For all these reasons, and because it is stimulating and educational for the doctor undertaking this work, it is felt that there is a real and continuing need for developing methods of collecting such epidemiological and clinical data from general practice.

If such records are to be developed then it is vital that some unified system of recording and nomenclature be devised, and it would be most appropriate that a conference, or some other steps, be organized at which the various interested bodies could inquire into future possibilities.

Summary

A report is presented of five years' work in a London suburban general practice. The importance of studying epidemiological and clinical data from this field lies in the information that can be obtained on the true patterns of disease as they occur in the community.

The basis of research in general practice and elsewhere is a sound system of record-keeping. In general practice any system has to be adapted to the peculiar features of the work. The methods used are described.

Over the period of five years (1952–6) there was a constant rate of attendance, with an average of 3.3 attendances per patient per year. Females were more frequent attenders by 6 : 5. The young (7.5 in infants) and the aged (6.1 in those over 70) required most attention. Almost three out of every four patients are seen each year and over the five years 91% of the practice were attended.

The great value of having full radiological and pathological facilities available is stressed. In any year an average of 13.5% of patients are sent directly for investigations, and a further 7.8% are referred for out-patient consultations and 0.7% for emergency admissions.

Respiratory infections of various types were by far the most common group of diseases seen in this practice, with a rate of 30% of the total. The next most frequent groups were digestive disorders (12%), skin disorders (10%), psychoneuroses (8.5%), "rheumatism" (6.5%), and cardiovascular disorders (6%). The age distributions of these groups are noted and their bearing on aetiology and management is discussed.

Of more importance is a study of the natural patterns of certain specific disorders. In frequency, respiratory infections are most important, but the very appreciable incidence of hypertension, peptic ulcers, and migraine is noted, all with an incidence of over 3%. Examination of epidemiological data on age incidence suggests features that might be of some help in elucidating aetiology and rational management of these common conditions. Thus it is probable that there is a peak level of incidence of the acute respiratory infections in childhood at 5–7 followed by a dramatic decline: this questions the usefulness of some of the more drastic remedies employed. "Hypertension" is so frequent and so symptomless that its abnormality is doubtful in many elderly patients. The natural history of the two psychosomatic conditions, migraine and peptic ulcer, suggests that there might be a tendency towards a spontaneous remission with age.

The need for developing the use of general practice records in the country as a whole is apparent, and steps to encourage these in a uniform manner are suggested.

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GONADAL DYSGENESIS: MODERN CONCEPTS

BY

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The syndrome of gonadal dysgenesis ("ovarian agenesis") has stimulated great interest in recent years. Knowledge accruing from the study of this subject has led to far-reaching developments in the understanding of the general field of sexual differentiation.

In the course of the past three years we have studied a number of patients with this condition. Arising from our investigations we wish to report certain observations.

The Concept of Gonadal Dysgenesis

Three main components make up the full syndrome.

1. *Sexual Infantilism.*—Fundamentally this is due to a failure of gonadal development. The gonads are represented by mere white streaks of primitive tissue lying on the posterior aspects of the broad ligaments. Primary amenorrhoea with failure of secondary sex characters is all but invariable. A raised level of follicle-stimulating hormone (F.S.H.) provides an important diagnostic criterion.

2. *Shortness of Stature.*—The majority of patients are between 4 ft. 6 in. and 4 ft. 10 in. (137 and 147 cm.) in height. This conflicts with the tall, eunuchoid stature generally found in cases of prepubertal gonadal failure. This shortness of stature is generally attributed to a distinct genetic anomaly (Albright *et al.*, 1942b).

3. *Associated Congenital Anomalies.*—A multiplicity of anomalies, affecting almost every organ or tissue of the body, have been described. Webbing of the neck, cubitus valgus, and coarctation of the aorta are the most widely known. These malformational anomalies do not all occur together. Individual patients show varying combinations; in fact, cases of proved gonadal dysgenesis have been noted without obvious congenital abnormalities (del Castillo *et al.*, 1947; Grumbach *et al.*, 1955; Greenblatt *et al.*, 1956).

Nuclear Sexing.—The recent recognition of male nuclear patterns in many anatomically female cases of "Turner's syndrome" (Polani *et al.*, 1954) has been explained in the light of Jost and other workers' experiments on animals (Jost, 1953). They have shown the female form to be basic or neuter, and male differentiation to occur only in the presence of functioning testes during embryonic development. This observation led to the adoption of the term "gonadal dysgenesis" in preference to "ovarian agenesis" and suggested that the syndrome was, in fact, a variety of intersexual development. Grumbach *et al.* (1955) have postulated a relationship between gonadal dysgenesis and male pseudohermaphroditism.

