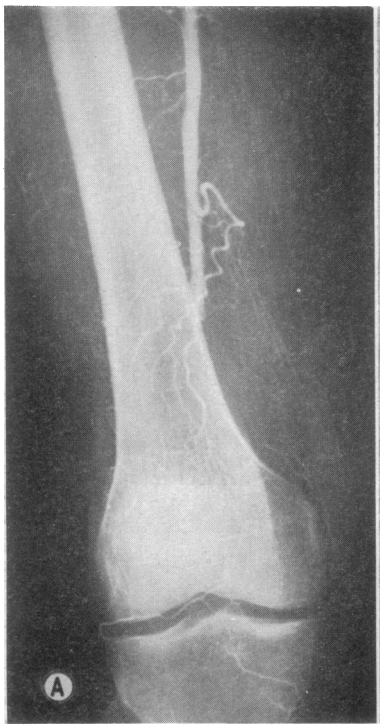
M. VERSTRAETE *ET AL.*: THROMBOLYTIC THERAPY WITH STREPTOKINASE



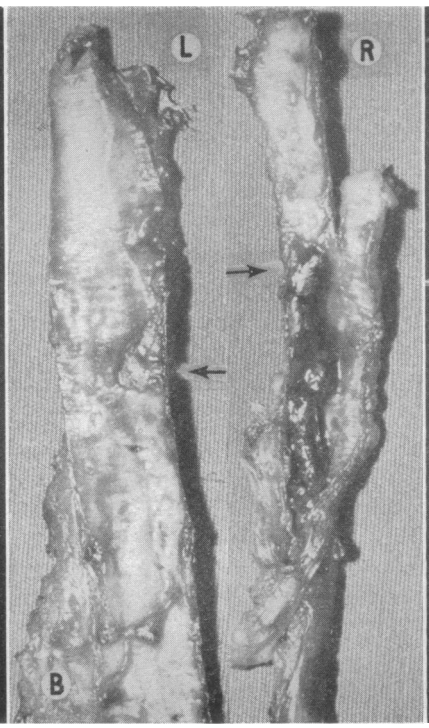


FIG. 5.—A Before. B After.

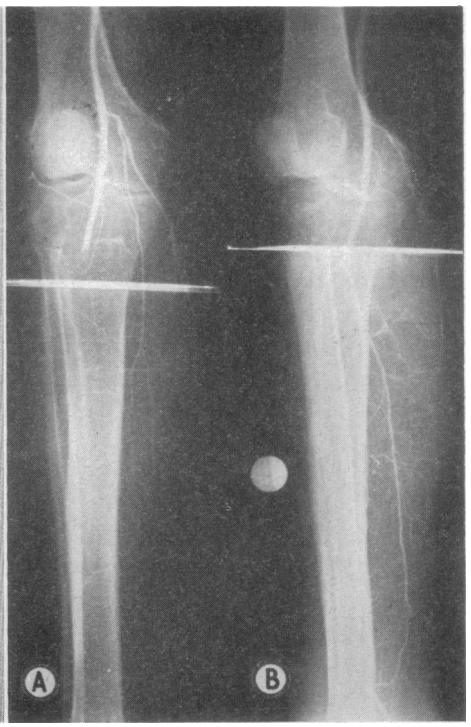
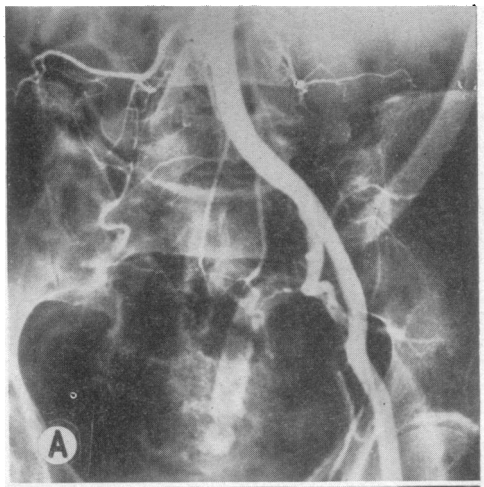


FIG. 7.—A Before. B After.



