TUMOURS OF THE OVARY

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FOREWORD

Neoplasms of the ovary present a widespread challenge. To the gynaecologist they are becoming increasingly important as they have gradually come to assume a dominant role in the causation of death from female genital cancer. The oncologist is frustrated by the paucity of knowledge of the aetiological factors in ovarian cancer and by the failure to achieve any notable reduction in the mortality rate from these neoplasms during the last few decades. The pathologist is often confused both by the profusion of neoplastic entities to which the ovary is host and by the wide variety of histogenetic theories that are profferred to explain their occurrence: both he and the gynaecologist are often in doubt as to the prognosis that should be offered for any particular tumour either because it is one for which the criteria of malignancy have not been adequately defined or because it is seen too infrequently in any one institution for its natural course to be known.

In this book it has been our aim to present an account of our present knowledge of ovarian tumours, basing this partly on a critical review of the literature and partly on our own experience of these neoplasms. Our own material consists largely of neoplasms from women treated at St. Mary's Hospital, Manchester, during the last 25 years but this has been considerably augmented by cases submitted to the Manchester Regional Ovarian Tumour Registry and by a large number of referred tumours. Further material has been obtained from the Manchester Regional Children's Tumour Registry and we have also had the opportunity to review the many neoplasms submitted to the Ovarian Tumour Panels of the World Health Organisation and the Royal College of Obstetricians and Gynaecologists.

We have attempted to review the literature on ovarian tumours in a fairly full fashion but we should stress that we have only read those papers and articles written in languages of which we have some understanding; therefore few of the many papers written on this topic in Eastern European, Hispanic or Oriental languages have been covered.

We have tried to deal fully with the histogenesis of the various neoplasms not simply because this is an interesting academic exercise but because of our belief that the greater our understanding of the true nature of a neoplasm the greater, eventually, will be the possibility of rational therapy. Although describing the pathological features of the tumours in some detail we have not felt it necessary to illustrate lavishly their morphological appearances; in particular, we have included few photographs of gross specimens for we feel black and white illustrations of tumour specimens to be rarely of value.

We have also considered the clinical features and therapy of ovarian neoplasms and here some may feel that we are, as pathologists, exceeding our remit. We make, however, no apology for detailing the clinical features partly because our comments on these are based upon the reading of numerous case notes of our own patients and of case reports in the literature and partly because of our belief that pathologists should consider a disease process in its entirety and not confine themselves solely to a study of morphology. It is true that therapy is not usually considered as the domain of the pathologist but we are often consulted by our clinical colleagues as to the indicated treatment for particular neoplasms and we feel that our relatively remote stance from practical treatment allows us to evaluate the results obtained by various therapeutic procedures with a dispassion that is not blunted by an adherence to, or an enthusiasm for, any particular form of therapy.

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Chapter 1

THE DEVELOPMENT OF THE GONADS

A study of the development of the human ovary and, to a lesser extent, of the testis is a necessary preamble to an understanding of the histogenesis of ovarian tumours. Unfortunately, concepts about the origin of the several cellular components have varied, and consequently the interpretations of the modes of development of the different tumour patterns. Thus it is necessary not only to describe the latest views of gonadogenesis but to outline their historical development in order to place the theories of ovarian oncogenesis in their proper perspective.

The early development of the gonad may be divided into four major phases. During the first, undifferentiated germ cells (primordial germ cells) become segregated and migrate from their sites of origin to settle in the genital ridges, which are bilateral thickenings of the coelomic epithelium ventral to the developing mesonephroi. The second phase occurs after the arrival of the germ cells in the genital ridges and consists in a proliferation of the coelomic epithelium and of the underlying mesenchyme. During the third stage the gonads become divided into a peripheral cortex and central medulla. The fourth phase, in the female, is characterised by development of the cortex and involution of the medulla and, in the male, by involution of the cortex and proliferation of the medulla.

The origin of the primordial germ cells

Two opposing views have been held regarding the source of the primordial germ cells: (1) that they arise in the gonadal tissue itself, or (2) that they arise in the yolk sac and migrate to the genital ridges.

Extragonadal primordial germ cells were first described by Fuss[17, 18] and by Felix[11] but their reports were brief and incomplete. More substantial studies were made by Politzer,[43, 44, 45] who described 17 human embryos, and by Witschi[54] who examined 23 human specimens varying in length from 3·5 to 8 mm. Cells, later to be identified as germ cells, arise in the yolk sac endoderm, but at this stage the primordial germ cells are difficult to identify with certainty. The paths by which these cells migrate from their site of origin to their final position in the genital ridges have been studied by standard histological as well as histochemical methods. Primordial germ cells are recognised histologically by their large size and histochemically by the presence of alkaline phosphatase.[35] In all vertebrates (excluding amphibians and birds) in which the zygote undergoes meroblastic cleavage, the primordial germ cells migrate to the region of the developing dorsal mesentery and later to the mesenchyme underlying the coelomic epithelium at the root of the mesentery. A concentration of primordial germ cells is thus formed ventral to the aorta, extending caudally from about the cranial limits of the developing mesonephroi. From this position the primordial germ cells migrate laterally to the genital ridges (Fig. 1.1).

