

SEPTICAEMIA DUE TO COLONIZATION OF SPITZ-HOLTER VALVES BY STAPHYLOCOCCI

FIVE CASES TREATED WITH METHICILLIN

BY

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In progressive hydrocephalus treated by a ventriculo-caval shunt using a Spitz-Holter valve, infection at the site of operation is apt to cause septicaemia. We are describing here five cases in which the problems of chemotherapy were closely studied, because (1) the valves were controlling the hydrocephalus perfectly, (2) the removal of the valve renders that internal jugular vein unsuitable for use later should a further shunt be required, and (3) the infants were not uncontrollably ill with the septicaemia. The clinical and the bacteriological approach to this study are described in separate publications (Cohen and Callaghan, 1961; Stewart, 1961).

Case 1

A male child born on March 8, 1960, with haemorrhagic disease of the newborn had a ventricular haemorrhage on the third day of life, and subsequently developed progressive hydrocephalus. Ventriculography on March 23 demonstrated a basal cistern block. A Spitz-Holter valve was inserted on May 19 to drain the cerebrospinal fluid from the right lateral ventricle to the superior vena cava. Post-operatively a 10-day course of penicillin G and sulphadiazine was given, but the temperature remained elevated—100–101° F. (37.8–38.3° C.). Tetracycline also had little effect in reducing the pyrexia. Two weeks post-operatively the temperature was fluctuating between 97 and 99.5° F. (Fig. 1), the spleen was just palpable, and *Staphylococcus albus* was isolated from the blood. The organism was resistant to penicillin G (10 µg./ml.), sulphadiazine, and tetracycline, but sensitive to methicillin,* which had a bactericidal effect at 2.5–5 µg./ml. This drug was given by six-hourly intramuscular injection in a dose of 100 mg./kg./day for 150 days. During this time there were several small spikes of temperature (Fig. 1), the haemoglobin fell from 85% to 60%, and the spleen remained just palpable. Blood cultures always produced staphylococci, and the strain of *Staph. albus* isolated after 150 days' treatment was fully resistant to 10 µg. of methicillin per ml.

Case 2

An oxycephalic boy born on May 12, 1959, presented at 9 months of age with signs of raised intracranial pressure. Ventriculography in March 3, 1960, demonstrated a sub-

*Previously referred to as BRL 1241 ("celbenin," "staphicillin").

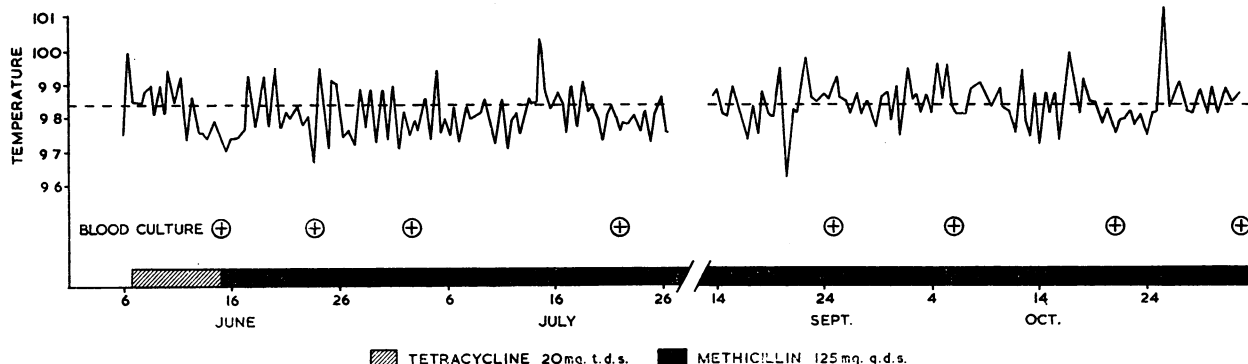


FIG. 1.—Effects produced by systemic tetracycline and long-term methicillin.

