

RECENT PROGRESS IN HORMONE RESEARCH

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PREFACE

The seventh annual meeting of the Laurentian Hormone Conference took place in September, 1950, at Franconia, New Hampshire. The Committee on Arrangements is indebted to the following contributors whose financial assistance made possible the arrangement of the meeting: Abbott Research Laboratories, Armour & Co., Ayerst, McKenna & Harrison, Ltd., Carroil Dunham Smith Pharmacal Co., Chemical Specialties Co., Inc., Ciba Pharmaceutical Products, Inc., Ciba Co., Ltd., Endo Products, Inc., Charles E. Frosst & Co., The Glidden Co., Hoffman-LaRoche, Inc., Frank W. Horner, Ltd., Lederle Laboratories, Eli Lilly & Co., Mallinckrodt Chemical Works, The Maltine Co., Merck & Co., Inc., The William S. Merrell Co., Nopco Chemical Co., Organon, Inc., Ortho Research Foundation, Park, Davis & Co., Schering Corp., G. D. Searle & Co., Sharp & Dohme, Inc., E. R. Squibb & Sons, Sterling-Winthrop Research Institute, Syntex, S. A., of Mexico, The Upjohn Co., and Wyeth, Inc. Their generosity allowed the Committee to have as its special guest Professor S. Zuckerman of the University of Birmingham, Birmingham, England, and the practice of inviting distinguished scientists from abroad to participate in the Conferences seems assured.

The Committee is grateful also to the various session chairmen: Drs. Dobriner, Hartman, Hertz, Kochakian, Noble, Schwenk, Thompson, and White, who are responsible for the lively and critical discussion which is so enjoyable a feature of the Conference. Miss Joanne Sanford, Mrs. May Sullivan, Miss Vivian Johnson, and Mrs. Gail Vavrick gave invaluable secretarial assistance to the Conference.

To the members of the Conference the Committee would like to express its appreciation of the spirit of friendliness and serious interest in the Conference objectives. However able as ears, eyes, and hands a Conference Committee may be, the speakers and membership are mouth, head, and heart. Working with us there have been wise heads, warm hearts and eloquent mouths.

GREGORY PINCUS

Shrewsbury, Massachusetts

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I. GONAD DEVELOPMENT AND FUNCTION

Embryogenesis of the Adrenal and the Reproductive Glands*

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I. INTRODUCTION

What contributions can embryology, a morphologic science, make toward progress in endocrine physiology? Admittedly, little should be expected that might help directly to improve clinical practice. However, scientific endocrinology meets embryology on common grounds when it concerns itself with the problems of the hormones within the organism: the places of their elaboration, actions, transformations, and elimination. Both embryologists and endocrinologists are interested in matters of tissue specificity and morphogenetic relationships, genetic constitution, and inductive activation.

Through the development of the science of genetics we have become once again neopreformists. We realize that by its constitution the fertilized human egg, weighing about one microgram, is essentially already the same person as the issuing adult, the 50 to 100 billion times heavier man or woman. Embryogenesis is only the translation of genetic potentiality into visible structure and functional manifoldness. As it proceeds, identical sets of chromosomes and genes are passed on to the nucleus of every cell. Differentiation of germ layers and of complex organs occurs on the basis of *cytoplasmic inequalities*. This traces back to a complicated micro-architecture of the uncleaved egg. There occur even grossly visible differences in cytoplasmic structure at opposite poles. But much more important and more elaborate microscopic and ultraviolet patterns of distribution of enzymes, proenzymes, special proteins, lipids, and so forth have been placed in evidence. Such substances, together with inductive agents entering the cell from without, form the *phenotypic milieu* of the nucleus, which by some unknown means must activate selectively the genes in proper spatial and temporal order.

*The investigations on which this report is mainly based were in part supported by grants from the National Research Council, Committee for Research in Problems of Sex, and from the American Cancer Society, upon recommendation of the Committee on Growth of the National Research Council.

