Patient R. W. had actinomycosis of the lung with an empyema. On admission a heavy and pure growth of *Actinomyces* was isolated, but after 21 million units of penicillin this organism disappeared and pus from the empyema gave a pure growth of penicillin-resistant *Staph. pyogenes*.

The question arises, Where do these penicillin-resistant organisms come from? In some cases—as, for example, patient R. C.—they are clearly present in the original lesion but overgrown by sensitive strains until penicillin treatment leaves them a clear field by getting rid of the latter. Hospital infection with *Staph. pyogenes* is, however, fairly common, and, as Harley *et al.* (1946) have shown, penicillin-resistant staphylococci occur far more often in patients who have been in hospital some time than in new admissions. In any hospital using large quantities of penicillin (and what hospital is not nowadays?) bacteria resistant to its action are probably increasing at the expense of those that are sensitive, and it seems not impossible that in time the resistant organisms will be the sole survivors. That a penicillin-resistant strain of *Staph. pyogenes* once it has got a footing in the hospital may spread from patient to patient is well illustrated by a series of cases occurring in a particular unit of this hospital, referred to hereafter as "Unit X." Throughout the two investigations the percentage of penicillin-resistant strains was higher in Unit X than elsewhere in the hospital (see Table I); five resistant and two sensitive cultures isolated from this unit during a single month were therefore sent to Dr. Allison and Dr. Hobbs for typing. The results are shown in Table III. It will be

TABLE III.—Strains of *Staph. Pyogenes* Isolated from Unit X

Source	Date of Isolation	Reaction to Penicillin	Phage Reaction	Serological Reaction
Breast milk	9/10/46	Resistant	6/47	III
" " " " " "	18/10/46	"	6/47	III
Caesarean wound ..	27/10/46	"	6/47	III
Cracked nipple ..	22/10/46	"	6/47	III
Sticky eye	4/11/46	"	6/47	III
Breast milk	20/10/46	Sensitive	Nil	I
" " " " " "	20/10/46	"	Nil	I

seen that all five resistant strains were of the same type and that the sensitive organisms were of the same type as each other but different from that of the resistant bacteria.

Detection of Penicillin-resistant Strains

From observations made during this investigation it seems that the best method for the detection of penicillin-resistant bacteria in specimens sent to the laboratory is to plate out the infected material direct on to a penicillin ditch-plate, using a concentration of about 10 units of penicillin per ml. of agar in the ditch (Figs. 1 and 2). Although this method is in fact used in many routine bacteriological laboratories the following two reasons for its superiority over other methods are not generally appreciated.

1. Most methods described for determining the penicillin sensitivity of bacteria ignore the size of inoculum used, as it was claimed that within wide limits this made little or no difference to the results (Fleming, 1942; Abraham *et al.*, 1941). As shown by Luria (1946) and Barber (1947), this is far from the case with penicillinase-producing bacteria. With such organisms a small inoculum may appear to be fairly sensitive to penicillin, whereas a large inoculum will grow in a concentration of 100 or more units per ml. This is well illustrated by plating out pure cultures of penicillin-sensitive and penicillin-resistant staphylococci on penicillin ditch-plates. Fig. 2a shows a sensitive culture which gives a fairly straight line of inhibition. Fig. 2b, on the other hand, shows a pure culture of penicillin-resistant staphylococci, and it will be seen that where the inoculum is heavy the organisms have grown right across the penicillin agar, but as the number of bacteria gets smaller an increasing amount of inhibition of growth occurs. Such a picture is seen only with penicillinase-producing organisms.

A bacterium, such as *Salmonella typhi*, which is resistant to penicillin but does not destroy it, when plated on a penicillin ditch-plate produces a straight line of growth which usually reaches the penicillin agar when a concentration of 10 units per ml. is used. Thus by this method some information on both the degree and the type of resistance is obtainable.

