is greater than the value of the L.F.L. Thus, if we require that the L.F.L. should exceed the minimum potency we wish to secure, the "desirable" potency, we shall be fairly safe in assuming that accepted batches are of satisfactory quality.

However, we do not know the "desirable" potency exactly, and we shall err on the safe side if we use the upper fiducial limits (U.F.L.) given in Tables IV and V: (a) assuming no deterioration (Table V), the "desirable" potency has a U.F.L. of 0.66 times the standard; and (b) assuming deterioration to have occurred (Table IV), the "desirable" potency has a U.F.L. of 3.2 times the standard.

If we now require that the L.F.L. of the *estimated* potency in a routine assay shall exceed one of these levels—namely, 0.66 or 3.2 times the standard—we shall have a high probability that the *true* potency of the vaccine exceeds the *true* value of the "desirable" level.

Furthermore, if we require that the L.F.L. in a routine assay shall be greater than 50% of the estimated potency, then we must set the requirement for estimated potency at about 1.3 and 6.4 times the standard. These are the two extremes. The choice might fall on either, or on some figure intermediate between them. As we have seen, whatever the choice may be, it must be arbitrary, and it must lie with the legal authorities.

We can, however, conclude that a measure of control is now practicable, and we would accordingly endorse the recommendation to this effect in the M.R.C. report.

The experimental work upon which this paper is based was carried out by Dr. A. E. Francis, of the Wellcome Research Laboratories, Beckenham, Kent, U.K.; Dr. M. Pittman, of the National Institutes of Health, Bethesda 14, Maryland, U.S.A.; Dr. A. F. B. Standfast, of the Lister Institute, Elstree, U.K.; and Dr. J. Ungar, of the Glaxo Laboratories, Greenford, Middlesex, U.K. We are greatly indebted to them for undertaking the work and for allowing us to quote from it.

REFERENCES

- Evans, D. G., and Perkins, F. T. (1953). *J. Path. Bact.*, 66, 479.
 — (1954). *Ibid.*, 68, 251.
 Irwin, J. O., and Standfast, A. F. B. (1957). *J. Hyg. (Lond.)*. In press.
 Jerne, N. K., and Perry, W. L. M. (1956). *Bull. Wild Hlth Org.*, 14, 167.
 Kendrick, P., Elderling, G., Hornbeck, C., and Baker, J. (1955). *Amer. J. publ. Hlth.*, 45, 1131.
 Medical Research Council (1956). *British Medical Journal*, 2, 454.
 World Health Organization (1953). *Wild Hlth Org. techn. Rep. Ser.*, No. 61.

SENSITIZATION TO P.A.S., STREPTOMYCIN, AND ISONIAZID

BY

PETER MACPHERSON, L.R.C.P.&S.Ed.
L.R.F.P.S.

Tuberculosis Physician, County of Argyll

During the latter part of 1952 several articles relating to the simultaneous development of sensitivity to P.A.S. and streptomycin were published in the *British Medical Journal* (Cuthbert, 1952; Julian, 1952; Jeffery *et al.*, 1952; Macpherson, 1952). The cases described were the first of this nature to be reported.

I have seen no previous record of a patient who proved more or less simultaneously hypersensitive to P.A.S. and isoniazid and possibly also to streptomycin.

Case Report

A man aged 62 was admitted to hospital on April 22, 1955, and found to have bilateral pulmonary tuberculosis. On May 17 a course of isoniazid, 300 mg., plus P.A.S., 15 g., daily was begun. On June 16 he developed a rash which was ascribed to P.A.S. sensitivity, and the administration of this drug was discontinued. The isoniazid was continued. By June 19 the rash had greatly diminished in intensity, and streptomycin, 1 g. daily, was substituted for the P.A.S.

The patient was transferred to the County Sanatorium, Oban, on June 22. As the rash was again increasing in extent and intensity drug treatment was discontinued. By June 27 there occurred oedema of the eyelids, exfoliative rash on the face and upper part of the trunk, swelling of the forearms associated with papular rash, and punctate erythema over the lower part of the trunk.

Desquamation of the whole face, head, upper trunk, and upper limbs occurred during the ensuing three weeks.

On July 28 a test dose of one 50-mg. tablet of isoniazid was given at 10 a.m., as it was assumed that this was the least likely of the three drugs to have caused the sensitization. No reaction followed, and another tablet was given at 6 p.m. At 9.30 p.m. he complained of headache. His temperature was 100.2° F. (37.9° C.) and he had a generalized erythematous rash. During the next few days he developed oedema of the right eyelid and a papular rash on the right forearm.