Investigations and Reflections

Twenty-seven cases of gonadal dysgenesis have been seen in the course of the past three years at the Endocrine Clinic, Groote Schuur Hospital. Many patients with primary amenorrhoea are seen and treated at other clinics. The number of cases in this series testifies to the frequency of occurrence of gonadal dysgenesis. The salient clinical features of each case are presented in the Table (see next page).

During the course of this study it became apparent that several concepts required extension.

Gonadotrophin Excretion and Gonadal Dysgenesis

A high level of gonadotrophin excretion is generally accepted as presumptive evidence of the diagnosis. Gonadal dysgenesis, however, occurs not infrequently with low levels of excretion. In the present series, five adult cases did not have increased levels. Several other workers have reported similar results (Dorff *et al.*, 1947; Hertz *et al.*, 1950; Sternlieb *et al.*, 1954; Carpentier *et al.*, 1956). In a separate paper (Jackson and Hoffenberg, 1956) we have suggested that primary pituitary failure during intrauterine life might explain the occurrence of gonadal dysgenesis with low urinary F.S.H. excretion. The animal decapitation experiments of Jost and others may bear some relation to this association.

Findings in 27 Cases of Gonadal Dysgenesis

Case No.	Age	Breasts	Pubic Hair	Axillary Hair	Tests of Adrenal Function	Urinary F.S.H. Excretion	Skin and/or W.B.C. Sexing	Comments	Height	
									in.	cm.
1	18	Flat	+	+	17-K.S. 2·4, 2·6 mg./d. I.T.T., Thorn, normal	+ at 96 m.u.	Male	Webbing of neck, asymmetrical eyes, low hairline. Good response to stilboestrol	56	142
2	17	,,	0	0	17-K.S. 4·2, 5·2 mg./d. I.T.T., Thorn, normal	+ at 192 m.u.	,,	Asymmetry of eyes, strabismus, nystagmus. Slight generalized osteoporosis; 4 lumbar vertebrae	50	127
3	9	Nil	0	0	17-K.S. 6·2, 3·8 mg./d. I.T.T., Thorn, normal Pl. hydrocortisone 4·5 µg.%	+ at 6 m.u. at 9 years	,,	Classical: webbing of neck, low hairline, coarctation of aorta, transient swellings of limbs. At 13 years: few downy pubic hairs; F.S.H. + at 48 m.u. Good response to stilboestrol		
4	16	Flat	Poor	Poor	17-K.S. 7·5 mg./d. Soffer, Thorn, I.T.T., normal	+ at 96 m.u.	Female	Corneal opacities, pigmented moles abundant. Transient hydrarthroses of knees	54	137
5	21	Large, small nipples	,,	0	17-K.S. 6·3, 9·7 mg./d. Soffer, Thorn, I.T.T., normal	− at 6 m.u.	Male	Large breasts (biopsy—fat only); poor nipples. Low F.S.H. Laparotomy: typical vestigial streaks. Later endogenous depression	55	140
6	22	Moderate	,,	0		− at 48 m.u. Two tests	,,	No increase in F.S.H. Breast biopsy done after oestrogen treatment. No anomalies, but pigmented moles plentiful	54	137
7	21	Hypoplastic	+	+		+ at 96 m.u.	,,	Attractive; no anomalies. 5 years of menstruation (oligomenorrhoea). Laparotomy: vestigial streaks. Good response to stilboestrol	58	147
8	30	Nil	+ +	+	17-K.S. 5·9 mg./d.	− at 48 m.u. 3 tests	,,	Manic-depressive psychosis. Moderate osteoporosis	54	137
9	40	Fatty	+	0	17-K.S. 7·2 mg./d. I.T.T., normal	+ at 96 m.u.	,,	Webbing of neck, low hairline. Severe osteoporosis with collapse of vertebrae	54	137
10	14	Nil	0	0	17-K.S. 5·1 mg./d. Thorn, I.T.T., Soffer, normal	− at 6 m.u. 2 tests	,,	Shortness of stature; no anomalies. Too young to assess hypogonadism. Episode of painless swellings of wrists and knees	44	112
11	22	Poor	+	+		+ at 96 m.u.	,,	Hare-lip; pigmented moles abundant; hypoplastic mandible	58	147
12	22	Flat	+	+		− at 96 m.u.	Female	Tall, attractive, "normal." Laparotomy: typical gonadal ridges	66½	169
13	12	Nil	0	0	Pl. hydrocortisone 10 µg./100 ml.	− at 6 m.u.	,,	Typical facies; short metacarpal. Not finally proved	51½	131
14	22	Flat	0	+			Male	Typical: webbing of neck, low hairline. Hypertension without clinical coarctation of aorta. Blue sclerotics	57	145
15	21	,,	0	Poor		37 r.o.u. (N. 8–9)	Female	Short metacarpal; numerous pigmented moles and café-au-lait patches. Blue sclerotics. Laparotomy: typical gonadal streaks	57	145
16	17	,,	Poor	,,			Male	No anomalies	53	135
17	17	Poor	,,	,,	17 K.S. 6·1 mg./d.		,,	No anomalies, but numerous dark facial moles. Laparotomy: typical vestigial streaks	59	150
18	51	Flat	Very poor	0	17-K.S. 6·5 mg./d.	11–12 r.o.u.	Female	Curious facies; shortness of stature. Severe osteoporosis with pathological fracture of femur. No anomalies	60	152
19	9	Nil	0	0			Male	Physical and mental retardation. No anomalies	46	117
20	19	Small	0	0	17-K.S. 5·8 mg./d.		,,	No anomalies. Laparotomy: gonadal streaks—occasional growing follicles	49	124
21	24	Nil	Poor	Poor		14 r.o.u. (N. 7–9)	Female	Shortness of stature. Large clitoris	50	127
22	22	Good	+	+		89 r.o.u. (N. 8–9)	,,	Shortness of stature; no anomalies, good breasts	61	155
23	29	Large	+	+		30 r.o.u. (N. 8–10)	,,	Shortness of stature; no anomalies; good breasts. Several spontaneous periods after 18 years. Laparotomy: typical streaks—few developing follicles	56½	144
24	13	0	0	0			Male	Shortness of stature. Sprengel's deformities of scapulae	51	130
25	23	+	Poor	+		9 r.o.u. (N. 8–9)	Female	No anomalies. Laparotomy: infantile ovaries, scanty follicles	61	155
26	18	Poor	,,	Poor			,,	Shortness of stature; no anomalies. Not proved	57	145
27	13	0	0	0		10 r.o.u. (N. 4–5)	Male	Typical facies		

