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TUBERCULOUS MENINGITIS: PROBLEMS IN PATHOGENESIS AND TREATMENT

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FOR many years it was assumed that tuberculous meningitis arose as a result of the implantation of tubercle bacilli in the meninges themselves in the course of generalised hæmatogenous disease. Rich and McCordock (1933) were the first seriously to challenge this theory. They had made two fundamental observations which did not fit in with this conception. They had observed that meningitis may be absent in even the most extreme miliary tuberculosis, and they had also noted that the age of miliary tubercles in other organs did not correspond with the age of the contemporaneous meningitis. This led them to search for a theory of pathogenesis which would be compatible with these observed facts. In 1933 they published an account of the post-mortem findings in 82 cases of miliary tuberculosis and tuberculous meningitis. In 77 out of the 82 cases focal caseous lesions, older than the meningitis, were found in communication with the meninges. In 56 cases the meningitis could be traced to a specific caseous focus in the brain which had ruptured into the subarachnoid space. In 17 cases the diffuse meningitis could be traced to caseous plaques in the meninges themselves. In 2 cases both cerebral and meningeal foci were present. In one case the focus was found in the choroid plexus and in one case meningitis had occurred as a result of the rupture of caseous material into the spinal meninges from a bony focus. Many authorities—most of them continental—have failed to find such antecedent foci in such a high proportion of cases. It must be stressed, however, that the identification of these caseous foci presents a considerable technical problem, demanding minute examination of numerous thin slivers of brain tissue. The work of Rich and McCordock, however, has been amply and beautifully confirmed by Macgregor and Green (1937). In the examination of the brains of 88 cases in which tuberculous meningitis was present, 78 of them (88·6 per cent.) showed tuberculomata which were antecedent to the meningitis, and in 74 per cent. this antecedent focus was clearly responsible for the meningitis.

These caseous brain foci are commonly 3 to 5 mm. in diameter. Macgregor and Green (1937) observed that the foci which gave rise to

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meningitis were commonly fairly small and acute with little attempt at fibrosis. The larger foci tended to be encapsulated. Such larger foci may have been seeded at a greater distance from the surface of the brain and consequently been checked by the defences of the body before they had become dangerous. There are frequently 30 to 40 such caseous foci. As many as 130 nodules have been observed in a single brain. It is evident therefore that the meninges may be infected by successively erupting foci. These caseous foci arise during the stage of hæmatogenous dissemination which is known to occur in the course of tuberculous infection. Yet in miliary disease caseous brain foci may be extremely sparse. For instance, 11 of Rich and McCordock's (1933) cases showed extensive disease of all organs with numerous soft caseating tubercles, but the brain and meninges showed rare discrete tubercles only. It is not clear why tubercle bacilli are retained and proliferate in the brain when the number of organisms is relatively small whereas, when numerous organisms disseminate in the course of miliary disease, few become established in nervous tissue.

Although a high proportion of cases appear to arise from the rupture of caseous foci into the subarachnoid space, there remain a number of cases in which such foci cannot be demonstrated. One possibility is that some cases do in fact arise directly from miliary disease and Macgregor and Green (1937) describe 8 cases in which they believed such a direct relationship to be present. Schwarz (1948) has suggested that spread to the meninges may take place by means of the Virchow-Robin spaces. He observed that the daughter tubercles around the central caseous focus in the brain corresponded in anatomical distribution to these spaces. The meninges could thus be infected from deep-seated caseous lesions.

One further problem must be briefly mentioned. Blacklock and Griffin (1935) contend that the evidence of Rich and McCordock (1933) does not fully explain the frequency with which miliary tuberculosis is found in association with tuberculous meningitis. In 297 successive autopsies they found this association in 68 per cent. of cases. Macgregor and Green (1937) found it as frequently as 83 per cent. A possible explanation is that the development of miliary disease gives rise to an allergic reaction in tissues already involved, causing reactivation of brain foci and leading to their rupture into the subarachnoid space. It is also possible that in some cases the tuberculous brain focus may itself be responsible for miliary dissemination.

Pathology of the Untreated Case of Tuberculous Meningitis

Before the problems of the management of tuberculous meningitis can be discussed, it is essential to make a careful study of the pathological changes which occur both in the untreated and in the treated case.

