it has settled, the area being kept well powdered. It is, however, very seldom that any discomfort is reported by the patient, and in no case has an oedematous balanitis developed. This really does seem, in fact, to be a safe and yet most reliable form of treatment, that can be carried out even by an untrained assistant.

It has been our experience that the harder and more chronic lesions are generally resistant to podophyllin, and usually require destruction by diathermy or electrocautery.

I should like to express my gratitude to Surgeon Commander H. L. Belcher, R.N., for his co-operation with regard to this therapeutic trial, and to the Medical Director-General of the Royal Navy for permission to publish.

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Medical Memoranda

Löffler's Syndrome Occurring During Streptomycin and P.A.S. Therapy

Toxic reactions encountered during treatment with sodium *p*-aminosalicylate (P.A.S.) include fever and pruritus (Hemming and Stewart, 1949), skin eruptions (Horne, 1949), haematuria (Nagley and Logg, 1949), hypoprothrombinaemia (Swanson, 1949), potassium deficiency (Cayley, 1950), and jaundice and enlargement of lymph nodes (Cuthbert, 1950). In the following case of Löffler's syndrome combined therapy with streptomycin and P.A.S. was given, the latter drug being held responsible. This is the first time, so far as I am aware, that this complication of P.A.S. therapy has been described in this country.

CASE REPORT

An unmarried girl aged 18 suffered from tuberculous endometritis (chest x-ray film clear). Previous illnesses were pneumonia in 1945, and mumps and measles in childhood. There was no personal or family history of allergy. Out-patient treatment with streptomycin (1 g. daily) and P.A.S. (12 g. daily) was begun on November 18, 1952. On December 13 she complained of general malaise of three days' duration associated with anorexia, vomiting, and vertigo. She had received 25 g. of streptomycin and approximately 290 g. of P.A.S. Specific drug therapy was discontinued. After admission to hospital later the same day she had a rigor and vomited. Her temperature was 99.6° F. (37.6° C.). Her face was flushed, and the conjunctivae were injected. An intensely itching maculopapular rash quickly developed on her trunk and forelimbs. The occipital, deep-cervical, epitrochlear, and axillary lymph nodes were enlarged. There was no icterus. The liver and spleen were not palpable. Diphenhydramine hydrochloride, 200 mg. daily, was given and lotio calaminae cum menthol. applied locally. For three days she had low irregular pyrexia—99.6° F. (37.6° C.). The itching gradually subsided and the rash faded.

On December 17 she was well; the rash had gone; the liver-function tests were normal; Hb, 13.3 g.; white cell count, 8,200 per c.mm. (differential count not performed). On December 22 the white cell count was 5,640 per c.mm. (polymorphs 53%, eosinophils nil). Diphenhydramine hydrochloride was discontinued. On the 26th streptomycin, 0.1 g. intradermally, produced generalized reaction with vertigo, tinnitus, and vomiting. Her face was flushed, there was no rash, and her temperature was not elevated. An area of induration and erythema, 3 cm. in diameter, at the site of injection later became ulcerated and persisted for two weeks.

Test doses of P.A.S., 1.5 g., 3 g., and 6 g., were given by mouth on successive days without ill effect. On January 2, 1953, a test dose of P.A.S., 6 g., was given by mouth. In the evening she complained of feeling hot, and developed a dry irritating cough. Her temperature was 105° F. (40.6° C.), pulse 120, respirations 30. Her face was flushed but there was no rash. Glands were palpable in the neck, axillae, and epitrochlear regions. The respiratory and cardiovascular systems were normal. Diphenhydramine was resumed.

Next day her temperature was normal, she felt well, and the cough was easier. X-ray examination of the chest revealed extensive coarse mottling throughout both lung fields, resembling a widespread bronchopneumonia. On the 4th she had no complaint; the cough was gone, and the drug was discontinued. Chest x-ray examination was repeated on January 8 and no pulmonary disease was seen.

Next day the Hb was 13.7 g.; white cell count, 9,800 per c.mm. (polymorphs 70%, including eosinophils 4%). Desensitization to P.A.S. was begun according to the schedule recommended by Madigan *et al.* (1950).

