facts than any other of the rôles attributed to these organs; (2) that they afford a sound explanation while including the views of other observers of the diseases of the ductless glands themselves, and account, in a logical manner, for the therapeutic results attained, and (3) that in their relations to the many general diseases in which from my viewpoint they take part (see Volume II), they readily fill gaps without which the pathogenesis of those diseases had remained obscure. One cannot group such a mass of heterogeneous material into a coherent and logical whole unless truth underlie the whole structure.

Before proceeding with the subject-matter concerning the adrenals, as I interpret their functions, and to facilitate its comprehension, the various subdivisions of our knowledge concerning origin and structure of these organs will be briefly reviewed. These subdivisions include: the chromaffin system; the histology of the adrenals; their blood-vessels, lymphatics and nerves; subsidiary adrenal and interrenal tissues such as the carotid, tympanic, etc. A feature which the reader should clearly apprehend therein is that the adrenals *per se* are but the major organs of a vast system, known as the "chromaffin system" which forms part of the sympathetic nerves and ganglia, the carotid glands, the pituitary body and other structures, referred to.

THE ORIGIN AND STRUCTURE OF THE ADRENALS AND THE CHROMAFFIN SYSTEM.

THE CHROMAFFIN SYSTEM.—The first observer to detect a characteristic color reaction of the adrenal bodies was Vulpian,[83] who, in 1856, found that ferric chloride when applied to their parenchyma caused it to become green. Henle[84] in 1865 noticed that when a solution of potassium bichromate was applied to the cut surfaces of human adrenals a permanent brown stain of the medullary substance resulted. This reaction was later called by Stilling the chromophile and, by Kohn, the chromaffin reaction, and was found to be due to the presence of adrenal active principle—epinephrin, or adrenalin—which,

[83] Vulpian: Comptes-rendus de l'Académie des Sciences, vol. xliii, p. 663, 1856.
[84] Henle: Zeitschrift für rationelle Medizin, 24, 1865.

by virtue of its reducing power, is capable of causing the formation of a brown precipitate in a solution of any chromium salt. The production of a green color in a solution of ferric chloride, and of a blackish discoloration with osmic acid, are additional evidences of the reducing power of adrenalin, and are also indications of the presence of this body in the subsidiary chromaffin tissues.

Apart from the adrenals themselves, the chromaffin reaction was first detected in 1872 by Sigmund Mayer,[85] who found the test positive in the tracts of cells accompanying the large abdominal sympathetic branches in amphibia and reptiles. In birds, Rabl[86] in 1891 found chromaffin cells in the sympathetic ganglia neighboring the adrenals, and in the following year Stilling[87] observed them in the carotid glands of several species of mammals. The same investigator, in 1899,[88] traced, along the abdominal sympathetic in the cat, aggregations of chromaffin cells which he asserted were identical with those of the adrenal medulla. Since then, similar aggregations have been located in man, and the power of adrenalin production therefore been found to extend to a large number of small cell groups outside the major organs set apart for this purpose.

That the sole function of the adrenals is adrenalin production is seemingly disproved by the fact that these organs contain two different types of tissue, formed independently from different sources. Whereas the cortex or outer portion of the adrenals, the cells of which contain lipoid (fat-like) substances, develops, in the embryo, from the "intermediate cell mass," or that portion of the mesoblast from which the mesonephros or primitive kidney is formed, the medulla or inner portion, which alone gives the chromaffin reaction, is produced by outgrowth *from the sympathetic system*, and is considered as consisting of profoundly changed nerve-cells. Even on naked-eye examination the division of the adrenals into two distinct segments differing in both color and consistency is striking. These two types of tissue exist in all vertebrates, but in mammals alone are they

[85] Mayer: Sitzungsberichte der k. Akademie zu Wien, No. 66, Abt. 3, 1-52, 1872.
[86] Rabl: Archiv für mikroskopische Anatomie, No. 38, S. 492-523, 1891.
[87] Stilling: Recueil inaugural, Lausanne, 1892.
[88] Stilling: Anatomischer Anzeiger, B. 53, 1899.