Abbreviations: 17-K.S. = 17-ketosteroids. I.T.T. = Insulin tolerance test. m.u. = mouse units (Bloomberg *et al.*, 1955). r.o.u. = rat ovarian units (Albert, 1956). N. = normal. Pl. = plasma.

Cortisone and F.S.H. Levels

The effect of cortisone and corticotrophin on urinary F.S.H. excretion has been investigated by several workers (Smith, 1951; Sohval and Soffer, 1951; Maddock *et al.*, 1953). In post-menopausal women with high levels of excretion, it has been found that cortisone administration has little or no depressant effect (Bishop, 1954). Recently Brown (1956) found changes in the ratio of F.S.H. to I.C.S.H. (interstitial cell-stimulating hormone) excretion, but the alteration in total gonadotrophin output was neither striking nor constant.

Cortisone, 100 mg. daily for 10 days, was administered to several patients in this series whose initial F.S.H. readings were high; no marked alteration in these readings was detected; in some the levels seemed to become higher. This finding in gonadal dysgenesis lends support to the view that cortisone in this dosage exerts no measurable suppressive effect on the pituitary gland with regard to its production of F.S.H.

Congenital Anomalies of "Turner's Syndrome"

In the diagnosis of gonadal dysgenesis considerable stress has been placed on the presence of certain congenital anomalies. The most notable of these include webbing of the neck, cubitus valgus, pes cavus, abnormalities of the cervical vertebrae, ribs, palate, fingers, eyes, and ears, the presence of pigmented moles and naevi, and, in particular, coarctation of the aorta. In the present series the relative infrequency of these phenomena has been striking.

Thus coarctation of the aorta was found in only one instance, webbing of the neck in four (Fig. 1), and cubitus valgus of minor degree in one. This latter anomaly presents particular difficulties, since very minor flexion of the elbow-joint allows considerable abduction of the forearm, which can closely simulate cubitus valgus in a photograph. Does this anomaly really exist in this syndrome? It appears that increasing familiarity with the vagaries of gonadal dysgenesis permits the diagnosis to be made more commonly: the incidence of the accepted anomalies thus diminishes.

