A large number of infectious diseases have undergone remarkable changes in their natural history since the introduction of penicillin. The duration of illness, incidence of complications, and fatality rates have been strikingly altered in those disorders for which this antibiotic has been effective. In addition, it has been possible, by applying this agent at the proper time, completely to inhibit the development of some infectious processes. An outstanding example of this general phenomenon is infective endocarditis. However, it is noteworthy that not all the changes in this syndrome have been related to therapy and that, in fact, problems unheard of not too many years ago are now often involved in the aetiology, clinical course, and final outcome of this kind of disease.

It is my purpose to review the clinical, microbiological and therapeutic features of infective endocarditis in the pre-penicillin era and in the present, and to comment on what appear to be likely problems in the future. Osler in 1885 pointed out the value of such an exercise in a Goulstonian lecture on endocarditis: ‘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, 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.’

MICROBIOLOGICAL FEATURES
A large variety of micro-organisms have been involved in the pathogenesis of infective endocarditis. In the pre-penicillin era, the green-pigment-producing streptococci (Streptococcus viridans) were the cause of at least 95 per cent of the subacute variety of infection, while Staphylococcus aureus, D. pneumoniae, Strep. pyogenes, Neisseria meningitidis, and N. gonorrhoeae were responsible for most episodes of the acute form. Valvular infections due to enterococci, non-haemolytic streptococci, various Gram-negative organisms, Listeria, diphtheroids, yeasts, and fungi were rare. A striking change in the frequency with which certain bacterial species are involved in endocarditis has occurred since the advent of penicillin (Lerner and Weinstein, 1966; Finland, 1969). At present, only about 50 per cent of subacute bacterial endocarditis
cases are caused by *Strep. viridans*; however, streptococcal species are still the most common offenders. Among the streptococci now frequently involved are micro-aerophilic strains (about 15 per cent of cases) and enterococci (8 to 10 per cent of cases). Physicians must be aware of these changes in the aetiology of the subacute disease because failure to do so may lead to errors in diagnosis, unless blood is cultured anaerobically, (micro-aerophilic streptococci), or inadequate therapy (enterococci). The agents involved in the acute disease have also changed to some degree; however, *Staph. aureus* remains the commonest cause of this type of valvular infection.

Unusual or ‘opportunistic’ organisms are presently responsible for an increasing number of cases of endocarditis. In part, this is related to improvements in microbiological techniques that allow isolation and identification of these species, and to appreciation of the existence of bacteria in forms other than the ‘normal’ ones. In addition, the use of antimicrobial agents, cytotoxic compounds and immunosuppressive drugs, and various types of cardiovascular surgery have contributed significantly to the frequency with which uncommon species of micro-organisms are involved. Thus, the incidence of endocarditis due to a variety of yeasts and fungi is now greater than it was twenty-five to thirty years ago. Infection caused by these is relatively common in narcotic users, especially ‘mainliners’, and in patients who have had valve prostheses and ‘patches’ inserted into the heart. Another bacterium now causing endocarditis more frequently and posing difficult diagnostic and therapeutic problems is *Staph. albus* (*Staph. epidermidis*). Since this organism is usually present on normal skin, it is often regarded as a contaminant when isolated from the blood. However, repeated recovery of *Staph. albus* from the blood of patients with manifestations of intracardiac infection should be accepted as indicating its causal relation and lead to treatment. It is paradoxical that, although this staphylococcus possesses little pathogenicity, it produces disease that may be of long duration when untreated (6 to 12 months or more), responds relatively poorly to the use of large doses of highly inhibitory antibiotics and frequently causes death even after prolonged treatment.

There has been an equally striking change in the organisms most commonly associated with acute infective endocarditis. While coagulase-positive staphylococci (*Staph. aureus*) remain the most frequent cause of this kind of disease, the gonococcus, pneumococcus, and *Strep. pyogenes* are now rarely involved. This is probably related to the rapidity with which the infections produced by these species at their portals of entry (acute urethritis or cervicitis, pneumonia and pharyngitis) are eradicated, and bacteraemia followed by metastatic implantation of heart valves prevented.
Among the uncommon bacterial species presently responsible for an increasing incidence of endocarditis are Enterobacteriaceae such as Escherichia coli, E. aerogenes and Proteus. Other unusual but increasingly frequent causes of valvular infections are Serratia, Salmonella, Listeria, Bacteroides, anaerobic diphtheroids, Haemophilus influenzae, Pseudomonas, and anaerobic streptococci. It is noteworthy that these are most often responsible for disease in individuals suffering from immunosuppressive disorders for which antibiotics and/or drugs that depress the activity of normal defence mechanisms are given. It is striking, however, that even in the face of bacteraemia due to Gram-negative bacteria, these organisms rarely produce infection of heart valves, even in patients who have underlying valvular disease.

