THE HUMAN ADRENAL GLAND

LOUIS J. SOFFER, M.D., F.A.C.P.

Attending Physcician and Head of Endocrinology, The Mount Sinai Hospital, New York City; Clinical Professor of Medicine, State University of New York College of Medicine in New York City

RALPH I. DORFMAN, Ph.D.

Director of Laboratories, Worcester Foundation for Experimental Biology, Shrewsbury, Mass. Research Professor of Biochemistry, Boston University Graduate School and Professor of Chemistry (Affiliate) Clark University

J. LESTER GABRILOVE, M.D., F.A.C.P.

Associate Attending Physician, The Mount Sinai Hospital, New York City; Clinical Associate Professor of Medicine, State University of New York College of Medicine in New York City

79 Illustrations and 1 Colour Plate

LONDON
HENRY KIMPTON
134 GREAT PORTLAND STREET, W.1
1961

Printed in The United States of America

Preface

THE past three decades represent an exciting period in the history of the development of our knowledge of the adrenal gland. This is the period during which there evolved a more fundamental understanding of adrenal function concomitant with the isolation and identification of a number of adrenal hormonal fractions as well as corticotropin and the melanocyte stimulating hormone. Extensive studies resulted in a better understanding of hypo- and hyperadrenocortical states, with improvement in their therapy and a change for the better in their prognosis. The management and outlook for patients with Addison's disease, Cushing's syndrome, and the adrenogenital syndrome have vastly improved as a result of these advances.

This has been primarily the era of the chemist. The isolation and identification of the adrenal hormones already referred to and the modification of the cortisol molecule with the preparation of various synthetic analogs of increased glucogenic and anti-inflammatory potency constitute a brilliant chapter of adrenocortical hormonal chemistry. This development represents the beginning of an even more fruitful period in which potent analogs may be developed lacking the undesirable side effects of the parent compounds. Imaginative approaches using more precise techniques have yielded firm insights into the various pathways of steroid hormone biosynthesis and the enzymatic defects responsible for the clinical manifestations of certain abnormal adrenal syndromes.

The clinician, too, has made his contributions during this exciting period. The happy application of glucogenic steroid therapy to a host of illnesses ostensibly unrelated to adrenal disease and the recognition of a new clinical syndrome, "primary aldosteronism," have provided impetus for new approaches in the study of edema and hypertension.

The studies of the adrenal medulla have also been marked by progress, perhaps less dramatic than that of the adrenal cortex but interesting and significant. The physiologic effects of epinephrine and norepinephrine, the metabolism of the catecholamines including biosynthesis and catabolism, and the utilization of this knowledge in the diagnosis and treatment of pheochromocytoma are but a few of the more important developments.

The details of these and other absorbing studies are discussed in this book. This seems to us a good time to pause, take stock, and incorporate the broad new knowledge into our thinking. There is, of course, a great deal still left undone and inadequately explored. The currently available background and the new technicological advances in this and related fields should provide the impetus for another forward surge.

LOUIS J. SOFFER
RALPH I. DORFMAN
J. LESTER GABRILOVE

Contents

The Human Adrenal Gland

Chapter 1

The Anatomy, Morphologic Structure and Embryology of the Adrenals

Gross Anatomy of the Adrenals.—The two suprarenal glands in man sit astride the upper poles of the kidneys. The convex surface of the kidneys produces a concave impression on the glands. The right suprarenal body is somewhat triangular in outline and its anterior surface touches the inferior vena cava posteriorly and medially and the liver laterally. The left adrenal is less triangular and more crescentic in outline, lies along the anterior medial border of the left kidney, and its lower half is in contact anteriorly with the posterior surface of the pancreas and splenic vessels. Frequently the left gland is elongated and may extend down to the hilus of the kidney, actually touching the renal vessels. It is somewhat nearer the aorta than is the right one and lies behind the lesser omental sac. Both glands are situated in the epigastric region at about the level of the 11th thoracic vertebra. The posterior surfaces rest against the lumbar insertion of the diaphragmatic leaves.

The glands are enclosed in a tough connective tissue capsule and embedded in adipose tissue. This connective tissue capsule penetrates into the deeper parts of the gland. It is contiguous with the septa which divides the organ into its characteristic zonal layers. In addition, the glands are surrounded by renal fascia to which they are quite firmly attached. The upper part of the lateral surface of the right gland is devoid of a peritoneal covering, while the lower half is covered by peritoneum. On the other hand, the upper anterior surface of the left adrenal is covered by the peritoneum of the omental bursa, while the lower area is free of such peritoneal covering.