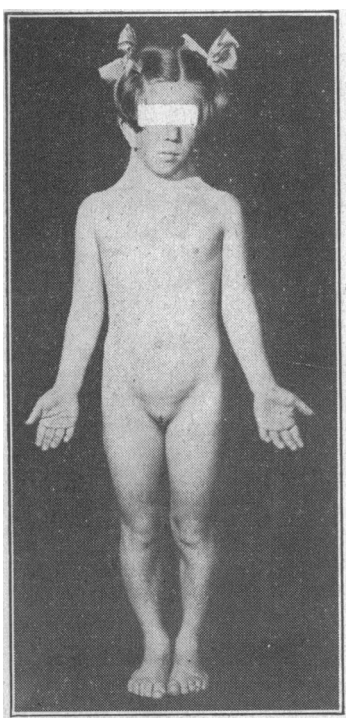

FIG. 1.—Case 3. A "classical" example of gonadal dysgenesis.

It is interesting to note two patients in the series with short metacarpal bones. In neither case was there a familial incidence of this anomaly, which has previously been described, particularly in the syndrome of pseudohypoparathyroidism (Albright *et al.*, 1942a). A case reported by Ezès (1949) showed the same defect.

Three patients gave a history of swellings or localized oedema. Case 3 had transient unexplained swellings of the limbs which persisted up to the age of 13; Case 4 suffered from intermittent hydrarthroses of the knees; Case 10 had an undiagnosed episode of swellings affecting the knees and wrists. These swellings are well documented in relation to gonadal dysgenesis (Silver, 1951; Haney, 1952; Skjelbred, 1953; Vulliamy, 1953; Keay and Lewis, 1954; Russell *et al.*, 1955; Barlow and Levin, 1955; Oberman, 1955); they have also been recognized as part of certain malformational syndromes affecting the musculo-skeletal system (described by Rossi and Caflisch, 1951).

Breast Development

Five patients in this series had good breast development when they first presented. One had received oestrogen therapy previously; the other four had not taken any endocrine preparations. Several cases with good breast development have been described (Wilkins and Fleischmann, 1944; Lisser *et al.*, 1947; Hertz *et al.*, 1950), although this is not to be expected in the absence of oestrogenic stimulation. As this finding seemed anomalous it was decided to perform biopsies of the breasts in two patients. In each case a representative core was taken from the central part of breast at depth. In the patient who had not taken oestrogen (Case 5, Fig. 2) her apparently normal breasts consisted of fat only, with no evidence of functioning mammary tissue. The breasts of the other patient (Case 6) showed some lobulation and "evidence of cyclical activity"; this biopsy was taken after a period of oestrogen therapy and the changes may reflect the influence of this hormone.

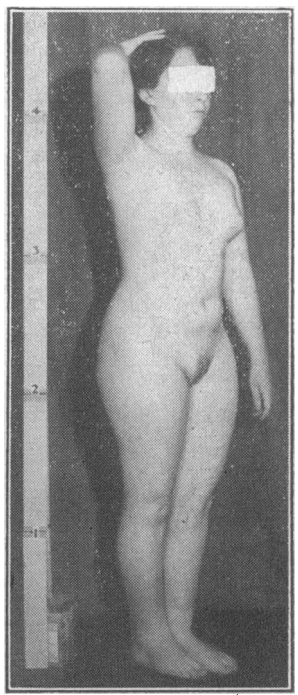

FIG. 2.—Case 5. Apparently well-formed breasts consisted of fat only on histological examination.

It is interesting that no functioning mammary tissue was found in a large biopsy specimen from the apparently well-developed breasts of Case 5. It is conceivable that in other reported cases the breasts have contained true glandular tissue, but biopsy data do not seem to be available. Evidence exists for some oestrogen secretion in occasional cases of gonadal dysgenesis. Whether this is derived from the adrenal glands or the primitive gonads is a matter for speculation.

Axillary Hair and Adrenal Function

Many, but not all, patients with gonadal dysgenesis show diminution or absence of pubic and axillary hair. Seven patients in this series had good sexual hair growth. It is commonly held that axillary hair is dependent on adequate adrenocortical function (Albright *et al.*, 1942b). In consequence it has been suggested that adrenocortical dysfunction exists in gonadal dysgenesis. We have attempted to assess adrenal function by means of Thorn* and Soffer tests, insulin tolerance tests, and determination of 17-ketosteroid excretion and plasma hydrocortisone levels. In patients so tested the results were normal (see Table) even where sex hair was deficient.

