

of drugs have to be tried out individually, a process that requires much time and patience. When this has been done and the patient has learnt to cope with intercurrent attacks, he need no longer be seen frequently in the outpatient department; one visit in one to three months will suffice. (The procedure is, in principle, similar to that adopted for the control of diabetics.)

In most cases definite improvement can be achieved and patients rendered fit for work who before had been regarded as semi-invalids. This is an aim well worth the effort, especially if one compares the doubtful effect of a long desensitisation course. The treatment may seem to be merely symptomatic, but it resembles rather a substitution therapy, and it should not be neglected in favour of desensitisation.

SUMMARY

Aleudrine (isopropyladrenaline) is effective in relieving attacks of bronchial spasm. It can be administered perlingually or inhaled.

The anti-histamine drug, anthisan, is also effective against bronchial spasm.

Tolerance to both substances is acquired by some patients.

The optimal dosages vary widely in different people, and they should be determined in every case by spirometry.

I am indebted to Dr. H. O. Schild for many valuable suggestions, and to Dr. A. Morland, in whose outpatient department most of the patients were seen. Messrs. C. H. Boehringer, Ingelheim, supplied the aleudrine and Messrs. May & Baker the anthisan.

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PENICILLIN THERAPY IN SCARLET FEVER AND COMPLICATING OTITIS*

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THE exact grouping and typing of hæmolytic streptococci after Lancefield and Griffith has thrown light on the epidemiology of scarlet fever, especially as regards complications, relapses, and reinfections. Gradually it has been realised that the treatment of scarlet-fever patients in a common ward irrespective of bacillary type, stage of disease, and possible complications is undesirable. Evidence has accumulated to the effect that all so-called relapses are due to reinfection, since the change in type of the infecting organism may be demonstrated immediately before, or simultaneously with, the "relapse." Similarly, many complications are probably due to reinfection, since a change in the type of the pathogenic organism has often been demonstrated in such cases.

As a result of such observations various improvements in the treatment of scarlet-fever patients have lately been suggested—e.g., private wards, type-specific wards, and home treatment. All these suggestions, however, have

encountered practical and economic difficulties. Besides, by adopting such measures it will not always be possible to avoid complications resulting from the primary streptococcal infection—and in previous reports from other countries as well as from Denmark 40–60% of all complications have been attributed to the primary type of streptococcus. Therefore an effort should be made to develop a form of therapy which will rapidly rid the patient of hæmolytic streptococci in the nasopharynx. In this respect the sulphonamide therapy hitherto employed has been disappointing, whereas penicillin soon proved to be most effective.

METHODS

In December, 1945, in the Blegdam Hospital we began treating scarlet-fever patients with penicillin. All the patients admitted on one day were given penicillin; and all those admitted next day were given sulphanilamide, and so on alternately. During their first five days in hospital the patients in both groups were all placed in small wards, so that no new patients were admitted to wards where others were already under treatment. On the sixth day the patients had a bath and their bedding was disinfected. Then the penicillin-treated patients were transferred to one "clean" ward and the sulphanilamide-treated patients to another "clean" ward.

Dosage

At first, to reduce the number of injections of penicillin as far as possible adrenaline was given with the penicillin—5 ml. of saline containing 0.3 ml. of 1 in 1000 adrenaline per 100,000 units of penicillin—to delay the absorption of penicillin. Deep subcutaneous injections were given just superficial to the muscular fascia on the anterior aspect of the thigh. Children under 1 year received 40,000 units, children aged 1–5 years 60,000 units, children aged 5–15 years 80,000 units, and adults 100,000 units thrice daily for six days. This dosage was used until 200 patients had been treated with penicillin and 200 with sulphanilamide. In a further 18 cases the course of penicillin was cut down to three days, but this was unsatisfactory (see below).