The pattern of the post-mortem changes in persons dying from untreated tuberculous meningitis is very much the same whatever the origin of the disease. The meningeal exudate is most marked at two sites. One is the site at which the original focus ruptures, the other is the base of the brain. Tubercles can be seen spreading from the original site of infection and are usually most evident along the line of vessels. The infection spreads by means of the C.S.F. from the original focus, the exudate tending to collect in the larger subarachnoid spaces such as the inter-peduncular fossæ. The spinal meninges are usually affected by downward extension of the disease. The meningeal exudate is at first slightly opaque or turbid and later is yellowish or greenish in appearance. Characteristically it is rich in fibrin. In acute cases it may be gelatinous. In the untreated case a degree of hydrocephalus is always present but is seldom marked. There is always involvement of the cerebral vessels which traverse the exudate. These show acute inflammation and fibrinoid necrosis, producing stenosis of the lumen of the vessel. In 88 untreated cases, however, Macgregor and Green (1937) found no ischæmic necrosis of brain tissue.

Distribution of Streptomycin in the Tissues: The Development of Streptomycin Resistance

The introduction of streptomycin therapy has brought about significant changes in the pathology of the disease, an understanding of which is essential to the treatment of the disease. There are, however, certain aspects of streptomycin therapy to which brief reference must be made at this stage.

Distribution of Streptomycin in the Tissues.—Like certain dyes and like serum bilirubin, streptomycin is unable to pass from blood to brain across the pia-glial barrier. Baggenstoss *et al.* (1947) give the following illuminating figures for streptomycin levels in one of their cases: Blood serum 120 μg./ml.; C.S.F. 15·8 μg./ml.; brain tissue, nil. When given intramuscularly the amount of streptomycin found in the C.S.F. is significantly less than that present in the blood serum. Published figures for the respective levels vary slightly, but it is generally agreed that the spinal fluid level is about one-twentieth of the serum level when the meninges are intact, but this amount is increased in the presence of meningitis to a figure of about one-seventh of the serum level. Levels of 5 to 10 μg./ml. are commonly found in the presence of tuberculous meningitis.

The Development of Drug-fastness.—The emergence of tubercle bacilli which are resistant to streptomycin is a very real therapeutic problem. Streptomycin is, unfortunately, a drug to which a wide variety of organisms, including the tubercle bacillus, readily become resistant. There are two theories—the mutation and the adaptation theory—advanced to account for such a development. The mutation theory appears to account for most of the known facts about streptomycin

resistance. Large populations of bacteria appear to possess minute numbers of cells which are able to thrive in concentrations of a therapeutic agent which are lethal to the majority of the organisms. The mutation theory contends that it is from these originally-resistant bacteria that the streptomycin-resistant population arises. Abraham (1950), however, warns that this theory must not be accepted entirely to the exclusion of the adaptation theory which suggests that drug-fastness depends upon a mechanism between organism and drug whereby organisms gradually develop a resistance to the therapeutic agent. Whatever the mechanism, the development of streptomycin-resistance is a very real menace to successful therapy. It is known that about two-thirds of cases of pulmonary tuberculosis can be expected to develop streptomycin-resistant organisms within 2 months. It is difficult to assess the incidence of streptomycin-resistance in tuberculous meningitis. For a number of reasons the isolation of tubercle bacilli from the C.S.F. in treated cases may be difficult. However, Cairns, Smith and Vollum (1950) and Cathie and MacFarlane (1950), who culture every specimen of C.S.F., report an incidence of serious streptomycin-resistance in 7·5 per cent. out of 80 cases and 8·3 per cent. in 60 patients respectively. There were no survivors among the patients who developed streptomycin-resistant organisms.

The Importance of an Intact Blood Supply.—If streptomycin therapy is to be successful, it is obvious that it is essential that the diseased areas must have an intact blood supply. Again, the effectiveness of streptomycin is seriously diminished when caseation occurs. Necrosis of tissue results in the interference with the normal cellular architecture which carries the blood supply. Caseation thus interferes with the transport of the drug to the diseased area. Not only that, it also interferes with the normal processes of the defence mechanisms of the body, including phagocytosis which, if it is to be effective, depends upon an adequate supply of oxygen.

Pathological Changes in Streptomycin-treated Cases and their Relation to Symptoms

The pathological changes observed in the streptomycin-treated case may be conveniently considered under four headings, the tuberculous exudate, the development of hydrocephalus, the changes in the cerebral blood-vessels, and the behaviour of the cerebral foci.

The Tuberculous Exudate.—Winter (1950) in a careful study of 30 cases of tuberculous meningitis unsuccessfully treated by streptomycin described changes observed in the tuberculous exudate. They may occur as early as the eleventh day of treatment. The polymorphs disappear from the exudate and the fibrin becomes liquefied though it remains abundant. This phase is followed by thickening of the

exudate by fibrous proliferation. Subsequently typical granulation tissue is formed by the growing in of capillaries. The exudate becomes woody in consistency and may form a thick layer. Caseous masses may persist within this fibrous membrane and tubercle bacilli may be present in large numbers. Lakes of cerebrospinal fluid may persist within the exudate and, if they communicate one with the other, circulation of the C.S.F. may still be possible. It will readily be seen that streptomycin will be ineffective in those areas in which impenetrable woody exudate is formed. Still more important is the fact that the exudate tends to form in certain vital anatomical sites, causing obstruction to the flow of C.S.F.