A case of "oestrogen-producing testes" (syndrome of Goldberg and Maxwell, 1948) has been tested in the same way and also failed to demonstrate adrenocortical impairment. In this syndrome the lack of sex hair is thought to be due to an end-organ failure (on the part of the hair follicles), and it has been suggested that this unresponsiveness is a genetic anomaly (Wilkins, 1950).

It is interesting that neither gonadal dysgenesis nor the syndrome of oestrogen-producing testes manifests adrenocortical dysfunction. In the latter syndrome the absence of sex hair is interpreted as a congenital anomaly. Is the hairlessness in gonadal dygenesis another congenital anomaly—like the others, erratic in its occurrence?

*Thorn tests included the response of the eosinophils, 17-ketosteroids, and, in some cases, 17-ketogenic steroids also to the intravenous injection of corticotrophin.

Osteoporosis in Gonadal Dysgenesis

Many authors have commented on slight osteoporosis in gonadal dysgenesis (Albright *et al.*, 1942b; Wilkins and Fleischmann, 1944; Lisser *et al.*, 1947; del Castillo *et al.*, 1947; Skjelbred, 1953; Jackson and Sougin-Mibashan, 1953). Marked osteoporosis seems to have been described only once—in a patient who also showed hypocalcaemia and tetany (Geffen, 1956).

In the present series three patients showed moderate to severe osteoporosis. Case 8 sustained a fractured vertebra during the course of electric convulsion therapy; her *x*-ray pictures revealed moderate diffuse osteoporosis. Two older patients (Case 9 (Fig. 3), aged 40, and Case 18, aged 51) had severe osteoporosis, with multiple vertebral collapse and, in Case 18, fracture of the femoral neck from slight trauma.

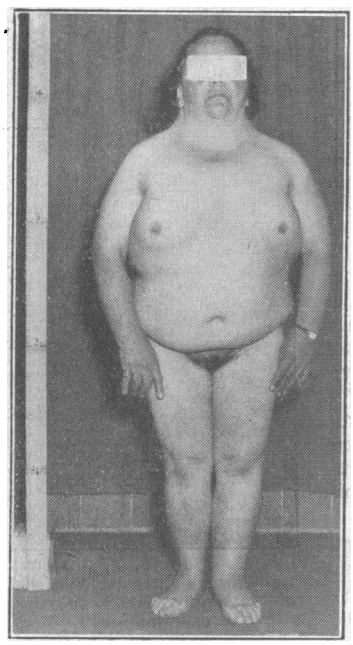

FIG. 3.—Case 9. Classical gonadal dysgenesis in an older patient.

The osteoporosis is generally attributed to oestrogen lack, analogous to the common form of post-menopausal osteoporosis. There is another possible explanation. Osteogenesis imperfecta tarda has been described as one of the congenital anomalies associated with gonadal dysgenesis (Lisser *et al.*, 1947; Oberman, 1955). Two patients in this series (Cases 14 and 15) showed strikingly blue sclerotics, but did not show "thin" bones. Many authorities regard osteogenesis imperfecta as a type of congenital osteoporosis (Dent, 1955). If the osteoporosis of gonadal dysgenesis is due to oestrogen lack, why does it not occur more commonly? Is it, instead, an associated congenital anomaly (that is, an incomplete form of osteogenesis imperfecta)? This may explain its capricious occurrence. Against this theory is the fact that inadequate bone formation is obvious at an early age in osteogenesis imperfecta; in gonadal dygenesis the osteoporosis is slight in young patients, severe degrees having been described only in older patients. This suggests a progressive lesion compatible with sustained sex-hormone lack.

"Ovarian Stroma," Follicles, and Clitoral Enlargement in Gonadal Dysgenesis

Ovarian Stroma

The histological reports on the gonads of three patients in this series refer to the presence of "adult ovarian stroma." While some authorities deny a distinction between ovarian and testicular stroma (Grumbach *et al.*, 1955), others accept that the two types are different. Gordan *et al.* (1955) found the female type of stroma in two cases with androgenic manifestations; Greenblatt and Carmona (1955) and Russell *et al.* (1955) report similar histological appearances in two patients, one of whom showed a male nuclear pattern. At first glance it appears curious that gonads which are testicular vestiges should show an ovarian type of stroma. But, possibly, in the absence of testicular function, the gonadal stroma shares the propensity of the rest of the genital tract towards feminization. In other words, the testis may exert a local effect on its own stroma which renders it distinctive.

