leading to thyroid hyperplasia; instead of the gland behaving as in hypothyroidism, the patient's diet intake may have contained enough iodine to overcome the blockage by sudden excessive formation and release of thyroid hormone (Paschkis *et al.*, 1941). Alternatively, all the cases so far reported might have had a transient period of hyperthyroidism followed later by hypothyroidism, which might have happened in our case had we continued with the drug for a longer period.

Summary

A case of P.A.S.-induced hyperthyroidism is reported. An attempt is made to explain the mechanism. The literature on hypothyroidism and thyroid enlargement caused by P.A.S. is briefly reviewed.

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GONADAL AGENESIS WITH TETANY AND SEVERE OSTEOPOROSIS

BY

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In 1938 Turner described a syndrome occurring in a group of 10 women, all of whom exhibited sexual infantilism, short stature, cubitus valgus, and webbing of the neck. Varney *et al.* (1942), reporting further cases, noted an increased excretion of urinary gonadotrophins. Albright *et al.* (1942) stressed the fact that the syndrome was associated with ovarian insufficiency, and that this was due to primary agenesis and was not secondary to pituitary hypofunction. In these and subsequent reports many further congenital abnormalities have been noted with varying frequency, and osteoporosis of a degree and distribution similar to that sometimes found in senile patients has often been observed. Much less commonly a similar syndrome has been described in men, and other cases have been seen in which one or more of the developmental abnormalities have been lacking.

One abnormality that has been found not infrequently in these patients is coarctation of the aorta. As this lesion occurs much more commonly in males, it seemed noteworthy to Polani *et al.* (1954) that it should be so often present in a group of people most of whom were women. They considered the possibility that their patients, though possessing genitalia of infantile female appearance, might in fact be genetic males. Animal experiments have shown that if the gonads are destroyed before sexual differentiation has occurred, the subjects will develop feminine genital tracts regardless of the true genetic sex (Jost, 1947). Polani and his group, using a method for sexing a subject by examination of the skin nuclei (Hunter *et al.*, 1954), found that three apparently female patients with Turner's syndrome and coarctation of the aorta were in fact genetic males.

If, as seems likely from these findings, most patients with Turner's syndrome are males, it is not surprising that efforts to treat their "ovarian" agenesis by substitution therapy with female sex hormones have failed to be very satisfactory. It also now seems preferable to use the term "gonadal agenesis" to describe the condition.

In the following case the patient suffered from gonadal agenesis and spontaneous tetany of unknown immediate cause. In addition, marked generalized osteoporosis was noted radiologically. This combination does not seem to have been noted previously, and so seems to merit description even though no good cause for the association can be suggested.

Case Report

A domestic servant aged 25 was referred to Dr. C. E. Dent at University College Hospital by Dr. B. Miles, of Hereford, for investigation of her tetany. She had never menstruated, but, apart from this, had felt normal until 1953, when she began to suffer from episodes of painful cramps and stiffness of the hands and feet, infrequent at first but gradually becoming more common and more severe. By the beginning of 1955 severe attacks were occurring every two to three weeks. She had been well otherwise, apart from a respiratory tract infection two months before admission. Complete dental clearance, apparently for caries, had been carried out early in 1953. She said that she was the backward member of her family. Her parents were not related, and they and five siblings were well and of normal stature.

On examination she was a co-operative but rather simple patient (I.Q. 75), who looked older than her years. No abnormality was noted in the cardiovascular, respiratory, or alimentary systems. Her height was 60 in. (152 cm.) and her span 61 in. (155 cm.). There was no webbing of the neck, but the carrying angle was increased and slight ptosis was present. The axillary hair was sparse, but there was a growth of fine downy hair on the trunk and limbs. The nipples were infantile and there was complete absence of breast tissue. Although she did not exhibit tetany spontaneously while in hospital, Chvostek's and Trousseau's signs were always positive. She showed no tendency to overbreathe.

Mr. G. R. Clare, who examined the patient under anaesthesia, reported: "The labia majora were firm and of normal shape. On the medial surface the labia minora were represented by two small skin tags which were about 2 cm. long. The clitoris was anatomically normal but smaller than usual. The vestibule, remnants of hymen, and vagina were normal in size, but the vaginal skin looked less well oestrogenized than usual for a woman of this age. The cervix and body of the uterus were infantile, measuring 2.5 cm. from external os to fundus uteri. The ovarian ligaments were palpable on both sides. The distal part of these appeared thicker. No separate gonad was palpable. The whole appearance of the genital organs was one of marked hypoplasia except for the vagina, which was of normal size."

Investigations.—Plasma electrolytes: sodium, 146 mEq/l.; potassium, 4.55 mEq/l.; chloride, 102.5 mEq/l.; bicarbonate, 25.4 mEq/l.; calcium, 8.4–9 mg./100 ml.; inorganic phosphorus 4–5 mg./100 ml.; magnesium, 2 mg./100 ml. Alkaline phosphatase, 10.2 King–Armstrong units; blood *p*H determined by Dr. Wynn, St. Mary's Hospital, 7.45; blood urea, 21 mg./100 ml. Electrophoresis of the plasma proteins was normal apart from a slight increase of alpha-globulin. Electrocardiogram: prolonged QTc (0.45 second) and T wave inversion in leads II and III and V_{1-5}. The patient absorbed 95% of her dietary fat in a five-day period. The 24-hour urinary output of 17-ketosteroids,

17-ketogenic steroids, and 17-hydroxysteroids (determined by Dr. J. D. Nabarro) was within normal limits. The 24-hour urinary output of gonadotrophins was between 20 and 80 mouse units. Reports on vaginal smear (Dr. G. I. M. Swyer): "Mainly mucus and debris. The few cells are of basal type—that is, very hypo-oestrogenic."