It seems probable that in man germ cells migrate by their own active amoeboid movements, possibly aided by histolytic action, although differential growth of germ layers may also play a part.[15] In the later stages of migration, when they are in the vicinity of the gonads, chemotaxis may

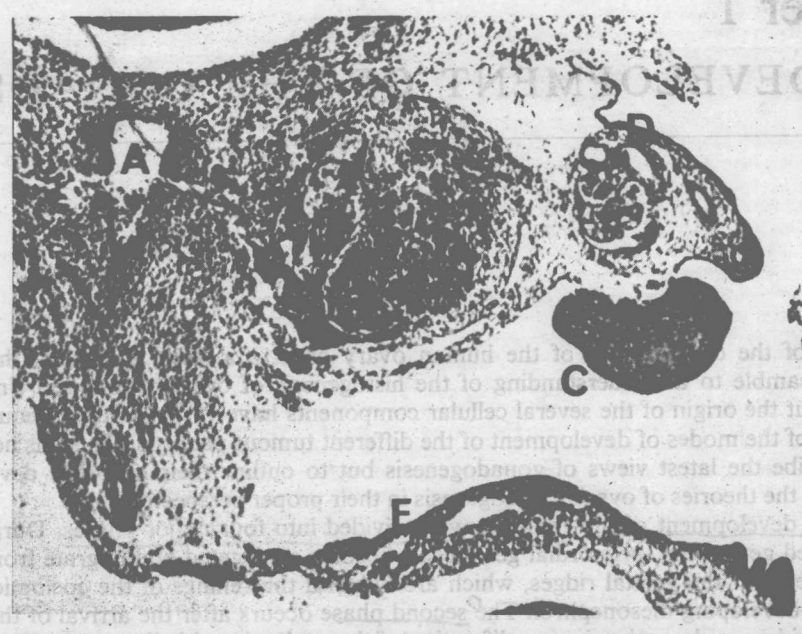

Fig. 1.1. A transverse section of a 14 mm fetus showing the urogenital ridge, comprising the gonad and mesonepheric apparatus, projecting into the coelomic cavity. A, aorta; B, adrenal; C, gonad; D, mesonephros and E, mesentery. (H & E × 72)

operate. Although the germ cells divide during migration[54] when they reach the genital ridges they undergo a period of more rapid mitotic division and normally the cells that fail to reach their destination degenerate and can no longer be identified. The persistence of ectopic primordial germ cells has been recorded in some teleosts[49] and in man may account for the occurrence of extragonadal teratomata.

Stieve[50] and Neuman[38] revived the theory that germ cells arise in the so-called germinal epithelium covering the ovary. Willis[53] has subscribed to this view and considered that the cells which Witschi and others have described as germ cells to be wrongly identified and that they are mitotic, pre-mitotic or degenerating cells of other kinds. The experimental evidence against this hypothesis has been reviewed by Franchi *et al.*[15]

The formation and differentiation of the gonad

The presumptive gonads first appear as bilateral thickenings of the coelomic epithelium which cover the ventro-lateral aspects of the developing mesenephroi between the root of the dorsal mesentery and the Wolffian ducts (Fig. 1.1). These changes occur at the 5 mm stage (fifth week) at about the same time as the germ cells reach this site. The gonadal primordium arises at the level of the upper lumbar segments and is composed of two elements—medulla and cortex. The origin and contribution of each of these constituents to the definitive gonad has been much disputed, and eight different views have been reviewed by Gillman.[21] Until recently it was believed that both were formed by proliferation and ingrowth of the coelomic epithelium covering the mesonephric ridge (the so-called first and second proliferations of the surface epithelium) but now it is thought likely that the medulla arises from the mesenchymal cells which lie beneath the epithelium and that only the cortex is derived from the coelomic epithelium. There still remain different views regarding the further development of these tissues; these are summarised in Table 1.1.

Table 1.1 *The Early Development of the Gonad*

	Witschi[55]	*Ohno*[39]	*Bulmer*[4]
Germ cells	Yolk sac	?Yolk sac	Yolk sac
Follicular cells	Cortex	Medulla	Cortex
Sustentacular Sertoli cells	Cortex	Medulla	Medulla
Interfollicular tissue	Medulla	Medulla	Medulla
Interstitial cell of testis and hilar cells of ovary	Medulla	Medulla	Medulla
Rete and somatic part of seminiferous tubules	Medulla		Medulla

Witschi[55] regards the cortex as a strip of thickened peritoneal epithelium which furnishes the primitive gonad with follicle cells which become granulosa cells in the ovary and Sertoli (sustentacular) cells in the testis. In his view the medulla shares with the adrenal cortex an origin from the medial mesonephric blastema. It differentiates into efferent ductules, rete tubules and the somatic part of the seminal tubules. In both sexes the medulla furnishes the interstitial cells and in the female contributes to the formation of the follicular theca.

