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A PROBLEM IN TROPICAL CARDIOLOGY*

BY

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I think it is fair to say that the environmental aspects of heart disease have not received the attention they deserve. This may be due to the fact that on the one hand those who have led the field of cardiology have in the main been concerned with the grosser end-stages of heart disease and with the isolated vignettes of consulting practice; opportunity for the study of heart disease during the course of its often slow evolution in its natural background has been infrequent. On the other hand, the family practitioners who have the opportunity to see the gradual evolution of a disease process in relation to the environment have not, with notable exceptions, possessed the necessary detailed knowledge and ability to turn the opportunity to the best advantage. Furthermore, we cardiologists have sometimes been slow to realize the importance of close association with the epidemiologist, the biochemist, the immunologist, etc., and have thereby overlooked many fruitful avenues of thought and development. I often think that cardiology is the very last specialty which should be sharply circumscribed in its dimension and served by jealous exclusive devotees. It flourishes best and advances fastest where its disciples have a broad foundation of scientific and medical knowledge and consistently and substantially retain an active interest in medical science and the unselected practice of clinical medicine.

The results of this self-imposed isolation are illustrated well by the extraordinarily long interval which elapsed between the recognition that myocardial necrosis associated with thrombotic occlusion was common and the development of any serious attempt to study the epidemiology of this disease, and the factors which caused blood to coagulate in the coronary arteries, or even to attempt to determine whether coronary thrombosis invariably precedes and causes the necrosis by ischaemia or whether thrombosis is ever secondary to necrosis. In fact, it is only within the last ten years that the epidemiological approach has been applied at all commonly to diseases other than those clearly due to infection. That such diseases as cancer, coronary thrombosis, disseminated sclerosis, and road accidents should have an "epidemiology" in the sense of being environmentally induced is one of the most exciting and productive intellectual attitudes of our time. The existence of the International Epidemiological Club and our presence here to-day is a practical expression of this "new look."

*From a paper presented in a discussion on the "Epidemiology of Heart Disease" organized by the International Epidemiological Club, supported by the Rockefeller Foundation and held in Cali, Colombia, from August 22 to 29, 1959.

Heart Disease in Africa

The broad outline of the classification of heart diseases as they present in Europe and North America has remained fairly stable for a long time. However, as the result of four years spent in the tropics and sub-tropics during the war I became dimly aware that in these areas there was much heart disease that did not readily fall into what may be called the northern pattern. This dissimilarity was sharply outlined by Bedford and Konstam (1946), who described a series of 40 cases of unexplained heart failure in African troops, mostly from West Africa. They presented with severe left heart failure or with combined pulmonary and systemic congestion and ascites. The rhythm was normal, extrasystoles were frequent, and the blood-pressure was low. The heart was generally enlarged.

General examination did not reveal the constant presence of any other disease or parasitism. The general nutrition was good and the diet adequate, though prior to recruitment they had inevitably been subjected to the nutritional inadequacies of Africa. Neither thiamine nor anything else produced any real improvement, and 17 died in hospital. Necropsy showed gross general enlargement of all cavities. There was no valvular disease, and the coronary arteries were healthy. In some cases there was extensive subendocardial fibrosis with areas resembling shallow infarcts adherent to which were organized thrombi. The authors pointed out that these cases were similar to the five cases reported by Smith and Furth (1943), all of which presented a similar picture during life and death. Their report states that one patient was Chinese, another of Italian origin, but there was no comment on the race of the other three. None of them could be regarded as having a satisfactory nutritional history, but thiamine did not influence the disease.

Endomyocardial Fibrosis

Williams, Ball, and Davies (1954) and Davies and Ball (1955), working in Uganda, have provided much information on what had by then come to be known generally as endomyocardial fibrosis (E.M.F.). They state that it is one of the commonest causes of heart failure in Africans in Uganda. Only hypertension, and that mainly renal, caused a higher proportion of heart failure. Pathologically the lesions were present in both sides of the heart and consisted of fibrosis of the endocardium and underlying myocardium. Firmly organized clot frequently lay over the fibrosed areas. The whole process often spread up to involve the chordae and the cusps of the mitral and tricuspid valves. Stenosis of the inflow tract of the right ventricle was sometimes present.

The disease can occur in African dwellers of European origin. Gray (1951) reported two fatal cases in Englishmen who had lived for nine and seven years in Nigeria. In all important clinical and pathological respects they presented the picture of E.M.F. Apart from residence in Africa their history yielded no aetiological clues. Edge (1946) reported a similar case in an Englishman stationed in West Africa.

Earlier this year, when I was in Northern Nigeria, Dr. Gordon Branch, of Jos, kindly asked me to see, rather for my own interest than for her benefit, a European lady who had had an illness which in all respects resembled E.M.F. except that she had made a surprising recovery, though there was still considerable cardiac enlargement.