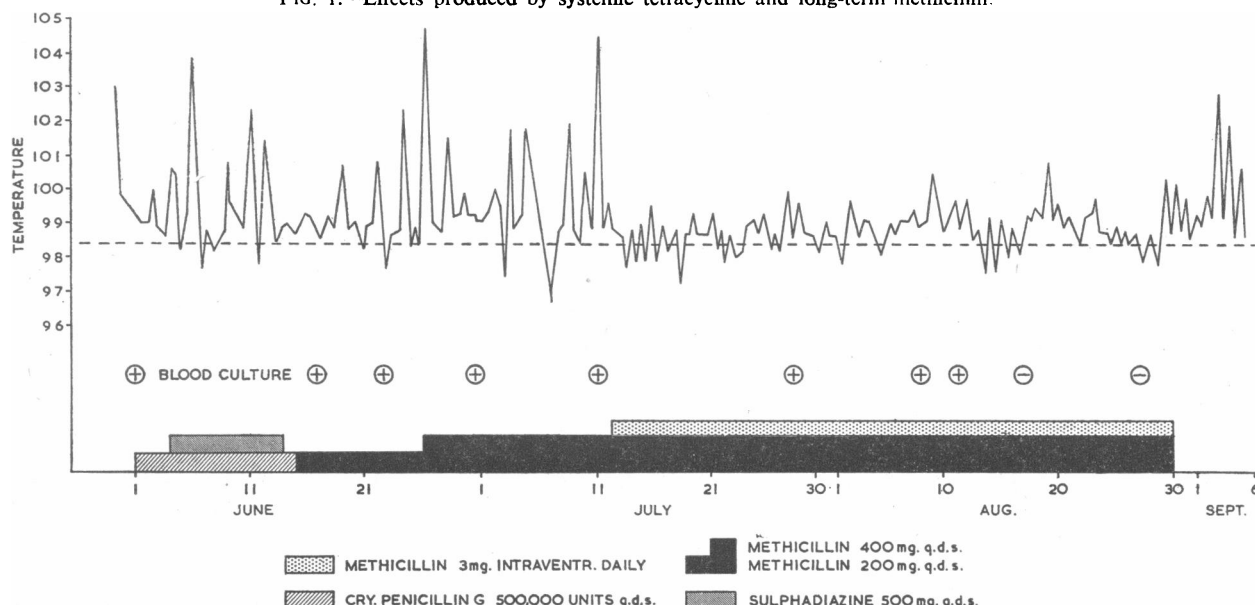


FIG. 2.—Intraventricular methicillin was the factor in reducing the pyrexia and sterilizing the blood.

tentorial block giving rise to gross internal hydrocephalus. A Spitz-Holter valve was inserted on March 10. Although penicillin G and sulphadiazine were given to cover the immediate post-operative 10 days, the infant's temperature remained elevated at 102° F. (38.9° C.), and it remained up when he was changed to a course of tetracycline. Two weeks after the operation the temperature was remittent—99–102° F. (37.2–38.9° C.)—and the haemoglobin had fallen from 87% to 67%. *Staph. albus* was cultured from the blood taken during the second and third weeks. At seven weeks the spleen became palpable. After this, staphylococci were again isolated from the blood on two occasions. These organisms were insensitive to tetracycline but sensitive to penicillin G and sulphadiazine. Another course of these drugs did not control the pyrexia (Fig. 2). By 12 weeks three blood transfusions had been required, the spleen had become palpable three fingerbreadths below the costal margin, and the temperature was still swinging.

Methicillin was then used, the organisms being sensitive to 1 µg./ml. On a dose of 100 mg./kg./day blood levels were 10 µg./ml. at one hour and 0.5 µg./ml. at five hours, but none was detectable in the C.S.F. As there was no clinical improvement after 10 days, the dose was doubled for a further 14 days. There was no change in the infant's condition when the drug was used systemically: the temperature was still swinging (Fig. 2), haemolysis was continuing (two transfusions required in a month), the spleen was the same size, and the blood culture was positive. On the doubled dose methicillin was still not detectable in the C.S.F. three-quarters of an hour after injection. Then, because the drug was not reaching the C.S.F. and therefore not percolating through the valve system, an additional 3 mg. was introduced into the C.S.F. daily for 50 days. This was done by a daily ventricular tap through the enlarged anterior fontanelle using 3 ml. of a 1% solution of methicillin in normal saline, and subsequently diluting it was 10 ml. of C.S.F. withdrawn immediately before injection. The ventricular puncture was always at the same site to avoid the risk of accidentally hitting a small blood-vessel if a different site were used each day.

There was a dramatic fall of temperature (Fig. 2), haemolysis ceased, and the spleen shrank to become almost impalpable. The infant was much brighter. During the last 20 days of this course no organisms were isolated from the blood. Five days after the drug had been discontinued the signs of septicaemia recurred. *Staph. albus* was again isolated from the blood, and at this stage, 76 days after treatment with methicillin and subsequently, it was resistant

to 5 µg. of methicillin per ml. Previously, after 50 days' treatment, the organism was noted to be resistant to 2.5 µg. of methicillin per ml.