2. Swabs from many staphylococcal lesions contain a mixture of sensitive and resistant strains. In some cases before any penicillin treatment has been started the number of resistant bacteria is very small, as illustrated by Case R. C., and they may be missed by simply testing a number of individual colonies. If, however, the material is plated direct on to a penicillin ditch-plate, as few as 1 resistant to 10,000 sensitive bacteria may be detected (Fig. 2c), and by comparison with known mixtures some idea of the proportion of resistant to sensitive strains may be determined. Thus the bacteria in the sputum of R. C. when replated (Fig. 2f) showed a similar picture to a mixture of 1 part resistant to 250 parts sensitive staphylococci (Fig. 2e).

Summary

In studying strains of *Staph. pyogenes* isolated from 100 cases of staphylococcal infection 38 patients were found to have penicillin-resistant strains; 10 patients had a mixture of penicillin-resistant and penicillin-sensitive staphylococci.

The source of these strains and the best method for their detection are discussed.

My thanks are due to Drs. Allison and Hobbs for typing, and to Drs. Anderson and Fullerton for the primary isolation of many strains.

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ALLERGY TO PENICILLIN WITH SYMPTOMS OF SERUM SICKNESS

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Toxic side-reactions and allergic symptoms following the administration of penicillin have lately attracted a good deal of attention in the U.S.A. Two papers published there dealing with this subject (Morginson, 1946; Holden, 1947) include a fairly comprehensive review of the literature. In this country Suchecki (1946) and Willcox (1946) described series of cases, and the former reviewed some of the literature. A number of single case reports have also been published in both countries, and these emphasize the variety of symptoms which may occur. One of the severest syndromes is a reaction similar to serum sickness, with some of the symptoms of anaphylactic shock. Feinberg (1944) and Rostenberg and Welch (1945), investigating the origin of this hypersensitiveness, suggest that, at least in the U.S.A., sensitization is brought about by ingestion or inhalation of *Penicillium* spores. These produce subclinical infections in approximately 5 to 6% of persons of allergic diathesis. No such data are available for this country. Feinberg's skin tests suggest that some batches of penicillin are tolerated better than others by allergic persons.

The following account of a case with severe and at times alarming symptoms is interesting for two reasons: (1) the same symptoms occurred twice, with increased severity on

the second occasion; and (2) the fact that intracutaneous sensitivity tests made it reasonably certain that the impurities in the penicillin preparations were implicated more than the penicillin in causing the symptoms.

Case History

On the night of July 24, 1945, a female patient aged 34, three weeks post partum, developed a sudden rigor. There was a painful induration and redness of the right lower quadrant of the right breast. During the next 24 hours her temperature varied between 102° and 103° F. (38.9° and 39.4° C.). From July 25 to 27 16,000 units of sodium penicillin were administered intramuscularly every three hours, together with sulphathiazole (2 g. stat., followed by 1 g. four-hourly for three days). Her temperature returned to normal within 48 hours and the local breast lesion cleared up completely within 72 hours.

Two weeks later urticarial weals appeared on the scalp. During the next five or six days there developed a massive urticaria and angioneurotic oedema of the face, trunk, and limbs, with severe pruritus. There was no rise in temperature. The patient complained of a feeling of tightness in the chest; she was very pale; the pulse was thin, with a rate of 80 to 90 a minute, her normal rate being about 60. Sitting up caused severe vertigo. Adrenaline and ephedrine were administered, but did not relieve the urticaria or the pruritus, and about 12 hours later paroxysms of tachycardia developed, with a pulse rate of 120 and upwards. Without further specific treatment the condition cleared up completely within five to six days. On account of the long interval between penicillin therapy and the onset of the allergic symptoms, penicillin was not suspected as a possible causative agent.

On Feb. 22, 1946, the patient complained of a red painful swelling in her right thumb. Within the next 12 hours the swelling increased rapidly and her temperature rose to 101.5° F. (38.6° C.). A course of 16,000 units of sodium penicillin intramuscularly at three-hourly intervals, together with sulphathiazole (2 g. stat., followed by 1 g. four-hourly), was started the next day. The first injection of penicillin into the gluteus maximus was extremely painful and the patient felt collapsed. The pulse volume was fairly good, with a frequency of 62 a minute. Recovery followed within half an hour. The penicillin injections were continued for five days without further untoward effects. The local and general condition improved rapidly, apart from a feeling of tightness in the chest on the fourth day of treatment, and after seven days the patient was quite well.