Bone *x*-ray films showed delayed epiphysial fusion. There was marked diffuse osteoporosis affecting both central and peripheral bones. This was most gross in the pelvic bones, spine, and long bones of the limbs, but the skull and small bones of the hands and feet also showed definite though less marked changes. There was no specific evidence of osteomalacia or hyperparathyroidism—that is, no signs of cyst formation or subperiosteal erosion and no Looser's zones. Report on biopsy from cortex of tibia (Dr. H. Sissons): "Osteoporosis. The cortex is thinned but is otherwise normal. No evidence of osteomalacia is present, and the histological appearance of the intracellular matrix of the bone is normal."

The patient's genetic sex was determined by Dr. Swyer by examination of the skin nuclei and those of the polymorphonuclear leucocytes, and proved to be male.

Course and Treatment.—In an attempt to exclude an endocrine deficiency as the cause of the tetany, methyltestosterone, 20 mg. daily for two periods of six days, and stilboestrol, 2 mg. daily for two periods of six days, were given. The calcium and phosphorus levels rose and fell slightly during this time, but the changes did not seem to be related to the treatment. The simultaneous calcium balance study also showed no significant changes, but was unfortunately very inaccurate owing to curious fluctuations in bowel function. Neither form of therapy nor the raising of the plasma calcium level to 9.7 mg./100 ml. with intravenous calcium gluconate succeeded in abolishing the Chvostek or Trousseau sign.

Discussion

There can be little doubt that this patient has gonadal agenesis in association with some of the other congenital defects of Turner's syndrome. Although such patients not infrequently have osteoporosis limited to the spine, generalized and marked osteoporosis such as this has not been mentioned, nor has the tetany. In the few cases in which serum calcium levels have been recorded they have been normal or slightly raised, as found by Albright *et al.* (1942).

The cause of this patient's tetany remains obscure. Although the serum calcium level was somewhat low, it was hardly low enough to produce tetany without the operation of some additional factor. Also the tetany persisted even when the calcium level was raised almost to normal. None of the other known causes of tetany was apparent in this case.

Although it seems reasonable to suppose that the coexistence of the rare condition of gonadal agenesis with the equally rare conditions of marked clinical tetany and generalized osteoporosis could hardly be a chance occurrence, no cause for the association could be shown.

Summary

A case of gonadal agenesis is described in which, in addition to many of the usual features, spontaneous tetany and generalized osteoporosis also occurred. No metabolic explanation for this association can be offered.

I am grateful to Dr. C. E. Dent, in whose department the balance studies were performed, for permission to publish this case and for assistance with the preparation of this paper.

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HAEMOLYTIC ANAEMIA IN SICKLE-CELL TRAIT

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It is generally accepted that cases of sickle-cell trait show no haematological abnormality other than sickling (Chernoff, 1955). Edington and Lehmann (1955), however, suggested that the trait itself may be "by no means harmless," and ascribed the cause of death in an African woman with the sickle-cell trait to a haemolytic crisis possibly precipitated by a superadded infection. Griffiths (1955) has referred to a sickle-cell crisis occurring in a case of sickle-cell trait during pregnancy. No details were given.

We give below an account of a patient with the sickle-cell trait in whom a haemolytic episode developed during a superadded infection.

Case Report

The patient, a 35-year-old Jamaican, was admitted to Whittington Hospital on February 17, 1955, complaining of general malaise and cough. Three days before admission he felt cold and hot in turn and had vague body pains. On the day before admission he had difficulty in breathing and developed a pain in the right side of his chest, with a cough which produced a small amount of white phlegm.

His previous history was difficult to obtain; all that could be elicited was that he had landed in England from Jamaica five months previously, that he had suffered from unspecified "fever" in his home country, and that he had been working with a fellow Jamaican who had a cough which produced a bloodstained sputum for which he was being treated as an out-patient at another hospital.

Physical examination showed the patient to be a well-nourished negro with a temperature of 105° F. (40.6° C.), pulse 100, and respiration rate 24. Examination of the chest suggested consolidation at the bases of both lungs, with scattered rales and crepitations over the lung areas. Abdominal examination revealed a barely palpable spleen. Examination of the other systems was negative.

Special Investigations.—The initial blood count was: Hb, 60% (8.9 g.); red cells, 3,110,000 per c.mm.; P.C.V., 28%; M.C.V., 93 cubic microns; M.C.H.C., 32%; reticulocytes, 4%; white cells, 3,100 per c.mm. (Standard techniques as in Wintrobe, 1951.) Examination of the blood film showed marked anisocytosis and increased polychromasia of the red cells. Some target cells, "raspberry"-shaped and spiculated forms, together with one normoblast, were seen. A sickling test with 2% sodium bisulphite was positive in 10 minutes. The E.S.R. (Westergren) was 9 mm. in one hour. The serum bilirubin was 1.4 mg. per 100 ml. and the urine contained a great excess of urobilinogen. The direct Coombs test, cold agglutinin test, and specific haemolysin tests were negative. Complement-fixation tests with the antigens of influenza A and B, psittacosis, and Q fever were persistently negative, and the M.G. streptococcus titre was negative at 1 in 4. The Wassermann reaction and Kahn test were negative. Paper electrophoresis of a haemoglobin solution (barbitone buffer *p*H 8.6, 0.06 M solution) revealed a pattern of haemoglobin A plus haemoglobin S, the latter pigment comprising one-quarter to one-third of the total haemoglobin mass. Foetal haemoglobin tested for by the alkali denaturation technique (Singer *et al.*, 1951) was 0.12% (within normal limits). No other abnormal haemoglobins could be demonstrated. Sternal marrow showed slight hypoplasia with active normoblastic erythropoiesis. The myeloid series and