On August 4 desensitization to isoniazid was begun: 12.5 mg. was given orally, the dose being increased by 12.5 mg. daily until he was receiving 200 mg.

As recrudescence and considerable worsening of the initial rash had occurred coincidentally with the beginning of streptomycin therapy, it was thought wiser to proceed with desensitization to this drug rather than risk a further recurrence of the sensitivity reaction. While the course of isoniazid was continued, 20 mg. of streptomycin in 0.06 ml. was injected intradermally on August 20 without upset. However, the dose of 40 mg. on the second day resulted in an indurated and erythematous reaction which persisted for 36 hours round the site of injection. The same dose was repeated the following day. Thereafter the daily dose was increased slowly to 1 g.

By November 27 he had completed a 90-g. course of streptomycin. Isoniazid was continued and desensitization to P.A.S. was begun, using sodium P.A.S. in the strength of 6 g. per fl. oz. (21 g. per 100 ml.). A test dose of $\frac{1}{2}$ dr. (1.75 ml.) at 9 a.m. produced no reaction. Further $\frac{1}{2}$ -dr. (1.75-ml.) doses were given at intervals of 2½ hours, until 9.30 p.m. During the next few days the single dose was increased to $\frac{1}{4}$, 1, 1½, and 2 dr. (2.6, 3.5, 5.2, and 7 ml.), and on December 3 to 3 dr. (10.5 ml.) six times daily.

On December 4 his temperature rose to 99° F. (37.2° C.) the respiratory rate increased, the face became flushed, and a punctate erythema appeared on the trunk, upper arms, and legs, and a papulo-erythematous rash on the forearms. P.A.S. was discontinued. On December 6 he was still moderately breathless. In view of the case reported by Cuthbert (1954) an x-ray film of the chest was taken, but there was no evidence of Löfller's syndrome. However, there was an eosinophilia of 11%.

Because the pulmonary condition merited long-term drug treatment a further attempt at desensitization was begun on January 20, 1956, and proved successful. On this occasion the daily dose was increased more slowly.

Discussion

Allied Chemical Compounds.—Mayer (1928) noted that sensitization to substances containing an aminophenol group may be caused by that group and not by the whole molecule. He showed that the skin transforms these substances into their derivatives and that it is to these that the reaction occurs. This is more common when the amine radical is in the para position. Jeffery *et al.* (1952) reported a case of P.A.S. sensitization which developed an acute generalized skin rash when 0.5 g. of "sulphatriad" was given, and another in which patch tests were markedly positive to 1% dilutions of P.A.S., para-aminobenzoic acid, sulphanilamide, procaine, para-phenylenediamine, meta-aminophenol, and para-aminophenol.

Antibiotics.—There appears to be some slight antigenic similarity among the members of the antibiotic group. Bedford (1951) reported that a patient known to be sensitive to penicillin developed a violent reaction to chlortetracycline.

Acquired hypersensitivity to streptomycin and penicillin, also to P.A.S., has been recorded by McKendrick (1951) and by Jeffery *et al.* (1952).

Heterogeneous Drugs.—Julian (1952) regarded the occurrence of simultaneous sensitization to streptomycin and P.A.S. to be most probably coincidental. Since then there has been a growing weight of evidence to suggest that a patient sensitive to one of these drugs is particularly apt to show sensitivity to others. I have noticed that, although various types of drug rash may result from sensitivity to either streptomycin or P.A.S., in a case where dual sensitization has developed the form of rash, and indeed the whole reaction, tends to be similar when each drug is tested separately. In the case described above isoniazid was likewise incriminated. It seems a reasonable assumption that a state of drug sensitization, once induced, in some way renders the individual at least temporarily more susceptible to other drugs with potential sensitizing properties. P.A.S. has been blamed as the most frequent precipitating agent in this type of multiple sensitivity state (Jeffery *et al.*, 1952). In the case reported above, the sensitization to P.A.S. was definitely the first to develop, though a further severe reaction to P.A.S. was not associated with the development of re-sensitization to isoniazid.

Conclusions

Sensitivity reactions to P.A.S., isoniazid, streptomycin, and probably other antibiotics may be identical, and if a combination of these drugs is given, any or all of them may be involved in a state of sensitization. Accordingly, in a sensitivity state associated with combined therapy one is no longer justified in assuming that a single drug is responsible. All drug therapy should be discontinued and a test dose of each drug given, if one would avoid risking further discomfort for the patient. In the case reported fairly severe subsequent reactions occurred to both isoniazid and P.A.S. before full dosage had been reached, despite the fact that the test dose with these drugs had proved negative. After a sensitivity reaction it is now our practice to carry out a modified desensitization programme where the initial test dose of a drug produces no reaction, as well as full desensitization to a drug which gives a positive reaction.

