positive Valsalva test, a patent foramen ovale was suspected. She died later from congestive cardiac failure, and post-mortem examination revealed a moderate-sized patent foramen ovale in addition to changes associated with pure pulmonary hypertension.

We have little experience in the use of the oxymeter tests in patients with cyanotic congenital heart disease, but preliminary work suggests that Fallot's tetralogy may be associated with a characteristic pattern of changing arterial oxygen saturation during Valsalva's manœuvre. One possible source of confusion in interpreting results from such patients may occur from individuals with cyanosis due to lung disease. We have found that patients with cor pulmonale and central cyanosis who perform Valsalva's manœuvre alter their arterial oxygen saturation considerably. During Valsalva's manœuvre the breath-holding that is entailed is associated with a fall in arterial oxygen saturation. Following the manœuvre the arterial oxygen saturation rises again, and often exceeds the resting value temporarily. This is probably due to hyperventilation that occurs as soon as the test is completed.

Conclusion

The oxymeter tests described appear to be both simple and reliable for demonstrating the presence of an atrial septal defect or patent foramen ovale. Having established the conditions under which the tests can be relied upon, we feel that it is not strictly necessary to record either the oesophageal pressure or brachial artery pressure provided that one is careful to follow a routine to eliminate false-negative results. We therefore record the arterial oxygen saturation with the ear oxymeter during Valsalva's manœuvre at rest. If the test is negative it is repeated after exercise; if a negative response is still obtained, then the Müller procedure, followed by elevation of the patient's legs, is carried out. In this way what appears to be an extremely reliable test is available for use in the clinic, with symptom-free patients of any age suspected of having an interatrial communication. The youngest child we have studied was 3½ years old.

We have so far not encountered an incorrect response to the tests in any patient in whom the diagnosis was proved by alternative means. In addition, an atrial septal defect was demonstrated by the tests in three patients in whom catheter data were equivocal, and confirmed the absence of an atrial septal defect in two patients with anomalous pulmonary venous drainage, where atrial defects could not be definitely excluded from catheter data. Provided that balanced pressures between the right and left ventricles do not exist, the tests appear to be negative with ventricular septal defects; and the response pattern also appears to be different in the few cases of Fallot's tetralogy so far studied. We are also studying a group of normal subjects after exercise to discover whether it is possible to recognize those who have a persistent foramen ovale.

Finally, we would like to express our gratitude to Dr. Raymond Daley and Mr. Kent Harrison, who allowed us to study patients in whom they had established an anatomical diagnosis by cardiac catheterization or at subsequent thoracotomy. This information formed the main evidence that the oxymeter test was a reliable procedure for diagnosis of inter-atrial communication.

Summary

Thirty-two patients suspected clinically of having atrial septal defects have been studied by means of the ear oxymeter during the performance of Valsalva's manœuvre.

Twelve of these patients in whom the diagnosis was proved by cardiac catheterization or thoracotomy had characteristic and reproducible changes in arterial oxygen saturation during and following Valsalva's manœuvre.

If the defect was small, exercise prior to Valsalva's manœuvre was required in order to obtain a positive oxymeter response.

Fourteen further patients gave positive oxymeter responses to the Valsalva test. These patients had catheter evidence of a left-to-right shunt at the atrial level but definite anatomical proof of an atrial septal defect was lacking. One patient with pulmonary hypertension, who became cyanosed on exertion and in whom cardiac catheterization was unhelpful in locating the site of the shunt, gave a positive response to the Valsalva test. Subsequent post-mortem examination revealed a patent foramen ovale.

Five patients gave a negative response to the Valsalva test. Two of these were subsequently found to have partial anomalous pulmonary venous drainage but no atrial septal defect. One patient had a ventricular septal defect; and two patients had congestive cardiac failure associated with atrial septal defects.

In the patients with atrial septal defect and cardiac failure, Müller's manœuvre or elevation of the legs caused a fall in systemic arterial oxygen saturation, enabling the correct diagnosis to be made.