Case 3

A boy born on December 12, 1959, had progressive hydrocephalus caused by a basal cistern block complicating a post-natal *Escherichia coli meningitis*. It was drained by a Spitz-Holter valve on March 31, 1960. Post-operatively there was a superficial stitch abscess due to *Staph. aureus*, which resolved completely on local measures and systemic penicillin G. While at home some more skin sepsis occurred and was similarly treated. Six weeks post-operatively there was a swinging temperature of 97–101° F. (36.1–38.3° C.), an anaemia (Hb 60%), a spleen palpable two fingerbreadths below the costal margin, and some local induration around the upper end of the valve. Blood culture yielded *Staph. aureus* (type 80), which was sensitive to penicillin G. After another course of penicillin G and sulphadiazine there was no clinical improvement, and then, as the organisms were no longer sensitive, a course of chloramphenicol and oleandomycin was given. Towards the end of this course the swing of temperature became more pronounced (Fig. 3). Thus at 12 weeks the temperature was still swinging, the spleen was palpable two fingerbreadths below the costal margin, and two blood transfusions had been required. The reisolated *Staph. aureus* was sensitive to methicillin (2.5 µg./ml.), which was given systemically (100 mg./kg./day) and intraventricularly as in Case 2.

Assay levels of the drug in the C.S.F. showed a 24-hour level of 3.4 µg./ml. and 5 µg./ml. rising to 11.2 µg./ml. half an hour after injection. While on this course the temperature settled apart from a few spikes of 99.5° F. (37.5° C.) (Fig. 3); there was no further haemolysis and the spleen became smaller. In the first two weeks of this treatment coagulase-negative staphylococci were isolated from the blood, but after this the cultures were sterile. On the sixth day after all treatment had been stopped, the swinging temperature recurred (Fig. 3). Then two attempts (each of 20 days) to eradicate the sepsis using methicillin systemically and in daily irrigations (3 mg. for the first attempt and 30–50 mg. for the second) through a silicone tube inserted around the valve failed, but they did partially control the swinging temperature (Fig. 3). As all attempts to eradicate the infection had failed, the valve was removed on October 27. The temperature rapidly subsided and no organisms were isolated from the blood after 48 hours and subsequently. Cultures from the valve, its silicone catheters,

