to his family or colleagues. With this in view, there is considerable scope for chemotherapy in certain types of more chronic patients whose only real disability is an infectious sputum, and this series of cases has shown that the sputum can be converted without interfering with the ordinary day's work.

Summary

Streptomycin and P.A.S. have been used for certain types of patient whose only adverse clinical sign was a positive sputum. Twenty-four patients, in four categories, whose sputum was consistently positive, were treated without interfering with their work or ordinary life.

In 23 cases the sputum was converted; in 14 of them it has remained negative up to two years. Five patients have since had an isolated positive sputum, and four have reverted to positive sputa after being sputum-negative for a period.

The value of such results is discussed when applied to the problem of employable chronic patients, so commonly attending chest clinics.

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The possibility of using high-velocity electrons and gamma rays for sterilizing pharmaceutical products was discussed by Government scientists and representatives of the pharmaceutical industry at a recent meeting at the Department for Scientific and Industrial Research. The method, according to Dr. R. S. Hannan, who has been studying the problem in America, has several advantages: it permits the sterilization of heat-sensitive materials; almost any type of sealed container can be used for the process; and it may lead to the preparation of new products, such as new vaccines. One of the disadvantages is the high capital cost of the generating equipment. Electron accelerators at present available in Britain, capable of treating 1 cwt. (51 kg.) of product an hour, cost between £25,000 and £50,000. A cobalt 60 source for producing gamma rays in sufficient quantity to sterilize 7 lb. (3 kg.) a day would cost £2,000, but gamma rays from fission products would be much cheaper. Other disadvantages, perhaps more theoretical than practical, are toxicity from unusual chemical by-products of irradiation and the failure to inactivate enzymes. The energies used for sterilization are insufficient to induce radioactivity in treated products. So far most of the work in this country on "electronic sterilization" has been done in relation to food; however, its uses in this field may be limited because of alterations to flavour.

ACQUIRED HYPERSENSITIVITY TO SODIUM P.A.S., STREPTOMYCIN, AND PENICILLIN

BY

BARBARA JEFFERY, M.B., B.S.

PETER BORRIE, M.D., M.R.C.P.

AND

NORMAN MACDONALD, M.B., M.R.C.P.Ed.

(From Clare Hall Hospital, South Mimms, Herts)

The administration of sodium *p*-aminosalicylate together with streptomycin is at present the most effective form of chemotherapy for tuberculosis. Toxic effects, while not infrequent, are usually of minor degree. Occasionally streptomycin produces a more severe reaction, such as exfoliative dermatitis or agranulocytosis, which may endanger life. The liver, however, generally appears to escape damage and jaundice is not a feature.

It was at first thought that the toxic effects of P.A.S. were mostly confined to the alimentary tract, the characteristic symptoms being nausea, vomiting, and looseness of the bowels; these disappeared rapidly on stopping the drug. Recently, however, it has become apparent that a small proportion of patients can develop an acute hypersensitivity with severe systemic upset, and a number of reports (Cuthbert, 1950; Livingstone and Street, 1950; Hess and Ismay; 1950) have indicated that P.A.S., in the form administered, is potentially hepato-toxic.

The case here reported is of a patient who developed a most profound systemic reaction following the administration of sodium P.A.S. and streptomycin, with exfoliative dermatitis, liver and kidney damage, and an intense bone-marrow response. Later she had a reaction to penicillin.

Case Record

A single woman aged 23 was admitted to hospital on January 25, 1950, with a cavity at the right apex; sputum positive. Thoracoplasty was recommended, but before it could be carried out the disease spread to the right mid-zone. To control this streptomycin (1 g. daily) and sodium P.A.S. (18 g. daily in divided doses) was begun on March 24.

Stage 1 (April 13–19): Prodromal Symptoms.—On April 13 the temperature rose suddenly to 100° F. (37.8° C.) and slight headache ensued. Both drugs were continued, as other patients had had similar reactions, which settled in a day or two. Temperature fell to 99° F. (37.2° C.) and patient felt better. On April 19 the leucocytes numbered 6,100 (eosinophils 10%).