On the anterior surface of both adrenals a faint groove is discernible, where the central vein appears on the surface. The adrenals have an unusually rich blood supply. The superior, middle, and inferior suprarenal arteries, which are branches of the inferior diaphragmatic artery, aorta, and renal artery respectively, penetrate into the interior of the gland to supply the cortex and medulla separately. The medulla, in contrast to the cortex, has a well developed venous supply, and eventually all the venous channels empty into one large central vein in the medulla, which exists at the hilus as the suprarenal vein. On the right side, this vein drains into the inferior vena cava, while on the left side it empties into the renal vein.

The lymphatic channels of the adrenals form two plexuses, one directly under the capsule and another one in the medulla. The peripheral plexus communicates with the efferent lymphatics in the perirenal capsule, while the central one follows the central and suprarenal veins. The lymphatics of the right adrenal drain into lymph nodes near the aorta and near the crus of the diaphragm. On the left side they connect with a lymph node situated at the origin of the renal artery and with nodes between the aorta and the crus of the diaphragm. Occasionally, the left-sided lymphatic channels will follow the splanchnic nerve through the diaphragm and empty into mediastinal nodes.

The adrenals are innervated chiefly by branches of the splanchnic nerves. These nerves then form the suprarenal plexus and connect with the renal and celiac plexuses and the celiac ganglia.

The combined weight of both adrenals in the human varies considerably, dependent on a number of factors discussed elsewhere in this book. The average weight of each gland is approximately 3 to 5 grams. They vary from 40 to 60 millimeters in length, 20 to 30 millimeters in width, and 2 to 8 millimeters in thickness, except at the bases where they are considerably thicker. The cut gland consists of an outer cortical layer and in inner medullary layer. The latter constitutes about 10 per cent of the weight of the gland. The cortex, or outer portion, is firm and distinctly yellowish in color, due to the presence of lipid filled cells, while the medulla is somewhat softer, more pulpy, and of a dark reddish-brown hue. The trabeculæ from the capsule penetrate into the gland and form septa. The cortex is divided into its three characteristic zones, the *zona glomerulosa*, the *zona fasciculata*, and *zona reticularis*.

Accessory Adrenal Tissue.—Such accessory bodies may be made up of cortical tissue or chromaphil tissue alone, or a combination of both structures resembling true adrenal glands in miniature. These *complete* accessory bodies are more common in some animals than in others, and have been reported with an incidence as high as 16 per cent in humans. They are relatively uncommon in the cat and the dog, but are observed fairly frequently in the mouse, the rat, and the rabbit. When present, they usually are found in the connnective tissue and fat immediately surrounding the adrenals, or in the cranial regions of the kidneys, occasionally actually embedded in the kidney substance or protruding as a nodule from the adrenal itself.[20,21]

In 100 human autopsies in which the region of the celiac plexus was carefully examined, Graham[20] found some accessory adrenal tissue in 32 instances. Sixteen of these consisted entirely of cortical tissue, while the remaining 16 accessory bodies were made up of both cortex and medulla histologically identical with that of normal adrenal tissue. The average size of these bodies was 7 × 4 × 3 mm. The majority of accessory bodies in this study were found to the left of the midline, although some were encountered to the right, several in the midline, and in 2 instances the tissue was bilateral. It is a question as yet unanswered, however, as to whether these accessory bodies could become sufficiently functional under suitable circumstances.

The medullary tissue of the adrenal glands is part of a widely distributed chromaphil system. Hence, in man, accessory chromaphil tissue may be diffusely located almost anywhere in the body, but does not constitute, in a true literal sense, accessory adrenal glands. Similarly, accessory cortical bodies, made up entirely of cortical tissue, are found not infrequently, and may be located in the adrenals themselves, in the connective tissue and fat surrounding the adrenals, and in almost any region of the abdominal