Since Oct. 1, 1946, all scarlet-fever patients admitted to the hospital have been treated with penicillin: 350 patients were given penicillin and adrenaline subcutaneously thrice daily for six days and discharged, on an average, after eight to ten days; and 142 patients were given penicillin (without any adrenaline) intramuscularly twice daily for six days. The dosage was as follows: children under 1 year received 60,000 units; children aged 1–5 years 90,000 units; children aged 5–15 years 120,000 units; and adults 150,000 units at each injection.

Controls.—As controls for the first 200 patients treated with penicillin, 200 other scarlet-fever patients were treated for eight days with sulphanilamide.

Follow-up.—From Oct. 1, 1946, during the first three weeks after their discharge from hospital all the patients of the uncontrolled series were under observation as outpatients, the following tests being performed every week: cultures for the presence of hæmolytic streptococci, microscopical examination of the urine, electrocardiography, and determination of erythrocyte-sedimentation rate (E.S.R.) and antistreptolysin titre. The 142 patients given intramuscular penicillin without adrenaline were further followed up for eight weeks.

RESULTS

Length of Treatment.—Since nearly all the penicillin-treated patients in the controlled series became free from streptococci within 24–48 hours, and since penicillin was scarce in Denmark in the early months of 1946, I tried to shorten the period of treatment from six days to three without changing the daily dosage. Altogether 18 patients

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were treated in this way, and they all became free from streptococci in less than 48 hours after the start of treatment (fig. 1). After a few days, however, hæmolytic streptococci were found with increasing frequency. Of the 18 patients, 11 were discharged while harbouring streptococci, and complications appeared subsequently in 7 of them (39%): tonsillitis in 3, tonsillitis and adenitis in 1, adenitis in 2, and otitis and mastoiditis in 1. Thus it is evident that the length of treatment is directly related to the results obtained with penicillin in scarlet fever.

E.S.R. and Antistreptolysin Titre.—In nearly every case in the controlled series the E.S.R. was estimated and an antistreptolysin test made once a week. The results are given in figs. 2 and 3. The E.S.R. (fig. 2) fell far more rapidly in the patients given penicillin.

INCIDENCE OF MASTOIDECTOMY IN SUPPURATIVE OTITIS MEDIA COMPLICATING SCARLET FEVER

Year	No. of cases of scarlet fever	No. of cases of otitis media	No. of mastoidectomies
1941	1529	256	53 (21%)
1942	2110	227	47 (21%)
1943	2345	195	71 (36%)
1944	2073	178	68 (38%)
1945	1674	125	30 (24%)
1946	1583	65 25*	23 (35%) 2 (8%)
1947 (6 months)	281	31*	0

* Treated with penicillin.

Fig. 3 shows that the great majority of the penicillin-treated patients did not form any antistreptolysin, no doubt because of the rapid and effective action of penicillin on streptococci. For the same reason the amount of specific antibody formed is small, so it is theoretically possible for reinfection with the same type of streptococcus to take place more easily. This possibility is illustrated by a scarlet-fever patient who was lately readmitted, a month after his discharge, with scarlet fever of the same type as on his first admission. So far as I am aware, no case of relapse or, more correctly, reinfection with a streptococcus of the same type has been published previously.

Use of Adrenaline.—In the uncontrolled series it was found that the results of treatment with intramuscular penicillin (without adrenaline) twice daily for six days were just as favourable as those obtained with three daily injections of penicillin and adrenaline for six days. Hitherto it had been thought necessary to maintain, so far as possible, a constant concentration of penicillin in the blood, whether by the use of beeswax or adrenaline, by giving injections every three hours, or with a continuous drip, or by adopting mechanical measures to slow absorption. The present material shows that equally good results can be obtained with only two intramuscular injections of penicillin daily. This makes it possible to simplify the treatment of scarlet fever so that it may be carried out at home, provided the home conditions allow of isolation for two days.