Of great interest and probable clinical importance is the demonstration that cell-wall deficient bacteria (L-forms, spheroplasts, protoplasts) may be responsible for endocarditis, especially in patients who have been treated with antibiotics that inhibit cell wall synthesis (Charache, 1968). These aberrant microbial forms will not grow in the media commonly employed for the recovery of ‘normal’ bacteria. Unless this possibility is appreciated and cultures carried out in hyperosmolar media, the diagnosis of active endocarditis will be overlooked and effective therapy (by drugs acting on protein synthesis) not instituted. It has been suggested that viruses, especially those of the Coxsackie group, may cause endocarditis (Burch et al., 1966; Burch and Colclough, 1969).

**Clinical Features**

There is a general impression that there has been a decrease in the incidence of infective endocarditis since effective antibiotics have become available. This has been thought to be related to a decrease in the frequency of acute rheumatic fever with carditis, and to the effective chemoprophylaxis of clinical situations that may predispose to the development of infections of heart valves. However, studies in Cleveland disclosed no change in the incidence of bacterial endocarditis in two consecutive six-year periods prior to the use of penicillin, and no significant reduction in its frequency over three six-year intervals after this antibiotic was introduced into clinical practice.

The clinical features of untreated infective endocarditis, especially the subacute variety, have undergone remarkable changes during the penicillin era (Lerner and Weinstein, 1966; Friedberg et al., 1961; Rabinovich et al., 1965; Tompsett, 1964; Uwaydah and Weinberg, 1965). These have been of such magnitude that the older classic descriptions are now of little diagnostic value. Failure to recognise that the natural history of this type of infection has altered to a very great degree, and reliance on old information is, in many
instances, a potentially fatal oversight. It must be emphasised that there is no evidence that the use of penicillin or any other antimicrobial agent has played an important role in this phenomenon. However, it is very clear that chemotherapy has greatly altered the course of events after it is undertaken.

Age Distribution. From 1913 to 1948, 10 to 25 per cent of individuals with this disease were over fifty years of age, and 2 to 10 per cent over sixty. Since 1948, 50 to 60 per cent of patients have been over fifty years old, and 20 to 30 per cent over sixty (Lerner and Weinstein, 1966).

Type of Underlying Heart Disease. Although rheumatic and congenital heart disease are still the commonest underlying disorders on which subacute infective endocarditis is superimposed, their frequency has decreased. As a reflection of the increased age incidence, arteriosclerotic valvular disease has become a fairly frequent lesion on which the subacute type of infection is implanted. In general, the background for acute endocarditis has remained essentially unchanged; from 40 to 60 per cent of patients have no previous cardiac disorders. The introduction of various types of surgery of the heart has added a group of iatrogenic lesions that may serve as foci for the development of both acute and subacute valvular infections. There also seems to be an increase in the frequency with which endocarditis is appearing in patients with acute myocardial infarction; the infection may be subacute or acute, depending on the nature of the organism involved, and may involve either the right or left side of the heart. Infections of the right side of the heart, usually of the tricuspid valve, but occasionally involving the lateral wall of the right ventricle or the right side of an intraventricular septal defect, are now being reported with increasing frequency.

Mode of Onset. The commonest manifestations that presently feature the early phase of subacute bacterial endocarditis before treatment are often so nonspecific that they fail to attract serious attention. Varying degrees of slight to moderate fever, progressive fatigue and loss of weight are the most frequent symptoms. Rigors are now quite uncommon. Arthralgia and, rarely, arthritis may appear early and persist even after effective therapy is undertaken. Progressive anaemia is a frequent but not a universal accompaniment of the disease; it is usually microcytic and hypochromic in character and advances rather slowly. Occasionally, decrease in haemoglobin is surprisingly rapid even in the absence of acute haemolysis. Now a great many patients with the subacute type of disease have normal white blood counts; shifts to the left are, however, common. The clinical manifestations of untreated acute infective endocarditis have changed little, if at all, since antimicrobial therapy has become available. High grade fever (103 to 104°F), severe rigors, rapidly advancing anaemia and the early appearance of embolic manifestations,
especially petechial and pustular skin lesions, are common. Although leucocytosis is frequently present, the number of circulating white blood cells may be normal or even low.

