REFRESHER COURSE FOR GENERAL PRACTITIONERS

SUBACUTE BACTERIAL ENDOCARDITIS

BY

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The effective use of antibiotics has not only changed the prognosis and clinical course of subacute bacterial endocarditis but has entirely altered the emphasis on early diagnosis. Ten years ago the diagnosis was seldom made until the disease was well established, while today any patient with a heart murmur and unexplained fever should be suspect. In my own wards patients suffering from rheumatic fever, cystitis, glandular fever, virus pneumonia, carcinoma of the stomach, periarteritis nodosa, haemolytic anaemia, and perianal abscess have been admitted with the diagnosis of subacute bacterial endocarditis, and in each case, although the initial diagnosis was shown to be wrong, the admission of the patient to hospital should be taken as evidence of good judgment and efficiency on the part of the general practitioner involved. Early diagnosis is of great importance to the patient, therefore a full investigation is indicated when subacute bacterial endocarditis is first suspected.

Early Diagnosis

It is unfortunate that the early clinical manifestations are not only variable but often vague and ill defined. Fever is probably the most reliable early sign, but the degree of malaise with which it is associated is often so slight that it may pass unnoticed. The first complaint is usually of fatigue, loss of appetite, and sometimes pains in the joints. The patient may feel chilly and slightly feverish, and the temperature is found to be raised. If the patient is examined at this stage some of the physical signs of the disease such as splenic enlargement, petechiae, or embolic phenomena may be found, but often these are absent and the diagnosis can be established only by blood culture. Less frequently the disease remains unsuspected until the sudden onset of rigors and fever or of embolism and infarction.

Early diagnosis is now important, since delay in treatment undoubtedly diminishes the chances of survival, not because the infection is less readily controlled but because damage to the heart is both progressive and dangerous. Any patient with valvular or congenital heart disease who has unexplained fever should be suspect, and it follows that in the differential diagnosis all conditions which give rise to prolonged fever have to be considered, particularly those associated with splenic enlargement. Urinary infection is a common source of error, and tuberculosis and typhoid, glandular, and other fevers may have to be excluded.

The most difficult disease to distinguish from subacute bacterial endocarditis is rheumatic fever, a difficulty which was emphasized by Horder over 40 years ago. "It is probable that all the symptoms and signs of infective endocarditis may be met with in rheumatic fever, save the isolation of micro-organisms from the blood. Recurring attacks of subacute rheumatism in patients who have previously developed valvular disease often give rise to considerable anxiety on account of the similarity which they bear to the symptoms of infection of the endocardium." It is now much more important than it was to distinguish between these two diseases, but unfortunately there has been no corresponding improvement in diagnostic methods during the past 40 years. Even if blood cultures are repeatedly negative the diagnosis may remain in doubt, and therapeutic tests, first with salicylates and then with penicillin, may

have to be resorted to. The response to cortisone should never be used as a guide, since this may be disastrous in patients with subacute bacterial endocarditis.

Treatment

A unique feature of this disease is its resistance to treatment, although the infecting organism, which is usually a streptococcus viridans, may be sensitive to penicillin and to a variety of other chemotherapeutic agents. Large doses of penicillin are now recommended, and, although accurate figures are not yet available, it seems probable that the infection can be controlled in 95% or more of the cases. When the organism is not more than twice as resistant to penicillin as the standard Oxford staphylococcus, 2,000,000 units a day for four to six weeks will almost always be effective. In about 10% of cases the resistance of the organism is approximately four times that of the Oxford staphylococcus, and in these the daily dose should be increased to about 4,000,000 units. In about 5% of cases the resistance of the organism is more than eight times that of the Oxford staphylococcus, and under these circumstances the system of dosage to be adopted should be decided only after careful consideration of each individual case.

It is with this group of patients that disappointing results have been obtained. Information is as yet inadequate on the system of dosage which should be adopted in the treatment of these resistant cases, but in general it is true that the best results are obtained when the daily dose, if given by continuous infusion, would maintain a concentration in the blood which is about 50 or 100 times as great as the concentration required to kill cultures of the organism. In some patients very large amounts of penicillin may be sufficient, either when given alone or when given with some substance such as probenid which delays the excretion of penicillin. As much as 40,000,000 units a day may be required, but when this degree of resistance is encountered the use of other antibiotics should always be considered, and it is in making this selection that mistakes are often made.

When antibiotics other than penicillin are used it should be borne in mind that bacteriostatic agents such as aureomycin and terramycin are seldom effective even when laboratory investigations indicate that the organism is highly sensitive. The practice of giving aureomycin because the laboratory report seems favourable and because the patient does not appear to be responding to penicillin should be condemned, since it seldom succeeds and usually only leads to delay in effective treatment. A more profitable line of approach is a combination of penicillin with streptomycin, which is also bactericidal, but it should be emphasized that combined antibiotics should be used only under close laboratory supervision. The interaction of antibiotics is a matter of great complexity, and the laboratory supervision of cases which are resistant to treatment with penicillin demands a high degree of skill and specialized knowledge.

For obvious reasons the patient should be confined to bed and the general principles involved in the treatment of any prolonged febrile illness should be applied. Anaemia should be given treatment appropriate to its severity, and it is important that an adequate state of nutrition should be maintained. Foci of infection should be searched for, and dental sepsis should if possible be eradicated while the patient is being treated with penicillin.

Response to Treatment.—The blood culture usually becomes sterile within a few days of the beginning of

treatment, but not infrequently fever persists longer, although it usually falls within a week. The danger of infarction and other embolic phenomena remains throughout treatment and convalescence, but in lessening degree. The spleen diminishes in size, often quite rapidly. In contrast, haematuria may persist long into convalescence. The erythrocyte sedimentation rate may remain high during treatment, but falls slowly during convalescence. In the absence of complications such as heart failure or major emboli it is usual to allow patients to sit in a chair for a week after the cessation of treatment, and then to encourage an increase in activity according to the patient's capacity.

