incapacitated with pain for three months—was able to return to his work as a milk-roundsman for the rest of his life (nearly seven months) and die easily of a haemorrhage. He needed only one injection of 50 ml. of proctocaine. The ballet dancer, aged 46, died quietly of cardiac secondaries from cancer of the cervix uteri after two injections of 40 ml. of proctocaine, the second injection being fortified with 5 ml. of absolute alcohol, nine weeks after her first visit to us. The duration of relief with one to three injections varied in 11 others from three weeks to four months; in all but four this marked their natural term. The four developed painful secondaries in other regions, and one of them had a neurectomy for this reason.

One other, a tough Welsh miner of wonderful physique with extensive invasion of the abdominal wall by a cancer of the bladder, died apparently from exhaustion and haemorrhage under thiopentone anaesthesia, given before attempting the caudal injection, as in no other way could the unfortunate man bear being turned on his side. This was our only disaster. Necropsy was refused, so that oil embolism could not be ruled out as the immediate cause of the sudden death shortly after the caudal injection was begun. He had suffered hideous pain for some weeks before.

Two women with pelvic secondaries from uterine cancer had apparently complete relief for a few days after injection, but on return of symptoms failed to be relieved by further injection. In one, intestinal obstruction by secondaries was proved at necropsy; in the other, massive abdominal and pulmonary secondaries proved fatal under opiates.

One man with prostatic cancer was not relieved at all; radiography had revealed spinal metastases, and he was kept under morphine for the few weeks left.

I have not observed or been told of any urinary or faecal incompetence following caudal injection of proctocaine, with or without added alcohol, in any of the patients treated.

I wish to thank Drs. Constance Wood and Lilian Walter, of the Medical Research Council Radium Centre in the British Postgraduate Medical School, for referring to me patients in their wards; my colleague in the Department of Obstetrics, Dr. Hilda Roberts, who assisted me with many of the injections; and my colleagues of the Department of Surgery for asking me to treat most of the male patients mentioned in this paper.

"Diet in Pregnancy" was the subject chosen by Prof. W. C. W. Nixon for his lecture at the Royal Institute of Public Health and Hygiene on Nov. 12. Sir Jack Drummond, F.R.S., was in the chair. In a community where diet was faulty or restricted, said Prof. Nixon, the mother, expectant and nursing, and children suffered first. Did the pregnant woman differ from the rest of the community regarding her dietetic requirements? Everyone agreed that in pregnancy those were increased. Natural foodstuffs were far better than synthetic tablets. It may be argued that, with the present food restrictions, it was impossible to attain anything like the ideal diet for a pregnant woman. However, a remarkably good diet had been planned by, for example, a Scotch hospital. The nutrients were obtained only from natural foods, but the margarine was fortified with vitamins A and D, and full use made of the additional rations available for pregnant women. Recent reports from America showed the benefit that resulted from increasing the protein intake during pregnancy. It had been found that the incidence of toxaemia in pregnancy was twice as great in one group of pregnant women, where protein intake was 60–70 g. daily, as compared with a similar group whose protein intake ranged from 110 to 120 g. daily. The health of a nation could be gauged by the vital statistics of pregnancy and infancy. He would like to quote from the Report of the Chief Medical Officer of the Ministry of Health on the state of the public health during the six years of war (1939–45): "The national provision of milk and vitamin supplements . . . together with rationing and the greatly improved quality of the national loaf, has contributed to the gradual decline in the maternal, neonatal, and infant mortality and stillbirth rates." Women of younger years were only too willing to be educated in health matters when these were explained simply. It was in this way that the mothers of our country would be guided to contribute to one of the greatest measures in public health—proper nutrition.

STAPHYLOCOCCAL INFECTION DUE TO PENICILLIN-RESISTANT STRAINS

BY

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The incidence of strains of *Staphylococcus pyogenes* that are grossly resistant to penicillin is clearly increasing rapidly. The rate of increase in this hospital at present is so rapid as to be somewhat alarming. In a previous study (Barber, 1947) all cultures of *Staph. pyogenes* occurring in the routine bacteriological laboratory were tested for penicillin sensitivity; out of a series of 200 patients yielding cultures of *Staph. pyogenes* penicillin-resistant strains were isolated from 25 (12.5%). Since then cultures have been tested for their reaction to penicillin only if they came from an infected lesion. In analysing a series of 100 patients with staphylococcal infection between February and June, 1947, it was found that as many as 38 yielded penicillin-resistant strains. Table I gives a comparison of the two series. In order to make a fair comparison, in Series 1 the figures for staphylococci isolated from cases of infection are given separately as well as figures for all specimens tested. In view of the high incidence of resistant strains in Series 2 it was thought worth while to record this second series, together with some observations on the source of penicillin-resistant strains and the best method for their detection.