It has already been emphasised that the exudate tends to form most abundantly in the areas of the subarachnoid which are greatly dilated—the cisterns at the base of the brain. The chief of these is the interpeduncular cistern bridging the space between the tips of the temporal lobes and containing the optic chiasma and the tuber cinereum. Lateral extensions of this cistern are formed in the Sylvian fissures, and postero-superiorly is the cisterna ambiens which embraces the mid-brain. The optic tracts lie along the medial walls of this cistern. It is of great importance also that the origins of all the major cerebral arteries lie at the base of the brain and this area may become a lake of exudate.

It is convenient at this point briefly to consider the nature and effects of the blockage of the C.S.F. pathways by tuberculous exudate. There are five sites at which obstruction chiefly occurs. The first three, which may be taken together, are (*a*) foramen of Monro ; (*b*) aqueduct of Sylvius ; (*c*) foramina of Magendie and Luschka. If obstruction occurs at any of these sites, the C.S.F. fails to escape from the ventricular system, there is little C.S.F. in the lumbar space and the pressure may fall. Dyes injected into the ventricles cannot be detected in the spinal C.S.F. Blockage at this site gives rise to " obstructive hydrocephalus." If, however, the cisterna ambiens becomes blocked with exudate, C.S.F. escapes from the ventricular system but cannot pass over the cerebral hemispheres whence it is absorbed. There is thus abundant fluid on lumbar puncture, and dyes injected into the ventricles pass freely into the spinal C.S.F.—but streptomycin injected intrathecally will be unable to pass into the cerebral subarachnoid spaces and ventricles. This gives rise to a " communicating " type of hydrocephalus. Finally, blockage may occur in the spinal canal. This can be readily detected, and it should be remembered that if it occurs administration of streptomycin by the cisternal route should be substituted.

Blockage of the C.S.F. pathways is, then, a considerable problem in the management of tuberculous meningitis. Fortunately, obstruction does not for some reason readily become complete and it sometimes is transient in duration. The ways in which the problem of the basal exudate may be tackled will be discussed shortly.

The Development of Hydrocephalus.—The way in which hydrocephalus may develop has been briefly discussed. The frequency with which it occurs is excellently illustrated in the Report of the Medical Research Council (1948). In the course of 53 autopsies, 46 instances of hydrocephalus were observed, the degree of hydrocephalus generally being more marked the longer the patient survived. The hydrocephalus was chiefly of the communicating type, emphasising again the fundamental part played by the basal exudate. De (1949) suggests that hydrocephalus following blockage by tuberculous exudate is independent of streptomycin therapy except indirectly in that it preserves life sufficiently long for blockage to occur. He believes that there is no convincing evidence that streptomycin increases the chances of this complication by stimulating the production of reparative tissue.

The Cerebral Blood Vessels.—Excellent accounts of the vascular changes are given by Doniach (1949) and by Winter (1950). Only the vessels traversing the exudate are involved, and generally the greater the amount of exudate, the more severe the arteritis. The changes occur mainly in the smaller calibre vessels. The adventitia is replaced by a thickened collagen ring, the media is usually unaffected. The intima is grossly thickened by fibrous tissue. Sometimes the artery is practically obliterated and always there is a reduction in the vessel's lumen. Again it is contended that these changes are independent of streptomycin therapy except indirectly by the prolongation of life. In contrast to the untreated case, however, ischæmic softening of the brain is frequent. The fact that the origins of all the main cerebral arteries are often bathed in exudate has already been emphasised. Its importance to functional recovery of the patient is obvious. The most easily recognisable effect of the vascular changes is of course hemiplegia and this is not infrequently recorded. Hypothalamic symptoms such as transient hypertension, glycosuria, and bulimia have been recorded by Cairns and Taylor (1949). Buenger and Geiger (1950) report two cases of obesity, hirsutism, and the purple striæ of Cushing's syndrome and attribute them to arachnoiditis occurring in the region of the optic chiasma. Mental changes, including several cases of Korsakow's psychosis, have also been attributed to the vascular changes.

