Occasional Survey

Infected Endocarditis: A Changing Disease*—I

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I have chosen for the subject of this Croonian lecture infective endocarditis in its subacute or chronic forms and have reverted to the original term rather than bacterial endocarditis as the disease may also be caused by rickettsiae, histoplasmas, fungi, and possibly viruses. This disease, although not common, has always had a fascination for the clinician, morbid anatomist, and bacteriologist, and I cannot do better than follow the precept of Osler,1 who, in his Goulstonian lecture on malignant endocarditis to the College in 1885, stated: “It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, and to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future.” Before this there were many descriptions in the literature of vegetative or ulcerative endocarditis, but Osler first showed clearly that these cases could be separated into two groups—septic endocarditis, which we now call acute, where there was an obvious septic focus with septicemia and infected infarcts, and so-called primary endocarditis, where the source of infection was not obvious, infarcts did not suppurate, and the disease ran a more chronic course.

Between 1885 and 1909 the infective nature of this type of chronic endocarditis was established with recovery of organisms, usually streptococci of low virulence, from the vegetations and blood stream, and it was realized that the disease affected patients with either chronic valvular disease or congenital malformations of the heart. The clinical features of the disease also became better recognized and were reviewed by Glynn2 in his Lumleian lectures of 1903.

Advent of Antibiotics

The year 1909 was a landmark in the history of the disease, as in that year Horder published his classic paper on “infective endocarditis with an analysis of 150 cases with special reference to the chronic form of the disease.” This was a remarkable publication, both in the excellence of its description of the clinical features and in establishing the importance of streptococci of low virulence as the usual cause of the disease and the correlation of clinical with necropsy findings. It had a dominating effect on thought on the disease for the next 35 years until the advent of antibiotic therapy in 1944. Until that time infective endocarditis was almost invariably fatal, with the exception of those cases with an infected patent ductus arteriosus, which were cured by ligation and chemotherapy. Bacteriological cure thus became a possibility, but after nearly 30 years of experience of antibiotic treatment and the availability of new antibiotics the results are disappointing and the disease still carries an early mortality of about 30%. Since 1944 the natural history of the disease has altered, quite apart from changes induced by antibiotic therapy. The clinical picture has altered; the traditional criteria for diagnosis are no longer adequate, and present methods of treatment require critical reappraisal in view of the continuing high mortality.

Accurate figures on the incidence of infective endocarditis are difficult to obtain, but such information that is available seems to indicate that there has been no decrease in numbers since antibiotic treatment became generally available. The Registrar General’s returns show that there were about 1,000 deaths per annum from infective endocarditis in the preantibiotic years, when the mortality was 100%. The number of recorded deaths in 1955 was 327 and in 1967 333. These figures include acute and subacute endocarditis, and if the 31% mortality in our own series can be regarded as representative the total number of cases each year is about the same as in 1939.4

The age incidence has shown a very striking change. Whereas Cates and Christie5 reported the maximum incidence in the second to fourth decades, at the present time the majority occur over the age of 50. Many factors are responsible for this change. The surgical correction of congenital defects which are subject to infection may have played a small part, but probably the major reason is the notable decrease in the incidence of rheumatic heart disease in patients under 40, partly caused by the greater use of antibiotics to control streptococcal throat infections and the virtual disappearance in Britain of florid rheumatic fever in young adults. As infective endocarditis is now largely a disease of the elderly an increasing number of patients have underlying arteriosclerotic heart disease, but rheumatic heart disease still remains the dominant factor, although in our own series6 the incidence dropped from 84% in 1956 to 65% in 1969.

Vegetations

A most striking change has occurred in the type of organism responsible for the disease. In pre-penicillin days 95% of cases were caused by Streptococcus viridans and other organisms were very rarely recovered. In 1969 in our series streptococci were still responsible for the majority of cases, but in 56

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cases with positive blood cultures only 44\% were *Str. viridans* and there was a rise in the number of non-haemolytic and microaerophilic streptococci and enterococci, many of which were resistant to penicillin. These figures are not representative, as many patients with organisms difficult to control had been referred from other hospitals. Improved bacteriological techniques had been responsible for the recovery of a wide range of unusual causal organisms, but streptococcal infections of one sort or another are still dominant. An unusual, but important type of infective endocarditis is caused by Coxiella burnetii (Q fever). This infection, which may be diagnosed by a rising titre of antibodies in the blood, will usually not respond to chemotherapy, and valve replacement during the active phase of infection may be necessary. Yeasts and fungi are very uncommon causes of "spontaneous" infective endocarditis although they occur with much greater frequency in patients subjected to cardiac surgery.