combined as a definite cortex and medulla separated by a clearly marked and continuous dividing line. In birds the two varieties of cells are intimately interwoven in one common tissue mass. In some reptiles, including snakes and lizards, separate groups of medullary cells are dispersed in the cortex, especially its ventral portion, while in others, such as the tortoise, the condition is analogous to that found in birds. In many amphibia, including the frog, the adrenals are seen as thin, linear, yellow organs in contact externally with the likewise elongated but more massive kidneys, while in other amphibia, such as the salamander, they are portioned off into small isolated masses, similarly in contact with the kidneys. The amphibian adrenals, like those of the higher verterbrates, contain aggregations of both lipoid-containing and chromaffin cells, the latter lying not in the interior of, but on the outside of, the former.

Vertebrates lower in the phylogenetic scale than the amphibia differ from all the others in exhibiting complete anatomical independence of the lipoid and chromaffin tissues. The former tissues constitute what is termed the interrenal body, while the latter compose what may be properly termed the adrenal or adrenalin-forming organs. In fishes the interrenal cells exhibit constantly a vesicular or tubular arrangement. In the selachian fishes the interrenal body is a homogeneous organ situated between the caudal termination of the kidneys; in the ganoids there are interrenal "corpuscles" disseminated in the interior of the kidneys, while in the cyclostomata, or eel-like fishes, the interrenal tissues occur as small cell groups extending from the head kidney along the animal's long, slender body to the tail and affixed to the posterior cardinal veins.

Wholly separate from the interrenal tissues in fishes are the chromaffin or adrenal organs, which, in the selachians, lie in proximity to the sympathetic ganglia, between the kidneys and the dorsal parietes in the caudal or tail portion of the animal's body. In the teleosts and the ganoid fishes, the adrenal organs lie actually in the walls of the cardinal veins, and in the cyclostomata they occur as band-like masses of tissue, interposed between the cardinal veins and the aorta. This unfailingly suggests the arrangement met with in mammals, in which the ad-

renals lie in close proximity to the inferior vena cava, into which their secretory product, adrenalin, is almost directly poured.

The essential difference between the interrenal and adrenal tissues appears still further when their embryological sources are inquired into. The interrenal cells are derived, in the embryo, from the mesoderm or primitive middle layer of tissue-cells. The organs they are destined later to constitute first appear as bud-like cellular elevations from the peritoneum, at a time when the sexual glands are likewise beginning to develop. Gradually assuming the appearance of definite, separate organs, the resulting tissues, already consisting of cells of characteristic interrenal type, migrate through the connective tissues to different situations, then undergo more or less complete degeneration and absorption at the cephalic or head end of the body and coalesce to form large interrenal glands at the caudal end.

The adrenal or chromaffin tissues, derived from the primitive ectoderm or outer cell layer of the young embryo, develop in close conjunction with the sympathetic nervous system. In the formation of the sympathetic ganglia, a part of the primordial tissue (*anlage*), instead of forming primitive nerve-cells, becomes set apart as the seat of origin of the subsequent chromaffin cells. So intimately are the two sorts of tissue originally blended that the chromaffin cells may remain either individually or in groups of less or greater size directly imbedded in the midst of the nerve elements. This, where it persists, represents the most primitive permanent relationship of chromaffin to sympathetic tissues. In the selachian fishes, however, the two tissues do not remain so intimately united. The chromaffin cells either collect together in a large group which remains at some point within the ganglion or leaves it to form a definite external mass which, nevertheless, always remains in the immediate vicinity of the ganglion. In, the amphibia and higher vertebrates, a further step in the separation of the two forms of tissue takes place, the chromaffin cell groups in part leaving the sympathetic completely and exhibiting no feature suggestive of a common origin with it. Even here, however, minor portions of the chromaffin tissue remain within or in close apposition to the sympathetic structures.