January 14, P.A.S., 1.5 g.: rise of temperature in evening—100.4° F. (38° C.); shivery, but no other complaint. January 15, P.A.S. withheld; temperature normal; chest x-ray film showed no pulmonary disease. January 16, P.A.S. resumed at 500-mg. dose; E.S.R., 12/19 mm. (Westergren). January 18, P.A.S., 1.5 g.: well; white cell count, 10,200 per c.mm. (polymorphs 70%, including eosinophils 8%). January 22, P.A.S., 3 g.: white cell count, 10,480 per c.mm. (polymorphs 61%, including eosinophils 10%). January 29, P.A.S., 6 g.: no ill effect; cold agglutinin titre 1 in 28. February 5, P.A.S., 9 g.: no complaint; cold agglutinin titre, 1 in 16.

COMMENT

The syndrome of acquired sensitivity to P.A.S.—namely, constitutional upset with fever and pruritic skin eruption—was first reported by Horne (1949) and has since been described and amplified by many workers. More recently (Jeffry *et al.*, 1952) it has become apparent that a similar syndrome occurring in patients receiving combined streptomycin-P.A.S. therapy may be evidence of acquired sensitivity to both drugs. The allergic nature of these reactions is indicated by the positive results of skin tests with the appropriate drug, by the eosinophilia reported by several authors, and by the effectiveness of desensitization.

There is no doubt that the above case was one of acquired sensitivity to both streptomycin and P.A.S. The main interest in the case centres on the reaction which occurred after the initial flare-up had subsided and which followed the administration of test doses of P.A.S. alone. The outstanding feature of this reaction was the absence of significant constitutional upset despite high fever (105° F.—40.6° C.). The only symptom complained of was an irritating cough which lasted nearly three days. The temperature returned to normal on the second day and remained at that level. Radiologically there was extensive patchy consolidation in both lungs, which had cleared completely five days later with no treatment other than diphenhydramine. The eosinophil count was not carried out at the height of the reaction, but one week after the onset of the reaction—that is, after resolution of the pulmonary infiltrations—eosinophils numbered 4% of 9,800 white cells per c.mm. and rose subsequently during P.A.S. desensitization to 10% of 10,480 white cells per c.mm. The occurrence in an allergic individual of such transient pulmonary infiltrations without significant general upset seems to justify a diagnosis of Löffler's syndrome.

This syndrome, as Löffler himself has pointed out, represents an allergic response of the body to an antigen, the lung being the shock-organ. In most of Löffler's cases the antigen was *Ascaris lumbricoides*, but, as Crofton *et al.* (1952) have shown in their very extensive review of the subject, a wide variety of other antigens have been incriminated from time to time. It is perhaps surprising that Löffler's syndrome is not seen more often in acquired sensitivity reactions to P.A.S. The not infrequent occur-

rence of jaundice in these reactions suggests that more often the shock-organ is the liver, probably because of the part played by that organ in the breakdown of the drug. It is, however, of interest to note that in two of the earliest descriptions of P.A.S. sensitivity reactions (Horne, 1949; Hemming and Stewart, 1949) one of the outstanding symptoms was an intractable dry cough; unfortunately, these patients were not x-rayed during their reactions.

The finding of cold agglutinins in the blood of the case reported above is of interest in view of the possible relationship suggested by Crofton *et al.* (1952) between Löffler's syndrome and other conditions, including tropical eosinophilia, which are characterized by the presence of pulmonary infiltrations and blood eosinophilia. Thus Viswanathan (1948) has drawn attention to the presence of cold agglutinins in the blood in tropical eosinophilia.

I wish to thank Dr. A. M. Sutherland for permission to quote from the hospital case record.

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Embolism and Secondary Thrombosis of the Bifurcation of the Aorta

Cases of embolism and secondary thrombosis of the bifurcation of the aorta are uncommon. Patients with mitral stenosis and auricular fibrillation especially are candidates for embolism of this nature. Herrmann *et al.* (1943) gave a full review of the literature and discussed the clinical picture and treatment. They record that Fry (1939) reviewed 135 reported cases of embolism of the bifurcation of the aorta. They described five cases of their own.

