GOITRE AND HYPOTHYROIDISM DEVELOPING DURING TREATMENT WITH P.A.S.

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Since the introduction of *p*-aminosalicylic acid (P.A.S.) for the treatment of tuberculosis by Lehmann in 1946, many thousands of patients must have received large doses of this drug for long periods. It is only during the past year or two that a few reports have appeared on the development of goitre and hypothyroidism in patients being treated with P.A.S. In these reports, as in the case here described, the circumstances are most suggestive that P.A.S. has a goitrogenic action in some individuals.

Case Report

A male medical student aged 28, with no personal or family history of thyroid disease, was admitted for treatment of pulmonary tuberculosis. On February 21, 1952, intramuscular streptomycin, 1 g. every three days, and P.A.S. (as the sodium salt), 10 g. daily, were started; later the dosage of P.A.S. was increased to 12 g. The patient's progress was satisfactory until, on July 29, after 56 g. of streptomycin and 1,600 g. of P.A.S. had been given, a symptomless diffuse non-tender goitre was noticed. Recently the patient had felt some impairment of appetite and possibly an increased susceptibility to cold; his upper face appeared puffy, but there was otherwise no clinical evidence of hypothyroidism. The serum cholesterol was 220 mg. per 100 ml.

On August 6 the basal metabolic rate was -10% , and on August 19 the streptomycin and P.A.S. were replaced by isoniazid. At this time the basal metabolic rate was -21% and the serum cholesterol 268 mg. per 100 ml. Radio-iodine studies seven days after discontinuation of the drugs suggested excessive thyroid activity with, however, no corresponding increase in the rate of organic binding of the iodine. This pattern is compatible with the incomplete removal of a thiouracil-like block of thyroid activity. Radiographs showed no recent increase in size of the heart. The electrocardiogram was normal.

Four weeks after discontinuation of streptomycin and P.A.S. the appetite and facies had returned to normal, the goitre was only just palpable, and the basal metabolic rate had risen gradually to -1% , although the serum cholesterol had fallen to only 245 mg. per 100 ml. Four months later the thyroid was still just palpable, the basal metabolic rate was $+5\%$, and the serum cholesterol was 215 mg. per 100 ml.

Discussion

The development of myxoedema during P.A.S. therapy was first described by Clausen and Kjerulf-Jensen in 1951. Three patients developed hypothyroidism and goitre after taking 610 g., 1,780 g., and 2,500 g. of P.A.S. respectively in the usual dosage. The endocrine state and the gland size returned to normal within two to four weeks of the cessation of this treatment. Shortly afterwards Komrower (1951) described the apparently sudden appearance of myxoedema and of a diffuse goitre in a girl aged 8 who had been given about 3,000 g. of P.A.S. during the previous nine months, the goitre and myxoedema disappearing within three weeks of stopping the drug.

Bergqvist and de Maré (1952) reported two cases of hypothyroidism with goitre and two cases of goitre without objec-

tive evidence of hypothyroidism in patients treated with simultaneous thiosemicarbazone and P.A.S. Streptomycin had been given to three of the patients for part of the time, but it would seem difficult to incriminate this drug. One patient died of myxoedema and cerebral oedema; at necropsy the thyroid showed a glandular hyperplasia identical with that seen after the administration of thiouracil. In two other cases the authors thought the thyroid condition improved when the thiosemicarbazone was stopped, the administration of P.A.S. continuing; while in the fourth the goitre had disappeared five months after simultaneous withdrawal of P.A.S. and thiosemicarbazone. These authors suggested that the thiosemicarbazone and P.A.S. may have a synergistic action or that the thiosemicarbazone may act by retarding the renal excretion of P.A.S. A further case of goitre following treatment with P.A.S. and thiosemicarbazone has been described by Librach (1952). Bergqvist and de Maré also quote a personal communication from Stavanow, who has seen "a few cases of goitre and one case of mild hypothyroidism following P.A.S. medication."

In animal experiments, principally on rats, Kjerulf-Jensen and Wolffbrandt (1951) showed that P.A.S. and its degradation product in the body, meta-aminophenol, produce a thyroid hyperplasia qualitatively comparable with, but quantitatively much less than, that induced by thiouracil. This hyperplasia can be prevented by the simultaneous administration of thyroid extract.

Hanngren (1952), in a preliminary communication on radio-iodine studies of three patients before and during P.A.S. therapy, showed that P.A.S. inhibited the uptake of iodine by the thyroid.

Astwood and his colleagues (1945) found that many aminophenol compounds, including 4-aminobenzoic acid, had a goitrogenic effect. It is not surprising, therefore, that P.A.S. (4-amino-2-hydroxybenzoic acid) has been shown to have a similar action.

Summary and Conclusions

A case in which goitre and mild hypothyroidism occurred during treatment with P.A.S. and streptomycin is described; the thyroid condition returned to normal within four weeks of discontinuing treatment.

The literature, in which at least 10 similar cases are mentioned, is reviewed.

It would seem that P.A.S. has a definite although feeble antithyroid action similar to that of the thiouracil drugs, and in a small proportion of patients receiving such treatment goitre and, possibly, hypothyroidism may develop without the dosage being excessive or the duration of treatment very prolonged. Fortunately, the process appears to be reversible if the situation is realized, and the administration of P.A.S. stopped, before the myxoedema is severe.

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The Annual Federal Conference of the Flying Doctor Service of Australia was opened in Sydney by Sir John Northcott, Governor of New South Wales, on April 20. During 1952 aircraft maintained at nine stations in the Australian outback made nearly 1,000 flights, covering just over 253,000 miles.