Coalescence of the interrenal and chromaffin tissues takes place first in the amphibia, and constitutes the last stage in the embryologic transmigrations to which they are subject. Thus, in amphibia, small masses of chromaffin cells, instead of remaining with the sympathetic ganglia, pass in an anterior and mesial direction to the interrenal bodies, with which they unite and become more or less intermingled. In the human embryo, when five weeks old, an analogous process takes place. Primordial sympathetic cells begin to migrate from the larger sympathetic group in the abdomen to the interrenal tissues, already aggregated in the form of definite organs, make an entrance through the capsules of the interrenal bodies, and become imbedded among the columnar and other cell groupings of the latter. The migration of sympathetic cells continues throughout fetal life. For a time the imbedded sympathetic cells remain in their primitive state. Only in the beginning of the fourth month, in the human embryo, is their chromaffin property developed. In birds, as already mentioned, the chromaffin tissue remains throughout interwoven with the interrenal cells. In mammals the interrenal tissue finally becomes definitely segregated as the cortex of the adrenals and the chromaffin tissue as their medulla.

Histology of the Adrenals.—The adrenal *medulla* in man consists of a loose network of columnar or rounded masses of cells situated in close contact with the blood-vessels. As a rule, the adrenal cells are separated from the lumina of the capillaries or venules by an endothelial cell membrane, though in some localities a thin sheath of connective tissue is interposed. No cavities exist between the cells forming part of individual columns or other groups, *i.e.*, there is no acinar arrangement. The columns are radially disposed around the large central vein of the adrenal, into which the secretory product or products of the gland are discharged.

The true medullary cells, for the most part, are polyhedral in form, and are separated only by a very thin cementing layer. Their nuclei, eccentrically situated (at the opposite side of the cell from the adjoining vascular channel) are poor in chromatin and present a vacuolar appearance. They are circular or oval in shape. The surrounding protoplasm in these cells, presenting a hyaline, highly refractile appearance in unstained specimens, nonetheless harbors numerous very fine granulations, sometimes closely packed together, at others sparsely distributed. After fixation with alcohol or formalin these cells present a paler appearance, upon staining, than do those of the adrenal cortex. The granules just referred to are of great interest in that they impart to the cells containing them their chromaffin property. They are soluble in water and in alcohol, but insoluble in ether, xylol, and glacial acetic acid. In unfixed preparations they can be made visible, though rather indistinctly at best, with iron hematoxylin. After fixation with Zenker's fluid, on the other hand, they can be stained fairly well, as a rule, with eosin. The granules are to a certain degree related, according to Biedl,[89] to nuclear coloring material. They are stained violet by a mixture of methylene blue and eosin, and pale pink by Ziehl's solution. The chromaffin property at once strikes the observer when a fixing solution, such as formalin, to which a salt of chromic acid has been added, is employed. A color varying from yellow to brown is at once imparted to the adrenal medulla as a whole. Some cells, however, are stained much less intensely than others, and even in individual cells the granules do not stain evenly. A peculiarity of this chromaffin property is that it is lost in a relatively short period of time after death; after twelve to, at most, thirty hours have elapsed, attempts to secure the brownish coloration completely fail. Once the brown color has been produced, on the other hand, it cannot be removed by washing with water. Another, less striking but classic reaction characteristic of the adrenal medulla is that of Vulpian, who, we have seen, noticed that upon application of a solution of ferric chloride, the cells of the medulla develop a green color.