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GONADAL DYSGENESIS IN NORMAL-LOOKING FEMALES

A GENETIC THEORY TO EXPLAIN VARIABILITY OF THE SYNDROME

BY

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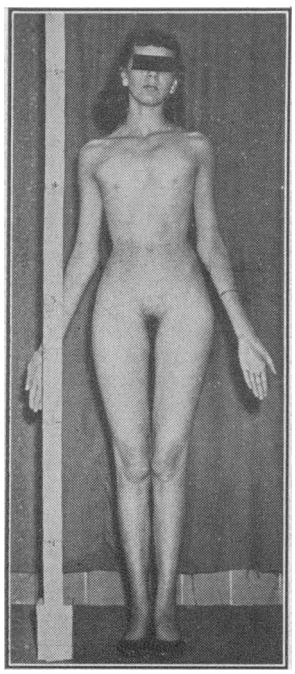
Swyer (1955) described two cases with an unusual clinical picture under the heading of "Male Pseudohermaphroditism: A Hitherto Undescribed Form." Briefly, these patients showed normal height with eunuchoidal proportions, female appearance, and female genitalia. They did not develop secondary sexual characters nor did they menstruate. Their nuclear pattern was male. They had no congenital anomalies of the Bonnevie–Ullrich–Turner type. Attempts to place these two patients into one of the recognized categories of intersex appear to have failed. In the *Year Book of Endocrinology, 1955–1956*, a précis of Swyer's paper is followed by an editorial comment which confirms this dilemma.

It is our contention that these patients suffer from a variant of the syndrome of gonadal dysgenesis. We present the case report of a patient showing a similar clinical picture but with female "genetic sex" in whom the presence of dysgenetic gonads was demonstrated at laparotomy.

Case Report

An attractive female school-teacher aged 22 presented with primary amenorrhoea. Her height was 66½ in. (169 cm.) and span 69 in. (175 cm.), and, apart from complete lack of breast development and eunuchoid proportions, she appeared a perfectly normal female (see illustration). Axillary and pubic hair were moderately profuse. The vagina was small, the clitoris not enlarged, and the uterus infantile on palpation; adnexae could not be felt.



Note eunuchoidal proportions and lack of breast development.

The family history was not contributory. There was no history of mumps or of other significant illness. The patient had not experienced hot flushes. The psychological orientation was completely female following a normal female upbringing and education.

The urinary gonadotrophin (F.S.H.) excretion was strongly positive at 6 mouse uterine units, but negative at 96 mouse units. A skin biopsy showed a normal female nuclear pattern.

At laparotomy typical primitive gonadal ridges were disclosed. Histology showed ovarian stroma, no follicles, but aggregates of cells resembling ovarian hilar cells (Dr. C. J. Uys).

Cyclical oestrogen therapy (1 mg. of stilboestrol daily) was instituted after the operation. Six months later the patient was extremelv pleased with the results: her breasts had grown considerably; monthly bleeding had ensued; the vagina had increased in size; general feminization of the contours had occurred; and she was engaged to be married.

Vagaries of Gonadal Dysgenesis

Several major advances over the past few years have widened the original concept of "ovarian agenesis." It has been recognized that patients may lack many of the classical features which have been associated with the syndrome. There are numerous reports of tall patients and even of attractive ones (Wilkins and Fleischmann, 1944; Lisser *et al.*, 1947; del Castillo *et al.*, 1947; Kerkhof and Stolte, 1956; Greenblatt *et al.*, 1956; Hoffenberg and Jackson, 1957), axillary and pubic hair are often normal in amount or even luxuriant (Hoffenberg and Jackson, 1957). The congenital anomalies of Turner's syndrome need not be present (del Castillo *et al.*, 1947; Grumbach *et al.*, 1955; Greenblatt *et al.*, 1956) and good breast development has been reported (Varney *et al.*, 1942; Wilkins and Fleischmann, 1944; Lisser *et al.*, 1947; Hertz *et al.*, 1950; Hoffenberg and Jackson, 1957). The urinary gonadotrophin, while generally high, may be normal or low (Dorff *et al.*, 1947; Hertz *et al.*, 1950; Sternlieb *et al.*, 1954; Carpentier *et al.*, 1956; Hoffenberg and Jackson, 1957); cases have been described with androgenic manifestations (Gordan *et al.*, 1955; Greenblatt *et al.*, 1956), and one proved case showed pseudohermaphroditic external genitals (Grumbach *et al.*, 1955); finally, we have encountered two patients who claimed to have menstruated for five and six years respectively (Hoffenberg *et al.*, 1957). The skin sex pattern in gonadal dysgenesis may be male or female.