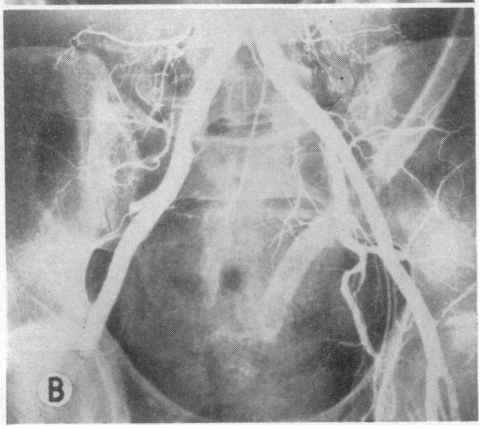


FIG. 6.—A Before. B After.

J. BOUTON *ET AL.*: B.C.G. DISSEMINATION IN CONGENITAL HYPOGAMMAGLOBULINAEMIA

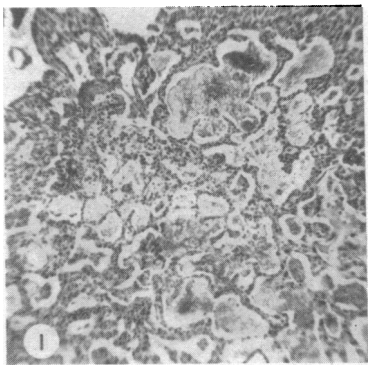
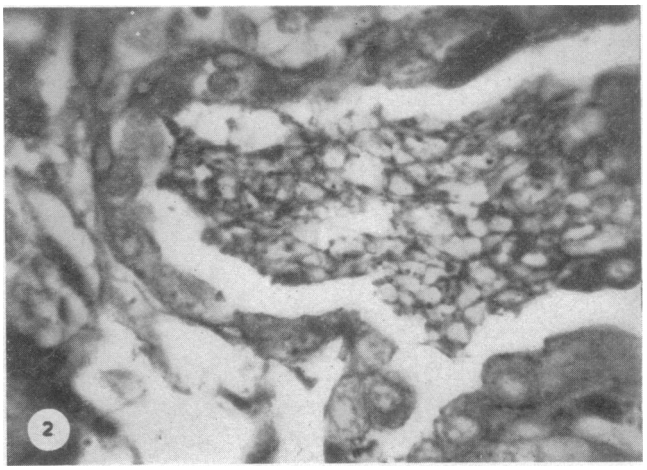


FIG. 1. — Section of lung showing alveoli filled by "honeycomb" exudate. (H. and E. ×52.)

FIG. 2. — Section of lung showing *Pneumocystis carinii* organisms, which appear as black dots surrounded by a pale envelope. (P.A.S. ×520.)



vessels beyond the reach of surgical methods of mechanical removal. Steroids should be given with the streptokinase, which should be followed by anticoagulant therapy. Local streptokinase therapy, which should be initiated by administration of an antibody-neutralizing dose, can be controlled thereafter by relatively simple laboratory tests.

Summary

Two patients with peripheral arterial occlusion have been treated by local perfusion of streptokinase. The first was a 33-year-old woman with thrombosis in the left brachial artery during the puerperium. The second was a 64-year-old man with thrombosis in the left superficial femoral artery.

Streptokinase was infused through a catheter into the artery above the thrombus and in each case the flow of blood was restored, after 30 hours perfusion in the first patient and 60 hours in the second.

It is concluded that streptokinase can be of benefit to carefully selected relatively fit patients with recent thrombotic or embolic arterial occlusion.

We are grateful to Professor W. A. Mackey and Professor E. M. McGirr for their interest in this work. Thanks are due to the Medical Research Council for financial support, to Miss S. Gale and Miss B. C. Bayley for technical assistance, and to Dr. Hans Dahlström for streptokinase. The illustrations were prepared by Miss M. Smith, Mr. P. Kelly, Mr. W. Towler, and Mr. J. Leiper.

