Memorandum on cerebro-spinal fever / Ministry of Health.

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MINISTRY OF HEALTH

MEMORANDUM ON CEREBRO-SPINAL FEVER

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In 1931 the Ministry of Health issued a Report on the Control of Cerebro-Spinal Fever (No. 65 in the series of Reports on Public Health and Medical Subjects) which amplified and replaced the memorandum issued by the Local Government Board in 1918 and was followed in March, 1932, by a memorandum on the administration of anti-meningococcus serum.

In view of the encouraging results recently obtained by chemotherapy it may now be opportune to issue a short memorandum briefly summarising the modern views on treatment of the disease. There are also included observations on the epidemiology of cerebro-spinal fever, the part played by the healthy carrier in its spread, the control of contacts, diagnosis, and general measures of prevention.

Epidemiology.

In England and Wales cerebro-spinal fever prevails chiefly in the late winter and spring, usually reaching a maximum in March or April and continuing with gradually diminishing intensity until May or June, but variations in the seasonal incidence occur from year to year.

There is good ground for the belief that outbreaks of cerebro-spinal fever are an indication and a consequence of widespread acute meningococcal infection of the nasopharynx in the general population. It is true that meningococci can be found in the nasopharynx of a large proportion of normal persons at times when the disease is practically non-existent; during 1931-7, for example, the percentage of such normal " carriers " in the staff of a London University Institution lay between 6 and 26 per cent. But their meningococci were distinguishable by agglutination tests from those isolated from patients in epidemic times, e.g., in the West Riding of Yorkshire in 1930-2. The latter were practically entirely (94 per cent.) of the serological Group I, whereas the former were almost all of Group II. The conclusion drawn* is that Group II is normally of low pathogenicity: it can produce meningitis, but as a rule only in highly

* Annual Report, Chief Medical Officer, Ministry of Health, 1931, p. 69.

susceptible subjects, especially infants, whereas Group I has much greater epidemic potentialities. For practical purposes, at the present time, only meningococci of Group I need be taken into consideration in efforts to control the spread of cerebro-spinal fever.

It was observed in 1938 that the proportion of Group I strains showed a distinct tendency to rise, and that this might foreshadow an approaching epidemic. Since October, 1939, not only has the proportion of Group I cases increased but this has been associated with an increased proportion of Group I infections of the nasopharynx as compared with Group II. The following figures have been collected by the Emergency Public Health Laboratories since October, 1939:—

Meningococci.	Group I	Group II	Not identified serologically.	Total	Per cent. of Group I
From cases of meningitis (by lnmbar puncture).	58	4	4	66	88
From the Nasopharynx of contacts.	20	7	11	38	53
From the Nasopharynx of non-contacts.	25	46	39	110	23

The percentage of " carriers " of meningococci Group I among different groups of the population at the present time has not yet been accurately determined, and it is not known whether a particular level of frequency is to be regarded as a danger signal foretelling the appearance of cases of cerebro-spinal fever. Moreover, the significance of carrier rates in relation to epidemic prevalence of cerebro-spinal fever is obscured by a factor which cannot yet be assessed by any laboratory test, namely the virulence of the " carried " meningococci, in the sense of their capacity to invade the blood stream and meninges.

Control of Contacts.

In view of the extent of infection of the general population with meningococci which cannot be distinguished from those actually producing cases of cerebro-spinal fever, search for " carriers " should be discouraged as a routine practice and undertaken only in quite special circumstances where it is thought necessary to trace the origin of an outbreak. It may be possible, by a nasopharyngeal swab* and the identification

* Swabs from the tonsil or fauces are practically useless.

of the meningococcus with that isolated from a patient, to show that a particular person has probably introduced the disease. In residential schools and similar limited communities, the occurrence of a case of cerebro-spinal fever may justify the bacteriological examination of swabs from the nasopharynx of those persons who have occupied beds adjacent to that of the patient, or who have otherwise been in close contact with him and the segregation of those found to be infected with a strain of meningococcus identical with that of the patient. It is prudent not to permit close association of children with any person who within three weeks has been living in a community in which the disease was present, until the person has given a negative nasopharyngeal swab.

Naval, Military and Air Force contacts will, of course, be dealt with as laid down by the Medical Departments of the Navy, Army and Air Force respectively. The isolation in hospital of civilian contacts or known " carriers " should not be attempted. They should be instructed to sleep alone, to avoid crowded assemblies and close contact particularly with children and young persons. To this end they should be in the open air as much as possible. Local treatment of the nasopharynx is probably useless. Treatment of " carriers " with sulphanilamide or sulphapyridine has been tried but in the present state of knowledge mass treatment of contacts by these drugs for this purpose should not be attempted. As a rule, " carriers " become free spontaneously in the course of two to three weeks simply with fresh air and exercise.

