intrathecal treatment. It is not possible to be dogmatic about this, as there has been no report of a properly controlled investigation in which concurrent cases were treated with or without intrathecal streptomycin, while receiving streptomycin systemically together with isoniazid. It is noteworthy, however, that in some series treated without intrathecal injections the number of deaths in the first four weeks of treatment is unduly high. These deaths cannot be regarded as inevitable, as the patients did not have the benefit of intrathecal treatment.

For these reasons it is thought that at present the optimum treatment of tuberculous meningitis should include intrathecal streptomycin therapy, although it might be possible to reduce the number of injections even further. As we cannot foretell which patients will survive without intrathecal treatment, it is preferable to give it to some of them unnecessarily rather than to withhold it from those who need it.

Use of Cortisone

We have no experience with cortisone or corticotrophin as adjuncts in the treatment of tuberculous meningitis. It is claimed that these drugs are useful in the prevention of obstructions in the C.S.F. pathways. There has not been, however, a single paper describing a controlled study of the value of cortisone. This does not mean that cortisone may not be of benefit in some cases or that it may not replace the intrathecal use of tuberculin. It must be borne in mind, however, that obstructions in the C.S.F. pathways very rarely develop with modern treatment. Only one case with a temporary spinal block has been seen in the 51 cases treated with isoniazid. Astonishing recoveries can occur from apparently hopeless situations without the use of cortisone, and such occurrences need not be attributed to cortisone treatment.

Effects of Earlier Diagnosis

Of the 69 consecutive unselected patients who were treated in the Children's Hospital, Sheffield, during 1952-4 inclusive, 59 (85.5%) are alive (Table IV). These figures include those

TABLE IV.—Results of Treatment of Tuberculous Meningitis, 1952-4

Year	No. of Cases	Survivors
1952	26	21 (80.8%)
1953	23	19 (82.6%)
1954	20	19 (95%)
1952-4:		
All cases	69	59 (85.5%)
Conscious on admission ..	59	54 (91.5%)

who died within a few hours of admission. The proportion of patients who are admitted in an advanced state has been progressively decreasing in the last few years, but some still arrive so late in the course of the illness that no method of treatment can be expected to restore them to normal health. Early diagnosis and efficient treatment should now result in a recovery rate which approaches 100%. In 1954 we lost no child who was conscious on admission, and of 59 consecutive children who were conscious when admitted between 1952 and 1954 inclusive, 54 (91.5%) are alive, although 18 of them received no isoniazid treatment. The need to refer cases to special centres has not been lessened by recent advances in treatment.

Summary

During 1954, 20 new patients were admitted with tuberculous meningitis. Of these only one child died. He was in status epilepticus on admission and never recovered consciousness. A reduction in the number of intrathecal injections to a minimum of 25 and an average of 32 did not result in any deterioration in the results of treatment as compared with a previous series, and the C.S.F. returned to normal as quickly as before. Only one of the survivors has serious neurological and

mental sequelae. As the reappearance of tubercle bacilli in the C.S.F. may still occur after a course of intrathecal treatment during isoniazid therapy it is thought unwise to abandon intrathecal treatment. Cortisone was not used.

Of 69 consecutive children who were admitted during 1952-4 inclusive, 59 (85.5%) are alive. Of the 59 who were conscious on admission, 54 (91.5%) survived.

All the 11 children who were admitted during this period suffering from uncomplicated miliary tuberculosis survived. None developed meningitis during or after treatment with isoniazid and streptomycin.

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MURMURLESS BACTERIAL ENDOCARDITIS

BY

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In 1870 Wilks pointed out that bacterial endocarditis may exist "even though we fail to detect any morbid sounds in the heart." The cases which he mentioned had neither signs nor history of a "primary heart affection," and several of them were examples of acute bacterial endocarditis. Rarely, subacute bacterial endocarditis also occurs in patients with no detectable heart disease, when, for instance, the infection involves a bicuspid aortic valve. To diagnose these cases before a murmur appears is obviously difficult, but it is particularly desirable, since prompt treatment could prevent them from developing valve lesions. In this paper the histories of four patients in whom bacterial endocarditis was at first murmurless are reviewed in an attempt to discover how the disease may be diagnosed before the valves become damaged. In two cases the condition was suspected and treatment was started before a murmur appeared, but in neither of them soon enough to avert valve damage.