We still do not know how vegetations are formed, although their site seems to be due in many cases to a jet effect, through either a regurgitant valve or an intracardiac shunt. Rodbard\* showed that infective endocarditis frequently occurs where there is a large pressure gradient between the two chambers behind or in front of a regurgitant stream, as in the small ventricular septal defect (Maladie de Roger) or aortic valve disease, whereas if the ventricular septal defect is large or in a secundum type of atrial septal defect, where there is little pressure gradient, infective endocarditis rarely occurs. Mitral regurgitation is the commonest lesion in infective endocarditis and it is cases with slight regurgitation which are usually affected. The jet effect may be elegantly shown by cineangiography in these cases, particularly those with a late systolic murmur from a posterior cusp defect who regurgitate in late systole only and are, perhaps, more vulnerable than those with any other type of lesion. Similar effects can be shown in mixed mitral valve disease whereas in patients with gross mitral regurgitation with a large left atrium and ventricle and heart failure no jet effect is seen and infective endocarditis is uncommon. Another example of the jet effect and turbulence in siting vegetations occurs in infective endocarditis of the aortic valve, where the regurgitant stream of blood impinges on the mitral valve leaflet or chordae tendineae, causing vegetations which may result in severe secondary mitral regurgitation.

Why vegetations form remains a mystery. The traditional view is that minute platelet thrombi settle on valves roughened by congenital or acquired defects or areas of endocardium damaged by jet effects and that bacteria of low virulence enter from the mouth or genitourinary tract, become established and grow in the platelet thrombi, and produce the pyogenic or non-pyogenic vegetations from which emboli are readily discharged. Anerit *et al.* suggested that the primary lesion is a thrombotic vegetation, bacterial infection occurring when it is well developed, and related infective endocarditis to non-bacterial thrombotic endocarditis, which so closely resembles it. In their view valve damage which may be progressive and cause valvular fibrosis and distortion may be initiated by stress, either specific from infection or allergic or non-specific from external stress to cold, altitude, or arteriovenous shunts or possibly hormonal. An interstitial valvulitis is followed by deposition of platelets and fibrin to form the vegetation of non-bacterial thrombotic endocarditis and then surface infection causes infective endocarditis.

The traditional view that non-bacterial thrombotic endocarditis is associated only with disseminated carcinomas, usually from stomach, lung, colon, or pancreas, or leukaemia and other terminal illness and that it usually affects the mitral valve is no longer tenable. It may occur without associated disease, usually in elderly patients although sometimes in young adults under conditions of privation or stress, as shown by numerous publications from Spanish authors after the Spanish Civil War. It usually affects the aortic valve and is characterized by a prolonged course, often over a year, with fever and bland emboli. Blood cultures are persistently negative, and yet at necropsy the friable vegetations are indistinguishable from those of infective endocarditis apart from the absence of organisms. Many patients with so-called bacteriologically negative endocarditis belong in this group, as although vegetations are found at necropsy a search for organisms in them is not always made.

It is difficult to understand why the introduction over a short period of time, such as during dental extraction, of organisms of low virulence should, in a well patient often with trivial heart trouble, initiate a disease so relentless in its course and destructive in its effects. More attention is now being paid to the host's responses to the infection rather than exclusively to the infection itself, and the variable clinical features and course are traditional features of infective endocarditis. Organisms of low virulence and identical in the laboratory may in one case cause valve rupture and heart failure within six to eight weeks from the onset of symptoms, whereas in another the disease is a true "endocarditis lenta," with febrile symptoms often for over a year, without embolism or progressive valve damage, and with a good response to penicillin therapy. This variability of host responses accounts for our own surprising finding that mortality was not in any way related to the duration of symptoms before treatment.

**Immunological Factors**

There is increasing evidence that immunological factors play an important part in the pathogenesis of the disease and its complications. High levels of circulating antibodies to the infecting organisms can be shown in most patients and in animals used for the production of antiserum; injection of the organisms when the antibody titres were high often produced chronic bacterial endocarditis. In most cases of infective endocarditis there is no precipitating cause for the illness and there must have been a bacteriaemias for an unknown period of time before the clinical illness occurred. During this period of high development of antibody formation antigen-antibody complexes are formed and are distributed throughout the body, where they may become attached to the endothelium of small blood vessels and elsewhere. This "immune complex" response is probably the cause of many of the so-called embolic phenomena, which are a classical feature of the disease.\*\*\*

The renal lesions of infective endocarditis are important in diuresis, treatment, and prognosis. Although frank haematuria from renal infarction is uncommon microscopic haematuria is almost invariable, and we regard this as a useful screening test for the presence or absence of the disease. The traditional view that focal embolic nephritis—the "fea-birren kidney"—is responsible for renal failure is no longer tenable. The renal lesion, which may cause death from renal failure, is histologically a true diffuse glomerulonephritis. The renal lesion also occurs in endocarditis affecting the right side of the heart, when a valvular embolus will not occur, and histological and immunological studies have shown that it is due to the deposition of immune complexes in the glomerular basement membrane, as also occurs in systemic lupus erythematosus.