A number of unusual manifestations may now herald the onset of subacute bacterial endocarditis. Among these are backache, meningitis (usually sterile), focal ‘embolic’ encephalitis, renal insufficiency and heart failure. Rarely, bacterial endocarditis, either acute or subacute, may be present together with acute rheumatic carditis. The clinical features of the early stage of right-sided endocarditis are often quite misleading. While fever, anaemia and other constitutional manifestations are usually present, the possibility of endocarditis involving the right heart is frequently overlooked because blood cultures are often sterile, especially when the disease is due to alpha or non-haemolytic streptococci. The most important clue to the diagnosis of this type of disease is repeated episodes of ‘pneumonia’ involving different areas of the lung; as a rule, these are infarcts. When the infection is due to organisms of relatively low invasive capacity, Strep. viridans for example, the pulmonary lesions are usually sterile; when Staph. aureus or other highly invasive bacteria are involved, they become infected and localised pneumonia or pulmonary abscesses develop.

**Clinical Signs**

While the nature of the hosts has changed, the clinical pictures of acute infective endocarditis have remained essentially unaltered. In sharp contrast to this have been the remarkable changes in the physical signs in individuals with subacute infections. These are so greatly altered that if diagnosis today is based on the signs considered ‘classic’ as short a time as twenty years ago, from 85 to 90 per cent of the cases would be overlooked.

Fever, one of the prime manifestations of endocarditis, may be absent, in some instances, throughout the course of the untreated disease. This is seen more often in older individuals, many of whom normally have relatively low basal temperatures.

The incidence of atrial fibrillation or cardiac failure or both, previously rare in the early stage of subacute endocarditis, is now relatively common. This is probably related to the empiric administration of short courses of antimicrobial therapy in the absence of a diagnosis. Such ineffective treatment may go on for weeks or months and lead to progressive cardiac damage with the establishment of congestive failure and/or arrhythmias.

‘Peripheral Signs’. The most dramatic change in the clinical picture has been the sharp decrease in the frequency with which the peripheral manifestations, the primary clues to the disease in the past, are now detectable. Osler
nodes are now rare in both the early or later stages of the disease. This is also true of the Janeway lesions, Roth spots and subungual haemorrhages. Although petechiae of the skin, mucous membranes and conjunctivae are still present in an appreciable number of cases, they are now less common.

Gross infarction of kidneys or spleen was a frequent complication of subacute infective endocarditis in the past; this was usually manifested by acute pain and haematuria (renal infarct) or increase in degree of splenomegaly, with or without friction rub (splenic infarct). Fatal myocardial infarcts due to deposition of emboli were also not rare. Such complications are today quite infrequent. However, necropsy studies still demonstrate multiple small infarcts of the kidneys, spleen and heart; it is noteworthy that these are usually not detected clinically.

Cardiac Murmurs. The presence of a murmur used to be considered the sine qua non for the diagnosis of subacute bacterial endocarditis. It has recently become clear, however, that a murmur may be absent early in the disease. In some cases, it appears only two or three weeks after therapy has been initiated and then becomes persistent. In others, it is absent at the beginning and throughout the period of therapy, becoming detectable only several weeks after cure has been accomplished. Uncommonly, a murmur is never heard. In such cases, positive blood cultures and the development of embolic phenomena such as hemiplegia or renal or splenic infarction in a young individual are sufficiently suggestive of endocarditis to warrant initiation of therapy.

It must be stressed that murmurs are absent in about one-third of patients in the early stages of acute endocarditis involving the left heart, and in either acute or subacute infections of the right heart. In most instances, however, murmurs are present during this kind of disease and may change in character with startling rapidity. This is usually due to perforation or tear of the infected leaflets, rupture of chordae tendineae or papillary muscles or development of aneurysms of the sinus of Valsalva.