Follicles

The vestigial streaks of gonadal dysgenesis do not show a uniform histological appearance. The most primitive have been composed of stromal tissue without primordial follicles; in others there has been more mature development with tunica albuginea, primordial follicles, and follicular cysts (Russell *et al.*, 1955; Kerkhof and Stolte, 1956). Presumably some ovarian maturation had occurred before development was interrupted by the responsible agent (genetic or acquired intrauterine). These latter subjects should show female chromatin patterns, since the gonads appear to be immature ovaries. In Case 20 growing follicles were seen; yet skin biopsy showed a male nuclear pattern. If these gonads were destined to be testes why did ovarian maturation ensue? Elsewhere we have outlined a theory which may answer this problem (Hoffenberg and Jackson, 1957b). In this theory we have postulated the existence of evocators which are responsible for differentiation of the primitive gonadal streak into testis or ovary. In Klinefelter's syndrome with female nuclear sex we suggested incorrect "male" evocation of the genetically female embryo to account for the development of testes. In Case 20 one could postulate abnormal "female" evocation in a genetic male: ovaries develop instead of testes: these ovaries are immature, as are the testes in Klinefelter's syndrome. The patient is thus genetically male (chromatin pattern), with partially developed ovaries; in reverse, the Klinefelter patient is genetically female with partially developed testes.

Clitoral Enlargement

Greenblatt *et al.* (1956) report the case of a patient with gonadal dysgenesis (proved by laparotomy), a large clitoris, and a female skin sex. Case 21 shows the same set of circumstances. On the theories of Grumbach *et al.* (1955) gonadal dysgenesis with androgenic manifestations—for example, clitoral enlargement—is really a variety of male pseudohermaphroditism in which the clitoral enlargement is thought to be a subtle token of the original genetic maleness of the subject. As in this form of intersex, these patients should show the male chromatin pattern. Yet in the two cases cited above a female nuclear pattern was found.

Clitoral enlargement implies androgen production. As the adrenal glands are not likely to be the source it must then be derived from the gonads. If these gonads are vestigial ovaries—as would be expected from the female chromatin pattern—then they constitute a variety of "androgen-producing ovaries" (the antithesis of "oestrogen-producing testes"). If, however, the gonads are vestigial testes, one can again invoke the influence of abnormal evocation to account for the presence of "testes" (albeit vestigial) in a genetic female. This condition may thus be an "early stage" of Klinefelter's syndrome: A genetic female, under the influence of a male evocator, develops testes. These fail at an early intrauterine age, so that feminization ensues; the failure, however, is incomplete, as evidence of some androgen production is provided by the clitoral enlargement. In some cases of Klinefelter's syndrome a genetic female is influenced by a male evocator; the resulting testes are less completely damaged (perhaps later); male body development (sometimes eunuchoidal) is permitted, but testicular abnormality is evident both clinically and histologically.

Menstruation in Gonadal Dysgenesis

Isolated patients with gonadal dysgenesis have been reported with scanty menstrual bleeds. Albright *et al.* (1942b) refer to a 21-year-old girl with a slight bloody vaginal discharge on a few occasions. Similar slight bleeds have been reported by Varney *et al.* (1942) and Lisser *et al.* (1947). Briggs and Kupperman (1956) refer to "a woman with amenorrhoea and the neck webbing typical of Turner's syndrome, who could not be said to have true gonadal dysgenesis since spontaneous menstruation had occurred in the past." The validity of this conclusion might be questioned in view of our experience.

In our series three patients claimed to have menstruated. In one instance this consisted of a single "show" lasting one day. Case 23 had several spontaneous bleeds. Case 7 stated that she had menstruated for five years from the age of 15, bleeding having occurred at one- to three-monthly intervals. Blood loss generally extended over three days, was moderate in amount, and unassociated with abdominal cramp or discomfort. Urinary F.S.H. excretion was raised and gonadal dysgenesis was proved by laparotomy with bilateral gonadal biopsy. The skin and leucocyte pattern was male. This patient has been reported elsewhere and the implications of her story have been discussed (Hoffenberg *et al.*, 1957).