TABLE I.—*Analysis of Patients Yielding Staph. Pyogenes*

	From Whole Hospital			From Unit X*		
	Total	Penicillin-resistant		Total	Penicillin-resistant	
		No.	%		No.	%
Series 1. Apr.–Nov., 1946:						
All strains ..	200	25	12·5	80	13	16·25
Strains from infected lesions ..	99	14	14·1	14	4	28·55
Series 2. Feb.–June, 1947	100	38	38	25	14	56

Analysis of Resistant Strains

The degree of resistance was in all 38 cases gross (see Fig. 1), and all, except one strain which was not tested, were shown to produce penicillinase; 36 of the strains were found to have a sensitivity to streptomycin approximately equal to that of the Oxford staphylococcus; one strain was not tested against streptomycin; and one strain, which came from a patient with tuberculous meningitis who was being treated with streptomycin was resistant to it.

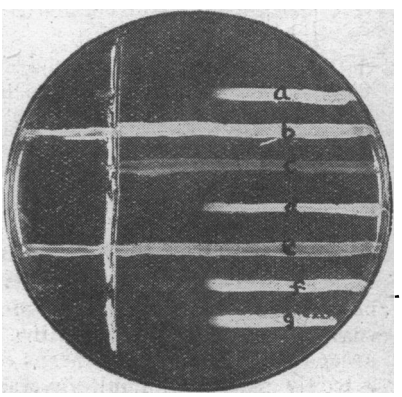

FIG. 1.—*a, d, f,* and *g* are penicillin-sensitive and *b* and *e* penicillin-resistant strains of *Staph. pyogenes*; *c* is a culture of *Salm. typhi*.

Table II analyses the patients according to type of infection. The case of septicaemia arose from an abscess in the buttock following injections for a refractory anaemia, and the outcome was fatal. The case of osteomyelitis was a chronic infection and gave a mixed growth of *Pseudomonas pyocyanea* and penicillin-resistant *Staph. pyogenes*.

TABLE II.—*Type of Infection in 38 Patients Yielding Penicillin-resistant Strains of Staph. Pyogenes*

Septicaemia	1	Otitis media	4
Extradural abscess	1	Infected operation wounds	3
Osteomyelitis	1	Puerperal infection (local)	2
Respiratory tract infections	8	Superficial lesions	5
Neonatal infections	12	Tuberculous sinus	1

The respiratory infections included bronchopneumonia, infected carcinoma of the lung, actinomycosis, bronchitis, and tracheitis. Several of these cases showed an interesting change in bacterial flora of the sputum during the course of penicillin treatment and will be referred to later. The neonatal infections consisted of four cases of ophthalmia neonatorum, two abscesses, one discharging ear, one buccal ulcer, and four superficial lesions. In most of the 38 cases *Staph. pyogenes* was the only, or at least the predominant, organism isolated; from 10 patients both penicillin-sensitive and penicillin-resistant strains of *Staph. pyogenes* were isolated from the same specimen.