II. EXTRAGONADAL ORIGIN AND CONTINUITY OF GERM CELLS

In the small crustacean *Tisbe* which may be used to illustrate this situation (Fig. 1) the distribution of visible cell inclusions is at first not very

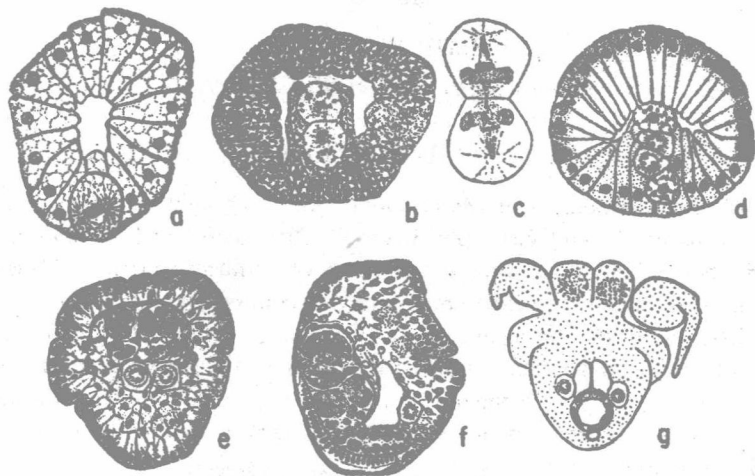


FIG. 1. Germ cell track in *Tisbe furcata*. C $\times 750$; others $\times 375$; after Witschi (29).

A. Blastula of 63 cells; stem cell at vegetal pole. B. Early gastrula; two stem cells, being carried into the hypoblast. C. Metaphase of unequal division of the two stem cells; mitochondrial ring goes to the inner cells. D. Gastrula; the stem cells have divided into two primordial endoderm cells and two (central) primordial germ cells. E. and F. Frontal and sagittal sections through embryos with two primordial germ cells; the endoderm cells have accumulated large yolk granules. G. Frontal section through Nauplius larva; the two germ cells lie next to body cavity and hindgut.

obviously unequal. Yet by the time of the sixth cleavage division a cell at the vegetal pole has accumulated special cytoplasmic inclusions and its mitotic rate has become slower than that of all other cells. During gastrulation this peculiar cell goes through two mitotic steps of which the second one is strikingly unequal as regards cytoplasmic inclusions. Of the four resulting cells, two are slightly smaller and contain the main mitochondrial mass: they turn out to be the primordial germ cells. The larger two contain vitellogenic granules and the later development shows that they are the primordial endoderm cells (Witschi, 29).

The early association of germ cells and endoderm is found in many animals and especially in all well-studied vertebrates. In *man* gonidia were discovered (1912) in the endoderm of the yolk sac just above the allantoic stalk by Fuss (7). In the course of the embryonic development they leave this site and migrate toward the medial edge of the mesonephric bodies. During this period the germ cells behave very much like parasitic amebae

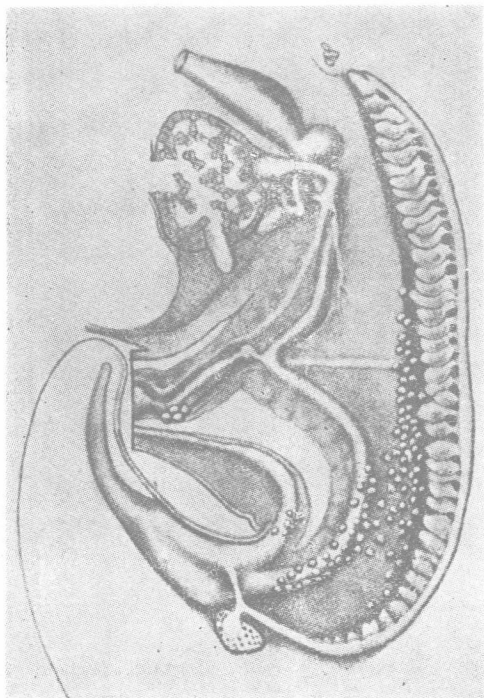


FIG. 2. Human embryo, 38 somites, 5.5 mm. Graphic reconstruction of nephric and endodermal organs of the lower body. The germ cells partly are still in the gut, partly already assembled along the medial border of the mesonephros; some are in the dorsal mesentery, migrating toward the mesonephros. In this particular embryo clusters of extraregional germ cells were found along the yolk stalk and the urachus (the germ cells are about twice their proportionate size); $\times 40$; after Witschi (33).