The mechanism of epinephrin secretion in the medullary cells is described by Stoerk and von Haberer[90] as follows: The chromaffin substance produced in the granules progressively augments up to a certain limit, when it begins to diffuse into the cytoplasm between the granules and even, sometimes, into the nucleus. When the entire cell has thus become sufficiently

[89] Biedl: Innere Sekretion, vol. i, p. 343, 1913.
[90] Stoerk and von Haberer: Archiv für mikroskopische Anatomie, No. 72, S. 481, 1908.

impregnated with the chromaffin substance, further diffusion takes place out of the cell into the blood of the neighboring small vascular channel. A rather complete discharge of the product is thus effected, the cell as a result temporarily losing its chromaffin property. In the adrenal venules the chromaffin substance appears as a mucoid material, colored yellowish brown and characteristically refractile, which passes down into the main adrenal vein and thence enters the general circulation in the interior vena cava. Small, brightly shining bodies, apparently distinct from the mucoid masses, have been noticed imbedded in the latter, and were formerly thought alone to represent the true secretion of the adrenals. Stoerk and von Haberer have shown that these bodies are, indeed, not identical with the surrounding mucoid material. No definite conception has as yet been formed, however, of their functional significance. The same is true of the large, rodlike, and wedge-shaped granules demonstrated in the cytoplasm of the cells of the medulla by the same investigators, who found them stained black when iron hematoxylin was used. Lipoid and pigment bodies, of unknown significance, have also been noticed in these medullary cells.

The *cortex* of the adrenals, which incloses the medulla on all its aspects, is a broad mass of tissue itself surrounded by a connective-tissue capsule which, at intervals, gives off radially disposed partitions extending down through the gland-tissue, and there progressively dwindling until so thin as to be hardly perceptible. These partitions themselves are joined, at a certain distance from the external capsule, by a fresh series of cross partitions, which form the inner limit of the outer or glomerular zone of the cortex. Proceeding farther inward from the periphery two additional zones, the fascicular and the reticular, respectively, are met with, the former relatively broad and the latter narrower, like the glomerular zones. More pronounced in some of the lower animals than in man, this division of the cortex into zones entails no fundamental difference between the cells constituting the several layers. In the glomerular zone the connective-tissue trabeculæ are so directed as to inclose spherical or oval groups of the columnar epithelial cells. In the broad fascicular zone, on the other hand, they run for the most part in a radial direction, marking off parallel

columns of epithelium, joined together only occasionally by oblique or transverse columns or connective-tissue strands inclosing capillary vessels. In the innermost or reticular zone, the connective-tissue strands have become distinctly attenuated, and inclose thinner cords of cells than exist in the middle zone, these cords, moreover, so anastomosing with one another as to form a coarse, irregular reticulum. The cells differ somewhat in size and shape in the several zones of the cortex. In the outer zone they are relatively small and of varying outline; in the middle zone, considerably larger, rounded, polygonal, or elongated, and in the inner zone, again smaller, and cubical or polygonal in outline. As in the medulla, the cortical epithelia lie in close relationship to blood-vessels, from the lumen of which they are separated solely by the endothelium of the vessels themselves, and occasionally, in addition, a thin layer of connective tissue.

Of firmer consistency than the medulla, the cortex of the adrenals presents, in contrast to the reddish vascular appearance of the latter, a yellowish tint, due to the extensive content of lipoid granules which characterize its epithelial cells. The granules ordinarily measure one to four microns in diameter, though occasionally they coalesce to form larger droplets—a condition which can be promoted by subjection of the tissues to strong acids or to potassium hydrate. Upon fixing adrenal tissue with formalin, sectioning with the freezing microtome, and staining with the ordinary fat stains, scarlet R or sudan III, the granules will be found to assume a red color. If osmic acid be used, however, the lipoid granules will not, like ordinary fats, be at once stained black, but will take on at first only a brown color, and become black only if later subjected to the action of alcohol. When thus prepared, the granules become insoluble in chloroform and benzol, but they remain soluble in ether and in xylol, which cannot, therefore, be used in the further treatment of the tissue specimen without causing their disappearance. Like other fatty substances, the adrenal lipoid is not stained by methylene blue or fuchsin stains. There are found, however, in the cells of the adrenal cortex other granules which do become stained in fuchsin—"Altmann's fuchsinophile granules." A special study of these has been made by Plecnik,[91]