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B.C.G. DISSEMINATION IN CONGENITAL HYPOGAMMAGLOBULINAEMIA

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[WITH SPECIAL PLATE]

The purpose of this paper is to report a case of congenital hypogammaglobulinaemia associated with widespread dissemination of B.C.G. organisms and a terminal *Pneumocystis carinii* pneumonia.

Case Report

The patient was born in February, 1961, the first child of healthy parents. The birth took place in a hospital which serves a part of Liverpool in which tuberculosis is relatively prevalent; all babies born there are vaccinated with B.C.G. unless parental consent is refused. The patient was vaccinated on the fourth day of life.

Six months later he was referred to Alder Hey Children's Hospital because a swelling had appeared in the left axilla five days previously. The lesion at the site of the vaccination over the left deltoid had developed when he was 6 weeks old and was still discharging. He was admitted for incision of the axillary abscess and a lot of thick green pus was evacuated. No organisms were seen in it or cultured from it by routine methods. At this time he weighed 14 lb. (6.4 kg.), although his weight had exceeded 15 lb. (6.8 kg.) a little while previously.

A month later neither the original B.C.G. lesion nor the axillary incision had healed. Hydroderm ointment (containing hydrocortisone, neomycin, and bacitracin) was applied locally without effect. The infant was readmitted at the age of 9 months. His weight had dropped to 12½ lb. (5.7 kg.) and there was a history of poor appetite and nocturnal cough for two months. For a fortnight he had been listless.

He was ill and unhappy, with a curious flush to the face. His skin was dry and rough, particularly on the extremities, and there were a few petechial haemorrhages on the legs. He had clearly lost weight. His muscles were very soft and he could not sit up. His B.C.G. ulcer and axillary sinus were still discharging.

A chest radiograph showed diffuse miliary shadowing throughout both lungs (Fig. A). The total white-cell count was 9,000/c.mm. with only 7% lymphocytes. The total serum protein level was 5.3 g./100 ml., of which just over half was globulin. Paper strip electrophoresis showed a raised α_2-globulin (1.02 g./100 ml.) and a very low γ-globulin (0.21 g./100 ml.). A swab from the axillary sinus showed large numbers of acid- and alcohol-fast bacilli. The Mantoux reaction was negative up to 1:100 old tuberculin.

On the basis of these findings the provisional diagnosis was felt to be congenital hypogammaglobulinaemia with either disseminated B.C.G. infection or *Pneumocystis carinii* pneumonia. Treatment was started with streptomycin, *p*-aminosalicylic acid, isoniazid, and γ-globulin. However, his condition continued to deteriorate with increasing respiratory distress and cyanosis. A chest radiograph on November 16 showed the shadowing to be more confluent (Fig. B), and he died later the same day.

Further investigations, some of which were not completed until after the infant's death, gave the following results.

Tibial bone-marrow: erythroid and myeloid series show normal maturation; megakaryocytes present; plasma cells not seen.

Serum protein immuno-electrophoresis (Dr. J. F. Soothill): γ-globulin 20 mg./100 ml. γ1-macroglobulin 6% of standard "normal" serum.

Blood group (Dr. D. Lehane): group A_2 Rh positive; weak anti-B demonstrated at 4.6° C. only.

Poliomyelitis antibody (two doses of Salk vaccine given four and five months previously) (Dr. G. B. Bruce White): type 1, 1/16; type 2, less than 1/8; type 3, less than 1/8.

Mother's serum γ-globulin 1.41 g./100 ml. Father's serum γ-globulin 1.38 g./100 ml.

Necropsy Report

The skin lesions have already been described. The tonsils were very hypoplastic and there were no adenoids. There were no carinal lymph nodes. The lungs were very fleshy in consistency, somewhat mottled in colour, and there were numerous greyish-white nodules of an average diameter of 1 mm., especially at both apices directly below the pleura. The cut surface of the lungs showed similar miliary nodules scattered throughout the substance. There were some confluent patches several millimetres in diameter.

