explanation has been offered by Boas and Scow (1954) for these results. They considered that the apparent exophthalmos was due to retarded body growth induced by cortisone. Essex (1955) also held the view that body growth is retarded by cortisone, while the eye, as an ectodermal structure, was little affected. Wyn Williams (1955) found that this cortisone-induced exophthalmos could be produced only in the growing animal. Moreover, it has been suggested that systemic cortisone might improve exophthalmos, and, although this was not borne out in a trial carried out under the auspices of the Medical Research Council (1955), no case was made worse by such treatment.

Although no definite mechanism can be implicated, the natural history of this case, with exophthalmos preceding the other signs of Cushing's syndrome, would suggest that the primary disturbance was hypothalamic or pituitary rather than adrenal.

Summary

A case of Cushing's syndrome with mental disturbance and malignant exophthalmos is described. A possible mechanism of the exophthalmos is discussed. It is suggested that the primary lesion of Cushing's syndrome was in the hypothalamus or pituitary rather than the adrenal glands.

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RENAL FAILURE DUE TO PARA-AMINOSALICYLIC ACID

BY

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Drug allergy has been said to have ousted syphilis in recent years as "the great imitator." Florid cases of allergic reactions to para-aminosalicylic acid (P.A.S.) have often been reported, but associated renal involvement has been uncommon and usually confined to patients who also had hepatitis. Accounts of allergic reactions to P.A.S. with renal failure and jaundice are given by Cuthbert (1950), Livingstone and Street (1950), Jeffrey *et al.* (1952), and Mann (1953). Two papers have also described renal failure in patients having allergic reactions to P.A.S. without jaundice, but in the earlier case (Le Melletier and Gerphagnon, 1950), the patient was already almost moribund with tuberculosis. In the other paper, Silverman *et al.* (1956) report a case of "toxic nephritis" without clinical but with biochemical evidence of hepatic damage. The following account is therefore the first authentic report of a case of renal failure due to P.A.S. without hepatitis.

Case Report

An Irishman of 31 was first found to be suffering from pulmonary tuberculosis, with a positive sputum, in April, 1956. In August, he was admitted to hospital, where he was given 1 g. of streptomycin daily with calcium B-P.A.S., 3.5 g. t.i.d., and isoniazid, 100 mg. t.i.d., for 83 days.

He was transferred to Colindale Hospital on October 30. On admission he was a healthy-looking man with a symptomless goitre. There was no clinical evidence of thyrotoxicosis. His temperature was 98.4° F. (36.9° C.), pulse 84, blood pressure 130/80. No abnormal physical signs were found in the chest or any other system. X-ray examination revealed bilateral apical pulmonary tuberculosis without cavitation. Sputum was negative for acid-fast bacilli on smear and culture. The E.S.R. (Westergren) was 3 mm. in one hour. The urine was found to contain sugar. Fasting blood sugar was 110 mg./100 ml. The glucose-tolerance curve was within normal limits. The blood count was normal; Hb, 106%.

There was no family history of asthma or other allergic conditions. His mother had a goitre. The patient did not remember ever having had a drug reaction. He had never had asthma or other manifestations of allergy.

On November 3 the patient started streptomycin, 1 g. three times a week, with daily sodium P.A.S. 12 g., and isoniazid 300 mg. by mouth. He made satisfactory progress until December 8 and 9, when the evening temperature was 99° F. (37.2° C.), and on December 10 it rose to 101.6° F. (38.7° C.). An injection of penicillin was given. Next morning a pink macular rash was noticed. The posterior cervical glands were enlarged, firm, and discrete, but not painful or tender. The patient was thought to be suffering from rubella. The evening temperature on December 11 was 103° F. (39.4° C.). Although no complaint of sore throat had been made the fauces were reddened. P.A.S. and isoniazid were continued, and streptomycin, P.A.S., and isoniazid were given the next day, December 12, as usual. That evening the temperature rose to 103.2° F. (39.5° C.) with enlargement of glands in the anterior triangles of the neck. Another injection of penicillin was given.

On December 13 the possibility of drug hypersensitivity was considered, and penicillin, streptomycin, P.A.S., and isoniazid were discontinued. A course of diphenhydramine hydrochloride was started. The same evening the temperature fell to 100° F. (37.8° C.), and by the evening of the 14th it was normal and remained so for over 36 hours, but the rash had become red and blotchy with considerable pruritus, and glands could be felt in the axillae and groins. The conjunctivae were suffused. The blood count remained normal. The Wassermann reaction was negative. No glandular fever cells were seen in the blood then or at any time. The Paul-Bunnell test and all other agglutination reactions were negative.

On December 16 and 17, while he was still on diphenhydramine hydrochloride, the temperature rose again to 99° and 102.2° F. (37.2 and 39° C.) respectively, and the drug was therefore discontinued.

On December 19 there was an evening pyrexia of 105° F. (40.6° C.) with a fresh crop of glands in the post-auricular regions, and the spleen was found to be palpable. One dose of chlortetracycline was given that night, but the drug was discontinued owing to vomiting. Although the rash gradually faded without desquamation, the urine became scanty and highly coloured. It contained sugar and a trace of albumin.