[91] Plecnik: Archiv für mikroskopische Anatomie, No. 60, S. 414, 1902.

who found them well marked even in the adrenals of embryos. For the most part of the same size as the lipoid granules, they occur most thickly in portions of the epithelial cells where the latter are most sparsely distributed, and exhibit a tendency to diminution in size as the nucleus is approached. A certain proportion of them disappears in common with the lipoid granules when the tissues are moistened with ether. No evidence that these granules can become converted into lipoid granules has been found, and their exact significance is unknown. The third and last type of minute inclosed bodies found in the cortical cells is that of the pigment granules, which occur, in particular, in the reticular or innermost zone. These remain behind when cells the lipoid bodies of which have been stained with osmic acid are treated with ether and iron hematoxylin, differentiation between the lipoid granules and the pigment bodies—the latter naturally yellow but now stained black by the iron hematoxylin—being thus effected in a striking manner.

The exact chemical nature of the doubly refractive substance present in the lipoid granules of the adrenal cortex has been the subject of repeated investigation and discussion. Aschoff's[92] view, supported by the chemical researches of Biedl, is that it is made up of cholesterin esters. This is the prevailing view. The functional significance of these cholesterin bodies, as well as of the cortical tissue as a whole, has given rise to much discussion, as yet with but little result. There is no evidence that the lipoids are discharged into the blood-stream as a secretion by the cortex. *In vitro* the cortical lipoids have been found capable of fixing and neutralizing toxins, and Bonamour[93] has advanced the theory that the cortex has for its purpose to absorb and neutralize toxic metabolic products. No demonstrative evidence to this effect has, however, been forthcoming. Biedl,[94] on the other hand, believes there is sufficient evidence to warrant consideration of the interrenal system as a true internally secreting organ, to be included in the group of organs which, like the thyroid, thymus, pituitary, and sexual glands,

[92] Aschoff: Ziegler's Beiträge zur allgemeine Pathologie und pathologischen Anatomie, S. 47, 1909.
[93] Bonamour: Thèse de Lyon, 1905.
[94] Biedl: Internal Secretory Organs, p. 292, 1913.

produce assimilatory hormones exerting an influence, directly or indirectly, upon general somatic and psychic development. This evidence consists of the observations pointing to the influence of the adrenal cortex on the development of the brain and sexual glands, upon body growth, and upon the changes taking place in the period of puberty.

The close anatomical relationship between the chief interrenal and true adrenal tissues has naturally given rise to speculation as to a possible functional relationship between them. The fact that the adrenal tissues lie, from the circulatory standpoint, immediately distal to the interrenal tissues, blood which has just circulated through the latter, passing into the former immediately after, suggests that the adrenal cortex supplies the medulla some material of value in the secretory process of the latter. As Mulon[95] points out, however, no such material is known, and the anatomical union of the tissues, while possibly advantageous, is not an absolute necessity, since there are many vertebrates in which the two tissues are some distance apart. Experiments purporting to show the presence of adrenalin in the adrenal cortex have been proven technically faulty. Voegtlin and Macht,[96] on the other hand, have detected in the cortex a body having a digitalis-like action and Iscovesco[97] also demonstrated in it a lipoid exerting a tonic effect on the heart. Langlois[98] has advanced the theory that the cortex chemically transforms the poisonous wastes arising in the metabolism of contracting muscular tissue and thereby prepares a substance from which the medulla elaborates adrenalin.

