological improvement, i. e. reduction of the amount of amorphous, interstitial material and areas rich in lipid. The six new cases were as follows:

Case l. Treatment with prednisone for 1 month, then discontinued for the last two weeks of life. Both adrenals were partially destroyed by massive haemorrhages (haemorrhagic infarct). In the remaining, intact areas the cells were of normal size, the cell groups of the cortex were crenated and interstitial spaces were large (Fig. 18).

Case m. Intermittent treatment with cortisone for one year, at first continuously for 7 months, then occasionally; no steroid treatment for the last 2 years. This young women of 23 suffered from rheumatoid arthritis for eleven years. Since her reactions to cortisone were severe, she was treated only sporadically with cortisone and during the last two years of her life, received practically no steroids. Both adrenal glands were in a state of severe degeneration. The cortices were thin and large areas were devoid of blastema and of zona glomerulosa so that only a thin, disorganized zona fasciculata remained. Fig. 19–21 show the healthiest areas of both glands. The few organized cell groups belong mainly to typus apertofollicularis (Figs. 19 and 21); but these groups were also a state of dystrophy and liquefaction. It should be noted that both Figs. 19 and 20 represent the cortex in its entire thickness. V = 1050 mm³ = 0.88 Vₚ.

On the other hand, the adenohypophysis (Fig. 22) exhibited hypertrophy and contained many colloid-filled follicles. A tentative interpretation of this phenomenon may be sought in an »attempt« by the hypophysis to stimulate the degenerated adrenal cortex.

Case n. Intermittent cortisone treatment during the last four years of life. Treatment interrupted because of side effects. The adrenal cortices were thin and slightly dystrophic. Nodule formation was observed frequently in both
glands. Zona glomerulosa duplex was noted at a few places (Figs. 23 and 24).

\[ V = 500 \text{ mm}^3 = 0.42 \ V_s. \]

*Case o.* Intermittent treatment with unspecified steroids and terminally, for two weeks, decadrone. Both adrenals were very small, and exhibited dystrophy
and liquefaction. Very large vacuoles were present in the zona fasciculata (Figs. 25 and 26). The anterior lobe of the hypophysis showed a very slight degree of atrophy, manifesting itself through dissociation of cells (Fig. 27).

Case p. Intermittent treatment with cortisone for 3 years; followed by meticorten for 2 years which was discontinued 3 months before death. This case is of particular interest because this patient received intermittent steroid treatment for five years, which was discontinued three months before her death.
The gland was very small as is typical for continuous steroid treatment and the cells were lipid depleted, dissociated and dystrophic with a large amount of interstitial material accumulated between them. Unlike the cells of totally »untreated« patients, these were small in this case (Figs. 28 and 29). $V = 480 \text{ mm}^3 = 0.4 \, V_s$. 
DISCUSSION

The adrenal cortices of 26 adult patients who died with (not from) rheumatoid arthritis, rheumatic heart disease and rheumatic fever were studied for their histological characteristics, and the volume of the entire gland was estimated through planimetry of the sections when possible.

The adrenal cortex of glands from patients not treated with adrenocortical steroids showed a typical change not encountered in any of 295 cases from pathological conditions other than rheumatoid diseases which had been previously studied (Elias & Pauly 1960 a, b). The parenchymal cells were depleted of lipid; they were enlarged and tended to undergo liquefaction. Between the parenchymal cell groups large amounts of optically amorphous interstitial material were present. This histological change is described as adrenocortical dystrophy. The entire adrenal glands of three of these patients were enlarged to 1 1/4–3 3/4 times the average normal volume. Of the adrenals of the other four cases, no measurements could be taken because the specimens were incomplete.

In the adrenal cortex of patients who had received continuous steroid treatment, a secondary change gradually appeared within 3–9 weeks after the beginning of treatment. The amorphous interstitial material disappeared, and the parenchymal cells were reduced to normal or subnormal size; but they appeared to be rich in lipid as suggested by the presence of numerous small vacuoles in the cytoplasm (Fig. 12). Adrenal glands (which were sufficiently complete to be measurable) from patients who had received continuous steroid treatment were reduced in size from 9/10–1/3 of average normal volume if treatment was given for one year or longer.

There was no consistency in structure and size of the adrenal gland in patients who had received intermittent treatment.

In general, it appeared that: (1) The adrenal cortex of rheumatoid patients not treated with steroids exhibited a characteristic dystrophic change. The gland as a whole was slightly enlarged. (2) In patients continuously treated with steroids until death, the adrenal glands were greatly reduced in size. However, this reduction in size was not a matter of atrophy, for the parenchymal cells appeared normal and even seemed rich in lipid (Fig. 12). This reduction in size is interpreted as hypoplasia. The cells of the adrenal cortex normally undergo necrosis in the zone reticularis while they are continuously or periodically replaced from a subcapsular blastema. Since there are no signs of degenerative change in the adrenal cortex of patients continuously treated with steroids, particularly after prednisone and prednisolone treatment, the reduction in total volume of the gland is ascribed to a subnormal production of new cells from the subcapsular blastema.
REFERENCES


Received on July 5th, 1965.

Acta endocr. 51, 1