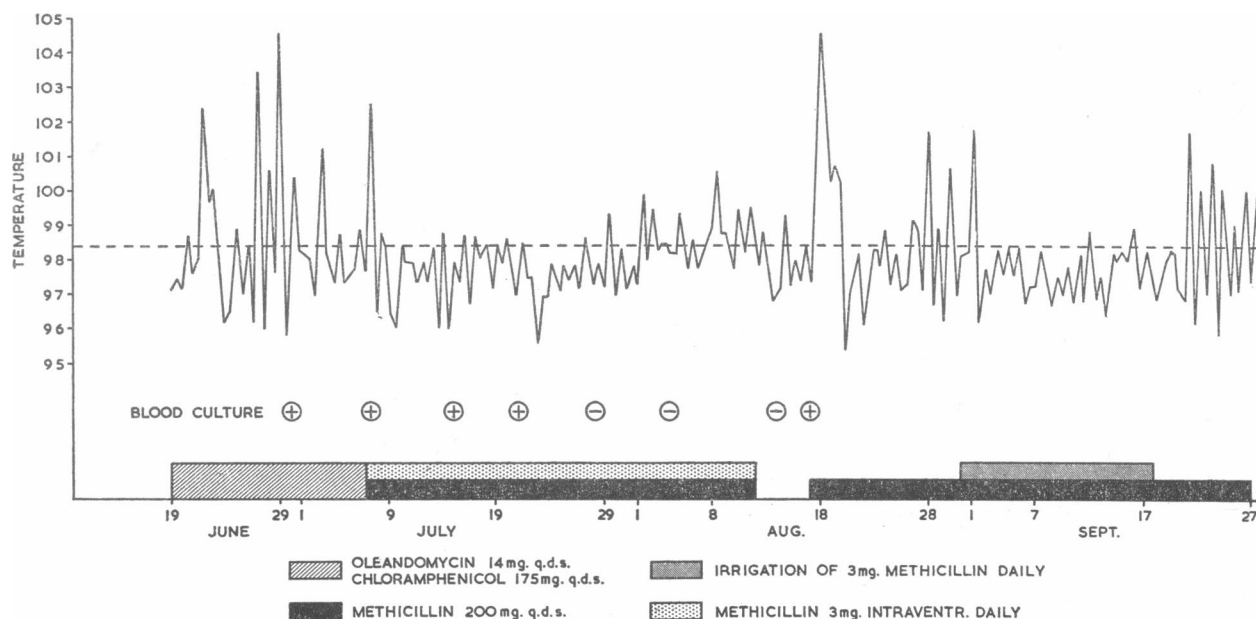


FIG. 3.—Similar results obtained by the intraventricular administration and by the local irrigation of methicillin.

and the surrounding tissues all yielded *Staph. aureus* with a sensitivity to methicillin 2.5 $\mu\text{g./ml.}$ unchanged after 110 days' treatment.

Case 4

A six-week premature girl (born on March 16, 1958) developed hydrocephalus after birth. A basal cistern block was demonstrated on October 5 and a Spitz-Holter valve was inserted on October 21. Post-operatively, while on a course of penicillin G and streptomycin, there was a mild pyrexia but no bacteriological evidence of septicaemia. When the patient was seen again 18 months later the haemoglobin was 29%, the spleen was enlarged to five fingerbreadths below the costal margin, and the temperature was spiking up to 99° F. (37.2° C.). Blood culture grew *Staph. albus* sensitive to penicillin G, which was given in a dose of 500,000 units by six-hourly intramuscular injection and 10,000 units intravenicularly daily. After 30 days on this treatment the temperature was swinging up to 102° F. (38.9° C.) (Fig. 4), the blood was being haemolysed, necessitating a further transfusion, and the spleen was slightly smaller. At this stage the *Staph. albus* isolated from the blood was resistant to penicillin G but sensitive to methicillin (1 $\mu\text{g./ml.}$). Methicillin was then given systemically and intravenicularly exactly as in Case 3. A small ventricular haemorrhage occurred on the twentieth day of this treatment. When this cleared one week later the temperature settled, haemolysis ceased, and the spleen shrank to two fingerbreadths below the costal margin. Immediately treatment ceased the temperature began to swing (Fig. 4) and haemolysis recommenced. The valve was removed on October 2, 1960. No organisms have since been isolated from the blood-stream, and after four days the temperature became normal. Cultures from the valve, its catheters, and the surrounding tissues yielded a *Staph. albus* with a sensitivity to methicillin now at 2.5 $\mu\text{g./ml.}$ after 50 days of treatment.

Case 5

In this case a hydrocephalic infant developed septicaemia after the insertion of a Spitz-Holter valve. The infecting organism was *Staph. aureus* (type 47/75) sensitive to 2.5 $\mu\text{g.}$ of methicillin per ml. The infant was treated with systemic methicillin for 30 days as in Case 1. During this time the blood cultures remained positive though the signs of infection were clinically controlled. The ward sister noticed that the infant's temperature rose sharply whenever the valve was pumped by digital pressure over its long axis. The valve was then changed and the operation field was irrigated with methicillin. *Staph. aureus* was cultured from the removed valve. Within a few days of this operation the blood cultures again became positive, and the same strain of *Staph. aureus* was repeatedly isolated. The sensi-

tivity remained unchanged (2.5 $\mu\text{g./ml.}$) after a total dose of 62 g. of methicillin given over 60 days.

Discussion

These are unusual cases of septicaemia, in which emboli of organisms pass directly from this "ventriculo-caval" channel into the heart. This fact has been shown in another case (Cohen and Callaghan, 1961), in which the withdrawal of the jugular catheter from the superior vena cava and connexion to external drainage cured the septicaemia but left the C.S.F. passing through the valve and its catheter infected, although that in the ventricle was sterile. Therefore a functioning valve is required to produce this type of septicaemia. They do not respond to long-term systemic antibiotics (Case 1), because most drugs, including methicillin, poorly penetrate a non-inflamed blood-brain barrier, and a bactericidal level of the drug does not pass with the C.S.F. through this channel to reach the source of infection (Case 2 before the drug was given intravenicularly). It is only when the antibiotic is given intravenicularly that a sufficient quantity passes along with the C.S.F. through this channel to sterilize it temporarily, as shown in Case 3, where the levels of methicillin recorded in the C.S.F. are well above the bacteriostatic level (2-4 $\mu\text{g./ml.}$) for staphylococci (Rolinson *et al.*, 1960). Thus the septicaemia could be controlled while the drug was administered systemically and intravenicularly (Cases 2, 3, and 4).