Our patient showed no recognizable congenital anomalies; she appeared, in fact, to be a normal thin female with poor breast development. Her F.S.H. excretion was not raised and her skin sex pattern was female. Yet, at laparotomy, typical dysgenetic gonads were found.

Sun and Rakoff (1956) include in a series of 15 patients with gonadal dysgenesis one who was 64 in. (162.5 cm.) tall and had normal skeletal proportions. She, however, had a high urinary F.S.H. excretion, and the diagnosis was confirmed at laparotomy.

Greenblatt *et al.* (1956) refer to another tall patient without the anomalies of Turner's syndrome, but with poor breasts, primary amenorrhoea, and otherwise normal female appearance, except for enlargement of the clitoris; her urine F.S.H. excretion was normal and skin sex was female. The diagnosis of gonadal dysgenesis was proved in this patient at laparotomy. Our patient displayed an almost identical picture. There was, however, no clitoral enlargement.

Reconsideration of Swyer's Cases

The two patients described by Swyer were apparent females with primary amenorrhoea; they had poor mammary development, eunuchoidal proportions, and normal axillary and pubic hair. The external genitalia were normal, except for clitoral enlargement in one. Each displayed a rudimentary uterus, a normal, non-oestrinized vagina, normal cervix, and apparently normal oestrogen levels. F.S.H. excretion was normal in one, low in the other. Blood smears showed a male pattern in both. Laparotomy was not performed.

Swyer considers gonadal dysgenesis in the differential diagnosis. He dismisses the condition on the grounds of numerous distinctions between his patients and those with the hitherto-accepted classical syndrome. However, in the light of the cases reported above, including our own, it is apparent that his cases differ in no specific manner from the less common variants of gonadal dysgenesis. The Table summarizes the salient features of "classical" gonadal dysgenesis, atypical gonadal dysgenesis, Swyer's "new" syndrome, and "classical" male pseudohermaphroditism. From a perusal of this Table it becomes apparent that Swyer's cases are, in fact, variants of the syndrome of gonadal dysgenesis. The difficulty in classification has arisen because his cases showed a number of atypical features, all of which have been described separately in other patients.

Genetic Considerations

These atypical cases of gonadal dysgenesis require some aetiological explanation. It has been suggested that the general Bonnevie–Ullrich–Turner syndrome might be produced by a primary intrauterine disturbance during early foetal life (Grumbach *et al.*, 1955). On the other hand, the type, multiplicity, and comparative constancy of the clinical features suggest that a genetic aberration is more likely. Thus this kaleidoscopic syndrome would resemble such states as mongolism, the Laurence–Moon–Biedl syndrome, and osteogenesis imperfecta, all of which show combinations of genetically determined anomalies. If the syndrome were caused by a mutation of dominant type occurring in one gene or in several closely related genes of a parental germ cell, no hereditary tendency could be observed because of the essential infertility of the sufferers.