When the embolus is large and the obstruction complete the clinical signs are well defined. In predisposed patients the occurrence of abdominal cramps should lead one to suspect movement of the emboli down the aorta. Lodgment of an embolus at the bifurcation of the aorta is characterized by sudden sharp pains in one leg and then in the other followed by paraesthesiae, coldness, blanching, lowered skin temperature, and absence of or greatly decreased femoral pulses. Herrmann *et al.*, however, emphasize that when the embolus is small and the obstruction incomplete a much less dramatic and less clear-cut clinical picture is presented. The length of time of survival, even after complete obstruction, the length of postponement of the development of gangrene, and the degree of gangrene are often surprising.

The following case is presented as an example of the insidious development of a clinical picture and of the possibly misleading nature of the initial symptoms and signs.

CASE REPORT

A woman aged 38, who had been complaining for a few days of pain in the region of the fifth metatarsal of the left foot, was seen by one of us (D. F. T.) on December 19, 1949. She had a history of rheumatic mitral disease and had had a right hemiplegia due to cerebral embolism in 1946. Examination revealed no swelling or deformity of the left foot itself, and no tenderness over the metatarsal region; definite pain on straight-leg-raising of the left lower limb; tenderness over the lumbo-sacral spine; and an ill-defined anaesthesia to pin-prick over the outer part of the foot. There was no evidence of interference with the circulation of the left lower limb. A differential diagnosis of left sciatic pain due to a lumbo-sacral lesion, or early thrombosis in the vessels to the limb, was made at that stage, and the patient was admitted to hospital. X-ray examination of the lumbo-

sacral region showed no abnormality. She was kept under observation and at first there was no change in her condition.

On December 28 tenderness over the metatarsal region of the foot was still present and there was also tenderness over the external popliteal nerve at the neck of the fibula. Straight-leg-raising on the left was still limited and painful, and the pain was felt in the foot. However, it was noted that, though the colour and temperature of the left foot were normal at rest, the foot became a little pale and cold after it had been moved passively for a few minutes. Mr. W. H. Bailey, who saw the case by request at this stage, agreed that no active treatment was indicated. On the following day the patient complained of increasing pain. Besides the pain in her leg and foot she also had pain in the left iliac fossa and left lumbar region. No pulse could be felt in either lower limb. There was tenderness in the left iliac fossa and in the left lumbar region. Her pulse was increasingly rapid. Later that day there was mottling of both lower limbs. Her respirations became rapid and laboured. She was obviously in severe pain. The following day she died.

Post-mortem Examination.—The body was well nourished. There was slight wasting of the right arm and leg, and some swelling of both ankles and feet. The right ventricle was moderately enlarged and hypertrophied. The left auricle was dilated and hypertrophied. The cardiac muscle was quite firm. The mitral valve was funnel-shaped, its orifice being extremely stenosed, the dimensions being approximately 1.5 cm. by 3 mm. There were no vegetations on the valve or on the posterior wall of the left auricle, nor were there any thrombi in either auricles or ventricles. In the aorta, from the level of the left renal artery to the bifurcation, was a firm ante-mortem thrombus which was firmly adherent to the wall of the vessel. A similar adherent thrombus was present in the left renal artery, and the smaller tributaries of the aorta. Below the bifurcation of the aorta, a recent red ante-mortem thrombus extended down the common iliac and into both external and internal iliac arteries. There was no atheroma of the aorta, its branches, the coronaries, or cerebral vessels.

Both kidneys presented many deep scars, the result of multiple infarction. The left kidney, with the exception of a small area at the inferior pole, presented the picture of recent complete infarction. The right kidney also contained a number of small recent infarcts. The spleen was deeply scarred and distorted and, if anything, was smaller than normal. The liver showed several large areas of congestion, the appearances of which were in keeping with recent infarcts. Both lungs showed large areas of collapse.

On opening the dura an encysted collection of cerebrospinal fluid was present over the left parietal lobe. Dissection of the brain revealed a large cyst of the left cerebral hemisphere occupying a subcortical situation, extending down to and destroying the internal capsule, and passing from the anterior part of the occipital lobe to the posterior part of the frontal lobe. Clearly this was the end-result of the infarction of three years ago.

Conclusion.—Mitral stenosis, hypertrophy of the right ventricle, infarction of the brain, liver, spleen, and kidneys, pulmonary collapse, embolism of the aortic bifurcation, and subsequent thrombosis of the aorta. The embolus was probably derived from a thrombus formed on the mitral valve, although there was no evidence of the thrombus formation on the valve when examined on the table.

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