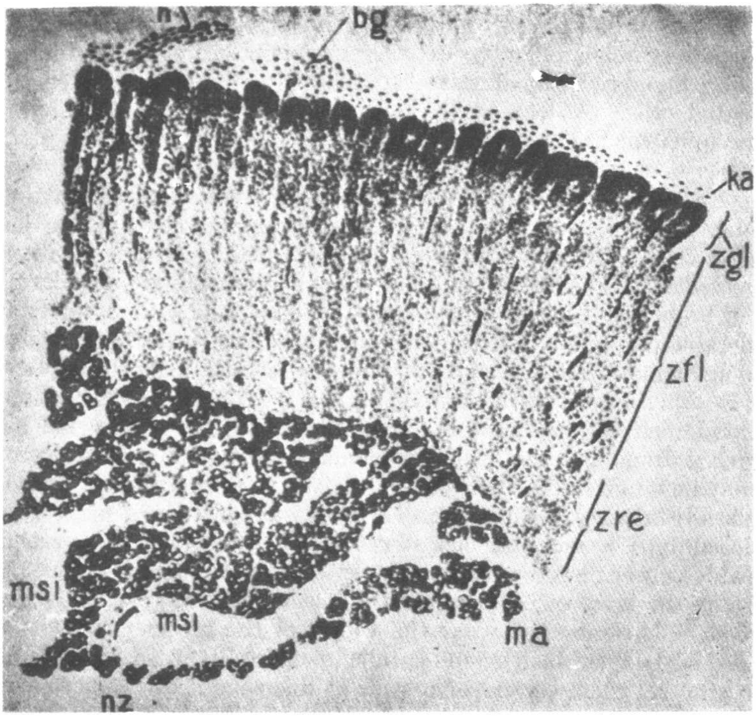

FIG. 1.—Section of adrenal of a child *ka*, capsule; *bg*, blood vessels; *n*, nerve trunk. Cortex; *zgl*, zona glomerulosa; *zfl*, zona fasciculata; *zre*, zona reticularis; *ma*, medulla; *msi*, medullary blood sinuses; *nz*, nerve cells. (After Krause, 1921.)

cavity. Such nodules have been found in the pelvis, in the broad ligaments of the uterus, along the course of the genitourinary tract, in the scrotum and the vaginal wall, and even in the liver and pancreas.

Histology of the Adrenals.—A cross section of the human adrenal reveals a deeply yellow outer portion, the cortex, and a central reddish hued area, the medulla. The medulla constitutes approximately one-tenth of the total adrenal cross sectional width. The entire gland is surrounded by a capsule consisting of a dense layer of fibrous connective tissue made up of collagen fibers running parallel to the surface of the organ. There is evidence that these collagen fibers can be stained with silver internally and periodically. Within this capsule, parenchymal cell groups occur in abundance.[47] The more superficial cells in these groups are small and dark staining. Those located deeper are of larger size. The closer these cells approach the zona glomerulosa the more they resemble the cells of the latter. These cells are referred to as the *capsular blastema*.[47] The cells of the cortex, although arranged in three layers from without inward, are actually one continuum of cells. The outermost layer, which is also the thinnest, is the *zona glomerulosa*. In this area, the cells are grouped rather loosely together in ill-defined clusters and consist of a large variety of structural types existing side by side. According to Elias and Pauly,[47] the cells of the glomerulosa are of varied appearance including small isodiametrical cells poor in lipoid, lipoid rich columnar cells, large lipoid rich isodiametrical cells, lipoid rich syncitia, and coarsely vacuolated cells. All the nuclei in the zona glomerulosa are approximately spherical and apparently free of nucleoli. The stroma of this zone consists of strong fuchsinophilic membranes reinforced by argyrophil fibers. In general the zona glomerulosa may be identified as that layer in which relatively large connective tissue compartments house large masses of cells. The layer closest to, and surrounding, the medulla is the *zona reticularis*. The cells in this region are arranged in an irregular network of branching interconnected cords, possess fine lipoid droplets and considerable pigment. These pigment granules are probably degenerative or aging manifestations and are probably identical with the lipofuscin found in other organs of the body. Aschoff has referred to this adrenal cortical pigment as the "wear and tear" pigment. The cells of this zone are dark staining and the nuclei frequently pyknotic. Isolated necrotic cells may be found in the lower part of the layer. The stroma of the zona reticularis is a very delicate fibrillar network which in some areas is condensed into a membranous structure. This stroma, however, is noticeably denser than that of the other two zones.[47] The *zona fasciculata* represents the layer of cells between the *zona glomerulosa* and the *zona reticularis*. This zone is by far the widest of the layers. Its cells are arranged in strands which extend parallel to one another from the glomerular to the reticular layers. The cells of this zone in the experimental animal are particularly rich in fat.[48] However, in the human adrenal cortex according to Elias and Pauly,[47] the zona fasciculata is almost devoid of lipoid substance, while the glomerular zone is particularly rich in this material. The stroma of the zona fasciculata is characterized by the presence of argyrophil fibers which are arranged in a basket-like network around the individual cells. The latter are organized in long parallel cords enclosed in thin membranous tubes.

