A STUDY OF ADRENAL CORTEX MORPHOLOGY *

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In our experimental studies on the physiology of the adrenal gland we looked for morphological criteria whereby we could determine the degree of activity and the state of exhaustion of the adrenal cortex.† The accepted methods did not entirely meet critical analysis. Variations in the amount and distribution of lipoids seemed to depend too much upon the technique of fixation and the care used in embedding and sectioning. The size and weight of the gland also proved to be of limited use in determining its functional state.

MATERIALS AND METHODS

The adrenal glands of normal frogs, mice, rats, guinea pigs, rabbits, cats, dogs, monkeys and humans ‡ have been studied as reference controls. These form the basis for a determination of the changes taking place under abnormal conditions. The latter have been experimentally produced and also observed in naturally occurring infections. A variety of experimental procedures was undertaken in an effort to produce specific cortico-adrenal lesions. Among the substances used were bacterial toxins, thyroxin, parathormone, adrenalin, histamine, mercuric chloride, and extensive body burns were also employed.

Although our own experimental material was prepared for microscopic examination by a variety of special techniques, the majority of adrenal glands which others have given us the opportunity to study were fixed in ordinary fixatives and stained with hematoxylin and eosin. A scheme of identification was gradually developed and tested with many series of "unknown" glands.

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† A preliminary paper was read before the American Association of Anatomists, March 1934. *Anat. Record*, 1934, 58, 43 (No. 4 and Suppl.).

‡ A human adrenal gland that is normal by our standards is very difficult to obtain.

OBSERVATIONS

Before undertaking a detailed description of the morphological changes accompanying certain physiological and pathological states we shall mention briefly our conception of the life history of the adrenal cortex cell. This is discussed in detail in a paper by Zwemer, Wotton, Nussman and Norkus.¹ We agree with Mulon,² Bogomolez,³ Goormaghtigh,⁴ and Hoerr⁵ that the adrenal cortex grows from without inward, new cells being formed at the periphery and destroyed in the reticular zone near the medulla. That the glomerular cells arise from indifferent connective tissue-like cells in the capsule is our additional contribution. These capsular cells lose their long processes, become short ovals and take up lipid droplets. A further increase in the amount of cytoplasm and a marked increase in cell fats mark the transition to the spongiocytes. The latter retain and emulsify their fat content as they are gradually pushed inward by the formation of new cells. After an experimentally induced discharge from these cells, lipid can be demonstrated in the blood stream in the form of small fat droplets by a special gelatin embedding lipid technique (Zwemer⁶). Direct observation of living frog adrenal glands, under normal and experimental conditions (Singer and Zwemer⁷), strengthens the view that lipoids may be extruded from the cells in droplet form as well as in non-visible secretions.

As the cells secrete, the ratio of cytoplasm to nucleus is greatly diminished, so that the innermost regions of the cell cords consist of rows of nuclei with very small remnants of cytoplasm still surrounding them. In the end stage the cell is represented by a pyknotic nucleus which is finally phagocytosed.

These studies show that the fundamental plan of adrenal cortex cell progression is the same for all species investigated. The differences between normal glands of various species appear to be due to changes in the relative proportions of the cell types. For ease in description we shall limit the detailed discussion to adult mammalian adrenal glands, with particular reference to those of carnivores and primates. The picture, as seen in a segment of a median section of the gland, will be described and illustrated.

A normal gland (Fig. 1) shows the capsule, a single or incomplete double row of glomerular loops, a moderately wide fascicular zone composed of spongiocytes in the outer half and smaller cells in vari-

ous states of discharge in the inner half. Internal to this region and near the medulla is the network of cell cords known as the "reticular zone." In its wide capillary meshes are found many macrophages; these assist in removing the cellular débris of exhausted and incompletely discharged cells.

The first modification of the normal picture reveals an unusually large number of spongiocytes present in the entire fascicular zone. The reticular zone is reduced to a small band of cell cords. This type of gland we have called the lipoid storage type (Fig. 2). A minor modification may show the capsule to be thickened and an increased number of circles and loops of cells is present in the glomerular zone. This latter picture is due to stimulation of the cortico-adrenal cells to hypertrophy and hyperplasia. It may occur as a result of anterior pituitary, mild thyroid, or other treatment.