Methicillin has been shown to be non-toxic (Douthwaite and Trafford, 1960; Stewart *et al.*, 1960). Although this drug will eradicate the usual staphylococcal infections in 5 to 10 days, in these cases it was used for long periods without toxic effects. Stewart *et al.* (1960) have recorded a case in which 50 g. of the drug was given to an infant over a period of 30 days. Of the present series, Case 1 had a total of 75 g. given over 150 days, Case 2 had 104 g. over 76 days, and the other three cases had similar but smaller doses. No infant had any nausea, vomiting, or skin rashes, nor was there evidence of any toxic effects on the bone-marrow or kidney. However, because of the frequency of the injections and the smallness of the infants' limbs, the injection sites became a little indurated and tender. One case developed an abscess at the site of injection, pus from which, when cultured, grew *Pseudomonas pyocyanea*, which is highly resistant to methicillin.

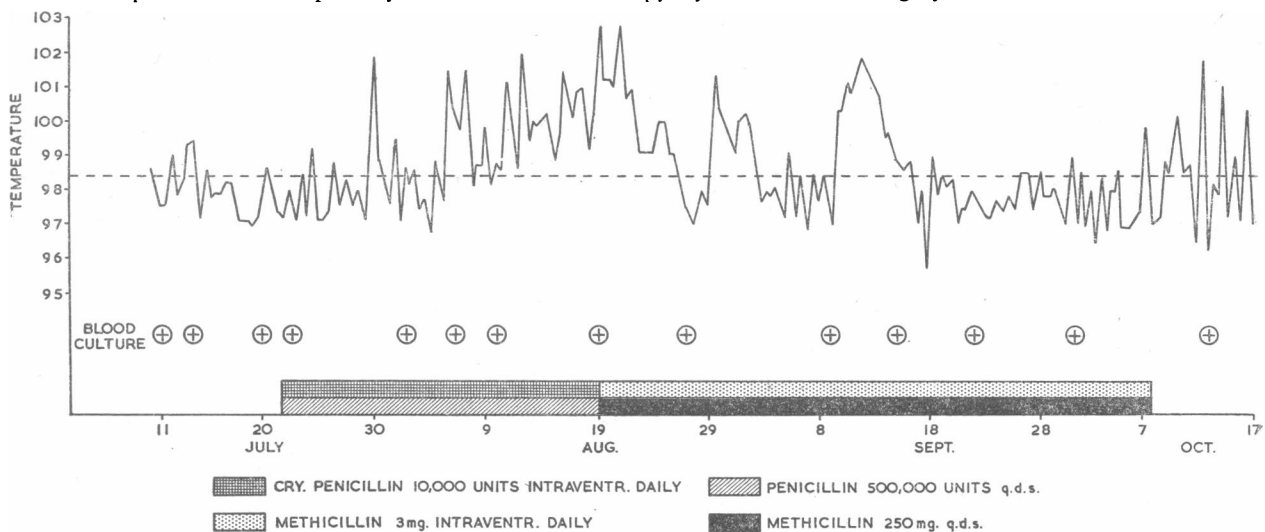


FIG. 4.—Effects produced by systemic and intravenicular penicillin G and methicillin.

To date there is no record of methicillin being given directly into the C.S.F. Douthwaite and Trafford (1960) have given it systemically to treat a staphylococcal meningitis and have used irrigations of it to treat an extradural abscess. We have given 3 mg. daily into the ventricle for 50 days in three cases. There has been no rise in the C.S.F. cell count or protein content, apart from that associated with a small ventricular haemorrhage in one of the cases.

Despite the unusually long periods of treatment with methicillin and the unique circumstances favouring persistence of the infecting organisms (Stewart, 1961), there was no evidence in the two cases of the *Staph. aureus* infection of the organisms developing any drug resistance. The reisolated organisms, however, in the three cases infected with *Staph. albus* showed a slight but definite trend towards resistance.

Summary

Four cases are described in which septicaemia developed as the result of colonization of Spitz-Holter valves by staphylococci.