The *vasculature* of the adrenal cortex consists of a subcapsular arterial plexus from which capillaries pursue a downward course into the zona glomerulosa where they form a basket-work arrangement. The capillaries widen as they course through the fascicular layer, but become thin once more when they enter the reticular zone, and finally penetrate the medulla at acute angles. In both the glomerular and fascicular zones the capillary networks are located in the membranous septa, while in the zona reticularis they are embedded in the fibrillar stroma. There are extensive anastomoses of the vertical capillaries in all the cortical zones. In addition, there are medullary arteries which run directly through the cortex to the medullary capillary network, as well as some arterial loops dipping into the cortex from the subcapsular plexus and returning to this plexus.[47] There is considerable evidence to indicate that new cortical cells are constantly being formed in the inner part of the glomerular and outer part of the fascicular layer,[17,18] and as they age they migrate towards the reticular zone from which they are finally removed.[78] Ingle[10] demonstrated the regeneration of adrenal cortical cells from the enucleated capsule following the continuous parenteral administration of adrenocorticotropic hormone in the rat. Greep and Deane[16] have confirmed these observations and demonstrated that the regenerated cortex actually includes all three zones. However, other evidence would tend to throw some doubt upon this view. It has been observed that cell division occurs throughout the cortex. Similarly, studies with intravital dyes have failed to demonstrate any cell translocation. Finally, the failure of various cortical cell types to undergo cytomorphosis in tissue culture suggests that the cortical cells arise, function, and die in one zone.[8]

The probabilities are that both views are correct, depending essentially upon the species, with particular regard to the presence or absence of a capsular blastema. In the human adrenal cortex where the capsular blastema is conspicuous, regeneration presumably occurs in good part from the capsule.[47] In those species where the capsular blastema is poorly developed, such as in the rat, regeneration from the capsule may play a subordinate role.[47] In this regard, it is interesting to note that the functional integrity of such regenerated cortices occurring after enucleation, may be impaired,[17,49] and indeed hypertension has been observed to occur during adrenal capsular regeneration in the rat.[50]

This general arrangement of cortical cells holds true for most mammals, although a well-defined division into its several layers is by no means universally true. In the rat there is an additional reasonably well-defined zone, the *zona intermedia*, located between the glomerular and fascicular layers and readily identified with the usual staining techniques. The cells of this zone are small and columnar in structure, containing elongated nuclei which are smaller and darker than those of the zona glomerulosa. This zone has also been identified in other mammals, such as the horse, cattle, sheep, pig, dog, cat, rabbit, guinea pig, mouse, and hamster, although in these animals it is generally not as clearly defined as it is in the rat.[51] Other investigators, while recognizing this zone, consider it either as the inner part of the zona glomerulosa or the outer part of the fascicular zone.[52] The lipid content of the intermediary zone varies with the species. In the horse, dog, and rat the zone is relatively fat-free, while in the rabbit and cat it is quite sudanophilic.[51]

The general thickness and structure of the adrenal cortex differs with age in humans. During fetal development the adrenals attain an enormous size, and at birth the cortex really consists of two parts, a large *fetal cortex, or X-zone*, and a considerably smaller outer layer of cortical cells identical with that observed later in life. The reduction in size of the adrenal cortex after birth is due essentially to the rapid degeneration of the fetal cortex, which disappears almost entirely during the first few months of postnatal life[1,22] leaving behind the true cortex which continues to grow and develop. The growth of the latter becomes considerably accelerated just before and during puberty, and continues to grow, al-

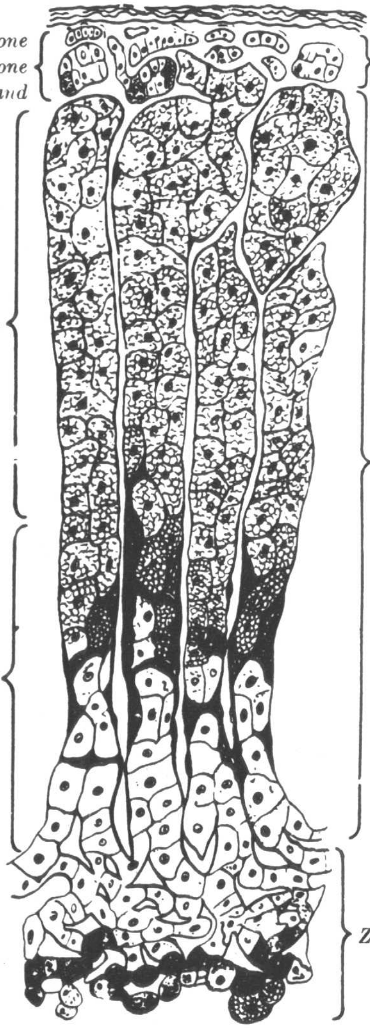

FIG. 2.—Schematic representation of adrenal cortex (after Goormaghtigh).

though at a much slower pace, probably until adult middle life. In aging men there is a narrowing of the inner zona fasciculata and a widening of the outer zona fasciculata and the zona reticularis. Although all zones exhibit a decrease in nuclear density and an increase in sudanophilia, the signs of atrophy are maximal in the inner zona fasciculata and min-