Immunological Phenomena. Although it was well known in the pre-antibiotic era that immunological reactions played an important role in the pathogenesis of subacute bacterial endocarditis, their potential importance has recently been emphasised (Cordeiro et al., 1965). Because the organisms that produce this disease possess relatively little invasive capacity, a large inoculum is required to initiate growth in, and invasion of, the primary cardiac lesion, the sterile platelet-fibrin thrombus that develops on the roughened surface of involved valves. High levels of agglutinating antibody for the causative agent are present in most if not all patients with subacute endocarditis. These agglutinate the organisms into large masses so that when they are trapped in
the valvular thrombus the numbers are high enough to initiate and continue
growth. The clinical effects of other types of immunological sequelae of the
infection are manifest in the sterile arthralgia or arthritis and renal involve-
ment (focal glomerulitis, chronic or rarely acute diffuse glomerulonephritis)
that develop in some patients. The incidence of these does not appear to have
been changed by effective chemotherapy. Although Osler nodes, Janeway
lesions and subungual haemorrhages have been thought to be embolic
phenomena in the past, they are now believed by many to be manifesta-
tions of a hypersensitivity state.

Recent studies of subacute bacterial endocarditis have indicated that most
patients develop higher titres of agglutinating, complement-fixing and
opsonising antibodies specific for the invading organism. All of these are
present in the 7S globulins; the 19S globulins contain only the agglutinins
and complement-fixing antibodies (Laxdal et al., 1968). Over 50 per cent of
patients develop some type of antiglobulin factor. A positive latex fixation
test is demonstrable in about 50 per cent of cases; it usually appears when the
disease has been present for six or more weeks.

**Therapy and Prophylaxis**

*The Pre-antibiotic Era*

The outlook for recovery from infective endocarditis was almost hopeless
before antimicrobial agents became available. The fatality rate of the acute
type of infection was 100 per cent. Although spontaneous cure of the subacute
disease occurred, it was rare; over 99 per cent of patients died. It is noteworthy
that the first cure of an infection of the cardiovascular system was accomplished
by surgery when an infected patent ductus arteriosus was ligated and eradicat-
ted the disease (Touroff and Vessell, 1940). Attempts to alter the course of
endocarditis by administration of sulphonamides were made prior to the
availability of penicillin (Schein and Baehr, 1948); fair to moderate success
was reported, especially when *H. influenzae* was the causative agent and massive
doses of sulphadiazine were given.

*The Antibiotic Era*

**Drug Therapy.** The development and use of antimicrobial agents has been
responsible for a most dramatic change in the prognosis of infective endo-
carditis. While there is an increasing need to use antibiotics other than peni-
cillin to treat this disease because of the increased involvement of unusual
organisms, it is striking that, even after more than twenty-five years, penicillin
and its semi-synthetic congeners are still the drugs most useful in the treatment
of infections of the heart.
Selection of antimicrobial therapy for infective endocarditis is directly dependent on the nature of the causative organism and its sensitivity to drugs. There is usually no need for immediate therapy in cases of subacute infection. A delay of two or three days is of little or no importance because many patients with this kind of disease have been ill for weeks or even months before the diagnosis is established. If death occurs before treatment is instituted in such cases, it is rarely due to the infectious process, but much more frequently to rupture of a mycotic aneurysm or an embolus in a major cerebral or coronary artery, complications not prevented by chemotherapy. In sharp contrast to this are the acute endocarditides, especially those due to *Staph. aureus*. Because of the rapidity with which rupture of valve leaflets, papillary muscles, etc. may occur, it is imperative that therapy be initiated immediately after appropriate blood cultures have been obtained. In the absence of bacteriological information, the diagnosis of this kind of disease must be based on the circumstances in which it developed and the clinical findings (e.g. pustular petechiae, demonstration of bacteria in smears of petechiae or the buffy coat of peripheral blood, high grade leucocytosis and severe constitutional reaction).

The specific choice of antibiotics for the management of the endocarditides is very often based on personal experience. The only requirement, whatever the agent employed, is that the organism be highly sensitive to it. In general, bactericidal compounds appear to be more effective than bacteriostatic ones. There are insufficient data at present to indicate optimal doses and duration of administration of any of the antibiotics used to treat endocarditis. Because of this, dosage is generally quite empiric.