(Figs. 2, 3). When actively moving, they form pseudopodial processes; when at rest, they assume a globular shape and become temporarily enclosed by endodermal or mesodermal cells (Witschi, 33). This property of inducing encystment is of great interest, because it leads to the formation of the final follicle cells, after the site in the gonadal folds has been reached. Today there remain practically no dissenters to the notion of the extragonadal origin of the primordial germ cells. Waldeyer, who in 1870 (22) had proposed the *theory of the germinal epithelium*, abandoned it in 1906 (23), accepting the accumulating evidence for extra gonadal origin. His recantation went almost unnoticed, and to our very day Waldeyer must suffer to be quoted as the classic representative of the theory of the origin



FIG. 3. Human embryo, 32 somites, 4.2 mm. Migrating ameboid germ cell. $\times 2,000$; after Witschi (33).

of germ cells within the sex glands, by differentiation from somatic cells. In fact, this theory has found repeated revivals, especially through students of the human ovary. The reason is only too obvious. Ovaries of mature women above 30 years contain relatively few ovocytes. At the same time they are very large, essentially a mass of fibrous tissue and difficult to cut in serial sections. Complete series are seldom prepared and more seldom studied. The casual observer of some sections easily gets the impression that at times germ cells are completely absent. Hence the conclusion that later ovulating ones should have to arise *de novo*. In fact, the ovaries of female fetuses of four months contain about 5 million ovocytes. At this time ovogonial multiplication comes to an end, and all ovogonia transform into primary ovocytes. Soon there begins the gradual decline of their number, mostly by degeneration. In the human, rarely over 400 may leave the ovary by ovulation during the reproductive period. The larger remainder of the 5 million degenerate until the disappearance of the last ones brings on complete sterility and menopause. Nature has imposed a rigid system of reduction of the reproductive index upon the human and to some degree

upon all amniote species: (1) by early termination of ovogonial multiplication and (2) by controlled follicular degeneration of the large majority of ovocytes.

III. SOMATIC CONSTITUENTS OF GONAD PRIMORDIA

When the germ cells arrive at the gonadal site, the primordial sex gland consists mainly of two somatic elements: *the cortical and the medullary rudiments*. They are separated more or less distinctly by a space which has been given the name of *primary gonad cavity*. However, this cavity is always filled by some loose mesenchyme of somitic origin which contains also the early entering blood vessels (Fig. 4). If reduced to a narrow space, it is sometimes designated as *albuginea*.

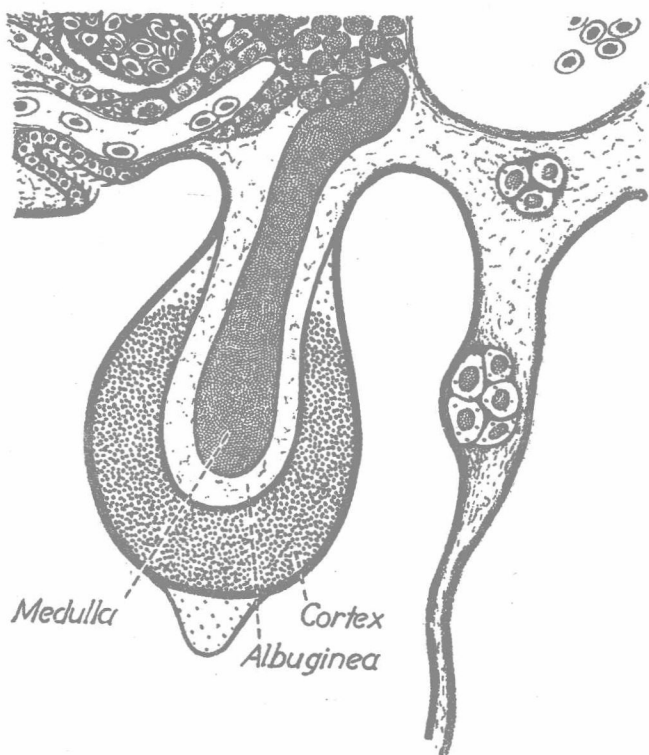


FIG. 4. Diagram representing the basic arrangement of cortex and medulla in the gonads of the higher vertebrates, as seen on a cross section. The crest as well as the hilar borders of the cortex are zones of low inductive value. Extraregional germ cells (in the diagram exaggerated in size) do not differentiate in either the male or the female sense. Mesonephric blastema cells are shown, indicating their relationship to gonadal medulla and adrenal cortex formation.

