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Key passages

STREPTOMYCIN TREATMENT OF TUBERCULOUS MENINGITIS

STREPTOMYCIN IN TUBERCULOSIS TRIALS COMMITTEE,^a
MEDICAL RESEARCH COUNCIL

IN September, 1946, the Medical Research Council appointed a committee to plan and direct clinical trials of streptomycin in the treatment of tuberculosis. Since the amount of the drug expected to be available for the trials was limited, the committee decided to restrict the tests at the outset to a few acute and usually fatal forms of the disease, including tuberculous meningitis in children and acute miliary tuberculosis. This report, the first to be made by the committee, is concerned with the results in tuberculous meningitis.

Three main centres were established in the first instance: Hammersmith Hospital (L.C.C.); Alder Hey Children's Hospital, Liverpool; and the Royal Hospital for Sick Children, Glasgow. Later, cases were also admitted under this scheme to the Hospital for Sick Children, Great Ormond Street; Guy's Hospital; the National Hospital for Nervous Diseases, Queen Square; and Highgate Hospital (L.C.C.). At the Radcliffe Infirmary, Oxford, some cases had been treated with streptomycin before the M.R.C. scheme was begun; this centre continued during 1947 to operate under M.R.C. auspices. Finally, when pressure for admission of cases was increasing, a few cases were admitted to centres established for other tuberculosis investigations in the M.R.C. streptomycin trials. Until July, 1947, only children under 9 years of age were admitted to the centres (except at Oxford, where there was no age limit); between then and the inception in September of the Ministry of Health scheme (see below) a few older children and adults were admitted as an emergency measure. In September, 1947, the centres at Alder Hey, Glasgow, Great Ormond Street, and Guy's were absorbed into the current Ministry of Health scheme, and the two largest centres, Hammersmith and Highgate, continued investigating special problems under M.R.C. auspices.

The first patients to be treated under the M.R.C. scheme were admitted in January, 1947, and 138 cases were admitted during 1947. This report is confined to the 105 proved cases admitted before Aug. 18, and the survivors observed to Dec. 15, thus giving a minimal observation period of 120 days (17 weeks). Of the 105

proved cases, 13 were treated at Oxford and are analysed in a separate report (Smith et al. 1948). For the other 92 cases the mean observation period in the survivors was 201 days (median 191 days), the maximum 325 days; the mean potential observation period (assuming survival of all cases) was 198 days (median 175), the maximum 334 days.

The centres kept uniform records and followed general recommendations regarding dosage, but there were necessarily considerable variations, particularly in rhythm of treatment, between different centres and between cases within each centre, because knowledge regarding optimal methods was so scanty that no hard and fast rules regarding treatment could be laid down.

This report does not present an exhaustive clinical analysis of the cases. By grouping the information from all centres it is, however, believed possible to reach conclusions more significant than could be derived from a study of a relatively small number of cases at one centre alone. It is hoped that the report may be followed by fuller clinical and pathological reports from individual centres.

The purpose of the present analysis is to ascertain the survival-rate in tuberculous meningitis under streptomycin treatment, to seek optimal techniques of treatment, to establish possible guides to prognosis, and to

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define the main outstanding problems. The general results (table I) and the over-all results of two methods of treatment (tables V and VI) refer to the total 105 proved cases; the more detailed analysis is concerned with the 92 cases treated in centres other than Oxford.

It had already become evident in the M.R.C. tests by the early summer of 1947 that streptomycin prolongs life and, at least temporarily, restores health in some cases of tuberculous meningitis, as previously reported from the U.S.A. The council thereupon recommended to the Ministry of Health that streptomycin should be made available for this condition as widely as supplies would permit. This recommendation led to the arrangement referred to above as the "Ministry of Health scheme," under which the streptomycin treatment of tuberculous meningitis (and acute miliary tuberculosis) can now be undertaken at many hospitals throughout the country (see *Lancet* 1947).