Gonadal Dysgenesis in Normal-looking Females

Attention has already been drawn to the comparative infrequency of the classical type of gonadal dysgenesis in our series. Case 12, whose case has been reported (Hoffenberg and Jackson, 1957a), appeared to be a normal thin female with poor breast development; there were no obvious congenital anomalies; she was not short; F.S.H. excretion was not raised; skin sex pattern was female. Yet laparotomy disclosed the typical primitive streak of gonadal dysgenesis. Similar patients have been reported by others (Swyer, 1955; Sun and Rakoff, 1956; Greenblatt *et al.*, 1956).

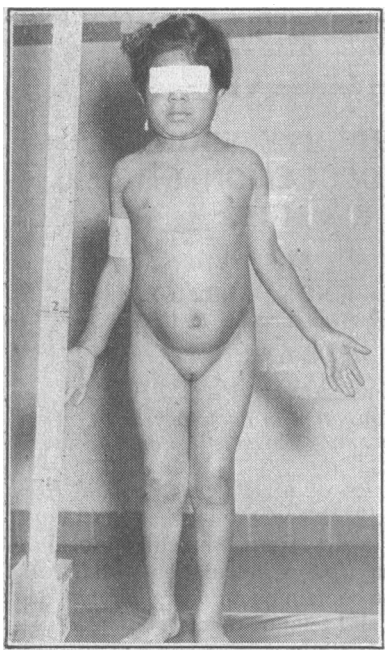

FIG. 4.—Case 10. Gonadal dysgenesis in a young patient with no anomalies.

Several other patients in this series appeared quite normal except for shortness of stature (Fig. 4). We wish to emphasize that gonadal dysgenesis must be considered as a cause of primary amenorrhoea, whatever the appearance of the patient.

Diagnosis of Gonadal Dysgenesis

From a consideration of our series and the cases reported in the literature it has become clear that many of the classical criteria need not obtain. Patients need not be short nor unattractive; axillary and pubic hair may be luxuriant and adrenal function unimpaired. The congenital stigmata of Turner's syndrome are often absent and good breast development may be found. The urinary gonadotrophin excretion need not be raised, and we have found the syndrome in a patient who claims to have menstruated for five years.

The diagnosis depends on a high index of suspicion. Gonadal dysgenesis appears to be the commonest cause of (1) primary amenorrhoea regardless of the patient's appearance; and (2) marked shortness of stature in the absence of gross disease or skeletal dysplasia.

Nuclear sexing (if male) probably provides the most reliable diagnostic criterion short of laparotomy. Few other conditions present the combination of male nuclear sex and female appearance: (1) Few reports are available of genetic sexing in true hermaphrodites. It is possible that a male nuclear pattern might be found in a patient with "normal" or "near-normal" female external appearance. (2) Male pseudohermaphroditism with bilaterally undescended testes may simulate gonadal dysgenesis with a large clitoris. Since these two conditions are regarded as extremes of the same aetiological spectrum (Grumbach *et al.*, 1955) this distinction is largely academic. (3) The syndrome of oestrogen-producing testes presents a distinctive clinical picture which makes the diagnosis ineluctable.

Apart from these few exceptions the diagnosis of gonadal dysgenesis is virtually certain in individuals with female appearance whose nuclear patterns are male.

The place of *urinary F.S.H. excretion* in diagnosis has already been discussed. Low levels are not of value in excluding gonadal dysgenesis. High levels indicate primary gonadal failure, but not its cause. Thus acquired prepubertal ovarian failure—for example, due to mumps—cannot be excluded. But such a patient should develop the tall eunuchoid proportions that generally accompany primary prepubertal hypogonadal states. The absence of this type of body build in an adult patient with prepubertal hypergonadotrophic gonadal failure therefore strongly suggests gonadal dysgenesis, in which shortness of stature is thought to be a separate linked congenital anomaly. For this reason four patients are included in this series despite lack of absolute proof of the diagnosis (Cases 13, 18, 22, and 26). Familiarity with the vagaries of the syndrome, coupled with knowledge of its prevalence, makes it likely that gonadal dysgenesis is the correct diagnosis in each of these patients. Laparotomy, vaginal culdoscopy, or peritoneoscopy is necessary finally to confirm or refute this conclusion.

Treatment of Gonadal Dysgenesis

Treatment cannot give function to the primitive gonads; but one can do much to aid the patient.

1. *Psychological Management.*—In an excellent psychological study Hampson *et al.* (1955) have shown that patients with gonadal dysgenesis are female in orientation irrespective of their chromosomal patterns. Support for this view is derived from experience with the present series. In fact two of our patients have married and apparently enjoy good female-type libido. Care must be taken to ensure that patients understand the basic physiological defect, which precludes any hope of pregnancy. Certainly the finding of a male chromosomal pattern should be withheld from patients and relatives, since this information can only give rise to distress and confusion. Therapy must be directed towards further feminization of these neuter individuals.