Ohno,[39] as a result of his study of cattle gonads, considered that a common blastema arising at the root of the genital ridge gives rise to the follicle cells of the ovary and the interstitial cells of the testis. At first the germ cells lie at the periphery of the gonad and the somatic blastema at the centre. In the male, when sex differentiation becomes apparent, the primordial germ cells invade the blastema and begin to organise seminiferous tubules whilst blastema cells outside the tubules become recognisable as interstitial cells. In the female, the majority of primordial germ cells remain directly beneath the surface for some time and the blastema sends out strands of cells towards them. These strands, representing the primordia of the follicular cells, engulf the germ cells which then move downwards, deeper into the ovary. Centrally well formed primordial follicles develop,

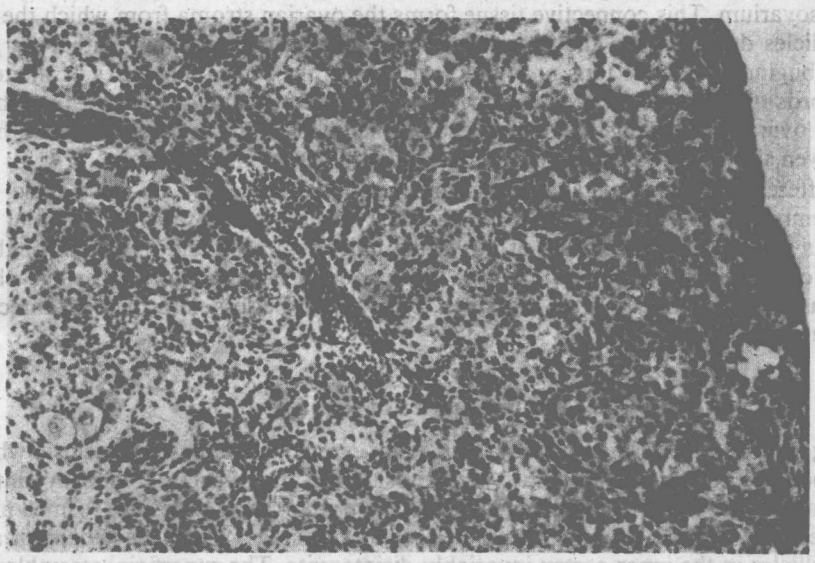

Fig. 1.2. A section of an ovary from a fetus of 16 weeks gestation. On the left the germ cells near the medulla occur singly, surrounded by circumferentially arranged stromal cells. On the right, beneath the surface of the ovary, the germ cells are arranged in groups separated from each other by strands of stromal cells. (H & E × 120)

each with a central germ cell and peripheral zone of follicular, or granulosa cells, arranged circumferentially (Fig. 1.2). However, the germ cells lying directly beneath the mesothelium which are not reached by the growing strands of follicular cells degenerate and disappear. It is of some interest that the germ cells which are alkaline phosphatase positive in the early phases of development become negative as they mature but the blastema becomes phosphatase positive and these differences in staining reaction were exploited by Ohno in his study of gonadogenesis. However, the theory he developed controverts Witschi's tenet of corticomedullary antagonism.

Bulmer[4] gives a somewhat different account of the development of the gonads. During the sixth week of embryonic life the indifferent gonad grows and forms a bulge projecting from the medial side of the mesonephric ridge (Fig. 1.1). Its attachment becomes constricted to form the mesogenitale which ultimately forms the mesorchium or the mesovarium. The cells of the medulla proliferate and form solid epithelial 'sex cords' which lie at right angles to the surface and extend to the mesogenitale. The cortex remains as a thickening of the overlying coelomic epithelium but separated from the medullary cords by a thin layer of undifferentiated mesenchyme. From about the sixth week the development of the testis and ovary diverge, differentiation of the testis occurring somewhat earlier than that of the ovary. In the testis the cortical primordium regresses to form the tunica vaginalis and the thin layer of mesenchyme, which originally separated the cortex from the medulla, becomes thickened to form the tunica albuginea. By about the 40 mm stage interstitial cells begin to appear in the mesenchyme between the medullary cords. The medullary cords become canalised to form seminiferous tubules and straight tubules in the gonad and the rete where they extend into the mesogenitale. In the ovary, in contrast to the testis, the cortex survives and proliferates giving rise to an ingrowth of cortical cords perpendicular to the surface and reaching to the peripheral ends of the medullary cords. The thin mesenchymal layer which originally separated the cortex and medulla disappears and thus the cortical and medullary cords become continuous. The medullary cords extend into the mesovarium where they form a rudimentary rete network. Up to about the end of the third month the ovary consists of an ill-defined mass of sex cords which incorporate primordial germ cells as well as somatic cells. At about the 70 mm stage the sex cords begin to break up into groups of primordial follicles coincident with the growth of interstitial tissue from the mesovarium. This connective tissue forms the ovarian stroma from which the theca of the Graafian follicles develops and the superficial layer beneath the coelomic epithelium gives rise to the tunica albuginea, which is thus not homologous with the tunica albuginea of the testis. As the medullary cords disintegrate in the mesovarium some cells probably persist to form the hilar cells of the adult ovary. According to Forbes[13] some medullary tubules located at the hilum of the ovary, and even showing germ cells, may persist until the 280 mm stage.

These different views of gonadogenesis arise from the necessity of using fixed and stained sections of embryos, in which the cells change their identifying features and spatial relationship with time. As yet we have no means of observing individual cells and tissues through successive generations of developmental interrelations. When cells have acquired certain characteristic features or associations they can be classified, but we can be less sure of their antecedents than their subsequent realisation.