In the mesentery were several small lymph nodes. The intestines were normal. The liver was slightly enlarged. Several miliary nodules were present on the anterior surface, more numerous in the left lobe, and the cut surface showed similar miliary nodules scattered throughout the substance. The spleen was small but firm, and there were several miliary nodules on its surface and in the substance. The left adrenal contained two miliary nodules.

Microscopical Examination

The "miliary nodules" in the liver and spleen were sharply delimited from the surrounding tissue and consisted almost entirely of pale-staining endothelioid cells. There was no necrosis or caseation and no cuffing by lymphocytes. Some nodules were older, and the endothelioid cells were largely replaced by fibroblasts. Ziehl–Neelsen staining, however, showed numerous acid-alcohol-fast bacilli in the centres of the nodules, even in the older ones which were almost fibrous scars.

In the lungs, in spite of sections through many sites, only one similar focus was seen—in a peribronchial group of lymph nodes. Ziehl–Neelsen staining revealed acid-alcohol-fast bacilli.

The rest of the lungs showed the characteristic picture of *Pneumocystis carinii* pneumonia (Special Plate, Figs. 1 and 2). The alveoli were filled by typical "honeycomb" conglomerates, staining lightly by routine haematoxylin and eosin and intensely by periodic-acid–Schiff, the latter also revealing the angular bodies of the parasite embedded in a mucoid envelope. The lining cells of the alveoli had become cuboidal and many were shed into the alveoli and appeared actively phagocytic. The absence of inflammatory cells from the alveoli, alveolar walls, and interstitium was very noticeable.

In the dermis and subcutaneous tissues at the site of the B.C.G. inoculation were numerous acid-alcohol-fast bacilli. There was no caseation and hardly any cellular reaction except by macrophages. The axillary lymph nodes contained no lymphocytes. They were completely replaced by swollen endothelioid cells, among which acid-fast bacilli were again very numerous. Sections through the regions of the tonsils and adenoids confirmed the almost complete absence of lymphoid tissue.

Mycobacteria were cultured from the liver and axillary sinus and were subsequently sent to Dr. J. Marks at the Tuberculosis Reference Laboratory, Cardiff; he reported: "Virulence tests on these cultures were negative in guinea-pigs. The animals were strongly tuberculin-positive. Identification of mild strains as B.C.G. can never be made with absolute certainty, but in this case is beyond reasonable doubt."

No growth was obtained from the spleen and lung. Death was attributed to pneumonia caused by *Pneumocystis carinii* in an infant with hypogammaglobulinaemia. In addition there was widespread dissemination of B.C.G. systemically and uninhibited proliferation locally.

Discussion

B.C.G. Dissemination and "B.C.G.itis"

B.C.G. vaccination in the normal person results in the development of a local lesion with involvement of the regional lymph nodes. The organism may then spread via the blood-stream to all organs. This was illustrated by Gormsen (1956), who described a series of necropsies on children who died as a result of some unrelated accident between six weeks and three and a half years after B.C.G. vaccination. He found epithelioid granulomata in various organs.

That such dissemination of B.C.G. organisms is not always benign is suggested by reports of fatal "B.C.G.-

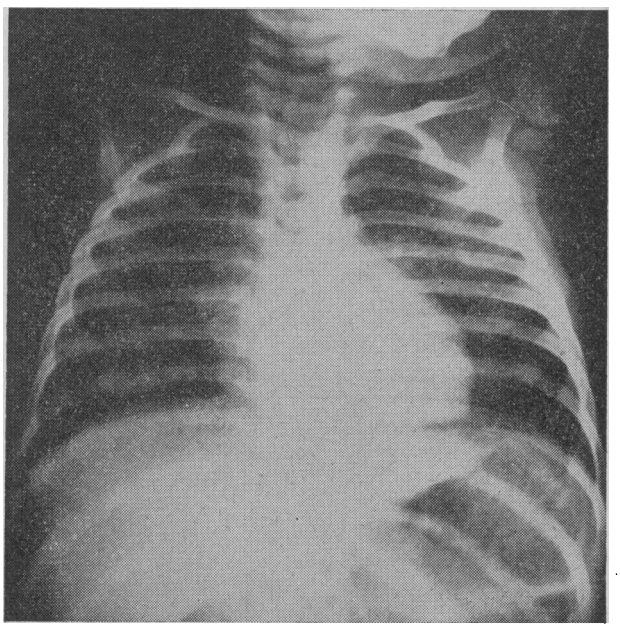

FIG. A.—Radiograph taken on November 8 showing diffuse miliary shadowing throughout both lungs.