Systemic drugs, including methicillin, failed to control the infection. The source of the infection could be reached by a combination of intraventricular (or local) and systemic administration of the drug. Thus the septicaemia could be controlled during the therapy, but recurred when it was discontinued. The complete cure necessitated removal of the valve.

Methicillin was given for long periods intraventricularly and systemically without signs of toxicity.

In the three cases of infection due to *Staph. albus* the organisms gradually acquired a degree of resistance to methicillin during the therapy; in the two cases infected with *Staph. aureus* the organisms showed no change in sensitivity to this drug.

We are indebted to Mr. G. H. Macnab for his advice in preparing this paper and for permission to treat these cases; to Mr. H. H. Nixon for the details of Case 5; to Beecham Research Laboratories for the supply of "celbenin"; to Sister Allen and staff for the extra work involved in treating these cases; to the pathological services of the Hospital for Sick Children, Great Ormond Street, for the many laboratory procedures undertaken; to Miss Jean White and Mr. R. J. Holt for technical assistance to Dr. Stewart; and to Mr. Martin for preparing copies of the graphs.

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At a February meeting of London County Council it was said that the total annual mileage travelled by the Council's ambulances in the last three years for which figures are available had risen from 4,173,784 miles in 1957, and 4,478,287 miles in 1958, to 4,504,336 miles in 1959. The percentage of accident and other emergency calls had remained around 13% during the three years. Between 1957 and 1959 the average time taken from receipt of the call to reach the scene of the accident had increased from 6.4 to 6.6 minutes, and the overall time from receipt of the call to reaching hospital with the patient had increased from 20 to 20.9 minutes, mainly owing to the increasingly heavy road traffic. The percentages of delays of more than one hour of the total numbers of non-priority cases removed increased from 2.6 in 1957 to 12.5 in January, 1961. These figures covered collection from home and return from hospital.

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CHANGES IN SENSITIVITY OF STAPHYLOCOCCI TO METHICILLIN

BY

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Reports from a variety of sources (Garrod, 1960; Branch *et al.*, 1960) have confirmed the preliminary findings of Knox (1960), Thompson *et al.* (1960), and Stewart (1960a) that the sodium salt of methicillin (BRL 1241; "celbenin"; "staphcillin") is uniformly active against *Staphylococcus aureus*, irrespectively of the resistance of this organism to penicillin G. Resistance to methicillin can, however, be produced artificially *in vitro* (Rolinson *et al.*, 1960; Stewart, 1960a; Barber, 1960), and it is obvious that the usefulness of the drug will be governed largely by the prevalence of comparable resistance *in vivo*.

The object of the present study is to examine some clinical and microbiological aspects of this problem, with regard not only to *Staph. aureus* but also to *Staph. albus*, which appears to be able to acquire resistance more readily (Stewart, 1960b).

Methods

The bacteriological methods employed were similar to those already described (Stewart, 1960a), with the following modifications:

Investigation of Resistance.—Induction of resistance *in vitro* was attempted by serial passage of the organisms, at intervals of 24–48 hours, (a) by the gradient-plate technique (Szybalski, 1953), and (b) by repeated subcultures in liquid media containing increasing concentrations of drug. Before each successive transfer the organisms were subcultured into drug-free broth for four hours to put them into the freely growing logarithmic phase. Assays of organisms thus treated, and of reisolated strains from patients and carriers, were performed by titrations in broth. The bactericidal effect was estimated from plate counts made after four hours at 37° C. and the overall bacteriostatic effect by reading the turbidity of the tubes after overnight incubation. In the case of an organism showing apparent resistance the assay was repeated in parallel with an assay of the parent strain, in comparable inoculum. By these criteria, resistance was identifiable when (1) there was no bactericidal action at the originally effective concentration, and (2) when the minimal inhibitory (bacteriostatic) concentration rose at least twofold. Tests for inactivation of methicillin and penicillin G were also carried out at various stages, as described below.

Spraying Experiments.—A small pavilion-type ward, in which staphylococcal cross-infection had already occurred, was selected for investigation of the consequences of spraying methicillin according to the technique of Elek and Fleming (1960).

Resistance to Methicillin *in vitro*

A number of strains of *Staph. aureus* and *Staph. albus*, freshly isolated from various routine specimens sent to the laboratory, were passaged repeatedly in liquid and solid media containing rising concentrations of methicillin. Tests on solid media were made by inoculating the organisms serially on to gradient plates containing