The author has found the following regimens successful in the management of various aetiologic types of endocarditis—

1. *Strep. viridans or non-haemolytic streptococci sensitive to one unit or less of penicillin G*: 10 to 12 million units of penicillin G per day in equally divided doses intravenously. For patients sensitised to this antibiotic, cephalothin, 1 g every 2 hours intravenously.

2. *Enterococcus*: 5 to 10 million units of penicillin G intravenously every 6 hours plus 0·5 g of streptomycin intramuscularly every 12 hours, or ampicillin alone, 200 to 300 mg/kg/day. Cephalothin has not proved effective, even when combined with streptomycin. For patients sensitive to penicillin:
   
   (a) erythromycin, 1 g intravenously every 6 hours,
   
   (b) careful desensitisation to penicillin followed by administration of this agent together with streptomycin, as indicated above, or
   
   (c) vancomycin, 1 g every 8 to 12 hours.

3. *Staphylococcus aureus*: for penicillin G-sensitive strains, 5 million units intravenously every 6 hours; for those resistant to this antibiotic, 1 g of
cephalothin or oxacillin intravenously every 2 hours. For persons hypersensitive to the penicillins, vancomycin, erythromycin or lincomycin, if the responsible organism is highly sensitive to these agents.

4. Other organisms causing acute endocarditis: for endocarditis due to the pneumococcus, gonococcus or meningococcus, penicillin G in the same doses as those used when Staph. aureus is the offending organism. For the rare case of acute valvular infection due to H. influenzae, ampicillin in the dose described above.

5. Unusual organisms: the choice of antibiotics for the therapy of endocarditis due to such species as Hafnia, Mimae, anaerobic diphtheroids, Staph. epidermidis (albus), Escherichia, Enterobacter, Klebsiella, Alcaligenes and Pseudomonas is based on the in vitro sensitivity of the organism recovered from the blood; the drug selected should preferably be bactericidal and given in the maximal tolerated and safe dose.

6. Fungi: amphotericin is presently the most effective drug for the management of endocarditis caused by the fungi and yeasts. Several dosage schedules have been used:

(a) 0·25 mg/kg the first day, 0·5 mg/kg the second, 0·75 mg/kg the third and 1 mg/kg the fourth and subsequent days until therapy is completed;
(b) 1·5 mg/kg every other day for the entire course of treatment;
(c) administration of quantities of the drug necessary to produce and maintain blood levels 2 to 4 times greater than in vitro inhibitory concentration (Drutz et al., 1968).

Surgical Therapy. A new dimension, surgery, has been added to the therapy of infective endocarditis. This may be life-saving in cases in which chemotherapy fails to produce total cure, or potentially lethal complications develop in the area of the infected valve. Indications for surgery in endocarditis are—

1. Disruption of valve leaflets or their supporting structures followed by congestive failure that fails to respond to vigorous medical measures.
2. Development of aneurysms of the sinus of Valsalva or the atrioventricular junctional tissues.
3. Infections that fail to respond after treatment with large doses of a highly active antibiotic.
4. Relapse of infection following two or more courses of therapy with an effective antibiotic.
5. A single relapse of fungal endocarditis; therapy a second or even third time is usually without effect.
6. The presence of an infected prosthetic valve or patch. If initial treatment is followed by cure, removal of the prosthesis is not necessary; however, if relapse occurs after completion of one course of therapy, replacement of the intracardiac foreign body is usually indicated.

When all the other criteria suggest the necessity for surgical intervention, the presence of active infection is not a contra-indication. It may be a mistake to temporise until the infectious process appears to be under control because with delay, tissue destruction may proceed to a point when operation becomes technically difficult or impossible. In this circumstance, chemotherapy must be maintained throughout the pre- and postoperative periods.

**Chemoprophylaxis.** Because of transient bacteraemia and the risk of endocarditis, patients with rheumatic, congenital, arteriosclerotic or syphilitic heart disease undergoing major dental procedures, surgical manipulation of the urinary or intestinal tract, gynaecological procedures and tonsillectomy should receive chemoprophylaxis. Two programmes have been employed for this purpose:

1. 250 mg of phenoxymethyl penicillin (penicillin V) orally 3 to 4 times a day for 2 days before, the day of and for 2 days after surgery. In addition, a dose of 600,000 or 1·2 million units of procaine penicillin is given on the day of operation.