Case 1. Acute Bacterial Endocarditis

In 1948 a 39-year-old policeman developed sudden fever, with severe malaise and headache. He had no symptoms of a respiratory infection, no joint pains, and no history of previous rheumatic fever. On treatment with salicylates he failed to improve, and later began to have rigors. When admitted to hospital after two weeks' illness, he was pale and sweating profusely (temperature 103° F.—39.4° C.) but no abnormal signs were found apart from tachycardia. The haemoglobin was 68%, the white blood count 9,800, and

the sedimentation rate 50 mm. per hour. Blood culture revealed a β -haemolytic streptococcus. The patient was given penicillin and his temperature returned to normal on the third day in hospital. On the fourth day a soft aortic diastolic murmur was heard and later there was a basal systolic murmur. They increased in intensity, and, despite prolonged treatment with penicillin, the heart enlarged, the diastolic blood pressure fell, and the jugular venous pressure increased. Nevertheless the patient recovered, although signs of heart failure persisted for six months. In 1954 he had a tooth extracted ten minutes after receiving a single oral dose of penicillin. Three days later he developed fever, which recurred after two short courses of penicillin. In hospital six weeks later he was found to have subacute bacterial endocarditis (*Str. viridans*), from which also he recovered after another six weeks' treatment.

Comment.—Although the first infection was virulent, and ultimately produced severe valve damage, a murmur did not appear in this case until the eighteenth day of illness. The diagnosis was delayed because the patient was at first thought to have rheumatic fever, and even when it was made rigors were the only evidence of septicaemia. The subsequent history emphasizes the need for adequate penicillin cover before tooth extraction in patients with valve lesions, and it shows that the diagnosis of the milder infection tends to be longer delayed.

Case 2. Subacute Bacterial Endocarditis

A 54-year-old naval officer was admitted to a nursing-home in 1950 with an undiagnosed pyrexia. He had been treated with antibiotics elsewhere twice in the previous six weeks, but on each occasion the fever had recurred. He complained of headache and nausea, and had an unproductive cough and slight stiffness of the finger- and elbow-joints. He was anaemic (Hb 80%) and febrile (temperature 100.8° F.—38.2° C.), but the only other abnormal signs were a respiration rate of 28 and crepitations at the base of the left lung. X-ray examination showed increased lung markings in this area. The white blood count was 15,400, the sedimentation rate 80 mm. per hour, and agglutination tests were negative. The patient was given chlortetracycline for ten days, but his condition did not improve, and his temperature, which had fallen to 99° F. (37.2° C.), soon increased again to 102° F. (38.9° C.). Fifteen days after admission a soft aortic diastolic murmur was heard and a penicillin-sensitive streptococcus was found on blood culture. During the first week of penicillin treatment the patient developed an Osler node and had pain suggestive of splenic infarction, but he eventually made a good recovery.

Comment.—This patient had pyrexia for at least eight weeks before a murmur appeared and the correct diagnosis was made. He showed none of the usual signs of infective endocarditis when first seen, and he was thought to have "atypical pneumonia." Repeated antibiotics certainly confused the picture, but the recurrence of fever after each course is, in retrospect, highly suggestive of bacterial endocarditis. Whenever the cause of pyrexia is at all doubtful immediate blood cultures should always be done.

Case 3. Subacute Bacterial Endocarditis

In 1952 a man aged 35 complained of aching muscles, fever (temperature 101° F.—38.3° C.) and a slight sore throat. A chest x-ray examination and white blood count were normal, but he was admitted to a hospital a week later because of continued fever. Physical examination, the sedimentation rate, and agglutination tests revealed no abnormality. After a further eight days' fever, two short courses of chlortetracycline were given, but on each occasion the pyrexia recurred two days later. After four weeks' illness he entered another hospital, still complaining of malaise but with no localizing symptoms or signs to account for a temperature of 99–100° F. (37.2–37.8° C.). The pulse rate and white blood count remained normal, but the sedimentation rate was now 28 mm. per hour, and he had

mild joint pains. The low fever and increased sedimentation rate continued for two weeks, and tonsillectomy was then performed because the tonsils were thought to be unhealthy.

On his return from convalescence, however, the patient had to be readmitted because he was febrile and the muscle pains were worse. He still appeared well and had no tachycardia or anaemia, but a soft aortic diastolic murmur was now audible and *Str. viridans* was found on blood culture. There was no clubbing of the fingers or evidence of emboli, the spleen was not palpable, and the jugular venous pressure was not increased. Penicillin treatment was started exactly three months after the onset of the illness, and the patient promptly recovered.