The *blood-supply* of the adrenals is extensive and is derived, as is well known, from no less than three sets of suprarenal arteries. The arterial trunks entering the capsule of the gland undergo, for the most part, an immediate division into small vessels which, after forming a network of capillaries to supply the capsule itself, pass inward in the connective-tissue septa and trabeculæ to supply each zone of the cortex, forming in each a capillary network which corresponds with the arrangement of

[95] Mulon: Paris médical, July 19, 1913.
[96] Voegtlin and Macht: Journal of the American Medical Association, Dec. 13, 1913.
[97] Iscovesco: Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris, Dec. 26, 1912.
[98] Langlois: Quoted by Mulon, *loc. cit.*

the connective tissue therein. After circulating through the entire cortex the blood passes into broad, sinus-like spaces in the medulla which are in intimate relationship to the chromaffin cells. From these it passes into narrower venules and thence into the central adrenal vein or veins. The medulla receives blood in addition from the "perforating arteries" of Srdinko,[99] which pass directly through the cortex from the capsule, without subdivision. This blood likewise is eventually discharged into the adrenal vein.

But little is known as to the precise distribution of the *lymphatics* in the adrenals. In a general way, the lymphatics follow the course of the blood-channels. Small aggregations of lymphocytes have been found in the connective-tissue stroma of the adrenals, likewise at times eosinophile leucocytes. Of special interest and possible significance are the elastic and smooth muscle-fibers also described in this tissue. According to Dewitzky[100] there exists in the adrenal medulla a network of elastic tissue having for its special purpose to hold the blood-vessels open.

The *nerve-supply* of the adrenals is very rich, even more in the medullary than in the cortex. In the capsule are to be found plexuses of non-medullated and, less abundantly, medullated fibers, connected with groups of sympathetic ganglion cells. Fine fibers pass from the capsular plexuses along the connective-tissue septa of the cortex into relationship with the columns of cortical cells, and terminate in elongated thickenings at the surface—not in the interior—of these columns. Through the cortex also pass larger and more numerous nerve-bundles destined for the tissues of the medulla, where they form a rich plexus the ramifications of which extend among the chromaffin cells and form arborizations around them. According to Dogiel,[101] to whom we are indebted for the most complete study of the adrenal nerve-supply extant, the nerve-fibers can be followed up to the venous walls themselves in the case of cells adjoining such veins. In relation with the plexuses of the medulla, and less abundantly with those of the cortex, are also

[99] Srdinko: Sitzungsberichte der böhmischen Kaiser-Franz-Joseph-Akademie, Prag, Nos. 12, 16, 28, 1905.
[100] Dewitzky: Ziegler's Beiträge, No. 52, S. 435, 1912.
[101] Dogiel: Archiv für Anatomie und Physiologie, S. 90-104, 1894.

to be found groups of sympathetic ganglion cells. Variable in size, these groups occur either along the nerve-trunks, at the boundary between the medulla and the cortex or, occasionally, in the fascicular zone of the cortex. These ganglion cells give off neurites and dentrites which form arborizations in the vicinity of other ganglion cells, but do not come into relationship with the parenchyma cells of the medulla themselves.

Subsidiary Adrenal and Interrenal Tissues.—The widespread distribution of both adrenal and interrenal tissues in the embryo and in adults of the lower animal forms in which these tissues exist finds expression in the adult mammalian animal in the presence of small, outlying masses of these tissues, entirely separate from the medulla and cortex of the adrenals. Of especial interest are the subsidiary chromaffin organs, grouped in conjunction with the medullæ of the adrenals under the term "paraganglia." These include, in particular, the carotid glands, the tympanic glands, and the parasympathetic organ of Zuckerkandl, situated in front of the bifurcation of the abdominal aorta.

The *carotid glands,* each of about the size of a grain of rice, lie in or near the crotch of the bifurcation of the common carotid arteries. Originally considered chiefly as vascular or glomerular structures, the true nature of the organs was discovered, as already mentioned, in 1892 by Stilling, who demonstrated the chromaffin property of the epithelium they contain. The cells are large and polyhedral, arranged in spheroidal groups, with very thin intervening cell-walls, and in close apposition to large, thin-walled capillaries, in which the narrow columns of epithelial cells are freely bathed. The source of the glands is in the embryonal ganglion cells of the intercarotid sympathetic nerve-plexus. The vascular and connective tissues of the glands augment with age, the epithelial cells, on the other hand, undergoing a corresponding diminution. As a rule, only a small proportion of the epithelial cells of the carotid glands are colored brown by chromium salts. This has been found to apply also to the epithelial tumors occasionally met with in these organs. At least two observers have even denied them, on the basis of personal experiments, any chromaffin property whatever, and expressed the opinion that these organs should no longer be grouped among the "paraganglia." At all events, their importance as components of the chromaffin system would appear to be, at best, slight.