Complications.—Fig. 1 shows that, in the controlled series, 73% of the sulphanilamide-treated patients still harboured hæmolytic streptococci at the end of treatment, and 53% on discharge from hospital. Complications appeared in 49.5% of this group. On the other hand, in the penicillin-treated group, only 4% of the patients harboured hæmolytic streptococci at the end of treatment, and complications appeared in

only 5.5%, there being no otitis or nephritis. The complications are analysed as follows:

Complications	200 cases treated with sulphanilamide	200 cases treated with penicillin
Adenitis	29.0%	0.5%
Suppurative otitis media	4.0%	0
Secondary tonsillitis	4.0%	2.0%
Secondary rhinitis	9.5%	2.5%
Sinusitis	0.5%	0
Nephritis	1.0%	0
Jaundice	1.0%	0
Myocarditis	0.5%	0.5%
Totals	49.5%	5.5%

In the uncontrolled series, to find how soon the streptococci disappeared from the nasopharyngeal cavity, cultures were made from 32 scarlet-fever patients every four hours day and night. More than half the patients (18 out of 32) were free from hæmolytic streptococci as early as twelve hours after the start of the penicillin treatment, and on the third day all the patients gave negative cultures. The streptococci disappeared from the discharge from the ears just as rapidly without local treatment. The sore throat subsided more rapidly in the penicillin-treated patients. In the penicillin-treated patients the primary temperature lasted on an average 4.5 days, in the sulphanilamide-treated patients on an average 7 days. The rash was not influenced by penicillin.

Up to now we have treated 1000 scarlet-fever patients with penicillin. Nephritis did not develop in any of them (4 were readmitted with albuminuria which proved to be orthostatic). No cases of secondary streptococcal otitis occurred (1 patient had pneumococcal otitis that subsided on renewed treatment with penicillin; and in 1 patient a Pfeiffer's bacillus otitis was found). In 4 patients adenitis appeared after their discharge from hospital, and in 3 of these a different type of streptococcus was found in the throat, wherefore it is reasonable to assume that the lymphadenitis resulted from a reinfection. These 4 patients were again given penicillin therapy, and the adenitis subsided promptly.

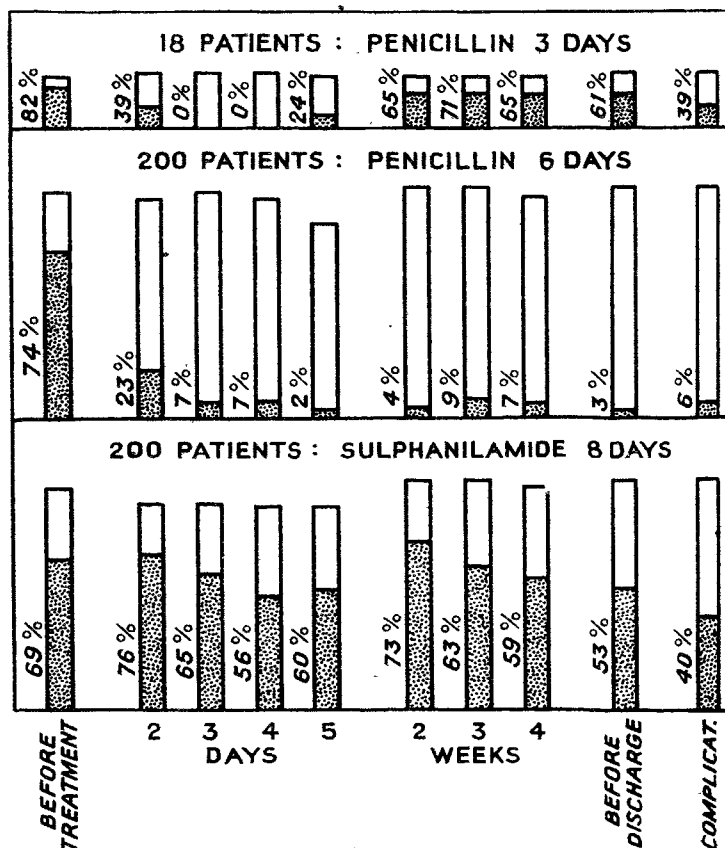


Fig. 1.—Results of tests for presence of hæmolytic streptococci in nasopharynx of scarlet-fever patients treated with penicillin or with sulphanilamide: stippled columns, streptococci present (expressed also by percentages); blank columns, streptococci absent.