Comment.—In this case the pyrexia was milder and the murmur first appeared between two and three months after the onset of symptoms. Recurrence of fever after antibiotic treatment was again a feature of the history. It is interesting that the sedimentation rate did not increase until the fourth week of the illness, and that the white blood count remained normal throughout.

Case 4. Subacute Bacterial Endocarditis

In 1955 a 54-year-old clerk developed sudden fever with very transient weakness of the left arm and leg. At hospital, five days later, no abnormal physical signs were found to account for the pyrexia, but the sedimentation rate was 68 mm. per hour and white blood count 11,000. Although symptomless, the patient did not look well, and he said that he had not properly recovered from two attacks of "pleurisy" suffered in the previous three months. (In these attacks he had pain in the shoulder and sweats, but no cough or dyspnoea. On both occasions he was given penicillin, and on the last one, a month previously, a chest x-ray film was normal.) One week later he again developed pain in the left shoulder and then began to have rigors. During one of these he suddenly became aphasic, and was found on admission to hospital to have a right hemiplegia. There were no other abnormal signs apart from fever (temperature 100° F.—37.8° C.). The haemoglobin was 93%, and examination of the cerebrospinal fluid and urine showed no abnormality.

A presumptive diagnosis of infective endocarditis was made, blood was taken for culture, and treatment with penicillin was started. The blood culture revealed *Str. viridans*, and eight days after treatment was begun a soft aortic diastolic murmur was heard. This was followed next day by a basal systolic murmur, and the blood pressure fell from 140/80 to 90/60. There was, however, no tachycardia or evidence of cardiac failure, and the heart was not enlarged. The infection responded to penicillin and the symptoms of the cerebral embolus slowly improved.

Comment.—This patient is thought to have had infective endocarditis for at least three months before the murmur began. The so-called pleurisy was almost certainly due to emboli in the spleen or elsewhere, since the pain was similar to that which occurred later on, and the initial sedimentation rate was higher than would be expected after only five days' illness. The absence of anaemia is therefore interesting, although once again the disease was modified by previous antibiotic therapy. The valve lesions developed a week after adequate treatment was begun, but it was of less moment than the cerebral embolus which occurred before the murmur appeared.

Discussion

In most cases of subacute bacterial endocarditis it is impossible to tell when the valves first become damaged, because they are already deformed by previous disease. The interval between the onset of symptoms and the development of a valve lesion can be accurately determined only in the rare cases in which the infection involves an apparently normal heart. Since the disease process is, however, the same in these cases, a similar interval presumably precedes valve damage in most patients with this infection. It is therefore important to decide the duration of this interval,

because valve damage can be prevented only by treating the disease during this time. In the three cases of subacute bacterial endocarditis described here, aortic incompetence appeared respectively 8, 10, and 12 weeks after the onset of symptoms. As often happens, the infection was modified in all of them by inadequate antibiotic treatment during the latent period. It thus seems likely that the disease must be recognized and treated within a very few weeks of its onset if significant valve damage is to be avoided. This is particularly difficult to achieve in the absence of heart murmurs, but even when they are present the diagnosis is often delayed.

In order to recognize subacute bacterial endocarditis in its earliest stages some reorientation of ideas is necessary. In the first place it should be remembered that the classical signs were formulated in the days when the disease was incurable, and that they are largely manifestations of its later complications. During the first few weeks of the illness patients often appear quite well and they do not present with obvious anaemia, clubbing of the fingers, or café-au-lait complexions. In none of the present cases was the spleen palpably enlarged even after two to three months of infection, and signs of emboli were only latterly detected in two of them. While it is important to examine the skin, conjunctiva, retina, urine, and peripheral pulses repeatedly for evidence of emboli, this tends to be done only when the diagnosis is already suspected and about to be confirmed by other means. In two of the cases described there was no tachycardia, in one no leucocytosis occurred, and in another there was no anaemia. The sedimentation rate increased in all of them, but in one case it did not do so for three weeks. The only constant early physical sign, other than a heart murmur, in fact, appears to be fever, and since this fluctuates it is easily missed if the temperature is taken on only one occasion.

