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HYPERTHYROIDISM DEVELOPING DURING P.A.S. THERAPY

BY

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AND

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Since the bacteriostatic effect of P.A.S. on tubercle bacilli in man was described by Lehmann (1946), its relative clinical value and toxicity have been amply confirmed. Among its many toxic effects one must include its effect on the thyroid gland. Medical reports on this subject are few. Madigan *et al.* (1950) were the first to mention an increase in skin temperature in patients who were receiving P.A.S. therapy, although the rectal temperature remained normal. They attributed the finding to the direct pharmacological effect of P.A.S. resulting in peripheral vasodilatation—an effect seen in febrile as well as afebrile patients. The increased heat loss in afebrile patients was compensated by an increase in the basal metabolic rate.

Komrower (1951) drew attention to the fact that P.A.S. was responsible for the thyroid enlargement in his patient, who developed clinical myxoedema during P.A.S. therapy over a period of about six months. Clausen and Kjerulf-Jensen (1951) reported somewhat similar findings in three cases, and four more cases were reported by Bergqvist and de Maré (1952). Further reports came from Librach (1952) and Davies and Galbraith (1953).

A series of 11 cases of thyroid enlargement during P.A.S. therapy was reported by Brinkman and Coates (1954) from the Trudeau Sanatorium, Trudeau, New York. Two of their cases developed myxoedema as well as thyroid enlargement. The enlargement appeared after 4 to 12 months' treatment with P.A.S., except in one case in which goitre appeared after seven weeks' treatment. In addition, Hamilton (1953) recorded an unusual finding of exophthalmos with a hyperplastic-hypothyroid type of enlargement.

The gradually increasing number of reports of the thyroid gland being affected during P.A.S. therapy are

all on the hypothyroid type. The following case presents the opposite picture—that is, hyperthyroidism, hitherto not mentioned, apart from the high basal metabolic rate alluded to by Madigan *et al.* (1950).

Case Report

A Thai married woman aged 32 attended the out-patient department for treatment of pulmonary tuberculosis in November, 1953. She had been treated by her doctor for the previous two years with apparently little improvement. Physical examination at that time proved the lesion to be in the left upper lobe, confirmed by x-ray examination. Sputum examinations were positive for tubercle bacilli. Her temperature was 37.7° C. (99.8° F.), pulse 118, respirations 24, and body weight 47.1 kg. (7 st. 5½ lb.). She was given P.A.S. (12 g. daily) and isoniazid ("rimifon") (300 mg. daily). After a pneumoperitoneum a few days later her condition improved steadily, and by December, 1954, her weight was 53.3 kg. (8 st. 5½ lb.), pulse 88, respirations 20, temperature 36.7° C. (98° F.), and sputum examinations were negative. However, she began to notice that her neck was somewhat enlarged, and by January, 1955, it was so obvious that she had to wear a scarf to conceal it. She felt easily tired, irritable, and hot even in relatively cool weather. Her weight dropped to 51.6 kg. (8 st. 1½ lb.) in spite of a voracious appetite.

The B.M.R. was +25.1%; cholesterol, 140.2 mg. per 100 ml.; neck measurement, 33 cm.; respirations 20; temperature 36.5° C. (97.7° F.); pulse 104. When the cause of the thyroid enlargement was realized P.A.S. was discontinued and streptomycin was given together with isoniazid. Subsequent to the withdrawal of P.A.S. the hyperthyroid state improved steadily—B.M.R. was +16.8%; cholesterol, 200 mg. per 100 ml.; neck measurement, 31 cm.—with no symptoms referable to hyperthyroidism. By November, 1955, the B.M.R. was +13.3% and the neck measurement 31 cm. (apparently her normal size).

Discussion

The clinical pattern and laboratory findings in this case leave us with no alternative but to conclude that P.A.S. caused thyroid enlargement and hyperthyroidism. It may be argued that the basal metabolism may be high even in afebrile cases, as previously noted by Madigan *et al.* in patients during P.A.S. therapy, but the fact that the B.M.R. changes in our case were correlated with blood cholesterol levels during and after cessation of the drug would be strongly in favour of hyperplastic hyperthyroidism. However, determinations of radioactive iodine uptake and of protein-bound iodine in the serum, especially the latter, could settle the problem, but unfortunately these were not available to us.

Isoniazid by itself is known to cause thyroid enlargement, but this was not the responsible factor in our case, as the drug had been given throughout the treatment period. Angel *et al.* (1955) discussed the role of P.A.S. in the production of thyroid enlargement with or without myxoedema. They investigated the iodine metabolism of the surviving thyroid slices, and were of the opinion that P.A.S. does not inhibit the accumulation of inorganic ¹³¹I in thyroid tissue, but is rather like thiouracil and somewhat weaker in action. P.A.S. inhibits the formation of di-iodotyrosine and thyroid hormone, and the action is a direct one, although the possibility of an additional indirect action cannot be entirely excluded. Macgregor and Somner (1954) and Brinkman and Coates (1954) found iodine ineffective in the relief of goitre due to P.A.S., but remissions of the symptoms and goitre were seen following the use of thyroid. Balint *et al.* (1954) reported some benefit from iodine.

The mechanism, outlined above, of the role of P.A.S. in the production of goitre does not seem to fit in with what happened in our case, undoubtedly a case of hyperthyroidism. It may be possible that in this case the P.A.S. in some way, (?) acting like thiocyanate, blocked the formation of thyroid hormone by excessive production of thyrotropin

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 pH 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 V₁₋₅. The patient absorbed 95% of her dietary fat in a five-day period. The 24-hour urinary output of 17-ketosteroids,