This conception is supported by Rossi and Caflisch (1951), who demonstrate beyond all doubt the hereditary nature of the various skeletal anomalies of the pterygium and Bonnevie–Ullrich syndromes, which are variably embodied in Turner's syndrome. Indeed, in some of the families they describe, cases of infantilism—that is, gonadal dysgenesis—actually appear together with non-infantilistic siblings who have, for instance, webbed neck, but who are capable of reproduction. The authors adduce evidence of direct parent–child transmission of anomalies, and claim, apparently on excellent grounds, that the hereditary trait concerned is dominant, of high penetrance, and of variable expressivity. Further confirmation of the hereditary nature

Varieties of Gonadal Dysgenesis and Classical Male Pseudohermaphroditism Compared

	Stature	Congenital Anomalies	Breasts	Sex Hair	Vagina	Cervix	Chromosomal Sex	Gonadotrophins	Oestrogen	Gonads
"Classical" gonadal dysgenesis	Short	Usual	Undeveloped	Usually scanty	Infantile	Infantile	Male or female	High	Low	Primitive streaks
Atypical gonadal dysgenesis	May be tall or normal height	Often absent	Usually undeveloped	May be normal	Small or normal	Infantile or normal	Male or female	High, normal, or low	Normal or low	May show some development
Swyer's "new" syndrome	Tall or normal	Absent	Undeveloped	Within normal limits	Normal unoestrogenized	Normal	Male	Normal	Apparently normal	?
Classical male pseudohermaphroditism	Normal or tall	"	Variable	Absent or scanty	Short; may be oestrogenized	Minute or absent	"	"	Low	Developed testes

of this syndrome is provided by the report of its occurrence in sisters (Davidson and Smith, 1956) and in twins (Solis and Schwartz, 1951).

It would seem possible to explain the varieties of this syndrome by postulating three closely connected genes situated on the same chromosome: one gene for infantilism —that is, intrauterine hypogonadism—called "I"; one gene for shortness of stature, "S"; and one gene or gene-complex for the various anomalies of musculo-skeletal, cardiac, cutaneous, renal, ocular, and other systems, "A." It is evident that the genetic factor A is very variable in its expressivity, since several different anomalies usually occur together, but never all in the same person. Now, if we imagine either that these three factors are not invariably inherited together or, alternatively, that they always occur together, but that the penetrance of each is not 100%, we can account for the complete syndrome and for the various partial ones. We thus have:

I+S+A (in genetic male or female)=Full Turner's syndrome.

S+A=Pterygium and other developmental syndromes, with short stature and normal sexual differentiation (Rossi and Caflisch, 1951).

A alone=Pterygium and other syndromes, with normal stature (Rossi and Caflisch, 1951).

I+S="Normal-looking" Turner's syndrome; with shortness of stature, infantilism, but no anomalies (Grumbach *et al.*, 1955; Hoffenberg and Jackson, 1957).

I alone=Apparent females of normal height with amenorrhoea and no anomalies (Swyer, 1955; Greenblatt *et al.*, 1956; Sun and Rakoff, 1956; and our case reported above). Nuclear sex may be male or female.

Grumbach *et al.* (1955) apply the experimental results of Jost and other workers to the problem of human intersex. The infantilism in gonadal dysgenesis results from very early failure of the developing gonad (our factor "I"), with consequent feminization of genital tract and body form. If gonadal failure occurs at a slightly later stage of male embryonic development, partial differentiation along masculine lines will already have taken place. Further development of the genital tract will be of female type, and so "male pseudohermaphroditism" will result. This is equivalent to our factor "I" coming into operation at a slightly later stage. Thus:

I alone (slightly later in genetic male)=Male pseudohermaphroditism.

I (slightly later in genetic male)+S+A=Male pseudohermaphroditism with short stature and anomalies (Grumbach *et al.*, 1955).

Stature in Gonadal Dysgenesis

The shortness of stature which is seen in most cases of gonadal dysgenesis conflicts with the tall eunuchoid proportions generally associated with prepubertal gonadal failure. It is best regarded as a distinct genetic anomaly. To test the validity of this hypothesis we have reviewed the reported cases of gonadal dysgenesis without shortness of stature.