The later stages of oogenesis

Female germ cells are termed oogonia until they enter the prophase of meiosis when they are designated oocytes. Oogonia proliferate by mitosis with diminishing frequency until the third month of fetal life and meiosis commences before the primordial follicles are formed at 4·5 to 5·5 months.[51] Death of oogonia or oocytes may occur at any stage in their development and the first primordial follicles in the inner cortex invariably disintegrate. The superficial resemblance between the histological appearance of the ovary at this stage and that of a dysgerminoma is worth noting. In the mature woman during the two weeks following menstruation several Graafian follicles usually begin to develop rapidly but, ultimately, only one survives and continues to enlarge, the

others becoming atretic and degenerate. Hence most of the ova with which the ovary was originally endowed degenerate *in situ* while only about 400 are ovulated during the entire reproductive period. Baker[2] has carried out a quantitative study of the number of germ cells and ova in the human ovary at different stages of development. At six weeks of fetal life 600,000 oogonia are present, at 20 weeks there are 7,000,000 oocytes declining to 2,000,000 at birth, 300,000 at 20 years and after the menopause the ovary is devoid of ova.

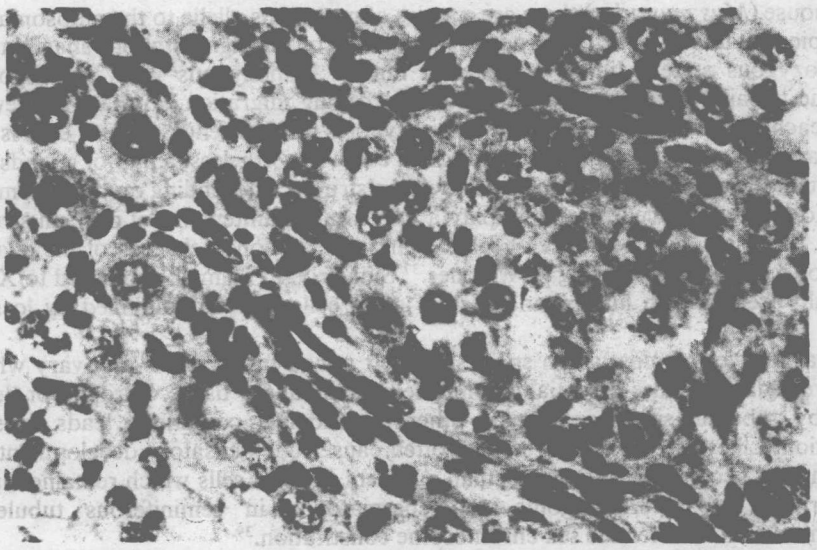

Fig. 1.3. This is a higher power view of a group of germ cells seen near the surface in Fig. 1.2. The nuclear chromatin in many of the germ cells forms slender strands. The appearances are probably indicative of the zygotene phase of meiosis; compare with Franchi *et al.* (15), Fig. 1.1, p. 60. (H & E × 300)

Meiosis is a special kind of cell division consisting of two divisions of the nucleus in the course of which the chromosomes divide only once and hence they are reduced to the haploid number. The first meiotic division begins with a lengthy prophase which can be subdivided successively into leptonema, zygonema, pachynema, diplonema and diakinesis (Fig. 1.3). Development of the ovum is arrested in diplonema and the next stage—diakinesis—does not take place until just before ovulation which may be many years later. This is followed by completion of the first meiotic division and reduction of the chromosome number to 23. The second meiotic division occurs only after the penetration of the oocyte by a spermatozoon. In the female the germ cells, whether oogonia or oocytes, have the distinction of never exhibiting a sex chromatin mass.

In the male meiosis does not commence until just before puberty and it is relatively rapid since there is no prolonged rest in the diplonema stage as in the female. The whole process of gametogenesis, running to the complete formation of spermatozoa each with 23 chromosomes, lasts 60 to 65 days. It is possible that the difference in the time of occurrence of diplonema and the duration of this phase may account for the different incidence of teratomata in the two sexes.

Factors controlling gonadogenesis

A number of abnormalities in the structure of the gonads and genital tract occur in man and some of these are associated with the presence of gonadal tumours. However, there is little direct evidence as to their mode of origin and our current understanding of this rests on an analysis of similar anomalies in other species.

The role of germ cells. It appears probable that the presence of germ cells is not necessary for the establishment of the gonadal anlage. The development of sterile gonads of both sexes has been recorded in frog larvae derived from eggs which were irradiated with ultraviolet light at their lower pole[3, 40] and also in chick embryos explanted *in vitro* without extraembryonic germ cells.[46] These gonads were small but the sex was recognisable, although Padoa[40] reports that the sterile ovarian cortex in frogs was better organised if the tadpoles were given oestradiol.

In the mouse (*Mus musculus*) there are a series of mutations allelic to the autosomal gene w and the pleiotropic mutants W, W^v, W^j produce an absence of fur pigmentation, anaemia and sterility in the homozygous state. Mintz[36] has shown that in homozygous W^vW^v embryos sterility is primarily due to failure of germ cells to proliferate during migration, so that very few primordial germ cells reach the genital ridges. In W W homozygotes the deficiency of germ cells is more severe and the gonads of the newborn are devoid of germ cells. Nevertheless, a pair of gonads is present in each individual of either normal testicular or ovarian structure depending on the chromosomal constitution.[7] However, germ cells probably play a part in the maintenance of ovarian structure since, for example, there is a disappearance of follicles and a reduction in the size of the ovary after loss or death of oogonia in mice bearing W W genes.[37] Similarly, in animals submitted to X-rays and in rats prenatally treated with busulphan[27] loss of germ cells was accompanied by loss of ovarian structure.