2. The author prefers to administer one million units of penicillin G intramuscularly one hour before and one hour after surgery. While two doses of antibiotic are probably sufficient when tonsillectomy or dental extraction is performed, it may be helpful to administer two or three additional doses, at 6-hour intervals, after other types of surgery. It must be emphasised that, while this kind of chemoprophylaxis appears to be effective in many instances, it does not completely prevent the development of endocarditis. This may be the case when penicillin-resistant organisms are responsible for the bacteraemia associated with the surgical procedure.

**CLINICAL COURSE OF TREATED ENDOCARDITIS**

The temperature may return to normal levels in some cases of endocarditis within 24 to 48 hours after initiation of therapy despite previous fever of appreciable degree for weeks or months but, more often, defervescence occurs after 7 to 10 days. It must be stressed, however, that low grade fever (100–100·6°F) may persist throughout the period of treatment and disappear only after drug administration has been stopped; in some cases, this is due to sterile inflammation at the sites in veins or muscles where the antibiotic has been injected. It is noteworthy that most persons with subacute bacterial endocarditis are aware of an improvement in their sense of well-being within
2 to 3 days after treatment is started, without relation to the level of temperature. Organisms disappear rapidly from the blood and are usually not recoverable after 24 to 48 hours of therapy. Leucocytosis recedes somewhat more slowly and an elevated ESR may not return to normal before three or more weeks. Anaemia usually improves slowly even when the general clinical response is good. The haemoglobin may not increase until the late phase of therapy or until one or two weeks after it has been stopped.

It must be stressed that embolic phenomena may supervene during the course of effective chemotherapy, or even several weeks after microbiologically-successful treatment has been discontinued. Death may result when small pieces of sterile thrombi are deposited in the cerebral or myocardial vascular tree. Rupture of mycotic aneurysms may be delayed and occur late in convalescence.

Manifestations of hypersensitivity, such as arthritis or renal dysfunction, may appear days or weeks after a good therapeutic response has been established; blood cultures are more often negative at this time.

The clinical course of acute bacterial and fungal endocarditis often differs remarkably from that of the subacute type of disease even when large doses of drugs highly active in vitro against the responsible organism are administered. Thus, in valvular infection due to Staph. aureus fever of high degree may persist in the absence of bacteraemia. This is usually due to metastatic infections in multiple organs and tissues, especially in the myocardium and kidney. Death is usual in such cases despite continued treatment. A common potentially-lethal event that may develop in this kind of endocarditis is intractable cardiac failure due to rupture of chordae tendineae or papillary muscles, or to tears or total disruption of valve leaflets. This may occur at a time when the infectious process appears to be under control.

The clinical course of fungal endocarditis treated with amphotericin may be very misleading. Experience indicates that, despite defervescence, negative blood cultures and increased sense of well-being, active infection of the involved valve may still be present, as indicated by relapse shortly after completion of an adequate course of therapy. Another important complication, limited to this type of endocarditis and unrelated to the clinical response, is sudden occlusion of a large artery. Because the infected valvular thrombi in fungal endocarditis are usually much larger and softer than those associated with bacterial infection, large fragments may break off and occlude a major vessel. The same problem may arise in atrial myxoma.

The prognosis of treated endocarditis
The outlook for endocarditis, while determined to a considerable degree by
host factors and type of therapy, is also unquestionably directly related to the nature of the organism responsible for infection. Valvular disease due to *Strep. viridans*, if detected early and treated with effective antimicrobial agents, should be cured in at least 95 per cent of patients. Delay in therapy, the presence of debilitating disease and improper selection of antibiotic or inadequate dose or duration of therapy worsen the prospects for recovery. The prognosis of acute endocarditis, especially that due to *Staph. aureus*, must always be guarded despite treatment with large doses of what appear to be highly active drugs because of the risks of ‘mechanical’ complications, diffuse metastatic infections, or continued activity of the process on the valve. Even in the best hands, the survival rate in this type of endocarditis does not approach that of disease produced by *Strep. viridans*. The outlook for endocarditis caused by *Staph. epidermidis (albus)* is also unpredictable. Despite the organism’s low level of pathogenicity, the death rate in treated cases remains high. Even with ‘effective’ chemotherapy, the course is often prolonged and marked by multiple remissions and relapses as drug is given and withdrawn, leading finally to the development of intractable heart failure and death. The prognosis for infection due to enterococci is not as good as for that caused by *Strep. viridans*, or quite as bad as that in which *Staph. aureus* is involved. Enterococcal endocarditis may be complicated by difficulty in eradication of organisms, rupture of papillary muscles and valve leaflets and, rarely, by metastatic infections, features characteristic of the disease produced by coagulase-positive staphylococci.