Probably one of these patients was reinfected from the mother, who in the past four months had been under otological treatment because of purulent discharge from the nose, resulting from a sinusitis. Cultures from the mother and child repeatedly grew hæmolytic streptococci of the same type. Then the mother was admitted to hospital and treated with penicillin 150,000 units intramuscularly twice daily for eight days. After that no hæmolytic streptococci were seen in the cultures, and the nasal secretion ceased after treatment with penicillin for four days.

OTITIS AND MASTOIDECTOMY

As mentioned already, no instance of hæmolytic streptococcal otitis occurred among the scarlet-fever patients treated promptly with penicillin early in the acute phase; but some patients were admitted with scarlatinal otitis. In 1946, 25 patients with scarlatinal otitis were treated with penicillin, two or three intramuscular injections being given daily, as in the other scarlet-fever patients, except that the treatment was continued longer—six to twenty-three days with an average of

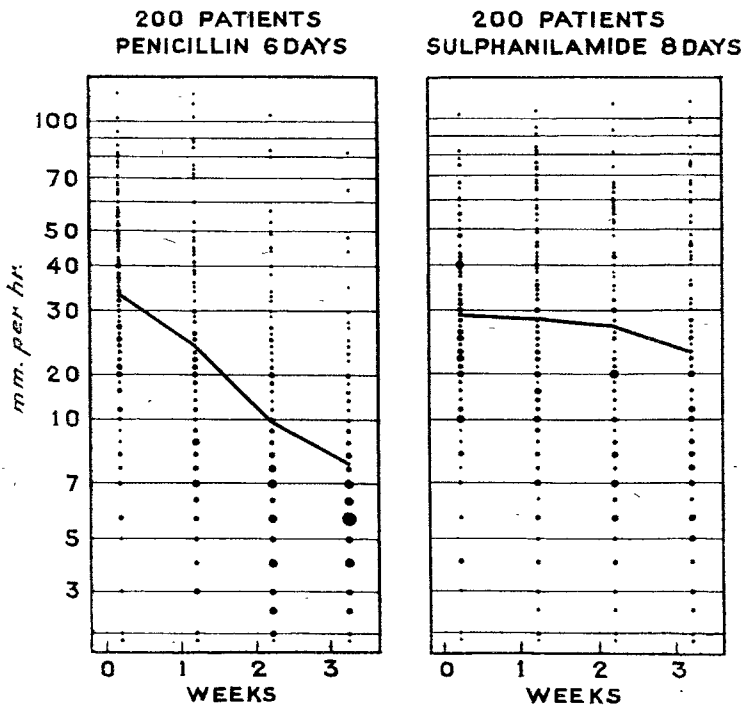


Fig. 2—Erythrocyte-sedimentation rates in scarlet-fever patients treated with penicillin or with sulphanilamide. Smallest dots indicate single cases. Larger dots indicate relatively larger number of patients. The mean readings are shown by curves.

nine days. In these patients the otitis had lasted an average of six days before admission (excluding 1 patient, in whom the otorrhœa had persisted for three months).

After the start of penicillin therapy it took, on an average, seven days for the otorrhœa to cease. In nearly all these cases the discharge was free from streptococci as early as the day after the start of penicillin therapy. In only 3 patients could hæmolytic streptococci be demonstrated in the discharge from the ear as late as three days after the start of penicillin treatment.

In the group of scarlet-fever patients treated with penicillin only 2 were submitted to mastoidectomy (in 1 of these a well-marked mastoiditis was already present at the start of penicillin therapy).

During the same period (1946), of 65 patients admitted with scarlatinal otitis and treated with sulphanilamide 23 (35%) required mastoidectomy. The hæmolytic streptococci persisted in spite of energetic treatment with sulphanilamide.