In normal females of most avian species, the left gonad functions as an ovary while the right gonad is a vestigial structure essentially composed of medullary tissue. Atrophy or destruction of the ovary by tuberculosis, neoplasm or other pathological conditions leads to spontaneous masculinisation. Likewise, left oophorectomy often causes compensatory development of the right gonad which now becomes a testis, and small numbers of germ cells which remained in this gonad are transformed into spermatogonia and spermatozoa in seminiferous tubules, but the spermatogonia retain their female sex chromosome constitution.[39]

These various lines of evidence indicate that the germ cells are not essential for the development of the gonad and that whether the germ cells develop into oocytes or spermatozoa depends on the gonadal milieu rather than on their chromosomal constitution. As a corollary it may be supposed that any germ cells which do not reach the gonad but remain dormant in extragonadal sites, remain sexually undifferentiated.

The role of hormones and allied substances. The 'hormonal theory' of sex differentiation was popularised by the beautiful studies of Lillie[33, 34] on freemartin cattle. He showed that when vascular anastomoses develop between the placentae of male and female calf embryos *in utero* the female becomes greatly modified in the male direction forming an intersex with testes and male ducts. Lillie interpreted this freemartin effect as the result of the transfer of testicular hormone from the male twin to the female, but the studies of Ohno[39] on germ cell chimerism suggest that this is an oversimplification.

A variety of other experiments in animals can, however, be cited in support of the hormonal theory of sex differentiation. Dantchakoff[8] produced full feminisation of genetically male birds by introducing oestrone dissolved in oil into the allantoic cavity on the fourth day of incubation. After hatching these birds developed as intersexes. Dantchakoff[9] also produced masculinisation of guinea pig embryos by use of testosterone propionate. More recent experiments showing the influence of extraneous sex hormones, gonadal grafts and parabiosis of heterosexual larvae have been reviewed and analysed by Jost.[31] All these studies indicate that hormonal factors can play a role in differentiation of the gonads, but whether, and to what extent, such factors are of importance in human gonadogenesis is unknown.

The role of genetic sex. In the human subject the presence of the Y chromosome ordinarily determines the masculine phenotype and an excess of X chromosomes in the presence of a Y chromosome (Klinefelter's syndrome) does not prevent the development of testes whilst an excess of Y chromosomes is compatible with testicular development. However, functional reversal of sex

in animals may be produced experimentally and reversal affects both the somatic and germ cell component of the gonad. This is beautifully illustrated by Haffen's[23] experiment in which male quails, which had been feminised during embryogenesis by oestradiol, developed ovaries and laid eggs. Although, as Jost[31] has pointed out, genetic sex may yield to hormonal factors during sex differentiation it may re-establish its significance later in life. Thus, cockerels[8, 56] and male newts,[19] which were feminised by oestrogens early in life, may revert to the masculine role later when adult. One of Gallien's[19] feminised newts laid eggs for two years, but later developed masculine behaviour, and when examined at the age of 11 years it was found to possess testes containing spermatozoa.

This brief review indicates that whereas normally the sex of the individual is determined by its genetic constitution the morphology of the gonad may be modified, especially by hormonal factors, and the germ cells may develop as ova or spermatozoa depending on the milieu of the gonad in which they are lodged.

The relation between the gonads and genital tract development

In view of the anomalies of the genital tract which may accompany a dysgerminoma, gonadoblastoma or Sertoli cell tumour, it is pertinent to consider briefly the influence of the gonad on genital tract morphogenesis. Much of the work elucidating this influence has been carried out by Jost and the following summary is based on a recent review[31] by him. The experiments, of course, have been carried out on a wide variety of animals and the results can only be transferred to man by inference.

Ovariectomy of female rabbit fetuses has little effect on the genital tract, but castration of a male fetus profoundly modifies the tract, the extent of the modification depending on the stage of differentiation at which the operation is performed. When male fetuses are castrated before initiation of somatic sexual differentiation (day 19), no male characteristics develop and the whole genital tract becomes feminine, the Wolffian ducts disappear and the Müllerian ducts continue to develop. Conversely, partial masculinisation is observed in females in which testes are grafted in contact with the genital tract. Thus, in mammals the 'neutral' or 'gonadless' type of genital tract developing in the absence of any sex gland is feminine whatever the genetic sex of the fetus. During development, the testis imposes masculinity on the various structures and inhibits feminine differentiation. In birds the gonadless type of somatic sex is masculine and the main sex differentiator is the ovary.

Carefully designed experiments indicate that there is an initial period in the development of the Müllerian ducts during which they are sensitive to the influence of the testis. Inhibition of these ducts was obtained only during a limited period of time, on day 13·5 in mice[52] and day 14·5 in rats.[42] In the human fetus the crucial period extends approximately from day 50 to day 60 after fertilisation.

The effects of the testis on morphogenesis are spatially restricted. Thus, unilateral castration of male rabbit fetuses at an early stage (say day 19) results in masculinisation of the genital tract on the side of the remaining gonad, but masculinisation on the castrated side may be absent or incomplete. In female rabbits testicular grafts do not influence the genital tract unless they are in direct contact with the structures. Unilateral masculinisation occurs when a testis is implanted on the mesoalpinx or ovary. Thus, the testicular morphogenetic substance is not distributed by the general circulation but spreads locally.