[NOTE.—The *coccygeal body*, first studied by Luschka in 1859 (Virchow's Archiv, B. 18) is a reddish-yellow organ of about the size of a small pea, situated in front of the apex of the coccyx. Though provisionally classed by this observer among the ductless glands, and since frequently compared, by reason of its structural peculiarities, with the carotid glands, pituitary body, and adrenals, the coccygeal body was shown by Stoerk in 1907 (Archiv f. mikrosc. Anat., B. 69) to present no chromaffin property, either in fetal or in extra-uterine life, and to be devoid of any relationship, from the developmental standpoint, with the sympathetic system. Recent embryological studies seem to have shown that the coccygeal body arises as a local thickening of the walls of the median sacral artery, with subsequent formation of an arteriovenous anastomosis and the production of a network of twisted blood-vessels. The earlier conception of the coccygeal body as a ductless gland has thus been abandoned.]

The *tympanic glands* are small groups of chromaffin cells situated in apposition to the nerve of Jacobson in the tympanic canal on either side of the body.

The most important subsidiary mass of chromaffin tissue is that constituting the *organ of Zuckerkandl,* which represents the lower, independent extremity of a large, elongated chromaffin body extending in the embryo from the level of the main adrenal bodies to the bifurcation of the aorta. In the newborn mammal the upper portion of this elongated body is, moreover, represented by a number of smaller chromaffin groups disseminated in the intervening space. Such groups have also been met with below the organ of Zuckerkandl, in the angle formed by the iliac arteries and on the lateral aspects of the rectum. The common embryological origin of the sympathetic nervous tissue and the chromaffin organs is even more strikingly shown in the fact that collections of chromaffin cells may be found imbedded in sympathetic nerve-ganglia, wherever the latter may be situated. Such collections have been frequently noted, for example, in the left stellate ganglion (Wiesel), and in various peripheral sympathetic ganglia, such as those of the celiac, abdominal aortic, inferior mesenteric, and superior and inferior hypogastric plexuses. Wiesel[102] (quoted by Biedl[103]) found a paraganglion 10 to 15 millimeters long at the root of the left coronary artery in a human heart. Other relatively uncommon sites noted have been the point of entrance of the superior vena cava into the heart, the pulmonary artery, the root of the superior mesenteric artery, the intestinal wall, the abdominal nerve-plexuses down to a point deep within the pelvis, the prostate gland, the ovary, the broad ligament, and the paradidymis. These subsidiary paraganglia may attain a size of from 3 to 20 millimeters and present a histological structure very similar to that of the main adrenal organ, consisting of a capsule of connective tissue and a parenchyma made up of rounded masses of cells, supplied with nerves and a rich capillary network. They are often easily to be mistaken for lymph-nodes, an error soon corrected when the characteristic yellow or brownish color appears upon application of a solution of potassium bichromate. In the sympathetic plexuses and ganglia, chromaffin cells may occur singly or in groups. The latter, inclosed, *e.g.,* in the ganglia, either may or may not be separated from the nervous tissue itself by a sheath of connective tissue.

[102] Wiesel: Wiener klinische Wochenschrift, 1906.
[103] Biedl: Innere Sekretion, vol. i, p. 358, 1913.