The Tuberculous Brain Foci.—As will be readily understood, the brain foci are unaffected by streptomycin therapy. The account of Baggenstoss, Feldman and Hinshaw (1947) is most revealing in this, and in other respects. Describing five fatal cases of streptomycin-treated tuberculosis, they observed that the minute, comparatively fresh miliary lesions in lungs, liver and spleen showed distinct evidence of healing. The healing took the form of a diffuse even fibrosis—a type of healing different from that which occurs in natural healing which is normally by encapsulation. By contrast, the larger caseating lesions in lungs, glands, bladder and prostate showed little evidence of

regression. Four of the cases showed involvement of the central nervous system; in three active progressive lesions were found in brain tissue.

The Development of Tuberculous Meningitis in Miliary Tuberculosis Treated with Streptomycin

One of the most interesting—and at the same time one of the most serious—problems in tuberculous meningitis is the development of meningitis during treatment of acute miliary tuberculosis with streptomycin. It is of especial importance because of the bad prognosis which attends such a development. In an account of one hundred consecutive cases of miliary and meningeal tuberculosis, Bunn (1950) reports the occurrence of complicating meningitis in 13 cases, none of whom survived. In the Ministry of Health Report on Streptomycin in Tuberculous Meningitis (1950), in which 369 bacteriologically proven cases are analysed, it is stated that one-third of the cases of miliary tuberculosis will develop tuberculous meningitis despite streptomycin treatment: that meningitis may develop as late as the seventh month of treatment and that "prophylactic" intrathecal streptomycin does not appear to prevent its development. These observations have been amply borne out in our own experience.

How does the meningeal disease arise, and why is it that so often it arises without meningeal signs? Choremis (1951) and his colleagues refer to it as asymptomatic or camouflaged meningitis. Why is it that its development is of such serious prognostic significance? The evidence of Baggenstoss, Feldman and Hinshaw (1947) that the brain foci progress despite healing of miliary disease in the lungs and elsewhere, suggests the obvious implication that the meningitis arises from the eruption of such a progressive focus into the subarachnoid space, life having been prolonged sufficiently by streptomycin for this event to occur. As has been pointed out, the concentration of streptomycin in C.S.F. is relatively low so long as the drug is given by the intramuscular route. If tubercle bacilli erupt into a medium which is inimical to proliferation but not actively bactericidal, it is possible that the meningitis produced may be—at least in the initial stages—of a mild type.

Rich (1946) suggests that the symptomatology of tuberculous meningitis is to some extent dependent upon a hypersensitive state of the meninges. There is some evidence that streptomycin depresses cutaneous tuberculin sensitivity, but the evidence is insufficient at the present time to be seriously accepted. If indeed the meninges do become less hypersensitive during streptomycin therapy, this factor could be one which affects the severity of the symptomatology of this type of meningitis.

The bad prognosis in such cases could theoretically be accounted for by the fact that organisms escaping into the subarachnoid were already streptomycin-resistant. As streptomycin does not penetrate

the brain foci, this occurrence is unlikely unless the cerebral focus is itself the result of the spread of streptomycin-resistant organisms. So far as I know, the finding of resistant organisms at the outset of tuberculous meningitis complicating acute miliary disease has not been reported. Whenever the sensitivity of the organism has been tested, it has always been found to be fully sensitive, even although tubercle bacilli isolated from other sources have already been resistant for as long as 46 days (McDermott, 1947). The organisms, however, may acquire resistance very rapidly when exposed to streptomycin by intrathecal injection. McDermott (1947) reports such an occurrence within four days of the recovery of a fully-sensitive organism.

Finally, it should not be forgotten that the development of tuberculous meningitis in the course of miliary disease under treatment may represent a basic failure on the part of the host to combat the disease.

In brief, in our present stage of knowledge there appear to be a number of factors which may influence the development of tuberculous meningitis in the course of miliary tuberculosis despite streptomycin treatment. It is not clear which of them are of importance. There is one important implication so far as treatment is concerned. All cases of miliary tuberculosis must have the C.S.F. examined for cells and chemical constituents regularly during treatment, preferably once weekly.

" Serous Tuberculous Meningitis "

Another interesting problem in the pathogenesis of tuberculous meningitis is the occurrence of what Lincoln (1947) describes as serous tuberculous meningitis. She describes the occurrence of meningeal symptoms in tuberculin-positive children, associated with an increase of pressure in the C.S.F., an increase in the number of cells, but no alteration in the chemical constituents. No abnormal neurological signs are present and no tubercle bacilli are found in the C.S.F. The children recover without specific treatment. In two such cases which have come to necropsy for one reason or another an area of healed non-specific meningitis has been found. She postulates that such phenomena are due to peri-focal reactions around Rich foci seeded in the brain during the primary and post-primary phases.

Macgregor and Green (1937) demonstrated tubercle bacilli in the C.S.F. of two patients who died of tuberculosis but in whom no evidence of miliary spread was seen. More recently Choremis and Vrachnos (1948) reported similar observations in children with primary tuberculous foci in the lungs.