Relapses, Prophylaxis, and Prognosis

Relapses.—These seldom occur more than a month after treatment, but a slight risk, amounting to about 2% of patients per annum, of relapse or reinfection remains. The treatment of patients who fail to respond to the usual dosage presents a special and difficult problem. A larger dose should be given, probably at least 5,000,000 units a day for a period of six to eight weeks, but, as already emphasized, the system of dosage should be carefully regulated according to the sensitivity of the infecting organism.

Prophylaxis.—Dental extraction and removal of other foci of infection have long been regarded as precipitating factors in this disease. In patients with rheumatic endocarditis or congenital heart disease a prophylactic course of penicillin for these minor operations should be insisted upon. A dosage of 500,000 units daily for three days is usually recommended, the first dose being given an hour or two before the operation. It is perhaps not generally realized that this system of dosage, which is the one generally used in prophylaxis, is based not on clinical trials but on an intelligent guess made many years ago when penicillin was in short supply.

Prognosis.—Death from heart failure is now a much greater hazard to the patient than the risk of failure to respond to penicillin. About a third of the patients who are apparently cured die in heart failure within two years of treatment with penicillin, and the outlook is particularly gloomy in those who have evidence of heart failure when treatment is started. If heart failure is severe the patient rarely survives more than a few months, and even if it is slight the chances against survival for more than two years are about four to one. Other adverse factors in prognosis are delay in treatment and relative insensitivity of the infecting organism to penicillin.

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Nova et Vetera

THE DISCOVERY OF INSULIN

The Nobel Prize was awarded in 1923 to Banting and Macleod "for the discovery of insulin." Macleod's contribution to this dramatic discovery has been for long disputed. It is widely thought to have been both considerable and direct, and nearly 20 years later, in 1941, the *British Medical Journal* obituary notice on Sir Frederick Banting referred to "experiments in collaboration with the late Professor J. J. R. Macleod and Dr. C. H. Best which led to the discovery of insulin." Macleod's close participation in the research would not have been surprising, for the absorbing interest of his academic life was the metabolism of carbohydrates. His first papers on experimental glycosuria were published in 1905, and a series of 12 papers under the general title of "Studies in Experimental Glycosuria" was published in the *American Journal of Physiology* between

1907 and 1917 in addition to a series of 18 papers between 1908 and 1921 dealing with other aspects of carbohydrate metabolism.

Yet his inclusion in the Nobel Prize award led to bitter criticism of the prize-jury's decision. It was alleged that Macleod had been away from Toronto when the decisive experiment was made, and that, although he had put the facilities of his laboratory at Banting's disposal, he had had no part either in the formulation of the hypothesis on which the discovery was based or in any of the experimental investigations by which insulin was isolated and evaluated as a therapeutic agent. Best, who was Banting's close and acknowledged collaborator, was not given a share in the honour. According to Göran Liljestrand (1951), Banting expressed his dissatisfaction by sharing his half of the prize with Best, whereupon Macleod gave a corresponding part of his to J. B. Collip, who had participated with him in the purification and standardization of insulin.

Some Simple Facts

Nearly 30 years after the event we can now read Best's version (1952) of the early days, given as his corrective to "a few interesting statements about the early development of insulin which I completely fail to recognize." In the Banting Memorial Lecture for 1952 he writes :

"The facts are simple and straightforward. The young surgeon formulated an hypothesis which was vital to his initiation of the work and it thus completely fulfilled its function. He obtained permission to explore this hypothesis in the Physiological Laboratory of his Alma Mater and he received some excellent general advice from the Head of the Department. The second working hypothesis was that an internal secretion of the pancreas existed and that it could be captured. This one Banting and I shared, and in its exploration we invested our time and energy. We formed a partnership which was based on the new knowledge and experience which we gained together. We had no stipends, but the facilities of Professor Macleod's deserted department were at our disposal. *We worked completely alone during the four summer months of 1921 without any verbal or written advice from any senior investigator and until well after the salient facts, consistent dramatic lowering of blood and urinary sugars and complete recovery of our moribund depancreatized dogs, had been repeatedly demonstrated.*" (There are no italics in the original.)

"Banting and I presented our work to the Medical Faculty at a departmental seminar in the autumn of 1921, and our findings were later published in two papers under our names in the *Journal of Laboratory and Clinical Medicine*. These papers give the first detailed account of our isolation of insulin. We were given an impression that a member's name was necessary for the acceptance of a paper to be read at the meeting of the American Physiological Society, and for this reason Professor Macleod's was added to the preliminary paper presented in December, 1921. Banting and I always hoped that our article on 'The Internal Secretion of the Pancreas,' which appeared in the February, 1922, issue of the *Journal of Laboratory and Clinical Medicine* and which we wrote for and presented to our Medical Faculty on November 14, 1921, would be universally accepted for what it in fact was, the original record of our work. The paper which bore, in addition, the name of the Head of the Department was a summary of the longer one. We prepared it later, but it appeared in print first."

Another commonly held misconception is also dispelled by Best—namely, that he was a medical student when he volunteered to work with Banting. He was, in fact, after five years of university study (and a year in the Canadian Army) a very recent graduate in the arts course of physiology and biochemistry. For family reasons he was particularly interested in diabetes and had been a part-time research worker on this subject and a demonstrator in physiology to medical students during 1920–1. He registered for an M.A. in physiology during the year that he and Banting worked together and was admitted to the degree in June, 1922. It was not until September, 1922, 16 months after the joint work on insulin had begun, that he decided to proceed to an M.D. and registered as a medical student in the University of Toronto.

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