Stage 2 (April 20–28): Exfoliative Dermatitis.—On April 20, after 27.5 g. streptomycin and 504 g. P.A.S., patient complained of nausea, dyspnoea, and pain in right side of chest. Temperature rose to 101.4° F. (38.6° C.). Next day she had a rigor and vomited; temperature 103.4° F. (39.7° C.). An intensely irritating maculo-papular rash appeared on the abdomen and rapidly became generalized, affecting particularly extensor surfaces of the forearms and legs, where it soon became vesicular and later haemorrhagic. Face swollen and puffy; glands in posterior triangle enlarged and tender. Tongue and inside of mouth became ulcerated; swallowing, even of fluids, was exceedingly difficult and painful. Motions were loose (no pathogens isolated); urinary output fell to 15 oz. (425 ml.) a day. Leucocytes numbered 44,000 (eosinophils 19%) on April 25, and 70,000 (eosinophils 19%) on

April 27. This high count was probably due in part to haemoconcentration, as erythrocytes rose at the same time by a million cells per c.mm.

Stage 3 (April 29–May 11): Liver and Kidney Damage.—On April 29 temperature again rose suddenly to 103.6° F. (39.8° C.), and remained elevated for three more days. Urine (May 1) contained albumin and numerous granular and leucocyte casts; on May 3 sclerae were yellow and the liver edge, though barely palpable, was tender. Urine (May 4) showed large excess of urobilin and urobilinogen, but no bile salts. Thymol turbidity (May 5), 20 units; serum alkaline phosphatase, 49 units. Van den Bergh reaction, direct positive. Stool pale in colour. Temperature rose to 103.8° F. (39.9° C.) on May 7, with subsequent deepening of the jaundice. E.S.R. (3/12 on April 21) rose to 78/104 on May 6. Patient showed signs of mental confusion, and complained of tingling in hands and feet. Right plantar response definitely extensor, left doubtful. Blood urea (31 mg. on May 5) rose to 99 mg. on May 9. On May 10 urine still contained albumin and casts, but leucocytes had fallen to 8,900 (eosinophils 14%).

Stage 4 (May 11 onwards): Recovery.—Temperature returned to normal. Skin began to peel extensively all over the body. Tongue improved greatly and patient was able to swallow normally. Jaundice faded and the liver lost its tenderness. Thymol turbidity test gradually fell to normal. Urine returned to normal. Hair on scalp fell out as the skin peeled, but later grew strongly. Skin remained roughened and itchy for several weeks.

During the whole period of the reaction there was no extension of lesions in the lungs, and a radiograph taken with a portable machine (April 21), with rash at its height, actually showed improvement, the previously noted spread in the right mid-zone having cleared. A film (May 12) after the period of jaundice and albuminuria showed no extension of disease, but a later film (June 9) revealed a new wedge-shaped area of consolidation in the right upper zone with a central cavity. Sputum increased from a trace (positive) to 5 oz. (130 ml.) (also positive), and cough became troublesome. Later this area slowly resolved and two-stage thoracoplasty was performed (December 6 and 21).

Post-operatively, an acute effusion developed within two days in the Semb space, and on January 9, 1951, aspirated fluid grew *Staph. aureus*. Penicillin, 1,000,000 units twice daily, was administered, but had to be stopped when widespread punctate rash developed on trunk, face, and limbs. The patient then made an uneventful recovery and was discharged from hospital well and sputum-negative on April 20.

Treatment

Streptomycin and P.A.S. were discontinued on April 20, when the generalized rash appeared. Diphenhydramine hydrochloride, 50 mg. twice daily, was given by mouth, and mepyramine hydrogen maleate cream applied to skin. Later, mepyramine, 100 mg. thrice daily, and promethazine hydrochloride, 25 mg. at night, were tried, but produced little significant change. Twice-daily intravenous injections of calcium gluconate (10 ml.) brought about temporary alleviation of the intense itching, but were otherwise unhelpful. Intravenous sodium thiosulphate produced no alleviation. Lotio calaminae with phenol 1% had a soothing effect locally. Following adrenaline, 0.5 ml. subcutaneously every six hours, the rash began to subside and the eosinophil count fell rapidly, but it would be unwise to conclude that the adrenaline was the responsible agent. It is worth noting that sunlight appeared to exacerbate the rash and increase the irritation.

The sore mouth was a distressing feature. Vitamin-B complex was given, and considerable relief was obtained by the patient retaining in her mouth for several minutes at a time a 1:6 solution of sodium sulphate. She was encouraged to take glucose and protein drinks. Potassium citrate, 30 gr. (2 g.), was given six-hourly.

Subsequent Investigations.—A series of patch tests was carried out on the forearms and repeated on the back.