On March 5, 1946, 12 days after the start of penicillin treatment, oedema of the eyelids was noticed, and the patient complained of a general feeling of weakness. In the evening she was in a state nearing collapse, with slight rigors. The temperature was 99.6° F. (37.6° C.) and the pulse was thin and rapid. Patches of urticaria appeared on the arms and back. The next day there was a generalized giant urticaria with angioneurotic oedema. The patient was somnolent and very difficult to rouse, took no food or drink, and passed no urine during the next 24 hours. The pulse rate was 80-90.

The drowsiness persisted on the following day, and the patient had pains in the wrists and feet, which were swollen. The next day she complained of soreness and tightness of the throat, and on inspection an oedema of the fauces, and of the uvula in particular, was noticed. This passed off within 12 hours. On the fourth day the general condition had begun to improve. The oedema of the face was less, but oedema of hands and feet was still pronounced. The patient now began to take food, and there was rapid improvement during the next few days. On the ninth day she was normal except for a general feeling of weakness, which persisted about two weeks.

Eight weeks after the allergic symptoms had subsided skin-sensitivity tests were carried out to determine whether penicillin or sulphathiazole had caused the severe reaction. Patch tests and intradermal injections were the methods employed. All patch tests with solutions of penicillin (20,000 units per ml.), "soluthiazole," and physiological saline were negative.

In the intracutaneous tests the following solutions were used: (1) a commercial preparation of impure penicillin (yellow); (2) a commercial preparation of pure crystalline (white) penicillin—both in a concentration of 16,000 units per ml.; and (3)

the disodium cinnamylidene dibisulphite derivative of sulphathiazole. The latter, known under the trade name of "soluthiazole," is in the form of a 45% solution, and was diluted one in five with sterile distilled water in order to obtain an isotonic solution. Quantities of 0.02 ml. of these solutions and of physiological saline as a control were injected intradermally into the upper arms, and the following reactions at the site of the injections were observed: penicillin (yellow), ++; penicillin (white), (+); soluthiazole, 0; 0.85% sodium chloride, 0.

The marked reaction to yellow impure penicillin strongly suggests that the impurities played the main part in producing the severe allergic condition, though the very weak reaction to pure crystalline penicillin also seems to implicate the penicillin as a rather mild allergen. The tests excluded sulphathiazole as a possible allergen.

Discussion

Although there are statements in the literature that renewed penicillin therapy does not necessarily produce a repetition of allergic symptoms, this case shows that the severity of the reactions may be increased considerably, and there is a possibility that each subsequent attack may tend to increase the degree of sensitivity still further. It is well to remember that there may be a considerable lag period between the administration of penicillin and the beginning of allergic manifestations. Occurrences as the one described should tend to discourage the use of penicillin in trivial infections which would clear up with the traditional conservative methods.

Willcox (1946) described the use of "benadryl" in cases with mild allergic symptoms, particularly those of urticaria after penicillin therapy. This was not freely available at the time. It remains to be seen whether severer symptoms such as the ones described in this case can be controlled effectively by antihistamine preparations.

We are indebted to Messrs. May and Baker Ltd. for a sample of "soluthiazole" and information regarding isotonic solution of the preparation; and to the Glaxo Laboratories Ltd. for a sample of white crystalline penicillin.

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CHRONIC BATTLE NEUROSIS TREATED WITH LEUCOTOMY

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From the time of Dunkirk onwards various ways of using physical methods in the treatment of acute and chronic battle neuroses have been a subject of research in this unit. Sleep treatment and barbiturate abreaction (Sargant and Slater, 1940), "front-line" sedation (Sargant, 1941, 1942), and modified insulin treatment (Sargant and Craske, 1941) have now found a generally recognized place in different stages of the rehabilitation of those breaking down under battle stress. The value of these treatments emphasizes the physiological aspects of many neurotic conditions, but so far there has been no report of the use of leucotomy in this particular group. It is the purpose of this paper to report a case in which great improvement resulted after this brain operation, one of the effects of which appears to be to reduce self-perpetuating tension within the nervous system.