The occurrence of a sensitivity reaction also indicates that care will be necessary in the future and that an initial test dose will be desirable before administering allied preparations or another antibiotic.

I am grateful to Dr. A. S. Hutcheson, consultant tuberculosis physician, Argyll Area, for criticism of this article and for permission to publish the case.

ADDENDUM.—Since this article was submitted for publication I have had a case similar to the one reported above. A man aged 37 was admitted from another hospital and stated that he had developed a streptomycin rash after having been for 80 days on a combined course of streptomycin, 1 g., and isoniazid, 300 mg., daily. Four months after his eruption we gave him a test dose of isoniazid and later of streptomycin. With both drugs he developed features which he reported were identical with his initial sensitivity reaction (fiery erythematous rash on the anterior aspects of the elbows and in the axillae, and oedema of the eyelids; mild eosinophilia was also present).

REFERENCES

- Bedford, P. D. (1951). *British Medical Journal*, 1, 1428.
Cuthbert, R. J. (1952). *Ibid.*, 2, 1205.
— (1954). *Ibid.*, 2, 398.
Jeffery, Barbara, Borrie, P., and Macdonald, N. (1952). *Ibid.*, 2, 647.
Julian, D. G. (1952). *Ibid.*, 2, 476.
Macpherson, P. (1952). *Ibid.*, 2, 723.
McKendrick, G. D. W. (1951). *Lancet*, 2, 668.
Mayer, R. L. (1928). *Arch. Derm. Syph. (Berl.)*, 156, 656.

CLEANSING OF HOSPITAL BLANKETS

BY

B. R. FRISBY, M.D.

*Senior Bacteriologist, Public Health Laboratory Service
(M.R.C.), Oxford, and Department of Bacteriology,
Radcliffe Infirmary, Oxford*

As part of the investigation into staphylococcal diarrhoea (Cook, Elliott, Elliot-Smith, Frisby, and Gardner, 1957) the bacterial flora of the blankets at the hospital concerned was examined.

In October, 1955, the criteria used for selecting blankets for washing were as follows: (1) a patient using them had died; (2) an obviously infectious patient had used them; and (3) they looked dirty. The latter contingency arose usually after the blankets had been in use some 12 weeks or more. These criteria are obviously unsatisfactory. The blankets from the bed of a patient who had died may be comparatively clean. Patients who are carriers of pathogenic organisms may contaminate blankets as heavily as an overt case. Finally, blankets may be heavily contaminated and still appear quite clean.

The blankets were washed in a Manlove and Alliott open pocket machine with intermittent rotation gear with the water at 37° C. and using a commercial detergent. They were sampled by the technique used by Blowers and Wallace (1955). The medium used for culture was horse-blood-agar, and an area of about 18 in. (45 cm.) square of each blanket to be tested was swept in ten forward-backward strokes of the plate.

In most tests the counts obtained from both the dirty and the clean blankets at this time were very high. Of 115 dirty blankets sampled, 44 (38%) yielded uncountable plates—that is, at least 500 colonies per plate. Scanty growths of *Staph. aureus* were obtained from 18 (15.7%) of the blankets. The corresponding washed blankets, of which 59 were tested, also gave high counts, the majority being over 100 colonies per plate, and 1 (1.7%) giving a scanty growth of *Staph. aureus* (see Table I). Most strains of *Staph. aureus* belonged to group III and were resistant to penicillin.

The number of bacteria obtained by this sweep-plate method was compared with that obtained by homogenizing a given area of blanket and performing total counts. Portions of ordinary dirty blanket 1 sq. in. (6.4 sq. cm.) in size were placed in 15 ml. of digest broth in an "M.S.E." homogenizer and run at 18,000 r.p.m. for 15 minutes with crushed ice in the cup-holder to prevent overheating. Dilutions of the homogenate were then made in broth and the organisms present counted by the pour-plate method, using nutrient agar at 22° C. and 37° C. These experiments showed that the sweep-plate picked up 1 in 10,000 to 1 in 20,000 of the organisms actually present. A blanket having a sweep-plate count of 200 would therefore have an actual count of 2 to 4 million organisms for each section 18 in. (45 cm.) square, giving a calculated count for the whole blanket of some 40–80 million organisms.

Experimental Tests

From these findings it was obvious that the blankets were a rich source of bacteria and that they harboured *Staph. aureus*. The "lissapol-cirrasol" method of cleansing blankets as described by Blowers and Wallace (1955) was then instituted experimentally. To facilitate sampling, distinctive peach-coloured blankets were issued to B ward