The prospects for recovery from fungal endocarditis are, on the whole, poor for the reasons discussed above. In fact, the survival rate in patients treated with amphotericin are so low that some investigators have suggested that in all cases, the most promising approach is chemotherapy until symptoms have been alleviated, followed by replacement of the infected valve by a prosthesis, and continuation of treatment for an appropriate period post-operatively. When Gram-negative and other unusual organisms are responsible for endocarditis it is impossible to make an accurate prediction regarding survival. This is so because patients with infection due to such opportunistic agents often suffer from disorders that suppress the activity of defence mechanisms, and the organisms often respond poorly to antimicrobial compounds.

**THE FUTURE**

It is impossible to predict future changes in the natural history of infective endocarditis with any reasonable degree of accuracy because this disease has undergone remarkable alterations in its behaviour for unexplained and
unpredictable reasons. However, on the basis of the problems that face the physician today, it is possible to point out the areas that still need laboratory and clinical examination, the results of which may, in great part, determine the nature of endocarditis and its effective and successful management in the future. It is not my purpose to discuss in detail the avenues of approach in continued investigation of this disease but merely to list the problems that still require study.

(a) Determination of the optimal dose, duration of use and route of administration of antibiotics. Despite years of experience with the treatment of infective endocarditis, there are still no universally acceptable data in these areas.

(b) Although there have been many studies of surgery in the management of cardiac infection, the exact indications for such therapy as well as improvements in technique and mechanical apparatus still need investigation.

(c) Problems related to an increasing frequency of valvular infections produced by unusual organisms, many of which are now resistant to a number of antimicrobial agents, will not only persist but probably become qualitatively and quantitatively more difficult as time progresses. This will undoubtedly necessitate a continuing search for new antibiotics to which, at least for a while, these species will be susceptible.

(d) Although it has been generally accepted that chemoprophylaxis of dental and other types of surgical manipulation in areas of the body in which bacteria are normally present prevents the development of bacterial endocarditis, there are no valid data to support this. The fact that 25 per cent of patients seen with valvular infections have had recent dental surgery does not indicate the true frequency of endocarditis after such operations. The question that has not been answered is how many people with acquired heart disease subjected to dental or other surgery (excluding the heart) will develop endocarditis, and whether the use of antibiotics prophylactically will actually prevent such infection.

(e) Very important for the future are studies of the potential clinical significance of the globulins and antiglobulins that develop in many victims of subacute bacterial endocarditis. It has already been shown (Cordeiro et al., 1965) that some of these attach to the basement membranes of the renal glomeruli, to myofibrils in the walls of blood vessels, to myocardium and to cell nuclei. It must be determined whether these are of importance only during the active and early convalescent phases of the disease, or whether the altered immunological state, once brought into being by the infection, has serious portent for the future in regard to chronic vascular, myocardial or renal disease.
CONCLUDING REMARKS

That infective endocarditis has changed remarkably over a relatively short period is clear to any who have studied it. The dramatic effects of antimicrobial therapy, especially penicillin, can only be appreciated by those who have experienced the hopelessness of the untreated disease. Morbidity and mortality have been so markedly improved by chemotherapy that young physicians often become disturbed when defervescence does not occur within 24 to 48 hours after initiation of treatment, and older ones are upset by a fatal outcome when, not too many years ago, they were amazed at a spontaneous recovery. This is not to infer, however, that all is well. Patients still die from endocarditis either because the disease is detected too late, treatment is inadequate, or highly invasive and destructive organisms, difficult or impossible to eradicate with any of the antibiotics available at present, are involved. Other patients have the good fortune to have their valvular infections cured but die from a mechanical accident such as deposition of a sterile embolus or rupture of a mycotic aneurysm situated in a vital area. It is obvious that infective endocarditis still presents problems for the future. Awareness of these is important and they should indicate, as Osler emphasised, 'in what direction we may look for fruitful investigations in the future'.

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