The second point which these cases illustrate is that the early symptoms of subacute bacterial endocarditis are fortunately often more obvious than the physical signs. However well patients with this disease may at first appear, they almost always complain of definite malaise, which is in part attributable to their fever. Headaches and muscle and joint pains unassociated with arthritis come and go as the pyrexia varies, and persistent sweating is usually noticed. Rigors are rare in the early stage of the infection, but when they occur they sometimes presage major emboli. Thus, one patient in the third month of his illness suffered a cerebral embolus during a rigor, before the cardiac murmurs appeared. Symptoms of minor emboli are often noticed when no signs of them are evident, and unless specific inquiries are made they may be overlooked.

A history of brief pains in the finger-tips or loins, for instance, or of transient pleurisy, paraesthesiae, or other neurological disturbance may be obtained quite early in the disease. There is a risk that such symptoms may be dismissed because there are no confirmatory physical signs, and, for the same reason, their exact cause is often in doubt. Pain in the shoulder, for example, may be due to a splenic or pulmonary embolus, but it had a different explanation in another case seen recently with a suspected bicuspid valve. The patient had coarctation of the aorta with infection of a stenosed aortic valve, and he presented with severe pain and stiffness of his right shoulder. An electrocardiogram showed a myocardial infarction, probably due to a coronary embolus from the aortic valve vegetations. Patients also often complain of recurrence of their febrile symptoms soon after inadequate antibiotic treatment, and this history is very characteristic of infective endocarditis.

Finally the subject of heart murmurs in early diagnosis must be considered. It is generally agreed that subacute bacterial endocarditis practically never involves an entirely normal heart and that it occurs almost exclusively in patients who are known to have acquired or congenital heart disease. Most of the exceptional cases without heart murmurs, like those described in this paper, eventually develop aortic

incompetence and are considered to have bicuspid valves. Bicuspid aortic valves may be of congenital or acquired origin, and they are said to account for 6–12% of all cases of subacute bacterial endocarditis (Koletsky, 1943). Very rarely, the infection may arise without a murmur in a scar on the mitral valve (Anderson and Staffurth, 1955), or the mural endocardium (Cates and Christie, 1951), or in association with a silent ductus arteriosus. The true incidence of murmurless bacterial endocarditis may have been underestimated, however, because such cases are apt to be thought to have pre-existing valve disease unless they are seen before murmurs develop.

In 65 cases of subacute bacterial endocarditis, Wedgwood (1955) found that the average duration of symptoms before admission to hospital was 10 weeks. As has been shown, this interval is quite long enough for valve lesions to appear in previously silent cases. This might partly explain the remarkable preponderance of males with isolated aortic valve lesions in the series reported by Cates and Christie (1951), since Koletsky (1941) found that bicuspid valves occur predominantly in male subjects. Experience of the present patients certainly supports Wedgwood's suggestion that the incidence of cases without heart murmurs is likely to be higher in the early stages of the disease. Furthermore, a relative increase in the proportion of murmurless cases must also be occurring if, as seems likely, the prophylactic use of penicillin in patients with known heart disease is effective. For these reasons it should be widely realized that subacute bacterial endocarditis may exist in the absence of "morbid sounds in the heart." The corollary to this—that healed subacute bacterial endocarditis should be regarded as a cause *per se* of persistent cardiac murmurs—was pointed out by Beebe and Meneely (1949) in their report of three similar murmurless cases.

Conclusion and Summary

Unless subacute bacterial endocarditis is treated within a very few weeks of its onset, structural damage to the heart valves inevitably occurs. Ultimate cure of the infection is then only a Pyrrhic victory, since the damage incurred may well shorten the patient's life. In the first few weeks of the disease physical signs are hardly ever conspicuous and the symptoms are often more helpful in suggesting the diagnosis. It should be suspected in every patient with undiagnosed pyrexia of more than a week's duration, whether or not a heart murmur is present. Blood culture is a simple and economical investigation, and it should be performed repeatedly whenever such suspicion exists. If the diagnosis remains uncertain, the patient should be given the benefit of the doubt and be promptly treated for this infection. Indiscriminate use of antibiotic drugs may seriously interfere with the proper management of these cases.

The occurrence of bacterial endocarditis in four patients without heart murmurs is described, and the problem of diagnosis in such cases is discussed.

Three of the patients had subacute bacterial endocarditis. In all of them the infection was modified by inadequate antibiotic therapy, but they nevertheless developed aortic incompetence 8, 10, and 12 weeks after the onset of symptoms.

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