Varney *et al.* (1942) describe the case of a patient 6 ft. (183 cm.) tall, with "eunuchoid elongation of the extremities." They also refer to patients reported by Pela in 1935 and Humphrey—the former 5 ft. 10 in. (178 cm.) tall with "long extremities," the latter 5 ft. 6½ in. (169.5 cm.) with "eunuchoid skeletal proportions." Wilkins and Fleischmann (1944) refer to a patient (reported by Kaliga) who was 5 ft. 9 in. (175 cm.) tall with "eunuchoid proportions." Del Castillo *et al.* (1947) cite a patient, 5 ft. 5½ in. (166 cm.) tall with the same arm-span. Greenblatt *et al.* (1956) state that their 5 ft. 10 in. (178 cm.) tall patient "resembles the tall eunuchoid male in appearance."

Of Swyer's two cases, the first is stated to have "definitely eunuchoid proportions," the second to have the general appearance of "a tall eunuchoid female." Our patient, referred to above, displays the same eunuchoid habitus.

Thus the majority of tall patients with gonadal dysgenesis show eunuchoidal proportions. This supports the view that the typical shortness of stature seen in gonadal dysgenesis is genetic in origin (our factor "S"). If this particular genetic aberration does not occur, patients show the body-build which is expected in individuals who are deprived of gonadal function before puberty.

Conclusion

From a consideration of our own case and a review of reported instances of gonadal dysgenesis, we conclude that the two patients described by Swyer are, in fact, suffering from a variant of this syndrome. His patients may be reappraised in the light of several other similar protocols. Consideration of the variable clinical picture in the syndrome of gonadal dysgenesis leads to the conclusion that this syndrome results from a genetic disturbance rather than a primary intrauterine disorder.

As the heterogeneous nature of gonadal dysgenesis becomes more widely recognized, we believe that this disorder will be found responsible for most cases of primary amenorrhoea—whatever the appearance of the patient.

Summary

A case of gonadal dysgenesis is reported in a patient who was tall and eunuchoidal, had no congenital anomalies, and had a female nuclear pattern. This and two other cases are compared with two cases reported by Swyer under the title of "Male Pseudohermaphroditism: A Hitherto Undescribed Form." Reconsideration of Swyer's cases suggests that they, too, suffer from a variant of the syndrome of gonadal dysgenesis.

The genetic aberration responsible for gonadal dysgenesis and its variants is discussed and a hypothesis is submitted to account for the whole syndrome and its less complete forms.

A reconsideration of reported tall patients with gonadal dysgenesis lends support to the view that the shortness of stature is genetic in origin.

We are grateful to Professor F. Forman for his constant interest and advice; to Professor James T. Louw, under whose care the patient was admitted; to Dr. W. H. Muller, who performed the laparotomy; to Dr. C. J. Uys for the histological reports; to

Professor H. Zwarenstein and Mr. D. G. Duncan for the gonadotrophin (F.S.H.) estimation; and to Mr. B. Todt for the photograph.

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HUMAN INFECTION WITH SALMONELLA CHOLERAESUIS

BY

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Salmonella choleraesuis differs from other salmonellae by the frequency with which it invades the blood stream, causing a generalized infection, and by its high mortality. Infection may manifest itself in three ways: as a gastro-enteritis, a typhoid-like illness, or a septicaemia. The septicaemia may localize in the lungs, bones, joints, or meninges. Reports of sporadic cases of the generalized type of infection have been published by Harvey (1937). He reviewed the literature, finding 50 cases, and added a further 21 cases. Goulder, Kingsland, and Janeway (1942) reported 11 cases, and Jager and Lamb (1943) six cases. Saphra and Wassermann (1954) analysed 329 cultures of *Salm. choleraesuis* from human sources submitted for identification to the New York Salmonella Center between 1940 and 1954. The organism had been isolated from the blood in 247 instances, and in only 26 from the faeces alone.

In this country only 12 cases of the generalized type of infection have been recorded. Nabarro, White, Dyke, and Scott (1929) and Schwabacher, Taylor, and White (1943) reported two cases each, and single cases were described by Boycott and McNee (1936), Herring and Nicholson (1939), and Guthrie (1941). Five cases of unusual manifestations of *Salm. choleraesuis* were reported in the *Monthly Bulletin of the Ministry of Health* (1950a, 1950b, 1951). These comprise two cases of septicaemia, a septic arthritis, and a cold abscess of the scalp, and in one case the organism was isolated from the urine. No clinical details were given.