There was a strong reaction to sodium P.A.S. 5%, to meta-aminophenol 1%, to streptomycin, and to dihydrostreptomycin. Sodium salicylate up to 20% produced no reaction.

A test dose of 3 g. P.A.S. by mouth resulted in a sharp rise of temperature to 101° F. (38.3° C.) associated with headache and reappearance of a papulo-vesicular rash on the extensor aspects of forearms and legs. A test dose of 0.5 g. streptomycin intramuscularly produced a generalized papular rash which faded within three days; there was no temperature reaction or eosinophilia.

Discussion

Acquired hypersensitivity to P.A.S., streptomycin, and penicillin has been recorded by McKendrick (1951), whose patient, a man aged 27, also developed hepatitis following a rash. As in the present instance, streptomycin and P.A.S. were given together. While it may be difficult to determine which drug was the original precipitating factor, there is evidence that the administration of P.A.S. is apt to result in liver damage. Streptomycin in the pure form now available seems to have little or no deleterious effect on the liver, either in human beings or in the experimental animal (Riggins and Hinshaw, 1949). P.A.S., on the other hand, has several times been said to produce hepatitis when administered alone (Cuthbert, 1950; Scott and McCann, 1950; Livingstone and Street, 1950). The reaction to P.A.S. seems to be violent and tissue damage severe, but a fatal outcome is generally avoided; indeed, complete recovery appears to be the rule, although it is highly probable that the state of hypersensitivity persists indefinitely. Desensitization is practicable, but should not be expected to be effective against drugs other than the one in question, and even then its action may not be permanent.

Sensitivity to streptomycin and penicillin, though not common, is to some extent explained by the fact that there is some slight antigenic similarity in the products of all fungi; thus Bedford (1951) describes a different example of the same thing—a violent reaction to aureomycin in a patient known to be sensitive to penicillin. Even the ordinary tinea infection of the feet and groins appears to possess this common antigenic property. The simultaneous acquisition of sensitivity to P.A.S. and streptomycin, however, seems to occur too often to be explained on the basis of an increased liability to develop multiple sensitizations in a potentially allergic individual. Nevertheless, at present there does not seem to be an alternative explanation. It is our impression, however, that a patient who has become sensitive to P.A.S. is particularly apt to exhibit toxic phenomena when other drugs are administered. Thus, another patient in this hospital who initially became sensitive to P.A.S. has since reacted violently to streptomycin, penicillin, and "sulphatriad" (but not to thiosemicarbazone).

It is also apparent that P.A.S. may cause hypersensitivity to certain chemically allied substances; this fact does not seem to have been stressed in previous reports on the subject. Mayer (1928) first noted that sensitization caused by substances containing an aminophenol group may on occasion be caused by that group and not by the whole molecule. He explained this by showing that the skin transforms all these substances to quinone-imines and di-imines, or their derivatives, and that it is to these that the reaction occurs. Although sensitization may occur in this manner with any aminophenol group, it is when the amino radical is in the *para* position that it is commonest. This cross-sensitization is illustrated by two further cases of P.A.S. sensitivity which we have seen. One developed an acute generalized skin rash when given 0.5 g. sulphatriad by mouth, while the other gave markedly positive patch tests to 1% dilutions of P.A.S., *para*-aminobenzoic acid, sulphamamide, procaine, *para*-phenylenediamine (the active ingredient in a well-known hair dye), *meta*-aminophenol, and *para*-aminophenol. The reaction to *para*-aminophenol was distinctly more pronounced than that to *meta*-aminophenol.

It is our belief that P.A.S. itself can be responsible for producing sensitization and that *meta*-aminophenol, some-

times present as a contaminant in P.A.S., need not be invoked as the guilty agent. Thus the use of freshly prepared solutions only, while desirable, will not necessarily prevent the development of P.A.S. sensitivity. For the patient's future safety we advocate patch testing in every known instance of P.A.S. sensitivity, at least against the drugs mentioned. These substances are commonly used in medicine to-day, and the list of drugs containing an aminophenol group is very long, including, among others, sulphadiazine, sulphaguanidine, and picric acid. Testing against the sulphonamide group of drugs is of special importance because of their wide general application. Procaine may be equally important, but we have used it as an anaesthetic agent in several P.A.S.-sensitive patients without apparent ill effect.