Diagnosis.

The incubation period is indefinite, but usually from three to five days. The maximum period may be as long as nine to ten days and in some fulminating cases as short as 24 hours. Suddenness is one of the usual characteristics of the onset but is not invariable. Before its confirmation by lumbar puncture the diagnosis is mainly determined by five symptoms; intense headache, vomiting, pyrexia (usually moderate and associated with a comparatively slow pulse), stiffness of the neck muscles, and Kernig's sign.

The patient appears to be more seriously ill than his moderate temperature and slow pulse would indicate; cerebration is usually slow or otherwise abnormal; stupor, delirium or coma may be present early in the disease. The vomiting is almost invariably associated with constipation. Stiffness of the neck muscles is an early sign, whilst retraction of the head comes later; forward flexion of the neck is more painful than rotation; Kernig's sign is pronounced and there is usually little difficulty in distinguishing this definite sign of meningeal irritation from its slight counterfeit which can sometimes be elicited in influenza or measles.

It must be remembered, however, that Kernig's sign sometimes appears gradually and may not be well marked until 24 or perhaps 48 hours after the onset of illness.

The rashes, which give rise to the term "spotted fever" are more common in some outbreaks than in others, such as the epidemic of 1921 in Denmark. They include petechiae, maculae, occasionally in the early stages rose red papules and large purpuric patches. Labial herpes is common and occurs late. Retention of urine with overflow may occur.

The clinical appearances in cases in which the invasion of the meninges of the brain and cord is of moderate severity are not difficult of interpretation, but this is not so either when the invasion is severe—the fulminating type in which the patient succumbs to a rapid intoxication—or when it is mild and the symptoms are chiefly those of a general infection. In epidemic times the great majority (probably 90 per cent.) of adult cases will show a fairly typical clinical picture. Among the remaining atypical cases there will usually be some 2 or 3 per cent. of "fulminant" cases in which the meningococcal septicaemia is so rapid and overwhelming that the patient scarcely has time to develop meningeal symptoms before coma and death supervene; in such cases the cerebro-spinal fluid may be clear or only faintly turbid. These cases often exhibit a purpuric rash.

Abnormal types of the disease are common among children. In infants stiffness of the neck muscles is seldom marked in the early stage and the slightest degree of rigidity of the neck is therefore significant.

Mild attacks lasting from six to nine days are occasionally met with at all ages, particularly towards the decline of an epidemic or as part of the sporadic occurrence of cerebro-spinal fever among adults. In such cases there may be malaise or sore throat followed by increasing headache and generalised pain; there may be vomiting. The mental condition is usually unaffected and the temperature reaches 100°F. to 103°F., with a gradual and steady fall to the normal. These cases may be mistaken at first for influenza or typhoid fever, but some degree of neck rigidity and Kernig's sign are usually present, and the cerebro-spinal fluid is slightly turbid with relatively few meningococci.

Sometimes a recrudescence or a second and more severe attack follows within three or four days of apparent recovery.

Examination of the cerebro-spinal fluid obtained by lumbar puncture will usually make the diagnosis certain. The services of the Emergency Public Health Laboratories set up by the Medical Research Council in collaboration with the Ministry of Health are available for this purpose.

Treatment.

Although one case of cerebro-spinal fever is rarely the direct source of infection of another case, removal to hospital will practically always be desirable, since treatment is highly specialised and requires expert medical attention.

Until recently the treatment of cerebro-spinal fever—apart from good nursing which is of the greatest importance—resolved itself into:—

(1) early and repeated lumbar puncture to relieve pressure and to promote drainage of the cerebro-spinal system; and

(2) the administration of anti-meningococcal serum either by the intrathecal route or by intravenous or intramuscular administration.

Recent advances in chemotherapy, however, give grounds for hope that the routine use of serum treatment may be dispensed with—even as an adjuvant to chemotherapy.