The fetal testis produces a morphogenetic secretion responsible for two effects: (1) it inhibits the Müllerian ducts, and (2) it stabilises the Wolffian ducts and stimulates the development of other male structures. The identification of the factor, or factors, which govern the sexual differentiation of the genital tract is not yet achieved. Jost[31] quotes investigations indicating that the fetal testis can produce androgens which may play a role in differentiation and that the fetal ovary displays steroid metabolism at a much later stage of development than does the testis. It seems probable that the

morphogenetic secretions are under the control of the genes determining sex, which may determine the production of the secretions and modulate the response of the tissues to these hormones.

Developmental abnormalities of the gonads

Abnormalities of the gonad may affect the whole organ, as in Turner's syndrome, or they may be focal, such as 'ring tubules'. The name 'gonadal dysgenesis' was introduced by Gordan *et al.*[22] to describe the gonads in Turner's syndrome, but the use of the term has been extended to other conditions and is thus rather imprecise.

Streak gonads. In this condition, the uterus and Fallopian tubes are small and the gonads form only streaks of tissue. Microscopically the streaks are covered by surface epithelium composed of low columnar cells and germinal inclusion cysts may be found. The substance of the streak consists of fibrous tissue similar in arrangement to normal ovarian stroma (Fig. 1.4) but lacking germ cells or associated structures in patients over the age of puberty. However, in such patients hilar cells can often be seen, and in the mid portion of the streaks remnants of the rete ovarii can be found. Mesonephric remnants may also be found in the broad ligament.

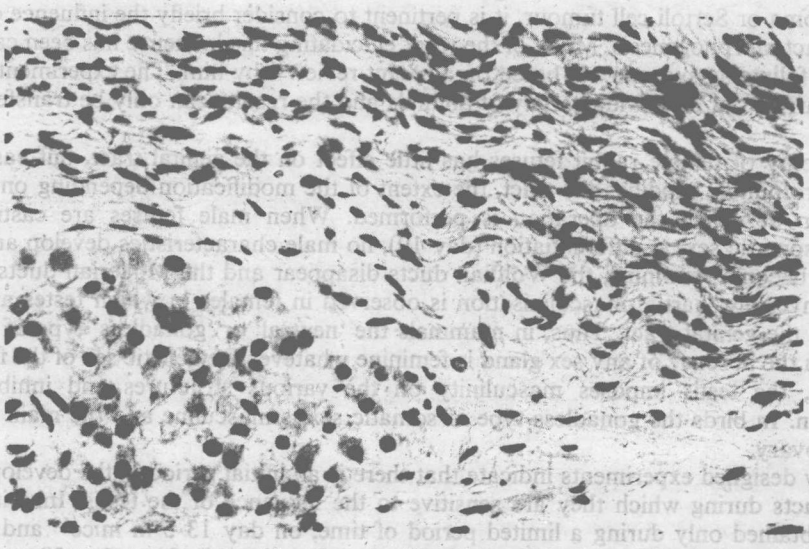

Fig. 1.4. Streak gonad. Fascicles of ovarian-like stroma are present together with a group of hilar cells (extra-testicular Leydig cells). (H & E × 300)

These streak gonads are not strictly aplastic structures. Examination of the genital ridges of embryos and fetuses and the gonads of new born infants which were apparently 45,XO[16,47] have shown that a few germ cells may be present in embryonic life but these disappear more rapidly than in the normal ovary, so that by the time of puberty they have disappeared.

Hermaphroditism.[30] Individuals bearing both recognisable ovarian and testicular tissue are regarded as true hermaphrodites, irrespective of how the internal ducts or external genitalia have differentiated. About one third of these individuals have an ovary on one side and a testis on the opposite side. Some have both an ovary and testis on each side, others an ovary and a testis on one side and an ovary or no gonad on the contralateral side, there may be an ovotestis on each side or an ovotestis on one side and either an ovary or testis on the other.

In an ovotestis the two components are usually separated by connective tissue, but occasionally the testicular and ovarian tissue are intermixed. In the testicular part there is generally poor germ cell development and after puberty the germ cells are quite degenerate. It seems that the testis is quite competent to influence Müllerian suppression whereas an ovotestis is quite incompetent and behaves in this respect like a normal ovary.

The paradoxical development of testicular tissue in the absence of a Y chromosome or of ovarian tissue with the male genotype cannot as yet be explained but various hypotheses have been advanced:

(1) In patients with 46, XX karyotype, Ferguson-Smith[12] has suggested that the ovum was fertilised by a sperm in which the male determining genes from the Y chromosomes were translocated during the first meiotic division to give a zygote with sex chromosomes XX^{Y}. According to the Lyon hypothesis this would result in two cell lines developing in the gonad one having X function which will develop into an ovary and one having XY function which will develop into a testis. However, using glucose–6–phosphate dehydrogenase as a gene marker, Jones[30] has shown that in the ovaries of the female heterozygote, the size of the pure clone of X inactivation was small (e.g. 2 × 2 mm or less) and would give rise to a mixed area of ovotestis rather than the distinctly separate ovarian and testicular structures usually found in an ovotestis. Nevertheless, it may be pertinent to suggest that a small area of ovotestis mixed with ovarian tissue might be regarded as a hamartoma and could be the site of origin of an ovarian tumour such as an androblastoma.