The streptomycin used in the present trials was in the form of the hydrochloride, obtained from one American producer; it had satisfied the requirements of the American Food and Drug Administration as regards identity, potency, purity, and toxicity (immediate lethal effects on mice, content of histamine-like depressor substances, content of pyrogens, &c.); tests on random

substances, content of pyrogallol, etc., were determined. The samples at the National Institute for Medical Research gave confirmatory results. The potencies of the preparations were within the range 550–650 μg . of base per mg. of material. All weights of streptomycin given here refer to active base (1 μg . of base is the equivalent of 1 S unit and of 1 provisional British unit). So far as possible each patient received the same batch throughout his treatment.

Summary of Results on Dec. 15, 1947

Of the 105 patients admitted to M.R.C. centres for streptomycin treatment before Aug. 18, 1947, 67 (64%) have died and 30 (28%) are making good progress after 120 or more days' treatment and observation (table 1). The condition of those making good progress is considered below.

It soon became obvious that the prognosis in children under 3 years of age was much worse than in older children; table 1 shows that the proportion of older children surviving and making good progress after four months

TABLE I—RESULTS OF STREPTOMYCIN TREATMENT RELATED TO AGE

Age (yr.)	No. of cases admitted before Aug. 18, 1947	Condition on Dec. 15, 1947			
		Good	Stationary or relapsed	Deteriorating	Dead
Under 3	33	4 (12%)	0	2 (6%)	27 (82%)
3–5 ..	26	10 (38%)	2 (8%)	0	14 (54%)
6–8 ..	25	11 (44%)	3 (12%)	0	11 (44%)
9 and over	21*	5 (24%)	1 (5%)	0	15 (71%)
All ages	105	30 (28%)	6 (6%)	2 (2%)	67 (64%)

*11 at Oxford.

was more than three times that in children under 3 years. An analysis of results reported by Debré et al. (1947) also shows a high fatality-rate in young children. The results in the age-group 9 years and over are not comparable with the rest, since 12 of the 21 received intramuscular treatment alone (see below).

Space does not allow comparison of results with those reported by Hinshaw et al. (1946), Dubois and Linz (1947), Cocchi and Pasquinucci (1947), Council on Pharmacy and Chemistry (1947), and Mollaret (1948). The last is one of a symposium of twelve papers reporting on a total of 615 cases of tuberculous meningitis treated in France.

Clinical Condition of Patients on Admission

Nearly a third of the patients admitted were in a clinically advanced condition when submitted to the centres for streptomycin treatment: some cases, on the other hand, were diagnosed at a relatively early stage. To assess how far the prognosis depends on the clinical condition at the time treatment was started, the 92 cases

TABLE II—RESULTS OF STREPTOMYCIN TREATMENT RELATED TO STAGE OF DISEASE

Stage of disease at start of treatment	No. of cases admitted between Jan. 18 and Aug. 18, 1947	Condition on Dec. 15, 1947		
		Good	Stationary, relapsed, or deteriorating	Dead
Early ..	26	11 (42%)	3 (12%)	12 (46%)
Medium ..	38	10 (26%)	3 (8%)	25 (66%)
Advanced ..	28	2 (7%)	2 (7%)	24 (86%)
Total ..	92	23 (25%)	8 (9%)	61 (66%)

treated in centres other than Oxford have been classified as follows:

Early.—Patients with mainly non-specific symptoms, with little or no clinical signs of meningitis, with no pareses, in good general condition, and fully conscious. Diagnosis established mainly on findings in cerebrospinal fluid (c.s.f.).

Advanced.—Patients obviously extremely ill, deeply stuporose or comatose, or with gross pareses.

Medium.—Patients in a condition between those of the first two groups.

A little less than half the early cases, two-thirds of the medium cases, and six-sevenths of the advanced cases have proved fatal (table II). Only 2 of 28 advanced cases are making good progress, † compared with 11 of 26 early cases. Though some early cases never responded to treatment, and 2 advanced cases did respond, on the whole the prognosis is closely related to the condition on admission.

Discussion

The streptomycin treatment of tuberculous meningitis, prolonging the course of the disease in most cases, producing considerable improvement in many and possibly clinical cure in a few, represents an outstanding advance. The problem of improving the results so far achieved raises numerous questions, many of which still remain unanswered.