With an acute demand for cortico-adrenal secretion (Fig. 3) there is a rapid change in the reticular and inner fascicular cords. The outer zones apparently remain unchanged and the adrenal cortex in some cases of death in the acute stage gives the appearance of having an ample store of cortical lipoids. In spite of this apparent store the bodily condition and blood chemistry may indicate a state of adrenal insufficiency and a careful study of sections stained for lipoid shows that the visible fat present is in much larger droplets and often stains differently from normal. This lipoid retention with insufficiency is perhaps a result of the time factor. If we suppose the existence of a polymer of cortin or a precortin, time would be necessary for this substance to be converted into the active hormone. In an acute demand adrenal insufficiency may appear before this change can take place. A very acute demand results in an exhausted gland with little indication of new cell formation (Fig. 4).

When the demand is mild and has existed for only a short period of time, the adrenal morphology is also different (Fig. 5). The glomerular zone is wider, but composed of somewhat smaller cells, spongiocytes have almost disappeared, and the inner fascicular zone is extensive with narrow irregular columns of small cells. The reticular zone does not show the accumulation of débris that is found with acute demand. If the mild demand has occurred for some time the hyperplasia may result in an adrenal that is larger than normal. The cell columns are very narrow and the larger capillaries may be congested (Fig. 6). In spite of an enlarged gland, the animal may suffer

from adrenal insufficiency. One can have a large depleted adrenal in addition to having a large, well stored gland.

A severe but not necessarily acute exhaustion of the adrenal cortex modifies the foregoing picture (Fig. 7). The capsule is thickened and in it accessory or "adenomatous" masses may be embedded. The glomerular zone is wide, quite irregular, and frequently has layers of cells which are crescentic in cross-section, the convexities being directed inward, as found by Hoerr.⁵ This directional curve can be seen best in adrenal glands that have been actively stimulated. The fascicular zone is irregular and is composed of small cells having a diminished amount of cytoplasm. The cell columns frequently are widely separated by large capillaries. The reticular debris accumulates faster than it can be removed by macrophages. In this type we see that in spite of the rapid formation of new cells there is little accumulation of lipoid (and its associated hormone). The life history of these small cells is probably extremely short, and an individual with this type of gland can easily be thrown into complete adrenal insufficiency by a slight additional demand for the vital secretion. A small accessory gland that is maintaining life in an experimental animal often has this appearance.

If a period of severe prolonged demand continues until death occurs from uncomplicated adrenal insufficiency, we see an exhausted adrenal (Fig. 8). This type of gland has no definite fascicular zone and there is a rapid transition from the accumulative to the degenerating phases. New cell formation is not sufficiently rapid to keep up with the secretory or discharge phase, and no storage is apparent.*

DISCUSSION

On the basis of our observations we have attempted to describe eight conditions present in adult mammalian adrenal glands. There

* A series of "unknown" adrenals from 200 human autopsies was very kindly put at our disposal by Dr. Seecof and checked by him from his and our records. A comparison of our classification with the pathologists' findings showed a close correlation of adrenal cortex morphology with the functional demands one might expect from the cause of death. In 80 per cent of the cases the group to which the gland belonged was easy to determine; the remaining 20 per cent of the cases were difficult to determine for two reasons. When the adrenals were from very young children the organization of the gland was incomplete. The sections frequently showed rapid multiplication of cells in the capsule and outer glomerular zone and there were also a number of so-called adenomas of cortical tissue. In young adrenals this appearance is due to portions of cortex that have failed as yet to become incorporated within the gland capsule. Another difficult group consisted of adrenals from cases of unusual causes of death.

are, however, gradations between these, and additional complicated types resulting from experimental procedures. An example of complication would be a gland that had been stimulated to hyperplasia and hypertrophy and then subjected to an acute demand.

The changes occurring in the adrenal cortex cells during normal metabolism seem to be accelerated by increased catabolism in other parts of the body.

To determine adequately the condition of a gland under consideration one must, of course, first know the normal proportions of the formative, loaded and discharging types of cells for the species studied. For example, in some species the normal gland seems at first to be composed entirely of loaded spongiocytes and the typical cell sequence becomes more apparent only after experimental procedure. For these species (frog, turtle) the storage type of gland seems to be the normal condition for certain seasons of the year. In other species, particularly among the mammals, there is a more rapid cell utilization, and cells in all stages can be found in a single segment of a median section. Among mammals there is a species difference in the amount of spongiocyte tissue normally found. This has been noted by others and expressed as the amount of visible lipoid found in the outer fascicular zone.