If we contrast the occurrence of " serous tuberculous meningitis " on the one hand with the finding of tubercle bacilli in the C.S.F. without clinical meningitis on the other, it is a pertinent reminder of how imperfectly we understand many factors in the pathogenesis of tuberculous meningitis.

Early Diagnosis

The importance of the early diagnosis of tuberculous meningitis requires no emphasis when one considers the vital necessity of arresting the disease before the proliferating tubercle bacilli become sealed off in caseating tuberculous tissue, before the exudate is sufficiently copious to block the vital cerebrospinal fluid pathways and before the vascular changes become sufficiently advanced to be dangerous to function and to life itself. We know that the results of treatment are correspondingly less successful as delay in instituting treatment occurs and this fact is emphatically borne out by published results. In the Medical Research Council Report (1948) concerning 92 cases of tuberculous meningitis 46 per cent. of the early cases died compared with 66 per cent. of the intermediate and 86 per cent. of the late cases. In the report of the Streptomycin Subcommittee of the Department of Health for Scotland (1949) concerning 81 cases, only 33 per cent. of the early cases compared with 54 per cent. of the intermediate and 88 per cent. of the late cases succumbed. Choremis *et al.* (1951) reporting 113 cases, found that 17 per cent. of his early cases died compared with 53 per cent. of the more advanced cases.

Early diagnosis may present very considerable difficulties especially in infants and young children. When headache, vomiting and neck and spinal rigidity are present the disease is well established. The prodromal symptoms are often indefinite and vague. Their true significance may be overlooked. Rarely the disease presents with a sudden onset such as convulsions or hemiplegia. Choremis *et al.* (1951) for instance, give an account of 4 cases in children occurring in this way. More commonly the onset is insidious. Irritability, somnolence, and ready tiredness ; fever, loss of appetite, constipation, sometimes loss of weight—these are the prodromal symptoms. Such symptoms may be a prelude to a number of conditions but if they occur in a child in a household in which contact with tuberculosis is known, or in a child who is known to have recently shown Mantoux conversion, their immediate investigation is necessary. It must be remembered that in Debré's 51 cases who developed tuberculous meningitis and in whom the date of onset of allergy was known, 42 (82 per cent.) of them developed this condition within six months of Mantoux conversion (Debré *et al.*, 1947).

Examination of the fundus oculi is very important ; papillœdema may be present in infants without other abnormalities and may be the first sign of relapse : the presence of choroidal tubercles indicates at least the presence of hæmatogenous infection. Radiological examination of the chest may show the presence of miliary disease or other sign of tuberculous infection. The tuberculin test is important in diagnosis. The vast majority of cases are tuberculin positive reactors but a negative test must not be allowed to rule out the diagnosis, for in severe infection the test is sometimes negative in the initial stages, becoming positive when improvement occurs following treatment.

Choroidal Tubercles

Of great value in diagnosis is the detection of choroidal tubercles and brief mention must be made of their nature and significance. The presence of choroidal tubercles is an extremely important diagnostic finding and consequently renewed interest has been taken in this subject, particularly as with streptomycin therapy the changes in the appearances of the tubercles can be observed as healing proceeds.

In the early stage the choroidal tubercle appears as a rounded pale-yellow area with a matt surface merging into the red background of the choroid. Choroidal tubercles may be solitary, but as many as thirteen have been seen in one fundus (Somner, 1951); three, four or five are commonly observed. They are to be seen in the posterior pole of the eye and are not connected with retinal vessels and may indeed be traversed by them. Numerous tubercle bacilli can be demonstrated in them on histological section.

It is interesting to note their frequency in miliary tuberculosis complicated by tuberculous meningitis. At the UNICEF Conference on Streptomycin in Childhood Tuberculosis (1950), Monbrun of Paris stated that in an analysis of over 1000 cases he found choroidal tubercles in 87 per cent. of cases of miliary tuberculosis plus meningitis but in only 17 per cent. of cases of meningitis alone. Illingworth and Wright (1948) record such tubercles in 65 per cent. of combined miliary and meningeal tuberculosis and only 6 per cent. in pure meningitis. Somner (1951) found no choroidal tubercles in his cases of pure meningitis but an incidence of 70 per cent. in meningitis accompanied by miliary disease. As the Department of Health for Scotland Report (1949) points out, the presence of choroidal tubercles seems to point to the severity of dissemination and in this way may be a better guide to prognosis than the appearance of the X-ray film of the lungs. Illingworth and Wright (1948) also warn that failure of the choroidal tubercles to show progressive healing may be of serious prognostic importance.