The cerebral lesions of infective endocarditis have many features in common with the renal lesions. Frank and major embolic cerebral infarction is common, but in many cases the manifestations indicate more diffuse cerebral vascular disease, usually in elderly patients although sometimes in young adults under conditions of privation or stress, as shown by numerous publications from Spanish authors after the Spanish Civil War. It usually affects the aortic
usual necropsy finding is a focal encephalitis and endarteritis. Most reports emphasize the absence of any evidence of embolism, and the vascular lesions with endothelial swelling and perivascular lymphocytes are very suggestive of immune complex disease. The so-called microembolic lesions causing petechiae, splinter haemorrhages, and the various eponymous signs—Oster’s nodes, Roth’s spots, and Janeway lesions—have all been subjected to microscopic examination in the past and in nearly all reports no embol or bacteria could be shown, but there was evidence of “vasculitis,” endothelial swelling, and proliferative and perivascular cellular infiltration.

Major embolism is obviously important and occurred in 43% of our cases, but immunological factors may well be responsible for the other small vascular lesions. High levels of agglutinating antibodies to the infecting organism can usually be shown in the blood, and in 50% of patients high titres of “rheumatoid” factors are present and after treatment the titre returns to normal. In some cases the changes in plasma proteins and the pressure of antiglobulin factors are suggestive of immune complex disease. This is a respect a comparison with the atrial myxoma, whose clinical features in so many ways resemble those of infective endocarditis, is interesting. In addition to major emboli many patients have a marked peripheral arteritis often causing incipient gangrene of fingers and toes, and yet within a few days of removal of the myxoma and presumed antigenic stimulus the peripheral circulation returns to normal.

**Diagnosis**

The classical criteria for the diagnosis of infective endocarditis are still the presence of heart disease, fever, emboli, and, finally, a positive blood culture. Infective endocarditis rarely occurs in patients with normal hearts, although in congenital aortic valve disease the diagnosis may not be possible until the murmur of aortic regurgitation develops. In congenital heart disease the cases are usually acentonic, an important exception being the high incidence of infection in the tetralogy of Fallot treated by a Blalock anastomosis. All types of acquired valvular disease may be infected, although in general lesions which are haemodynamically not severe are particularly at risk, whereas patients with severe heart disease, with cardiac enlargement and congestive failure, are rarely affected. Because of the increasing age of patients and the prevalence of arteriosclerotic heart disease aortic valve infec tions are now more frequent, and pre-existing atrial fibrillation, which was formerly regarded as rare, is now not uncommon (10% of our series). Febrile symptoms often dominate the clinical picture, and clinical diagnosis is made easiest in those cases where the symptoms indicate the presence of fever, although frequently the disease is suspected only when the fever recurs after the indiscriminate use of short courses of antibiotics, which may sterilize the blood stream for as long as four weeks. More commonly the onset is insidious, with vague general symptoms such as malaise, and the presence of low-grade pyrexia is unsuspected.

The changing pattern of symptomatology of infective endocarditis is well shown by the change in peripheral manifestations; it is more intelligible if one accepts the thesis that these may be either obviously embolic or more commonly may be caused by diffuse vascular disease, whether this be due to microembolism or, as now seems more probable, immune complex disease. Overt embolii tend to be small rather than large and frank splenic or renal infarction is rare. Oster’s nodes occur infrequently and are almost never seen except with underlying rheumatic valve lesions. Petechiae and splinter haemorrhages are no longer of diagnostic significance, although the painful finger pulp is still of diagnostic importance. Clubbing of the fingers is probably the most useful peripheral manifestation as it is so rarely found in diseases with which infective endocarditis may be confused. Its significance was emphasized in a symposium on subacute bacterial endocarditis in 1920 by a galaxy of stars including Thomas Lewis, Horder, Libman, Carey-Coombs, and Gibson and was placed on a firm footing by Cotton in 1922, who also emphasized the difficulty in distinguishing it from congenital clubbing. It can occur quickly, and the persistence of a boggy oedematous nail-bed is important evidence of active infection.

It is common for the early symptoms of infective endocarditis to be regarded at psychoneurotic, and many of these patients had been under psychiatric care. In some cases there are frank psychotic symptoms or symptoms thought to be due to cerebral arteriosclerosis in the elderly. Heart murmurs in these patients are often regarded as insig nificant although in many the infection is localized on a sclerotic aortic valve, which causes the aortic ejection systolic murmur so common in the elderly. The response of those patients with diffuse cerebral vascular involvement to antibiotic therapy is good. In those with cerebral infarction secondary to major embolism there may be considerable neurological deficit even when the infection is cured. Diagnosis is often difficult when musculoskeletal symptoms are dominant, and cases may mimic rheumatic fever, rheumatoid arthritis, or polymyositis rheumatica.