All investigators agree that the cortical rudiment arises from the celomic epithelium. It is of a very specific nature. Accidentally or experimentally displaced *extragonadal germ cells* never form a cortex with any other part of the celomic epithelium. Also, it must be assumed that this particular part of the epithelium emits early an inductor substance which guides (attracts) the germ cells during their migrations.

About the *origin of the medulla*, the expressed opinions are widely divergent. The literature has often been reviewed, recently again by Gilman (10). While indeed the microscopic pictures present some difficulty for interpretation, the *literature* has become a hopeless imbroglio of truth, error, and terminology. The available sources obviously are the celomic epithelium, the mesenchyme of somitic origin, and the nephric blastema. Since the medulla, from its inception, is separated from the celomic epithelium by the mesenchyme of the primary gonad cavity, the celomic epithelium is immediately ruled out. The misconception that the medulla might arise as a "first proliferation" from the "germinal epithelium" could only arise from the study of mammalian materials, where the gonad cavity is reduced to a very narrow space or albuginea. In amphibians the cavity is wide and the initial separation is unmistakable [Fig. 4, Witschi (26, 27)], but even in human embryos of the early indifferent stage a fine cleft between the two components is always recognizable (Fig. 5). The alternative between

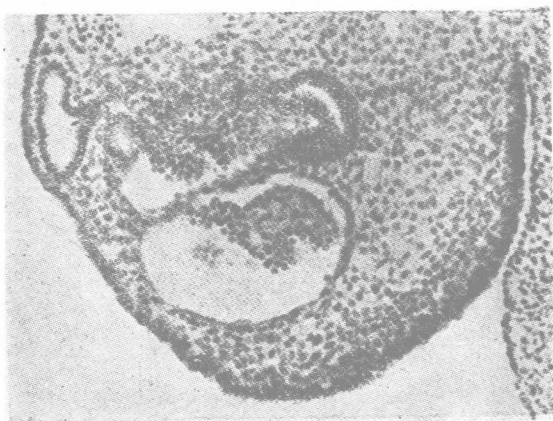


FIG. 5. Human embryo 7.4 mm. Cross section through left urogenital fold: indifferent gonad stage. The cortex consists of the much thickened celomic epithelium and contains several germ cells. The medulla is made up of a nucleus of blastema cells, more or less distinctly organized as about eight cords, radiating from the mesonephros toward the cortex. A narrow albuginea with only a few mesenchyme cells separates cortex and medulla. $\times 200$; after Witschi (33).

mesenchyme or mesonephric blastema is easily decided in favor of the latter—by direct observation (Fig. 5) as well as by corroborative evidence of various nature. By continued condensation of blastema cells the medulla finally establishes solid connections with mesonephric corpuscles or tubules, the *primordial efferent ductules*. In amphibians and in birds they usually form over the full length of the gonads, in pseudosegmental distribution (Witschi, 27, 31). In mammals and especially in man such connections differentiate and persist only in the uppermost region of the gonad. In the middle and lower regions the medulla develops merely a system of intra-gonadal rete cords which connect with the mesonephros indirectly, by their attachment to the upper parts of the medulla. While the tubular character of rete and efferent ductules in itself suggests a close relationship with the nephric organs, this becomes even more drastically evident by the not infrequent differentiation, within the medulla of amphibian sex glands, of short, isolated segments of true nephric tubules. In human fetal gonads the medulla of the hilar region sometimes encloses also vestigial renal corpuscles and almost regularly it is connected with peritoneum and body cavity by one or two nephrostomes (Fig. 6). Such occurrences would be incomprehensible on the basis of the assumption, that the medulla arises by proliferation from the cortical peritoneum. They give, however, clear evidence of the close morphogenetic relationship between gonadal medulla and mesonephros. I can see splendid *experimental evidence* for the nephrogenic origin of the medulla in Willier's (25) work on transplantation of parts of chick blastoderm to the chorio-allantoic membrane. Pieces including the primitive node and closely neighboring parts, not the prospective lateral plates, develop into defective embryos without celomic cavities or epithelia, but with mesonephric bodies, adrenals, and "sterile testes." The latter are purely medullary structures, embedded in mesenchyme except where they touch the mesonephros. In the absence of peritoneal epithelia, they serve as crucial evidence of the *non-celomic derivation of the entire medullary part of the sex glands*. Last but not least one also should mention evolutionary evidence, namely, the fact that the gonads of cyclostomes and of the many teleosts, which do not develop a urogenital connection in the male sex, consist merely of cortex and gonad cavity. Homologues of the medulla of the higher classes are missing.