The Clinical Problems Associated with Streptomycin Treatment

One of the chief problems of streptomycin therapy is that the drug is potentially extremely toxic.

Toxicity.—Numerous toxic effects of streptomycin have been reported but few of them occur with any frequency nowadays and consequently few of them are of practical importance. Such toxic effects as headache, nausea, vomiting, skin rashes including exfoliative dermatitis, eosinophilia, renal irritation and so on fall into this group. Of major importance is the neurotoxic effect upon the 8th nerve. Both portions of the nerve—vestibular and auditory—may be involved. The precise site and nature of the pathological disturbance responsible for these effects is not known for certain. The incidence of

toxicity is greater with higher dosage, as would be expected, and it is also greater the longer the drug is administered. Consequently, neurotoxicity is a major problem in the treatment of tuberculous meningitis as high dosage is given over long periods.

The vestibular damage associated with streptomycin therapy is a well-known phenomenon. Even although no vestibular symptoms are observed in the bed-patient, if vestibular function is tested by the cold caloric test significant loss of function will be found in a high percentage of cases if treated for 3 months, reaching 100 per cent. in those treated for 6 months. On the whole, dihydrostreptomycin is less injurious in this respect than streptomycin. Most patients compensate adequately although in the majority the loss of vestibular function is permanent.

The development of deafness is, however, a serious complication, especially in young children who have never possessed the faculty of speech. The incidence of deafness is variously reported. Debré *et al.* (1947) report deafness in 15 of 72 survivors, Cairns, Smith and Vollum (1950) report 5 cases of deafness in 60 patients. Choremis *et al.* (1951) report 1 case in 81 survivors and this low figure is of interest in view of the fact that they never use more than one gramme of the drug daily. Of greater importance, however, than the dose of the drug is the preparation used. There can no longer be any doubt that dihydrostreptomycin when used over long periods gives rise to deafness in a high percentage of cases. If I quote only one reference it is because of lack of time and because it is in accordance with our own recent experience. O'Connor, Christie and Howlett (1951) report that, out of 21 patients receiving dihydrostreptomycin for pulmonary tuberculosis for a period of six months or longer, 16 showed impairment of auditory function. Two were totally deaf and three showed moderate to severe impairment. By contrast, none of 12 patients receiving streptomycin for the same period showed any impairment of hearing. Deafness may supervene after treatment with dihydrostreptomycin has stopped.

Neither the development of loss of hearing or of vestibular function must outweigh other considerations in the treatment of tuberculous meningitis, but it can be said emphatically that dihydrostreptomycin in its present form must not be used where treatment over long periods is contemplated. None of the reported advantages of dihydrostreptomycin can alter this view.

Streptomycin: Dosage and Duration of Treatment

Streptomycin is the sheet-anchor in the treatment of tuberculous meningitis. The problems associated with its administration—chief of which are the tendency for the development of drug-fast strains and the neurotoxic effects of the drug—have already been discussed. There remains the question as to how much streptomycin should be

given and for how long. There is still not unanimity regarding this problem, especially in relation to its intrathecal administration.

Intramuscular.—When streptomycin was first employed it was used in a dosage of 3 or even 5 or 10 grammes a day intramuscularly, the total dose being divided into four fractions given 6-hourly. When given in this dosage its toxic effects were severe and it was sometimes impossible to determine which of the clinical manifestations were due to the disease and which to the cure ! The adult dose now advocated is 1-2 grammes daily. Many authorities recommend the higher dose, but it is of interest that Choremis *et al.* (1951) who never exceed a daily dose of one gramme of the drug at one occasion report a recovery rate of 61 per cent. in 132 cases—one of the highest recovery rates reported. Of the 81 survivors, only one is deaf. Streptomycin is bactericidal (Garrod, 1950). No advantage seems to accrue from giving divided doses. The drug is normally given once daily except in wasted children when the dose may be fractionated in order to lessen the amount of solution injected.

As to duration of intramuscular therapy, the Ministry of Health Report (1950) states emphatically that better results are obtained when intramuscular therapy is continued for at least 6 months. This appears to be current practice in this country at the present time. The danger of development of streptomycin-resistance and of the more serious toxic effects are increased with prolonged dosage, but the improvement in the recovery rate more than outweighs these disadvantages. Intramuscular streptomycin should be resumed in the event of recrudescence or relapse of the disease or if a fresh hæmatogenous spread of the disease becomes apparent.