**Multiple Culture Technique**

The diagnosis of infective endocarditis is often easy, but because “atypical” symptoms are often more prominent than the classical febrile or major embolic symptoms the diagnosis is frequently delayed, often for periods as long as a year. The diagnosis must be considered in any patient of any age with any type of heart disease who has persistent or recurring fever. This is one disease where the closest collaboration is necessary between the laboratory and the clinician for diagnosis, and more particularly in the planning of effective treatment. Bacteremia in infective endocarditis is persistent rather than intermittent, and it is our practice to take four to six blood cultures over a period of a few days rather than continue to take cultures over a longer period, as it is unusual for organisms to be grown from later cultures if they have been absent in the earlier ones. A multivariate technique was employed including the preparation of pour plates and provision for anaerobic growth. Organisms from positive cultures were identified and anterior treatment was started as soon as the diagnosis was confirmed by another blood culture. Bacteriological examination was continued with tube dilutions against penicillin and other antibio tic or antibiotic combinations until a satisfactory bactericidal level was obtained.

Positive cultures have been obtained in 70% of our patients with clinical infective endocarditis, and in spite of improved and more elaborate bacteriological techniques the figure has not altered since 1956. The changing pattern of the bacteriological flora of the disease has already been discussed—many of the present organisms are more resistant to antibiotic treatment and new unusual organisms are being recovered.

The group of patients (30%) with persistently negative cultures is of great interest. Many of these have had recent short courses of antibiotics, which may sterilize the blood for up to four weeks. Some may be infected with cell-wall deficient bacteria (L-forms or protoplasts) which will not grow in the usual media. Others are examples of non-bacterial thrombotic endocarditis, which is clinically indistin-
Regional Hospital Boards to Regional Health Authorities

FROM A SPECIAL CORRESPONDENT

In 1974 as regional hospital boards disappear from the scene, regional health authorities will make their entrance. Mr. R. Dobbin, secretary to the Newcastle Regional Hospital Board, explained to me what this will mean in his region. The present regional hospital board is responsible for 32 hospital management committees covering the counties of Northumberland, Cumberland, North Westmorland, Durham, and part of the North Riding. In the reorganization the regional health authority will become responsible for the Barrow area and Westmorland, which is now administered by the Manchester region; on the other hand, the Northallerton H.M.C. in the North Riding will go to the Leeds regional health authority. Nevertheless, the population of just over 3 million served by the regional health authorities will remain about the same as at present.

The new authority will encompass nine area health authorities, four of which will be co-terminous with the new local authority counties of Northumberland, Cumbria, Durham, and Cleveland; and five with the new metropolitan districts of Newcastle, North Tyneside, South Tyneside, Gateshead, and Sunderland. The area joint liaison committees will probably recommend that these five will be areas-without-districts, whereas the county area health authorities are likely to be divided into something like 12 districts based on district general hospitals or groups of hospitals providing a district general hospital service.

All staff of the regional hospital board will be transferred to the regional health authority, except for those who may have been appointed to the top posts—some of which are being advertised at present. The preamble to the H.L.S. Reorganisation Bill says that the reorganization should not itself lead to an increase in staff, but Mr. Dobbin thought that, as the Department had been encouraging the development of personnel and training services, an increase of staff would be needed. Nevertheless, this increase was a tendency that already existed, and was not due solely to the reorganization.

Planning Processes

Mr. Dobbin estimated that the new planning processes at district and area level would take perhaps three to five years to come fully into operation and that they should not produce any significant extra work at regional level. The hospital building programme, for example, was already outlined for the next ten years—though new thoughts on community hospitals might alter the plans a little. But planning at area and district level would initially be concerned with redeploying and making better use of staff and services, as well as organizing the new service.

Plans for expanding the actual premises of the regional hospital board were already being considered, and the offices were thought to be suitably sited for the headquarters of the new regional health authority. Currently every year the board was spending about £80 million on the hospital services—of which 70% went on salaries (a third of this on the nurses). But as the new regional health authority would also have to finance the community services the future budgets would not be strictly comparable with those at present.

In the past the regional hospital board had usually taken the initiative in liaising with the local health authorities—particularly on building requirements. But in future, Mr. Dobbin suggested, most of the liaison would take place at area level through the joint consultative committees. So far as professional liaison was concerned, the Act did require regional professional advisory committees, but he thought that these would not be composed of the same people who would serve on the area professional advisory committees. On the other hand, quite possibly the regional health authority might continue with the system of specialist advisers to the regional hospital board and the same specialists might

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