Another spike of pyrexia—101.4° F. (38.6° C.)—occurred on December 23 with a transient erythematous rash on the trunk. The general condition remained good, but the patient was still vomiting, and only 2 oz. (57 ml.) of urine had been passed in the previous 24 hours. This was solid with albumin and contained leucocytes, erythrocytes, and hyaline and granular casts. Culture was sterile. The blood urea was

found to be 150 mg./100 ml. Fluids were immediately restricted by mouth and penicillin was started. No pitting oedema was observed at any time. Daily blood-pressure readings never rose above 150/90. At no time was there clinical evidence of hepatic involvement. The blood count remained normal throughout. The blood urea rose to 245 mg./100 ml. on December 27 and thereafter fell, until by January 7, 1957, it was normal. (Urea concentration test was also normal on January 7.)

By December 30 fluid balance had been re-established and the spleen was no longer palpable. (The glands subsided more gradually, the last disappearing on February 13.) Urine was clear of red cells by December 31, casts by January 11, and albumin and leucocytes by January 21. Glycosuria persisted. A 24-hour specimen of urine contained no acid-fast bacilli on Löwenstein culture. Serum protein electrophoresis still showed a slight decrease in albumin and increase in α_2 and γ globulins on January 7.

Despite courses of penicillin and chlortetracycline the temperature subsided very gradually and did not settle finally until the middle of January.

Test doses of chlortetracycline and penicillin during March gave no reaction, nor did isoniazid or streptomycin.

On March 8, 4 g. of sodium P.A.S. given orally at 10 a.m. was followed by a prickling sensation in the skin during the afternoon. The temperature at 5 p.m. was 100° F. (37.8° C.). 50 mg. of diphenhydramine was given. At 10 p.m. the temperature was 101.8° F. (38.8° C.) and the patient vomited. Diphenhydramine, 100 mg., was then given and the temperature fell to normal. There was a deficit of 40 oz. (1,140 ml.) in urinary output during the next 48 hours. Blood urea was 30 mg./100 ml. The urine contained no albumin.

The patient was discharged home well on April 4.

Discussion

By far the commonest serious complication of P.A.S. therapy is hepatitis, an excellent review of which is given by Hensler *et al.* (1957). Hepatitis usually accompanies a severe allergic reaction characterized by fever, rash with pruritus, sore throat, conjunctivitis, eosinophilia, and enlargement of glands and spleen, or most of these signs.

It was noted by Lichtenstein and Cannemeyer (1953) and Cannemeyer *et al.* (1955) that 0.3% of their patients treated with P.A.S. had reactions of some sort, but in over 3,000 cases none had renal complications. This infrequency is confirmed in the literature reviewed here. P.A.S. remains a comparatively safe drug whose usefulness outweighs the possibility of occasional severe complications.

It is noteworthy that the patient described here took calcium B-P.A.S. for 83 days without mishap. After 35 days of sodium P.A.S. his severe allergic illness developed. Unfortunately, after recovery, a test dose of calcium B-P.A.S. was not tried. All the allergic reactions already alluded to were due to sodium P.A.S. (Cuthbert, 1950; Livingstone and Street, 1950; Jeffery *et al.*, 1952), or P.A.S. itself (Le Melletier, 1950; Mann, 1953; Silverman *et al.*, 1956). Phillips *et al.* (1957) has described three cases in which the patients exhibited allergic reactions to sodium P.A.S. and

were subsequently able to take calcium B-P.A.S. uneventfully. As calcium B-P.A.S. is of comparatively recent introduction, it remains to be seen whether it does in fact reduce the incidence of allergic reactions. Pharmacologically there would appear to be no reason to expect this.

Summary

A review of the literature of renal complications of P.A.S. therapy is given. The frequency of association of renal with hepatic complications is discussed.

A case is described of severe renal failure due to sodium P.A.S. as part of an allergic reaction to the drug. The diagnosis was confirmed by subsequent test doses. The patient made a spontaneous recovery some time after the drug was stopped.

The rarity of renal complications of P.A.S. therapy is mentioned. There would appear to be no indications for using P.A.S. less frequently than is at present the custom.

The possible relationship of P.A.S., sodium P.A.S., and calcium B-P.A.S. to allergic reactions is briefly considered. It is possible that calcium B-P.A.S. is the safest of the group available for routine use at the present time.

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LEIOMYOMA OF OESOPHAGUS

REPORT ON TWO CASES SURGICALLY TREATED

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Leiomyoma is the most common benign tumour of the oesophagus. Until recent years most cases were discovered at necropsy. Lewis and Maxfield (1954) reported 47 surgically treated and 108 post-mortem cases in their collection of 150 cases from the world literature. Whether priority of surgical treatment belongs to Sauerbrück or Ohsawa, it is clear that there has since been a new chapter in the field of practical treatment and consequently an increase in the number of surgical cases. Storey and Adams (1956) collected 110 cases of these tumours surgically treated: 16 before 1948 and 94 from 1948 to 1956.

We do not propose to review the whole literature, as this has already been done recently by several authors. However, the infrequency and the successful operative treatment of leiomyoma of the oesophagus gives us reason to present our two personal cases.