(2) At least four hermaphrodites have been described[6, 20, 30, 41] in which haematological studies revealed erythrocyte chimerism. It may be postulated that this was caused by double fertilisation by dispermy. Fraccaro *et al.*[14] have demonstrated a rare type of mosaicism in a case of true hermaphroditism and postulated that all true hermaphroditism may be due to hidden chromosomal mosaicism, but this is probably too wide a generalisation. Chimerism in this context is the presence in the same person of two genetically different cell lines derived from different zygotes which subsequently fused, whereas mosaicism is the presence in the same person of two genetically different cell lines derived from the same zygote.

Minor malformation and heterotopia. The above conditions, streak gonads and hermaphroditism, affect the gonads diffusely but there are local anomalies of development, which

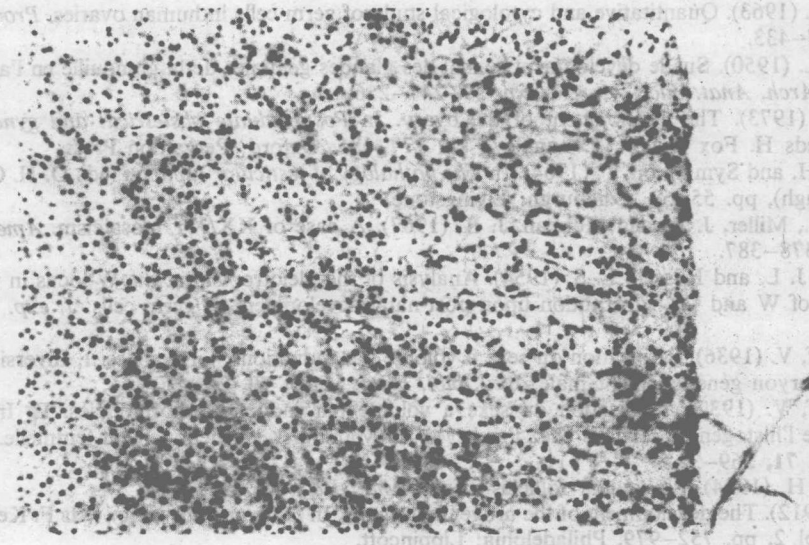

Fig. 1.5. Ectopic adrenal tissue adjacent to the ovary. (H & E × 120)

should probably be regarded as hamartomata. Polyovular follicules occur in many species of animals and have also been recorded in women.[1, 10, 26] In Arnold's[1] case there were many follicles in each ovary containing 2 to 13 ova. These probably represent ova which have retained their intercellular connections beyond the usual stage.

It is of some importance to remember that heterotopic nodules of adrenal tissue (Fig. 1.5) may be found in the mesosalpinx, mesovarium or broad ligament in women and in the spermatic cord, epididymis and tunica albuginea of the testis. Willis[53] has reviewed such examples of heterotopia and pointed out that they may sometimes simulate gonadal tumours so that on rare occasions a tumour designated 'arrhenblastoma' may turn out to be a juxta-ovarian adrenal cortical tumour.

Intratubular spherical bodies have frequently been noted in ectopically situated or in abnormal testes since their first description by Lecene and Chevassau.[32] These bodies are usually homogeneous, but sometimes they have a laminated or shell-like structure and histochemical analysis indicates that they are composed chiefly of masses of protein, rich in acid mucopolysaccharides, but containing no iron or calcium. Sometimes these spherical bodies are multiple and located in dilated segments of tubules lined by a double row of epithelial cells forming the so-called 'ring-tubule'. The structure of these ring-tubules in the cryptorchid testes of children has been carefully studied in serial section by Huber *et al.*[28] It is difficult to be certain whether the spherical bodies lie within the tubule or outside in a cup-shaped depression in a dilated portion of the tubule.

In normal testes multiple concretions may be found in a group of hypoplastic tubules; such structures have been described as foci of Sertoli cell hyperplasia,[5] Sertoli cell tumours[24, 25] or 'immature seminiferous' tubules.[48] Huber *et al.*[29] have examined a number of such structures in serial section and found that the hypoplastic zones are parts of normally developed seminiferous tubules in which the epithelium is replaced by a solid cord of cells with dense nuclei which is coiled up within the tunica propria. The cord often swells up and encloses small concretions. The appearances of these structures closely resembles those of the dysgenetic gonad associated with gonadoblastomata.

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Chapter 2
GONADAL ENDOCRINOLOGY

A significant proportion of ovarian neoplasms appear to be endocrinologically active, and neither their true nature nor their clinical manifestations can be clearly understood without some knowledge of the normal mechanisms and sites of steroid biosynthesis in the ovaries. Some hormonally active tumours of the ovary are, however, thought to be formed of cells of a type normally present not in this organ but in the testis, and hence the student of functioning ovarian neoplasms has also to consider testicular physiology and biochemistry.

No attempt will, however, be made to describe in this chapter anything more than a very simplified outline of gonadal endocrinology, for this is a highly complex, and often controversial, subject a detailed consideration of which clearly lies outside the scope of this book.