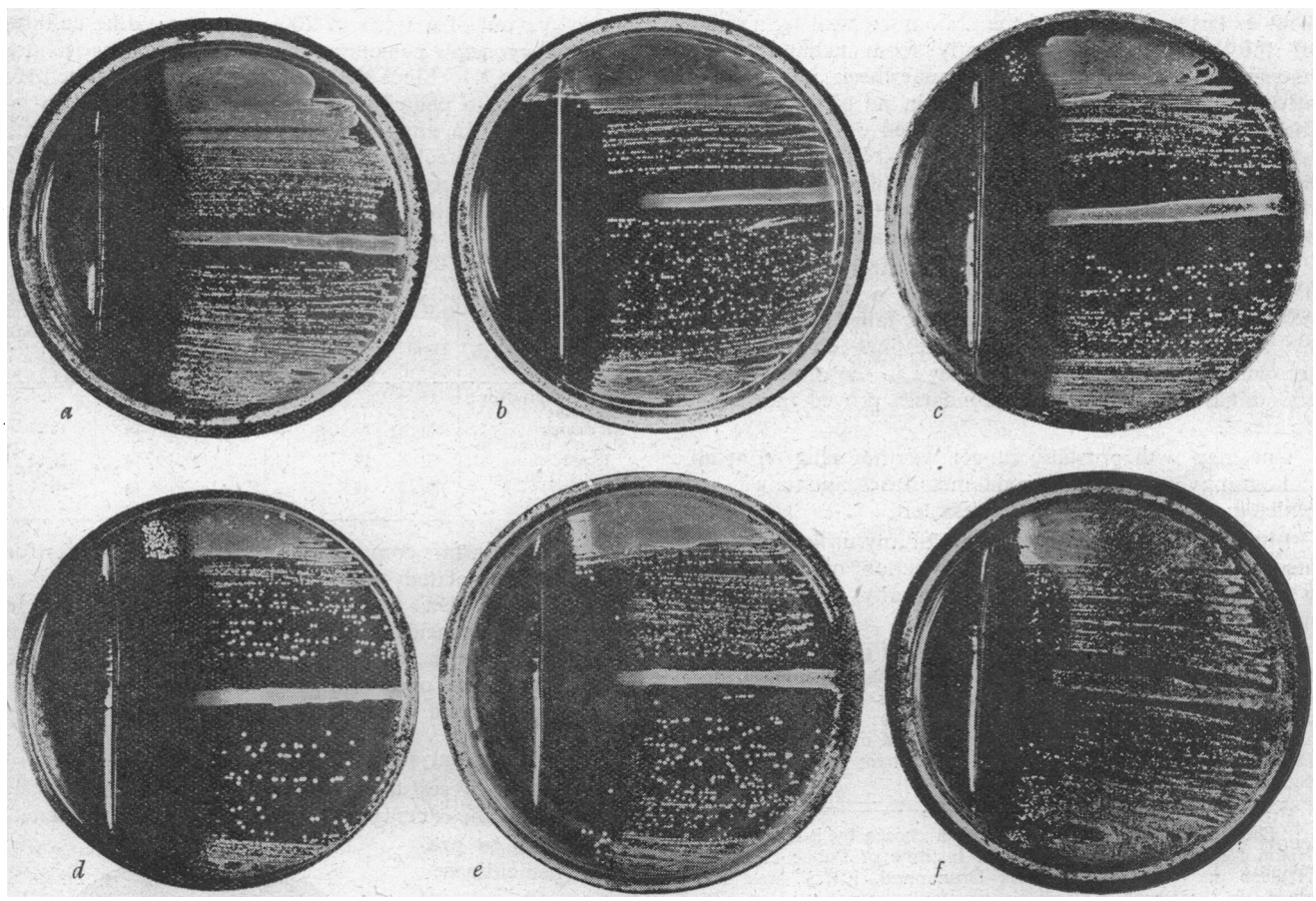

FIG. 2.—Emulsions of bacteria in broth plated out on penicillin ditch-plates with a central streak of the Oxford staphylococcus. (*a*) Pure culture of a penicillin-sensitive *Staph. pyogenes*. (*b*) Pure culture of a penicillin-resistant *Staph. pyogenes*. (*c*) One part penicillin-resistant to 10,000 parts penicillin-sensitive *Staph. pyogenes*. (*d*) One part penicillin-resistant to 5,000 parts penicillin-sensitive *Staph. pyogenes*. (*e*) One part penicillin-resistant to 250 parts penicillin-sensitive *Staph. pyogenes*. (*f*) Emulsion from sputum plate culture of patient R. C. replated on to penicilliin ditch-plate, showing that approximately 1 in 250 of the staphylococci were penicillin-resistant.

Source of Penicillin-resistant Strains

It is obvious that the main cause for this increase in penicillin-resistant strains of *Staph. pyogenes* is the widespread use of penicillin, although a patient yielding such an organism may not himself have ever had any. In the present series 28 of the 38 patients with penicillin-resistant staphylococci had had a fair amount of penicillin before the specimens were taken, two had had a few doses, and eight had had none. For the reasons stated in the previous paper (Barber, 1947) it is my opinion that these strains are not originally sensitive staphylococci which have acquired a resistance to penicillin by contact with it but are naturally resistant strains which survive by a simple process of selection in penicillin-treated infections. That such changes in bacterial flora do take place during the course of penicillin treatment is becoming increasingly clear, and is well illustrated by five of the cases of lung infection in this series.

Patient R. C., a case of carcinoma of the lung, had a sputum heavily infected with *Staph. pyogenes* shortly after admission to hospital; 30 colonies picked from the original culture plate were as sensitive to penicillin as the Oxford staphylococcus, but when a mixed emulsion from this plate was replated on to a penicillin ditch-plate it was seen that a number of penicillin-resistant organisms were present (Fig. 2*f*). Twelve days later, when the patient had had 2.8 million units of penicillin, the sputum again yielded a heavy growth of *Staph. pyogenes*, but 30 colonies tested were all found to be penicillin-resistant. Subcultures from three sensitive and three resistant colonies (one from the first sputum and two from the second) were typed by Dr. Allison and Dr. Hobbs; all three sensitive cultures were phage type 29/52 and serological type I, whereas all three resistant cultures were serological type III and were not typable by the phage method.

Patients N. H., M. H., and M. S. all had bronchopneumonia. From each the first sputum tested contained no colonies of *Staph. pyogenes*. After 15.9, 11, and 4.8 million units of penicillin respectively, the sputum of all three patients yielded a heavy growth of *Staph. pyogenes*; in patients N. H. and M. H. all the colonies tested were penicillin-resistant, but in patient M. S., who had had the least penicillin, nine colonies were found to be resistant and one sensitive to penicillin.

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 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.

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

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. 2*a* shows a sensitive culture which gives a fairly straight line of inhibition. Fig. 2*b*, 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. 2*c*), 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. 2*f*) showed a similar picture to a mixture of 1 part resistant to 250 parts sensitive staphylococci (Fig. 2*e*).

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

BY

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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