Intrathecal Streptomycin.—There is considerable divergence of opinion regarding the intrathecal use of streptomycin. Levinson (1949) considers that intrathecal therapy is unnecessary, and reports 10 survivors out of 33 cases. The Ministry of Health Report (1950), however, in analysing 369 cases stated that the percentage of recoveries was generally greater with more intensive intrathecal therapy and that only exceptionally was a satisfactory response obtained with intramuscular treatment alone. It is current practice to employ intrathecal streptomycin.

The dosage employed varies from 25-100 mgm. daily. It must be remembered that streptomycin is an irritant substance when injected intrathecally. Cathie (1948) instances a substantial rise—about one thousand—in the number of cells, and in the protein, after injection of 100 mgm. of the drug into the normal theca. Choremis *et al.* (1951) stress that sensitivity to intrathecal streptomycin varies from individual to individual and adjust the dose accordingly with great care, using as little as 5 mgm. in some instances.

After intrathecal treatment nausea, nystagmus and drowsiness are not uncommon. Intracisternal and intraventricular streptomycin may be followed by severe reactions, including gross nystagmus and occasionally collapse and coma.

The Use of other Chemotherapeutic Drugs

In an effort to improve the recovery rate, it seems reasonable to try the effect of other known tuberculostatic drugs. None of them, with the exception of the continuous intravenous use of para-aminosalicylic acid (Paraf *et al.*, 1948), are effective in the treatment of tuberculous meningitis. Several have been tried together with streptomycin in the hope that they might have a synergistic action or help in the prevention of the development of streptomycin-resistant strains. Three such drugs must be briefly considered.

Sulphetrone.—Sulphetrone is a drug which does not diffuse into the C.S.F. and must be given intrathecally. It mixes readily with streptomycin but has potent toxic effects if a dose of 50-100 mgm. is exceeded. In this country Calnan *et al.* (1951) and Cathie and MacFarlane (1950), and Fouquet *et al.* (1949) in France, are satisfied that sulphetrone is of no added value in the treatment of tuberculous meningitis.

Promizole.—Promizole has also been used. Lincoln and Kirmse (1950), using promizole with streptomycin in a series of 18 cases, report a recovery rate of 72 per cent. Pasquinucci (1949) employing streptomycin and sulphone in 183 cases reports a recovery rate of 47 per cent. Promizole does not apparently prevent the emergence of streptomycin-resistant strains.

Para-aminosalicylic Acid (*P.A.S.*).—The discovery that the administration of P.A.S. (which is itself effective as a tuberculostatic agent) along with streptomycin significantly reduces the emergence of resistant strains (Medical Research Council, 1950) is an extremely important one. In 49 cases of pulmonary tuberculosis treated with streptomycin alone for six months, an incidence of 67 per cent. of streptomycin-resistant strains was observed. In 48 cases treated with streptomycin together with P.A.S., only 9·6 per cent. showed resistant organisms, and in 2 of the 5 cases only one resistant culture was found. It has already been shown that the development of streptomycin-resistant organisms may be a significant cause of failure. The administration of streptomycin alone is therefore no longer justifiable.

The Therapeutic Problems of the Basal Exudate

Considerable emphasis has already been laid on the problems presented by the basal exudate. Obviously early diagnosis and the institution of immediate therapy will minimise the risk of the formation of copious exudate in the basal cisterns. Attention has also been paid to substances which will liquefy the exudate.

Heparin.—Heparin was the first substance to be tried but its use was soon given up as it was ineffective. Cathie (1949) published a preliminary report on the use of streptokinase and a few months ago (Cathie and MacFarlane, 1950) a further account of its use was published.

Streptokinase is an enzyme produced by certain groups of hæmolytic

streptococci, and, as used by Cathie, it was found *in vitro* to lyse fibrinous exudate taken from the brain at post-mortem. It is given in half to one c.c. amounts at the time of intrathecal injection. Cathie and MacFarlane (1950) report two series comparable in many respects. Of 20 cases treated with streptomycin alone, only 25 per cent. survived ; in 40 cases treated with streptomycin and streptokinase 58 per cent. have survived. The comparative figures are impressive, but it seems to me that certain important differences in the series may not have been taken into account, not the least of which is the fact that the 40 cases treated with streptokinase were admitted subsequent to those treated without streptokinase. I have no doubt that experience in the management of tuberculous meningitis is an important factor in the results achieved. The results obtained in Cathie and MacFarlane's series are not significantly better than in some series in which streptokinase has not been used. Streptokinase must be used from the beginning of treatment, and its value must not be judged from cases in which it is used as a last-ditch effort in therapy. The value of streptokinase remains equivocal.

In the meantime, further reports have appeared of substances which are capable of liquefying exudates, but I am not aware that any of these have been tried in the treatment of tuberculous meningitis.