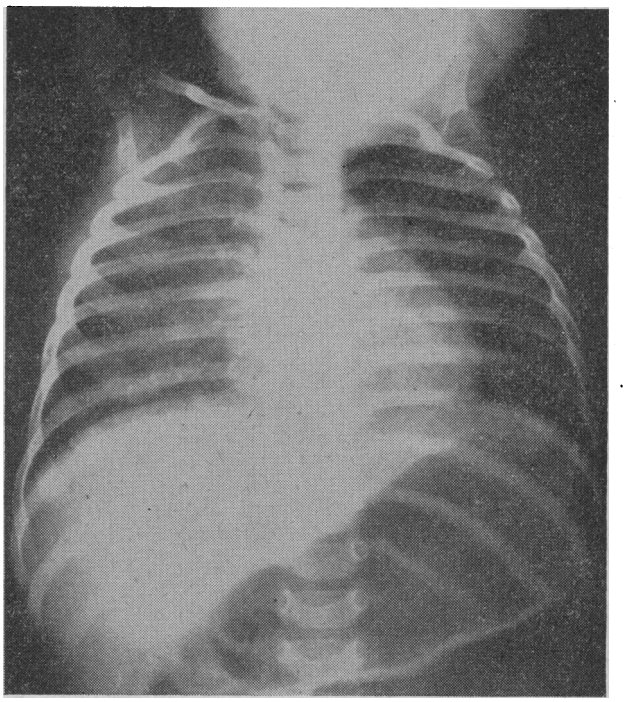

FIG. B.—Radiograph taken on November 16 showing shadowing to be more confluent.

itis" from Scandinavia and South America. Falkmer, Lind, and Ploman (1955) described the case of a boy who was vaccinated on the thigh on the fourth day of life, developed inguinal adenitis at 6 months, and died shortly afterwards. Microscopical examination showed myriads of acid-fast bacilli at the site of the vaccination and in the regional lymph nodes, and smaller numbers of organisms in other organs. The organism cultured was considered to be B.C.G.

These authors quote a similar case reported by Hollström and Hård (1953) of a girl who was vaccinated two days after birth and died 15 months later with widespread tuberculous abscesses. The organism cultured was thought to be B.C.G.

Meyer and Jensen (1954) described the case of a boy who was vaccinated with B.C.G. at the age of 7½ years and died 18 months later with widespread tuberculosis involving the lymphoid system only. Again the organisms were considered to be B.C.G.

Wallgren (1957) drew attention to the possibility of some abnormality of the serum γ-globulins in these patients. No γ-globulin levels were reported for the two infants quoted above. Meyer and Jensen's case had normal values. However, the appearance of the photomicrographs of the lungs from the case described by Falkmer *et al.* (1955) is so suggestive of *Pneumocystis carinii* pneumonia that one of us (J. B.) wrote to Dr. Falkmer about it. He not only confirms this diagnosis; he tells us that the child had a brother born 10 years later who recently died from hypogammaglobulinaemia.

The deaths of two children who developed local skin lesions and regional lymphadenitis after B.C.G. vaccination were reported from Uruguay (Ramon-Guerra, Queirolo, and Temerio, 1958). These cases are of interest in that both children were members of families known to be affected by congenital hypogammaglobulinaemia. These infants died as a consequence of acute chest infections, and one of them was found to have a mixed fungal infection, *Candida albicans, Candida tropicalis,* and *Torula histolytica* being isolated. In neither case was B.C.G. isolated from the lungs. Local skin lesions and regional lymphadenopathy seemed to be the only complications directly attributable to B.C.G. The γ-globulin levels of these two children were not estimated.