During 1923–53 *Salm. choleraesuis* was isolated from 66 food-poisoning incidents in England and Wales out of a total of 14,847 due to salmonella organisms.

The following two cases are put on record because they present features not previously reported in this country.

Case 1

A personnel manager in a bakery firm, aged 53, was admitted to Sefton General Hospital on December 16, 1954, with a history of an influenza-like illness and backache one month earlier, followed by swelling of his ankles. There was no history of gastro-enteritis, but three months previously, in the course of his work, he had been in contact with the contents of a large tin of ham which was obviously decomposed and was in fact condemned, although no record of a bacteriological examination is available.

On admission his temperature was normal. Oedema of the ankles and sacrum was present, but no cause for this could be found. Three days after admission he had a temperature of 100–104° F. (37.8–40° C.). Four blood cultures were taken over a period of 24 hours, and an organism of the salmonella group was isolated from three. These were identified by Dr. Joan Taylor at the Salmonella Reference Laboratory as *Salm. choleraesuis* var. *kunzendorf*.

The patient was transferred to Fazakerley Hospital on December 24. He was treated with chloramphenicol, 500 mg. six-hourly for seven days. His temperature settled. On January 8, 1955, he complained of pain in the right loin and dysuria. *Salm. choleraesuis* was cultured from the urine. On January 14 he was again pyrexial, and on January 26 a further course of chloramphenicol, 500 mg. six-hourly for seven days, was started. His temperature settled. An intravenous pyelogram showed normal excretion of the dye.

On February 19 he complained of pain in both loins and was found to be tender over the lower dorsal vertebrae. *X*-ray examination of the spine showed diminution of the disk space between D 9 and 10 with erosion of the adjacent vertebral margin and a paravertebral abscess, presumably due to *Salm. choleraesuis*.

Stools cultured 23 times between December 25, 1954, and March 3, 1956, failed to grow *Salm. choleraesuis*. The urine was frequently cultured, and was found to be sterile except on January 8.

The patient was eventually discharged from hospital on November 16, 1955, wearing a spinal support. The stools of relatives were examined but no carrier was found.

An *x*-ray film taken on August 21, 1956, showed the destructive lesion between the ninth and tenth dorsal vertebrae to be healed. There was very little destruction in these two vertebrae, but the intervertebral disk had been destroyed. The paravertebral abscess had almost disappeared. He was still wearing a surgical support.

Case 2

A woman confectioner aged 23, suffering from idiopathic thrombocytopenic purpura, was admitted to Sefton General Hospital for splenectomy on February 1, 1955. There had been no history of gastro-enteritis, and a chest *x*-ray examination showed the lung fields to be clear.

Splenectomy was performed on February 11, using a transthoracic approach through the bed of the tenth rib, and the chest was closed without drainage.

On the second post-operative day the patient became febrile. A chest *x*-ray film showed a left basal opacity. She was treated with penicillin, 500,000 units six-hourly by intramuscular injection, and her temperature settled slowly. On February 22 she again became pyrexial. On clinical examination there was an impaired percussion note at the left base and air entry was diminished. Chest *x*-ray examination showed consolidation of the left lower lobe. Penicillin was stopped and chlortetracycline, 250 mg. six-hourly, was given. Chest aspiration carried out three days later produced 3 fl. oz. (85 ml.) of dark straw-coloured fluid. Microscopical examination showed an excess of leucocytes, but the fluid on culture was sterile.

The patient remained pyrexial and exploration of the chest was carried out on March 17. A posterior loculated empyema was found and a drain inserted. An organism of the salmonella group was isolated from the pus. This was identified by Dr. Joan Taylor as *Salm. choleraesuis* var. *kunzendorf*. Treatment was begun on March 19 with chloramphenicol, 0.5 g. four-hourly for eight days. Her temperature settled after six days. An organism of the salmonella group was isolated from the pus draining from the chest on April 4 and 6.