In the fulminating type of case, or if the patient when first seen is nearly comatose, the administration of a suitable serum may be considered. It may be given intrathecally at the first lumbar puncture and a large dose may also be given intravenously with a view to neutralising the circulating toxin pending a sufficient concentration being attained in the blood stream and cerebro-spinal fluid of one of the drugs which are mentioned later. Serum which is more than six months old and has not been kept in cold storage or which is not known to be specific against the current epidemic strain is likely to be relatively ineffective. There is evidence that even acute and fulminating cases of the disease have frequently been rapidly cured by chemotherapy without the use of serum at all. On the other hand, although there appears to be no convincing clinical evidence that the use of serum is necessary, even as an adjuvant to chemotherapy conducted in accordance with the principles outlined below, nevertheless some recent animal experiments suggest that better results may be obtained by combining the two forms of treatment.*

The drugs which now seem to have revolutionised treatment and radically improved the prognosis in cerebro-spinal fever are two derivatives of the sulphonamide series—(i) M. & B. 693, or Sulphapyridine, and (ii) Sulphanilamide (trade synonyms Sulphonamide P., Colsulanyde, Streptocide, Prontosil album). Group I and Group II Meningococci appear to be equally susceptible to these drugs, the only agents which have been shown to be highly active against meningococcal infections in laboratory experiments and in large series fully curative in man.†

Sulphapyridine is the drug of first choice because it possesses one important advantage in comparison with sulphanilamide namely, it is not only as effective in the treatment of meningococcal and streptococcal infections as is sulphanilamide but is unique in its action in pneumococcal infections. This is an advantage since at the bedside the practitioner can rarely make

* For details of serum therapy see Ministry of Health Public Health and Medical Subjects, No. 65, pp. 13–19.

† Banks, H. S., Lancet, 1940. I. 42.

a more precise diagnosis than that the patient is suffering from a purulent meningitis.

The object of chemotherapy in meningococcal infections is to secure with the minimal delay and to maintain in the body fluids an adequate concentration of the selected bacteriostatic agent. *The two essentials of this method of treatment are early administration and adequate dosage. Directly a clinical diagnosis is made chemotherapy should be commenced without waiting for bacteriological confirmation.* It should be remembered that irritability and deepening coma may quickly render the administration of fluids difficult, and, as soon as the clinical diagnosis is made, the patient should, also, be given a plentiful supply of fluids. Neither of these measures should be delayed until the patient has been admitted to hospital. *A note of the drug used, the amount, route and time of administration should invariably be sent with the patient to the hospital.*

Dosage.

The aim should be to maintain in the cerebro-spinal fluids a concentration of the drug equal to 5 mg. per 100 c.cm. for three days and a diminishing concentration for a further period of five or six days. Low initial dosage is unsafe. *Large doses in the first forty-eight hours is the most important factor for success* as high values at a later date may be comparatively ineffective.

During the first 2½-3 days of treatment, Banks* employs the following dosage for Sulphanilamide or Sulphapyridine although there is evidence that a somewhat lower dosage of Sulphapyridine will often be successful:—

Age Period in Year ...	0—	2—	5—	10—	15+
Daily Amount in Grammes	3	4½	6	7½	9

The spacing of the dosage is important and the compound should be given four-hourly *night and day* during the first few days, and, thereafter, if considered desirable, six-hourly. *In adults,* at the commencement of treatment, the first two single doses may be increased to a maximum of two grammes each. Thereafter, the four-hourly doses should not exceed one and a half grammes each, or a total twenty-hour dose of nine grammes. This initial twentyfour-hour dosage should extend over a period of 2½-3 days and the dose should then gradually be reduced over the next 4 to 6 days. This scheme will generally ensure that the drug is administered for some days after the disappearance of clinical signs and so prevent a recurrence

* Banks, H. S., Lancet, 1939. II. 921.

of the infection. The drug treatment should be completed in 7 to 9 days in order to avoid the more dangerous toxic effects. It is important, moreover, that the administration should not be interrupted on account of minor toxic effects, e.g. cyanosis, nausea, vomiting, or mental confusion.

The oral route should be employed for preference. If a dose is vomited it should be repeated and a suspension of the drug in pure mucilage of tragacanth may be more easily tolerated. If vomiting is repeated once or twice it is a good plan to change from sulphapyridine to sulphanilamide, which is generally retained under these circumstances. Alternatively Sulphapyridine Soluble may be given as a *deep* intramuscular injection (for an adult 3 cc. = 1 gramme). In delirious or semi-comatose patients who cannot be induced to swallow and in those who are completely comatose, the drug must either be administered by nasal or stomach tube (a method which enables fluids to be given at the same time) or by intramuscular injection. The latter route is also applicable to those rare cases of severe head retraction in which swallowing is for a time impossible owing to mechanical constriction of the oesophagus. A change back to oral administration should be made at the first opportunity.

As indicated in the dosage table, the initial dosage for infants and young children should be much higher proportionately than for adults. Banks* reports that infants tolerate easily 3 grammes a day for the first three days. This is, relative to body weight, a very high dose and must be reduced within three days. For the same reason, it is not advisable to " load " the first two doses as in adults.