Intrathecal Tuberculin Therapy.—Everyone who treats tuberculous meningitis very soon becomes familiar with the tragic clinical picture of the unsuccessfully-treated case—the child who, despite continuous treatment and after weeks of deadlock, becomes comatose and passes into a state of decerebrate rigidity, with chewing and sucking movements, grinding of teeth and gross opisthotonos. Such cases were always found to have a thick collar of exudate around the mid-brain and infarction of the basal ganglia. These cases presented a seemingly insoluble problem. Smith and Vollum (1950), however, having observed the spikes of cells and protein which followed streptomycin therapy, postulated that such changes might result from the liberation of breakdown products of the tubercle bacillus (*e.g.* tuberculin) into the C.S.F. of the sensitised patient. They proceeded to confirm that tuberculin, when injected into the theca of a Mantoux-positive individual produced just such a reaction whereas no such changes occurred in the Mantoux-negative reactor. In the summer of 1949 Dr Honor Smith treated three apparently hopeless cases of the type which I have described with intrathecal tuberculin. Miraculously, two of them made a complete recovery. The third one died after five months of treatment—but at post-mortem the cisterns and the Sylvian fissures were free from exudate.

It seems that, in some specific way, tuberculin is responsible for the lysis of the exudates. One of the objections to the use of tuberculin therapy is that it is capable of producing exacerbation and dissemination of the disease, but the use of streptomycin makes this a less valid objection. Intrathecal tuberculin therapy, however, is potentially

dangerous and should not be embarked upon without knowledge of and skill in its use, and without facilities for surgical drainage of the ventricles. The discovery of intrathecal tuberculin therapy may be an important contribution to the treatment of tuberculous meningitis but it is too early for its place in therapy to be fully evaluated.

Neurosurgical Treatment

Discussion of methods designed to deal with the formation of tuberculous exudate is not complete without reference to neurosurgical methods of treatment. Sir Hugh Cairns and his associates at Oxford have made outstanding contributions to our knowledge in this respect. They believe (Cairns *et al.*, 1950) that there is much to be said for making frontal burr holes in all cases at the outset of treatment and there should never be a day when one does not have free access to the cerebro-spinal pathways for purposes of administering streptomycin, withdrawing C.S.F. for relief of intracranial pressure, or for purposes of investigation. These advantages are fully discussed by Smith *et al.* (1948). At the other end of the scale Choremis *et al.* (1951) state that, though they have been unable to secure the assistance of a neurosurgeon, they have yet been able to secure a recovery rate of 61 per cent. in 132 cases. They believe that the procedure they adopt—intramuscular dosage limited to one gramme, the careful gradation of intrathecal therapy and the use of intravenous tuberculin in severe cases—minimises the danger of blockage of the C.S.F. pathways by exudate. They agree, however, that some of their fatal cases would have benefited from surgical intervention. Wherever full neurosurgical facilities exist the routine making of frontal burr holes may be an advisable procedure ; where such do not exist there is no doubt that wherever it is indicated the institution of ventricular drainage can be life-saving and should be carried out without delay. Access to the ventricles is essential when intrathecal tuberculin therapy is contemplated.

General Treatment

A study of the pathogenesis and pathology of tuberculous meningitis readily demonstrates the need for attention to general treatment of the disease. The rather dull basic requirements of treatment are often neglected amidst the glitter of intrathecal therapy, ventricular drainage and laboratory procedures—vital though these things are. Rest must be prolonged and must be measured in terms of many months to ensure that not only the meningitis is healed but also the tuberculous focus from which it sprung. It must be remembered that in the Medical Research Council Report (1948) it was observed that in 42 out of 51 cases dying of meningitis active caseous lesions were found in lungs and in hilar and abdominal glands. The physician must ensure that nutrition is adequate ; this may require the prescription of protein supplements or tube feeding or adjustment of fluid balance ;

the tuberculous patient needs extra ascorbic acid. The management of tuberculous meningitis places a great strain upon all concerned—greatest, perhaps, upon the nursing staff. The fretfulness, the incontinence, the frequent vomiting, the helplessness of the patient with tuberculous meningitis over a period of many weeks make heavy demands upon the patience and time of the nursing staff. Their skilled and devoted care gives immeasurable help in the return of health to the gravely ill patient and eases the last days of the doomed child.

The advent of a drug which can reduce the inevitable fatality of a disease by approximately 50 per cent. is surely one of the greatest advances of our time but this drug has opened up innumerable problems which still lack solution and there is much to be done before we can be satisfied that we are using it to its full and proper advantage. The pathological problems which defy treatment are related essentially to the stage of disease at which treatment is started and if the recovery rate is to be increased it can only be by earlier diagnosis. That is a problem that remains with us to-day.

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