2. *Oestrogens.*—Even small doses (0.5–1 mg. of stilboestrol daily for three to four weeks, alternating with gaps of one week) assist by stimulating mammary growth, feminizing the body contours, producing cyclical menstrual bleeds, and furthering the development of the uterus and vagina. Premature ageing, osteoporosis, and possibly coronary atheroma may be prevented. Gratifying results have been obtained in all patients treated in this way. A very striking result of treatment has been the claim of many patients and their relatives that oestrogens have stimulated greater energy, drive, and enthusiasm. It is probably undesirable to administer oestrogens before the age of 12, in view of the psychological effect of mammary growth and menstrual bleeds. We believe, without final proof, however, that small doses of oestrogens may help a little in increasing height, so that this hormone should certainly be given before the time of epiphysial closure draws near. Recently it has been suggested that oestrogens strongly stimulate epiphysial closure and thus cause ultimate shortness of stature (Escamilla, 1956). For this reason larger doses should not be employed. A very considerable darkening of nipples and areolae (and sometimes of facial colour) usually develops shortly after oestrogens have been started. In two cases the colour has reverted to normal on continuation of the same dosage. An occasional difficulty is the development of intermenstrual discharge. This usually goes away

after a time in any event, but the oestrogen dosage may be halved or temporarily abandoned if desired. The further addition of progesterone does not appear to have any value in the treatment of gonadal dysgenesis.

Conclusions and Summary

A series of 27 patients with gonadal dysgenesis is presented. The absence of raised levels of urinary gonadotrophin excretion in this syndrome is shown to be a not uncommon finding. Cortisone was found not to reduce high excretions of gonadotrophin when these were present.

Attention is drawn to the comparatively infrequent occurrence of the classical congenital anomalies of "Turner's syndrome." Scepticism is expressed about the existence of cubitus valgus. Several patients in this series had good breast development when they were first seen. Biopsy in one untreated patient showed the breasts to consist of fat only. Tests of adrenocortical function displayed no impairment—even where sex hair was deficient. This tends to refute the view that the adrenal cortex alone governs axillary hair growth. Three cases are described in which moderate-to-severe osteoporosis occurred. This finding is discussed.

The presence of "ovarian stroma" and developing follicles on histological examination of the gonadal streaks is considered in relation to nuclear sexing of these patients. The anomalous finding of clitoral enlargement in "genetic" females is mentioned. Reference is made to patients who claim to have menstruated and to "normal-looking females" with gonadal dysgenesis.

The diagnosis of gonadal dysgenesis is discussed with particular reference to nuclear sexing. It is pointed out that this syndrome is probably the most common cause of primary amenorrhoea—whatever the appearance of the patient.

The treatment of gonadal dysgenesis is outlined.

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MORBIDITY FROM T.A.B.T. INOCULATION IN R.A.F. RECRUITS

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Several clinicians at Royal Air Force schools of recruit training have gained the impression that a variety of morbid conditions, apart from immediate local and general reactions, may follow inoculation with T.A.B.T (a phenolized vaccine containing *Salmonella typhi, Salm paratyphi A* and *B*, and tetanus toxoid).

Robertson and Leonard (1956) stated that the conditions usually affected the joints and reticulo-endothelial system, and very occasionally seemed to initiate a cycle of events leading to a syndrome resembling the "collagen disorders." They suggested that infective conditions of all kinds, including upper respiratory infections, were more common during the seven to ten days following inoculation. They postulated that "all the immunological processes are disturbed at this time, giving rise to a general lowering of resistance to infection." These claims clearly called for a full investigation, for if they were substantiated the justification for routine inoculation of Service personnel would need careful reconsideration. This paper reports the results of such an investigation, carried out at five R.A.F. schools of recruit training over a period of one year. The opportunity was also taken to record the incidence of local and general reactions following inoculation.

Materials and Methods

At each of the five centres arrangements were made for recruits with even Service numbers to receive the usual doses of T.A.B.T. (0.5 ml. subcutaneously followed by 1 ml. four to six weeks later), and for those with odd numbers to be left uninoculated until arrival at their next unit. Both groups continued to be vaccinated against smallpox. Special records of sickness were kept on all recruits during their eight weeks of training, and a pathologist (J. D. E. K.) was