Since Jan. 1, 1947, all cases (31) of scarlatinal otitis have been treated with penicillin, and none has needed mastoidectomy. On the other hand, in 1941-45, when most of the patients were treated with sulphanilamide, mastoidectomy had to be performed in 21-38% of all the cases of scarlatinal otitis (see table).

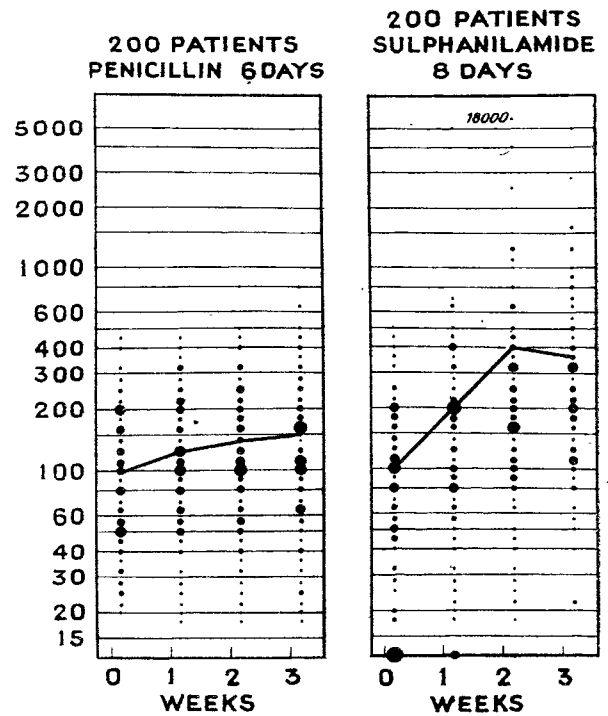


Fig. 3—Antistreptolysin titre in scarlet-fever patients treated with penicillin or with sulphanilamide. Dots and curves as in fig. 2.

SUMMARY

Since December, 1945, a total of 1000 patients with scarlet fever have been treated with penicillin in the Blegdam Hospital and followed up carefully.

Intramuscular injection of 90,000-150,000 units of penicillin (according to the patient's age) twice a day will rid the nose and throat of hæmolytic streptococci within 48 hours.

It is unnecessary for this purpose to maintain a bacteriostatic concentration of penicillin in the blood by giving injections three-hourly or by injecting the penicillin with pea-nut oil, wax, adrenaline, &c.

To prevent the reappearance of the streptococci the penicillin treatment should be continued for 6 days.

Under this treatment sore throat subsided rapidly. The average febrile period was only 4.5 days, compared with 7 days in controls treated with sulphanilamide. No complications (otitis, nephritis) developed. The average stay in hospital was only 8 days. Accordingly the saving in hospital days was very great (in Denmark it has been estimated to be about 300,000 days a year, with an average annual scarlet-fever morbidity of 14,000 cases).

The reduction of injections to two daily makes home treatment possible where conditions allow the patient to be isolated for a few days.

The rash of scarlet fever is not influenced by the treatment.

In the patients admitted with a streptococcal otitis treatment with penicillin in the same dosage gave very good results. In 1941-45, in spite of energetic treatment with sulphanilamide, 21-38% of patients with scarlatinal otitis had to undergo mastoidectomy. With penicillin therapy, of 56 patients admitted with scarlatinal otitis only 2 required mastoidectomy, and in 1 of these mastoiditis was already present at the start of penicillin treatment.

ADDENDUM

Since this paper was submitted for publication a total of 2000 scarlet-fever patients have been treated with penicillin. No change has been made in the dosage (90,000-150,000 units twice a day for 6 days). The patients have been discharged from the hospital on an average 8 days after admission. The results of treatment have been just as favourable in these later cases as in the earlier ones. On follow-up examination of the penicillin-treated scarlatinal patients, none of them has been found to have any complication in the form of scarlatinal otitis or nephritis.