Hormones produced by the gonads

In general terms the principal endocrine function of the ovary is to produce oestrogens and progesterone, whilst that of the testis is to secrete androgens. The situation in reality is, of course, not as clear cut as this, for the ovaries also produce androgens whilst oestrogens are synthesised by the testes. Indeed, although the principal ovarian secretions are oestrone, oestradiol and progesterone, the ovary also secretes practically every steroid that occurs as an intermediate along the synthetic pathway from pregnenolone to oestradiol, for testosterone, androstenedione, dehydroepiandrosterone and 17-hydroxyprogesterone are all present in higher concentration in ovarian venous plasma than in the peripheral plasma.[2] The levels of sex steroids in the peripheral plasma of healthy adults during the reproductive years are shown in Table 2.1, the figures being an average of those reported by various workers.[2, 3, 4, 8, 13, 14, 18, 19] These figures should not only be regarded as approximations but should also be treated with some caution, partly because slight differences of techniques can give somewhat variable results and partly because there is a considerable individual variation from person to person. Further, these plasma levels are the result of a balance between

Table 2.1. *Average Steroid Levels in Plasma of Men and Women* (in ng/ml)

Steroid	*Men*	*Women (Follicular Phase)*	*Women (Luteal Phase)*
Oestradiol-17β	0·02	0·07	0·17
Oestrone	0·06	0·06	0·12
Progesterone	0·3	0·5	10
17β-dehydroxyprogesterone		0·4	1·5
Testosterone	6·6	0·37	0·37
Androstenedione	0·9	1·6	1·6
Dehydroepiandrosterone	5	—	—
5α-dihydrotestosterone	0·5	—	—

numerous variables; these including adrenal secretion of steroids, binding of steroids to proteins in the plasma, metabolism and conjugation of steroids in the liver and elsewhere, biliary and urinary excretion and, perhaps most important, peripheral inter-conversion of steroids either in the plasma or in the cells of target organs.

In females, nearly all of the active oestrogenic substance, oestradiol, is derived by direct ovarian secretion; a small amount is derived from oestrone, but there is no significant adrenal secretion of this hormone. About a fifth of the circulating oestrone is formed from circulating androstenedione whilst up to a third is derived by conversion from oestradiol; the small amount of circulating testosterone is also formed largely by peripheral conversion from androstenedione, this latter being secreted by both the ovaries and the adrenals.

In males the principal androgens found are, in descending order of biological activity, dihydrotestosterone, testosterone and androstenedione; testosterone is probably secreted solely from the testes whilst androstenedione is derived mainly from the adrenals. The testes secrete only a small quantity of the highly potent dihydrotestosterone, this being largely produced within the cells of target tissues from testosterone.[7] About 20 per cent of the circulating oestradiol in males is derived directly from the testes, the remainder being formed by peripheral conversion from testosterone and oestrone; the circulating oestrone is partly secreted by the adrenals and partly formed by conversion from androstenedione.

In both sexes the circulating sex steroids are largely bound to plasma proteins. Much is bound to albumen which has a high capacity but a low affinity for these steroids whilst both oestradiol and testosterone bind to the same specific beta-globulin which has a high affinity but a low capacity for steroids.[4] Progesterone, androstenedione and testosterone are bound to the same globulin which binds cortico-steroids. The effective concentration of a steroid hormone is a function of the free unbound level which is clearly related to the level of specific sex steroid-binding globulin.

Most steroids are metabolised in the body, principally in the liver, to water soluble conjugates of sulphuric and glucuronic acid; some sulphated conjugates do, however, appear to be secreted directly by the gonads though their function, if any, is obscure.

Gonadal synthesis of sex steroids

The synthesis of gonadal steroid hormones is now, in its broad outlines, reasonably well understood.[18] The pathways of steroid synthesis are similar in the testes and ovaries and are all based on a common carbon skeleton—the perhydrocyclopentenophenanthracene ring in which carbon atoms in three cyclohexane and one cyclopentane nuclei are adjoined (Fig. 2.1). These atoms are

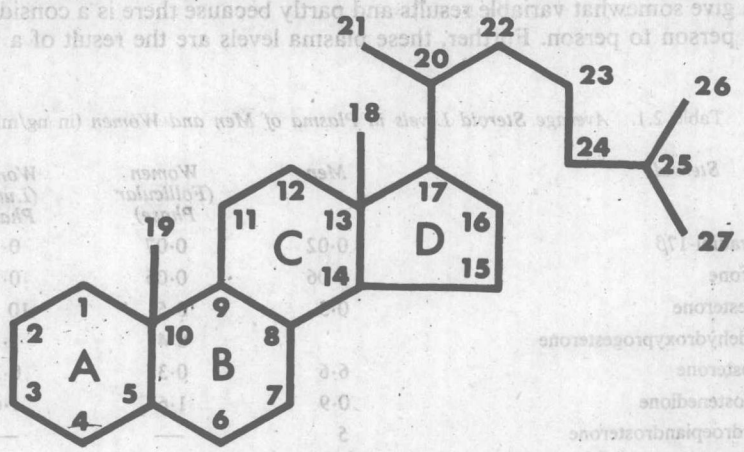

Fig. 2.1. The perhydrocyclopentenophenanthracene ring.