Ariztia, Moreno, Garces, and Montero (1960) studied an infant who died at the age of 4½ months. He was vaccinated at 2 days and local suppuration was noted a month later. Investigations included a Mantoux series which was negative to 1:10 old tuberculin, and γ-globulin estimation (0.55 g./100 ml.). Necropsy showed that in addition to a local deep ulcer at the injection site and granulomatous changes in the regional lymph nodes there were inflammatory changes in the lungs and spleen. Organisms cultured from all these sites were identified as B.C.G.

Various estimates of the mortality from "B.C.G.-itis" have been made. Barclay (1959), while acknowledging the difficulty of establishing accurate figures, suggests an incidence of 2 cases per 10,000,000 doses of B.C.G. given. The morbidity rate is of course far higher. So far, in none of the cases in which death has been attributed either wholly or in part to "B.C.G.-itis" has there been any definite evidence of hypogammaglobulinaemia, although in some cases the circumstantial evidence is strongly suggestive.

Response of Hypogammaglobulinaemic Subjects to Tuberculosis and B.C.G.

There are very few published cases of tuberculosis in children with congenital hypogammaglobulinaemia. Elphinstone, Wickes, and Anderson (1956) described the cases of two brothers with congenital hypogammaglobulinaemia. The elder was found to have a primary complex at the age of 6½ years. The illness ran a normal course and the Mantoux test 1:100 became positive. The younger brother was given B.C.G., and his Mantoux reaction became positive.

Good, Zak, Condie, and Bridges (1960) refer to a single case of tuberculosis in a hypogammaglobulinaemic child in whom the Mantoux reaction became positive.

Garvie and Kendall (1961) described the case of an infant who developed pulmonary tuberculosis at the age of 6 months. The illness responded to antibiotics and the tuberculin reaction became positive. Hypogammaglobulinaemia was diagnosed after the onset of the illness.

Kulneff, Pedersen, and Waldenström (1955) gave B.C.G. to three patients with hypogammaglobulinaemia. The Mantoux reaction became positive in two but remained negative in the third.

Porter (1957) gave B.C.G. to a 2-year-old boy with a serum γ-globulin level below 10 mg./100 ml. Ten weeks later the Mantoux reaction was positive to 1/10,000 old tuberculin. From the limited evidence available Good *et al.* (1960) concluded "that agammaglobulinaemic patients deal with tuberculosis very well."

Pneumocystis Carinii Pneumonia in Normal and Hypogammaglobulinaemic Subjects

Patients with hypogammaglobulinaemia are especially prone to *Pneumocystis carinii* pneumonia. This has been well known in Central Europe for many years under the name "plasma-cell pneumonitis." It occurs especially in premature and debilitated infants, is often epidemic, and appears to be unrelated to hypogammaglobulinaemia. The causative organism was demonstrated by Vaněk (1951).

Few cases of *Pneumocystis carinii* pneumonia in childhood have been reported from Great Britain. White, Saxton, and Dawson (1961) found seven in the literature, five of whom had hypogammaglobulinaemia. They added one case—that of a child of 2 years with Letterer–Siwe disease. They also reviewed cases reported in adults and added two further examples. Of 15 cases, nine had a malignant disease of the reticulo-endothelial system (lymphosarcoma, Hodgkin's disease, or leukaemia).

It seems possible that the fundamental predisposing factor to infection by *Pneumocystis carinii* is a disorder of the reticulo-endothelial system, particularly that part which is concerned in the production of lymphocytes or plasma cells. In congenital hypogammaglobulinaemia the low level of γ-globulin is only a reflection of the poorly developed lymphoid system. Either lymphocytes are not being produced or they cannot differentiate into γ-globulin-carrying plasma cells.

Summary and Conclusions

The case is described of an infant whose death was attributable to *Pneumocystis carinii* pneumonia consequent upon congenital hypogammaglobulinaemia.