So long as these compounds are being administered the intake of fluids must be adequate to maintain a reasonable balance between blood concentration and urinary excretion. For adults on sulphanilamide, approximately three pints of fluid a day are desirable but with sulphapyridine a larger amount should be aimed at (e.g. 4 pints) to avoid the danger of hematuria due to the deposit of crystals of the acetyl derivative of the drug in the kidneys.

During the first 24-48 hours difficulty may be experienced in administering the requisite amount of fluid especially if vomiting occurs. In comatose cases it is usually necessary to administer fluids by nasal or stomach tube for 24-48 hours until the drug has time to act. In extreme cases, it may even be necessary to give a general anaesthetic in order to administer a pint of fluid. Infants and small children frequently become dehydrated and it is imperative to administer saline without delay,

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* Banks, H. S., Lancet, 1940. I. 42.

preferably as a continuous drip by the subcutaneous or rectal route.

It is generally held that eggs and sulphur-containing foods should be excluded from the diet. Saline purges and drastic purgatives should be avoided. The most satisfactory laxative is liquid paraffin and the action of the bowel may be aided at first by enema and later by glycerine suppository.

Toxic effects of the drugs.

The toxic effects of the drugs in the treatment of cerebrospinal fever appear usually to be of a minor nature. With sulphanilamide on the scale of dosage indicated above, cyanosis constantly appears within 24 hours and, especially in adults, is generally quite deep in 36 hours. It remains as a rule until the dosage is substantially reduced and is due in most cases to methaemoglobin and occasionally to sulphaemoglobin. Except in such conditions as severe anaemia or dyspnoea from concurrent respiratory disease, cyanosis, unless extreme, is not necessarily considered an indication for reducing the dosage.

Other toxic effects of sulphanilamide are drowsiness, disorientation, mental confusion (probably distinct from that produced by the disease), occasionally hallucinations and rarely papular rashes. Nausea and vomiting are uncommon.

With sulphapyridine, cyanosis is much less marked but nausea and vomiting, malaise and general depression may be troublesome especially in adults. Transient haematuria has been noted. In these conditions the drug should be changed to sulphanilamide in similar dosage. If haematuria persists, the drug may be reduced or stopped for 12 to 24 hours as considered desirable. At the same time the administration of fluids should be increased and the urine kept alkaline by the administration of citrate.

Generally it may be said that patients on high dosage of sulphanilamide look ill, owing to cyanosis, and those on sulphapyridine feel ill, owing to depression and nausea.

The danger of agranulocytosis in this disease seems to be more remote than in some other infectious diseases such as puerperal fever and pneumonia, provided that the period of administration of the drug is restricted to nine days. It will, however, be at least a wise precaution to perform a white blood count after the third day of treatment and to repeat it in a few days. In hospital practice, analyses to determine the drug content of the body fluids should be made during treatment so that an accurate control may be exercised in relation to the clinical condition of the patient.

Lumbar Puncture.

After an initial lumbar puncture for diagnosis, further puncture should not be done except to relieve pressure symptoms (intense headache, etc.), and on alternate days, to verify the effective action of chemotherapy. A clear fluid which, on microscopic examination, is found to contain few cells and these mostly lymphocytes will indicate satisfactory progress.

General Measures of Prevention.

The measures of disinfection required in connection with a cerebro-spinal fever patient are simple; practically they can be limited to articles likely to have been soiled by discharges from the nose and mouth. Table utensils should be carefully boiled.

Observance of the general rules of hygiene, particularly in regard to fresh air and avoidance of "droplet" infection, is the best general safeguard. Masks should be worn by nurses in attendance on cases with a view to the prevention of massive infection. This applies particularly when assisting at lumbar puncture or otherwise giving attention to restive patients. The path of meningococcus infection being by way of the nose or mouth, the general precautions to be taken are such as are appropriate to prevent the spread of catarrhal diseases.

Local outbreaks are favoured by overcrowding, especially in sleeping quarters, and insufficient ventilation. On the appearance of cerebro-spinal fever in a residential institution, the nearest approach to open air life by day and night should be aimed at. Overcrowding in sleeping quarters, particularly in cold weather, has been proved by repeated experience to constitute a powerful factor in the spread of cerebro-spinal fever; in dormitories the space left between adjacent beds should be as great as can be obtained and not less than three feet. If the distance between the beds is less than 3½ feet, every alternate bed should be turned round, so that each occupant sleeps with his head opposite his neighbour's feet. Extra space can also usually be obtained by pulling some of the beds into the middle of the room.

All children of school age who have been in contact with a clinical case should be excluded from school for three weeks.

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