IV. STERILE GONADS

The gonadal ridges or folds have scarcely begun to organize when, in the normal course of events, the germ cells begin to arrive. In frogs they first settle exclusively in the cortex, in salamanders and probably in all amniotes, some also enter the medulla directly. The question has been



FIG. 6. Human fetus of 180 mm., 21 weeks old. Cross section through testis, mesonephros, vestige of oviduct and vascular plexus. The rete testis is connected with the celomic epithelium by a vestigial nephrostome (arrow). The major blood vessels pass between the seminal tubules and branch in the albuginea, directly beneath the surface epithelium; $\times 20$.

raised, whether or not well-defined gonads may form in the complete absence of germ cells. Answers have been sought by experimental methods, especially making use of chick embryos. Dantchakoff as far back as 1908, working on early blood development, found in the diploblastic area in front of the head of very early embryos large, ameboid endodermal *migrating cells* (Wanderzellen) which later entered the blood vessels. Swift in 1915 (20), unable to trace the germ cells to earlier than 22-somite stages, noticed the similarity of the primary gonia with Dantchakoff's migrating cells. He conceived the idea that the two were identical and that the germ cells after a short journey in the blood stream left the vessels again to become settled in the splanchnopleure, where Firket and other early observers had already seen them. Dantchakoff enthusiastically adopted Swift's interpretation, though, according to her description, the germ cells would leave the vessels directly at the final gonadal site. These somewhat baffling specula-

tions stimulated a considerable volume of experimental work. Here I shall mention only investigations that were carried far enough to bear on the problem of gonad organization. Dantchakoff (4), having destroyed the "germ crescent" with a hot needle, got embryos which at the age of four days had no gonads formed whatsoever. She concludes that germ cells provide an essential stimulus for gonad differentiation. Willier, as already mentioned, with his method of transplantation received "sterile testes." He points out that his transplantations of the restricted primitive node region cannot be taken as crucial evidence for the reality of the "germ crescent." For, if he transplants the entire blastoderm, including the crescent region, he still gets only sterile gonads (25). However, in the latter case, since lateral plate material was included, the embryos acquire celomic cavities and epithelia. The "sterile testes" now have a covering celomic epithelium; but it is a thin single-layer membrane without semblance to ovarian cortex.

In comparing the results obtained by Willier and Dantchakoff one must take into consideration that Willier's embryos were nine days old when preserved; Dantchakoff's only four. Evidently Dantchakoff was only examining for the presence or absence of a sterile cortex. She does not discuss the condition of the mesonephric blastema. Willier and Dantchakoff agree, therefore, in their statements about the lack of cortical differentiation.

A seemingly contradictory result was reported by Dulbecco (5). He irradiated early embryos with gamma rays (radium), usually for a period of twenty-four hours (600 r). At termination of the treatment, the embryos had reached the 20 to 25 somite stage. Probably in all cases some of the germ cells survived long enough to enter the gonad primordia. Dulbecco reports that all fourteen cases that survived until the eighth to the sixteenth day were female fetuses with sterile ovaries. His figures indicate, however, that the cortex is always very thin. Considering this case together with Dantchakoff's and Willier's experiments, it seems not unlikely (1) that the differentiation of a thin cortex in Dulbecco's chicks is due to the initial presence of a few gonocytes, and (2) that cortical development depends on the initial presence of gonocytes.

In my work on the effects of uterine overripeness on amphibian eggs, the germ cells are seen to suffer similarly as by radiation. The issuing larvae often have near-sterile gonads, with some completely sterile segments. The case of the toad (28) is particularly interesting because the upper part of the gonad is a purely cortical territory. If here gonocytes are completely absent due to overripeness, nothing more develops than a single-layered peritoneal epithelium (Fig. 7, *right*). If, however, some remnants of degenerating eggs are still present, one also finds sterile cortical cords, i.e., anovular follicles (Fig. 7, *left*).