It should be noted that the cell columns in different segments of a single section may vary considerably as a result of intermittent blood circulation. An estimation of the state of the gland as a whole depends, of course, on the condition present in most of the sections. If one wishes to determine minor changes, some commonly used quantitative measurement of relative proportions of cell types may be employed. This may be by cell counts, by polarplanimetric measurement of different cell type areas, or by weighing paper outlines of areas.

One of the fundamental features of the normal adrenal cortex in all types studied is the large cell containing much visible lipoid in a finely divided state. The lipoids are undoubtedly there for some purpose. This point needs no emphasis since the functional state of the gland has long been gauged by its lipoid content. Furthermore, chemical studies have shown that the vital hormone, although somewhat water soluble, is extracted with the lipoids by organic solvents. One can conceive the spongiocyte lipoid to be either the raw substance from which the hormone is made, or the vehicle in which it is

stored. Perhaps both functions are performed by the lipoids. If the hormone were not stored in a protected and relatively inactive form it might well affect the structure of the cells by which it is formed (cf. gastric secretions and postmortem autolysis). By conceiving that the spongiocyte is the cortico-adrenal lipid storage cell, one admits the presence of accumulating and discharging cells. The rapidity with which new cells are formed is one factor in an increase in gland size, but the rapid hypertrophy of these new cells as a result of their lipid storage also contributes to the increase. If lipoids are continuously stored the gland size increases quite rapidly. On the other hand, if the discharging phase predominates, one could expect to find a small gland with very few of the loaded, spongiocyte cells. If cell proliferation, however, might give rise to a large gland. As in the thyroid gland, an increased activity results in a different morphological appearance from that seen in storage, although in both cases the glands may be enlarged.

This broad plan of viewing adrenal cortex changes taking place under natural conditions was applied to specific lesions induced by bacterial and other toxins. In these cases the adrenal gland morphology depended on the extent of the infection, the amount of hormone injected or produced, and the rapidity with which death occurred, i.e. the length of time over which the toxin had acted.

No attempt has been made to discuss fully the pathology of the adrenal glands. This has been extensively reviewed by Goldziher.

SUMMARY AND CONCLUSIONS

The morphology of the adrenal cortex seems to reflect the demands imposed by body needs.

An excess of hormone over normal requirements is shown by an increase in the number of storage cells.

An acute demand discharges the mature cells but does not immediately affect the accumulative cell types.

Prolonged demands stimulate new cell formation, which may not be able to counteract the cell utilization of the discharging phase.

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DIAGRAM OF CORTICO-ADRENAL TYPES

The accompanying schematic diagram may aid in an understanding of the plate by indicating the relative proportions of cell types generally present in the different morphological states of the adrenal cortex.

Horizontal lines at the top of a figure indicate the capsule.

Circles and arches are used for the small proliferating new cells (zona glomerulosa).

Vertical lines represent the columns of cells bounded by capillaries (zona fasciculata).

(a) If the lines are widely spaced the cells are large and loaded with lipid droplets (spongiocytes).

(b) If the lines are close together the cells are of the active secreting type.

Cross-hatched areas correspond to the inner network of cell cords with its sinusoids, macrophages and cellular debris (zona reticularis).

DESCRIPTION OF PLATE

PLATE 15

- FIG. 1. *Normal* secreting adrenal cortex with a balance between accumulating and discharging cell types.
- FIG. 2. *Lipoid storage* with the accumulative cells predominating.
- FIG. 3. An *acute demand* results in a rapid cytoplasmic diminution in the inner zones.
- FIG. 4. A *severe acute* demand depletes the gland with little or no indication of new cell formation.
- FIG. 5. A *mild stimulation* to discharge is indicated by a decrease in the number of lipid-loaded spongiocytes.
- FIG. 6. *Prolonged activity* is associated with an increase in accumulative and discharging cell types and an absence of lipid storage cells.
- FIG. 7. In a *severe* condition, new cell formation and discharge follow each other rapidly and the normal, regularly arranged cell columns no longer are present.
- FIG. 8. *Severe prolongation* of the demand results in an atrophic adrenal with groups of cells separated by fibrous connective tissue which no longer resembles the reticular tissue usually present.