B.C.G. organisms were widely disseminated, and it is difficult to assess the significance of this. Some degree of systemic spread must be accepted as a normal sequel to B.C.G. vaccination. The extensive spread in this child seems to have been the consequence of his ill-health rather than the cause. In some of the cases of "B.C.G.-itis" to which reference has been made there appeared to be no predisposing illness. However, three of the five reported cases in infants had a family history of hypogammaglobulinaemia. It is clearly desirable that any future cases should be thoroughly investigated with this possibility in mind. B.C.G. has already had to live down one scandal for which it was not responsible: it would be unfortunate if it were to be blamed for deaths which should be laid at another diagnostic door.

With regard to the liability of hypogammaglobulinaemic patients to *Pneumocystis carinii* pneumonia, it is suggested that the cellular defect is more important than the deficiency of γ-globulin. In adults with this infection the level of γ-globulin has been found normal whenever it has been estimated, but in most instances there has been malignant disease of the reticulo-endothelial system.

We wish to thank Dr. J. Marks, Dr. J. F. Soothill, Dr. D. Lehane, and Dr. G. B. Bruce White for technical help. We are also grateful to Dr. E. G. Hall for his helpful advice.

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EFFECT OF TOPICAL FRAMYCETIN ON STAPHYLOCOCCAL NASAL CARRIAGE

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The carriage of coagulase-positive staphylococci by patients and hospital personnel is one of the important factors contributing to the development of infection by these organisms. Many studies have demonstrated the prevalence of nasal carriage in hospital patients and the close association between this carrier state and the occurrence of staphylococcal infection (McNeill *et al.*, 1961). To reduce the incidence of staphylococcal sepsis attempts have been made, by the use of antibiotic nasal creams, to eradicate nasal staphylococci in patients admitted to hospital and to prevent the development of nasal carriage of these organisms, particularly of antibiotic-resistant "hospital" types, during the period of hospitalization. These attempts, however, have been only partially successful in the elimination of nasal carriage and in the prevention of infection (Henderson and Williams, 1961). The report from Australia of Stratford *et al.* (1960) that framycetin sulphate ("sofra-mycin") spray (containing framycetin 1.25% and gramicidin 0.005%) rapidly and completely cleared staphylococci from the nose suggested that an effective method of treating nasal carriage was available. Some of the findings in this report, however, differ from those of other workers.

Stratford *et al.* (1960) used deep nasal swabs to detect the presence of the carrier state and to assess the results of treatment with topical antibiotics. This technique was employed because a survey of 103 patients had indicated that deep swabbing was 17% more effective than superficial swabbing in the detection of nasal carriers. This finding, however, is not in accord with other reports which claim that superficial swabbing more frequently demonstrates the presence of nasal staphylococci. Indeed, Williams *et al.* (1960) state that "nothing will be gained by swabbing the higher reaches of the nose, and in fact mistakenly swabbing beyond the vestibule may produce artificially low carrier rates."

Other studies on the effectiveness of framycetin, such as that of Barber and Warren (1962), have shown that not all patients carrying staphylococci ceased to do so under treatment with framycetin, and although in many cases the staphylococci disappeared from the nares they subsequently returned despite continuation of treatment.

As Stratford and his co-workers did not carry out phage-typing of the staphylococci isolated from nasal swabs it is not possible to ascertain whether nasal recolonization after cessation of framycetin was due to environmental contamination by different strains of staphylococci or to persistence of the same organisms in the nose. The investigation of Jarvis and Wigley (1961) would suggest that the latter explanation is the more likely.

In the investigation reported here evidence is presented on the frequency with which nasal carriage of staphylococci occurs in the hospital environment; on the accuracy of superficial as compared with deep nasal swabbing in the detection of the carrier state; and on the effectiveness of topical framycetin in the prevention and treatment of nasal carriage.

Materials and Methods

The investigations detailed below were carried out in a male general surgical ward in which staphylococcal infection had already been studied (McNeill *et al.*, 1960).