With regard to the more specifically tuberculous aspects of streptomycin-P.A.S. sensitivity, the possibility of this development can no longer be ignored when considering the application of chemotherapy in a patient suffering from tuberculosis. Besides the risk of damage to the liver, kidney, skin, and other organs (including possibly the central nervous system) further treatment may be prejudiced—particularly resection, should this be required. P.A.S., because of its alleged harmlessness, has perhaps been employed rather more freely than would otherwise have been the case, but present knowledge of the profound bodily disturbance it may cause emphasizes the need to avoid indiscriminate chemotherapy.

It should be mentioned that our patient had no previous history of allergic phenomena other than a mild upset, possibly due to food, during childhood. The hypersensitivity appeared to develop purely as a result of drug administration. The severity of the reaction which occurred is all the more disturbing because there is no direct clue regarding which patients are likely to prove susceptible. When administration of the drug has begun, however, *particular attention should be paid to any unexpected rise of temperature, especially during the period two to four weeks after the beginning of treatment*, which appears to be the usual time for reactions to develop. In patients who have had P.A.S. previously, hypersensitivity may of course occur much earlier.

Finally, the possibility that P.A.S.-sensitive patients may develop local sensitization phenomena must be remembered. Our patient had a severe effusion into her Semm space following thoracoplasty, and, in retrospect, the possibility of its being due to the sulphathiazole-penicillin powder dusted into the space at operation has to be considered, although no generalized rash developed at the time. It is, on the whole, perhaps advisable to avoid using sulphathiazole powder or tablets in this way in P.A.S.-sensitive patients.

Treatment of the condition with A.C.T.H. was considered, but at the time it was felt that the danger of producing spread of the tuberculous lesion was best avoided. If A.C.T.H. had been administered it would have been difficult to avoid the charge that it was responsible for the spread of disease in the right lung, which did, in fact, occur after the acute reaction had settled down. Even so, the employment of A.C.T.H. in carefully graded doses remains a possibility in patients with tuberculosis who have developed acute drug-sensitivity.

Summary

The case history is given of a patient who suffered from a severe general toxic reaction to combined P.A.S.-streptomycin. Skin, alimentary tract, liver, kidney, and bone marrow all gave evidence of considerable damage, and the central nervous system may also have been affected. The patient later developed hypersensitivity towards penicillin.

Treatment adopted is outlined. Particular attention should be given to the mouth and to the protection of the liver by the administration of glucose in the early stages. The patient's skin should be protected from direct sunlight.

As a preventive measure it is important to stop P.A.S. as soon as any unexpected rise of temperature occurs; in susceptible patients this usually occurs two to four weeks after the beginning of treatment.

If sensitivity to P.A.S. has already developed it would seem that reaction to other drugs may more readily occur, particularly those containing an aminophenol group in the *para* position—for example, certain sulphonamides, picric acid, hair dye. The routine patch testing of P.A.S.-sensitive patients towards such drugs is advocated; it is preferable to begin with a 1% solution of each. The patient should be told what drugs to avoid.

The mechanism whereby hypersensitivity to a heterogeneous group of drugs becomes established is not properly understood and requires further elucidation. The mechanism of desensitization would also repay fuller investigation.

The development of drug hypersensitivity imposes limitations as regards future treatment; this aspect further emphasizes the need to avoid indiscriminate chemotherapy.

A description of this case from the nursing point of view, by Sister J. Kenshole, appeared in the *Nursing Mirror* of November 16, 1951, p. 151.

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TECHNIQUE OF JELLY (TUBERCULIN) TESTING

SOME FURTHER OBSERVATIONS

BY

J. D. LENDRUM, V.R.D., M.B., Ch.B., D.P.H.

Medical Director of the Portsmouth Mass Radiography
Unit of the South-west Metropolitan
Regional Hospital Board

Recent correspondence in the medical journals shows that all physicians are not yet satisfied with this test. This may be due to technique, for it has been shown (Lendrum, 1951) that the test as described gives better results than the 10 T.U. (tuberculin units) Mantoux test, although fewer positive findings than the 100 T.U. test—perhaps an advantage when the non-specific element of the latter is taken into account (Long and Seibert, 1937; Furcolow *et al.*, 1941; Furcolow and Robinson, 1941; W.H.O., 1948).

When Dick (1950) described the technique, using flourpaper and P.P.D. jelly, he noted a discrepancy in results between P.P.D. and O.T. jellies which he was unable to explain and which I, having noted the same discrepancy independently, suggested was due to insufficient lapse of time before the test was read.

The investigations reported here are considered to be of importance, as they explain the discrepancies in results, as well as the dissatisfaction of some physicians.