Gradual retrogression and diminution in size of many of the subsidiary paraganglia begins after birth. This applies in particular to the organ of Zuckerkandl, so that by the fifth to the eighth year of life its chromaffin property has been entirely lost. The chromaffin inclusions in the sympathetic ganglia, however, according to Wiesel, retrogress only very slowly and still exist in aged individuals. Special significance attaches to the subsidiary paraganglia in cases of malformation of the adrenals proper, where the former tissues may retain sufficient of their pristine importance and size to make up for deficient epinephrin production in the latter.

The *subsidiary interrenal tissues,* or *adrenal rests* often erroneously termed "accessory adrenals" formerly, the fact being overlooked that they contain no tissue corresponding to that of the medulla of the adrenals, arise either as persistent bits of that portion of the original interrenal tissue which ordinarily undergoes absorption when the cortex of the adrenal is formed, or by splitting off of small masses of the developing adrenal cortex through the intrusion of sympathetic cells or of bands of connective tissue. Their existence was known as far back as the seventeenth century. According to Schmorl[104] no less than 92 per cent. of all human cadavers, if carefully examined, will be found to show small or large aggregations of interrenal cells in various parts of the body. Histologically these consist, like the adrenal cortex, of a connective-tissue stroma in which are supported columns of cortical, lipoid-containing cells, usually arranged so as to form an outer glomerular, an intermediate fascicular, and occasionally also an inner reticular zone, as in the suprarenal organ itself. Like the adrenal cortex, moreover, these subsidiary interrenal bodies are capable, where the demand exists, *e.g.*, after excision of the adrenals, of undergoing a marked compensatory hypertrophy.

Three groups of subsidiary interrenal organs have been recognized by Poll.[105] The first group includes those found in the region of the adrenals and kidneys. Some occur in the substance of the adrenal cortex and medulla themselves. These may lie firmly imbedded at the surface of the adrenals and, when numerous, give the latter a nodulated appearance, or they may possess stalks connected with the interior parenchyma of the organ, or, again, they may lie more deeply, completely surrounded by parenchyma, even, *e.g.*, in the very center of the medullary tissue. They may be situated outside of the adrenals, in the adjacent connective tissue, or at the surface or in the interior of the kidney, in which location they sometimes become the source of the tumors known as hypernephromas. Along vessel walls they may be found in contact with the adrenal artery or vein, the inferior vena cava, or the renal vein, as well as between the vena cava and the aorta. They may also be noted in close relationship to the sympathetic nerve-plexuses, in the transverse mesocolic ligament (between the transverse colon and spleen), on the under surface of the liver or in its right lobe, and, lastly, in the pancreas. Poll's second group comprises subsidiary interrenal bodies found in the retroperitoneal space, below the inferior poles of the kidneys, along the internal spermatic veins, on the iliopsoas muscles in the vault of the pelvis, and on the sacroiliac synchondroses.

The third group consists of the interrenal tissues occurring

[104] Schmorl: Ziegler's Beiträge, 9, 1891.
[105] Poll: Quoted by Biedl: Innere Sekretion, vol. i, S. 356, 1913.

in relation to the reproductive organs. Thus, in the male subject, such tissues may be found anywhere along the spermatic cord, above, below, or within the inguinal canal. They may occur between the testicles and epididymes. Wiesel[106] found such a collection of cells at the junction of the duct of the epididymis and the vas deferens in 76 per cent. of newborn babies; this tissue often persisted throughout life. Interrenal tissue has also been found imbedded in the testicular tissues and in the paradidymis. In the female subject, interrenal organs have been detected in the broad ligament, lying in contact with the Fallopian tube, and in the substance of the ovary. Biedl calls attention to the fact that subsidiary interrenal organs are encountered with relative frequency in the reproductive organs in the young and but seldom in old subjects, while Marchetti[107] makes the opposite assertion in the case of interrenal tissues in the vicinity of the adrenals themselves.

[106] Wiesel: Sitzungsberichte der k. Akademie zu Wien, S. 108, 1899.
[107] Marchetti: Virchow's Archiv, No. 177, p. 227, 1904.