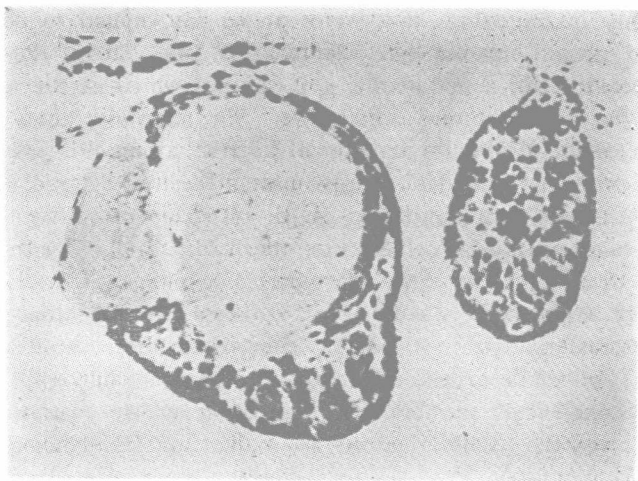


FIG. 7. Sections through cortical organs of the toad. Sterility produced by uterine overripeness of the egg. In the case at the left, germ cells were originally present (see degenerating remnants) and formation of the cortical cords or anovular follicles at the crest was presumably induced by such ovocytes. In the case at the right, sterility is more complete and no anovular follicles have formed; $\times 300$; after Witschi (28).

All these observations on sterile and near-sterile gonads indicate that *the presence of germ cells is indeed essential for the formation of a true ovarian cortex*. The germ cell seems to have the quality of an inductor of follicle cell formation. Shortly after its arrival as a naked ameboid cell in the gonad primordium, it becomes encapsulated, *usually by a single cell*. The exact origin of these cells, whether from the celomic epithelium or the mesenchyme of the gonadal rudiment, is not finally decided. The second alternative seems to be in better accord with all observed facts. The importance of this inductive competence of the primitive germ cell is evident in view of the fact that later the follicle cells become the granulosa cells of the ovarian follicles and the sustentacular cells of the seminal tubules. *Radiation experiments* with female rats, as well as the basic facts of *menopause*, show that even in the ovary of the adult the formation and persistence of granulosa cells depends on the presence of germ cells. Degeneration of follicles and cessation of estrogen production follow rather closely the disappearance of the last ovocyte.

V. COMMON ORIGIN OF ADRENAL CORTEX AND GONAD MEDULLA FROM MESONEPHRIC BLASTEMA

For the study of the origin of the adrenal cortex, *birds and reptiles* are more suitable materials than either amphibians or mammals. In bird embryos of the third and fourth days of incubation, the blastema cords along the median borders of the mesonephric bodies gradually separate into dorsal and ventral strings of cells. The former develop nodular concentrations around each one of the efferent venules where they enter the subcardinal veins, forerunners of the inferior caval vein. They are the primordia of the *cortical elements of the adrenals*. They are joined and later invaded by batches of adrenal medullary cells of sympathetic origin (31). The ventral strings of blastema cells participate in the formation of the primordial gonad folds, contributing the *medullary rudiments*. Alternating with branches of the efferent venules, this blastema also forms pseudosegmentally arranged blastemic connections with the mesonephric capsules, about twelve along each gonad. These are primordial *efferent ductules*. Later about half of them regress without ever developing a lumen. In birds and in reptiles adrenal and gonadal medulla maintain for a long time, or even permanently, close connections. Blood vessels may be seen running from one organ directly into the other. In anurans, the adrenals remain permanently incorporated in the persisting mesonephros. They move, however, in the course of larval development from the dorsomedial edges to the ventrolateral surfaces of the kidneys. If larvae are raised in water containing relatively high concentrations of estradiol (Padoa, 18) or equilenin (200 to 1,000 $\mu\text{g./l.}$) the adrenals develop prematurely, fuse in the midline between dorsal aorta and caval vein, and retain this central position permanently. So far, nothing is known about physiologic consequences of this experimentally produced anomaly. In mammals the adrenals become early separated from the gonads and the mesonephric rudiments. However, they originate essentially as in the other vertebrate classes.

In the development of the sex glands the primitive medulla gives origin not only to the tubular urogenital connecting system but also to the medullary endocrine glands: interstitial cells of the testis and theca cells of the ovary. The relative ease with which some of the endocrine organs that derive from the mesonephric blastema can interchange their functions is one of the best supports for the concept of common origin and close morphogenic relationship. It is well known that the adrenal cortex under pathologic conditions may produce excessive quantities of androgenic hormones. Some investigators maintain that in the rat, under experimental conditions or even in normal fetal and postnatal life the adrenals rather than the testes stimulate and maintain the development of the secondary male sex char-

acters (Burrill and Greene, 2; Price, 19). For the rabbit this is, however, definitely ruled out by the experiments of Jost on intrauterine castration (14). Wells (24) in similar experiments with rats "did not find any evidence of the production of androgen by the adrenals of fetuses." That the adult rat ovary, even under normal conditions, produces some androgenic hormone may be seen from the slightly stimulated condition of female prostates, where such are present (Witschi, unpublished). But its output is considerably increased if the ovaries are transplanted into the ears (Hill, 12) or into the tip of the tail (Hernandez, 11). The histologic studies of Hernandez show that rats with tail grafts maintain estrus as long as the ovaries still have ovular or anovular follicles; in other words, as long as granulosa cells persist. On the other hand, the prostates decrease with the reduction of the theca-interstitial cell component and assume castrate condition, when the interstitials disappear. These responses to separate survival of one or the other endocrine tissue attest to the gynogenic character of the granulosa and the androgenic character of the theca cells.

It has variously been noticed that adrenalectomy in female rodents is followed by an increase of ovarian interstitial tissue, and Hill (13) made the startling observation that in mice, ovaries transplanted into the ears maintain life after adrenalectomy. That the ovary under this condition (i.e., lowered temperature) substitutes for an essential adrenal function is clearly proved by the fact that such mice presently die after removal of the graft ovary.

VI. OVARIAN AND TESTICULAR HOMOLOGIES

According to the so far developed picture, the mature ovarian follicle must be homologous to a segment of testicular seminal tubule. Its theca corresponds to the interstitial cells that surround the tubule. The granulosa is the homologue of the sustentacular cells. It is, therefore, to be expected that the ovarian medulla maintains some relationship with the thecal elements of the ovary, as indeed is the case. In fetuses of the third and fourth month, medullary cords approach the ovocyte layer dividing it up into cortical cords, the "egg tubes" of Pflüger. Later, and even in the adult, the individual follicles are found to maintain these contacts. In case of degeneration of the granulosa, centrally located follicles often establish an open connection and release degenerating eggs into the lumen of a rete tubule. This is a process entirely analogous to spermiation (Figs. 8, 9).

The homology of ovarian and testicular medullary cords would be more readily recognized, if at the fetal stage luteal transformation occurred in the female as well as in the male sex glands. In human testes, the interstitial cells early exhibit an excessive luteinization. In human ovaries nothing similar is observed before theca luteinization sets in, at much later stages.



FIG. 8. Ovary of a young rat. Near the center a degenerating follicle has opened into a tubule of the ovarian rete; $\times 87.5$.

However, true lutein cells occur in the medulla of ovaries of the armadillo (Newfang, 16). The medulla in this species is especially well developed. In fact, the armadillo ovary exhibits an interesting form of intersexuality. Some of the cortical cords near the hilum do not divide up into individual ovocytes. On the contrary, like sex cords in testicular development, they detach themselves from the cortex and move into the medullary space. In the adult ovary they exhibit a condition intermediary between a seminal tubule and a polyovular follicle; however, they contain not only ovocytes but also gonidia which still undergo mitotic division. Such intersexual tubes demonstrate most clearly the homology of cortical cords and ovarian follicles, with the seminal tubules.

The intersexual tubes of the armadillo furnish also renewed evidence for the homology of granulosa and sustentacular cells. It is, therefore, of interest to find this relationship likewise borne out by endocrinologic observations. It is well known that stallion testes produce considerable amounts of estrogens. The fact that the human male excretes estrogens, which however practically disappear after castration, indicates an estrogenic function also of the human testis. This raises the question of the site of estrogen production. Some years ago we (Witschi and Mengert, 36) described a human hermaphrodite with almost purely female secondary sex characters and nor-