So far as I know no closely comparable example of this condition has been reported from Asia, Australasia, or South America. I think it can be taken that E.M.F. has occurred in Europeans who have no obvious ethnic or other connexion with Africa. Löffler (1936) described two cases which corresponded in all respects to the E.M.F.-concept, except that eosinophilia was present (in one of these the eosinophils reached 12,600 per c.mm.). No satisfactory explanation was found for this curious feature, though variable eosinophilia features in some of the African reports, this being regarded as due to the wellnigh universal state of parasitism of man in the tropics. Gallavardin and Gravier (1929) report a typical case and mention three others.

So far as I can ascertain there is no evidence of there ever having occurred a case in all respects similar to E.M.F. in an inhabitant of Great Britain who has not been abroad. In making this statement I must emphasize that I am taking, quite arbitrarily, the presence of massive endocardial fibrosis as the hallmark of classification, though it may well turn out to be an end-stage common to several aetiologically different processes. The phenomenon is in itself so striking that its occurrence could hardly fail to be noted, especially in latter-day Britain, where the keen competition for professional advancement ensures that few opportunities of making a striking contribution to knowledge are neglected.

Myocarditis

The whole question of myocarditis is very complex, and has been the subject of several able reviews, notable among which are the St. Cyres Lecture of Wallace Brigden (1957) and that of Chapelle and Kossmann (1954). Quite apart from the myocardial damage that results from ischaemia, rheumatism, acute infections (especially viral), familial heart disease, alcoholism, amyloidosis, collagen disease, endomyocardial fibro-elastosis, etc., a substantial proportion of people develop progressive cardiac failure, and at necropsy are found to have in their myocardium evidence of damage in the form of small connective-tissue scars, areas of hydropic degeneration of heart muscle, or even collections of cells suggestive of an inflammatory reaction. There is an inevitable tendency for these cases to be regarded as being atypical examples of the effects of coronary disease, rheumatism, hypertension, collagen disease, etc. However, the important point is that they do not show massive E.M.F.

It may well be that the gross morbid anatomical change is only an advanced stage of a much commoner disorder. There is some support for this belief in that throughout Africa there seems to be a high incidence

of cardiac failure which, while it is clinically indistinguishable from those eventually shown to have gross E.M.F., fails to show this change to a marked degree. Gillanders (1951), in a report on heart failure among Bantus in Johannesburg, describes 30 cases which, while they clinically resemble cases of E.M.F., had concomitant evidence of liver disease of the type commonly regarded as due to malnutrition. Treatment with a variety of procedures, including thiamine, had no effect, but striking improvement occurred on a well-balanced diet, and relapses were consistently induced by reverting to the sort of diet to which they were accustomed—that is, porridge made from highly refined maize supplemented with white bread, tea, and sugar. Relapse was common on discharge from hospital, and eight patients died. Necropsy on these showed great enlargement of the heart, with an absence of obvious disease of the heart valves, coronary vessels, or aorta. “No convincing evidence of subendocardial necrosis or fibrosis was found in any.” Sections showed inter-fibrillary oedema of the myocardium, hypertrophy of fibres, no hydropic degeneration, and minimal interstitial fibrosis. Whether these cases have any aetiological communion with E.M.F. is a matter for speculation.

My own experience of this syndrome is essentially that of the spectator rather than the serious investigator. It is peripatetic, superficial, and unreliable, being based mainly on three long medical tours in Africa undertaken during the last three years. These journeys have ranged through most of the territories of the British Commonwealth between the Sahara and the Cape, and have included not only visits to big centres but innumerable leisurely ward rounds in rural hospitals. I am immensely indebted to so many people who gave me freely of their time, knowledge, and hospitality. Nowhere did the pattern of heart disease resemble that seen in Britain. Many of the differences were at least partially understandable. Myocardial infarction was almost unknown, at least among Africans. Rheumatic heart disease as judged by the frequency of mitral stenosis was relatively rare, and I suspect that many of the cases regarded as such were in reality cases of “myocarditis” perhaps with E.M.F.

Not infrequently I was taken to see cases of what were regarded as chronic rheumatic heart disease, but the absence of auricular fibrillation and any evidence of mitral disease other than incompetence struck a false note. In many respects these cases resembled constrictive pericarditis; some of them may have been, as tuberculosis is rife; others, again, may well have been “constrictive endocarditis”—that is, E.M.F. Luetic aortitis was naturally not uncommon. Acute beriberi heart disease was seen in the “coloured” people in Capetown, where extreme alcoholism was the main cause. Hypertensive heart disease was very common, but the commonest of all seemed to be cardiac failure of the E.M.F. type. Apart from the university centres, notably the University College of East Africa in Uganda, where Professors Davies and Williams work, few pathological data were available. Over many territories, notably Northern Nigeria, the Islamic faith made necropsies rare, and pathological services were in general rudimentary by European standards and quite incapable of shedding much light on such a problem.

I hope I have convinced you—supposing, that is, that any of you are not fully alive to the problem—that there exists a form of heart disease which in its effect on the

efficiency and life expectancy of Africans is fully comparable with myocardial infarction or rheumatic heart disease in other lands. A perusal of current European and American cardiological literature and the proceedings of cardiological meetings in these continents shows that the problem received little attention; in fact, it is not the sort of problem that is likely to be advanced along the conventional lines of clinical cardiology as it is generally understood. It requires an approach widely based on internal medicine, epidemiology, and pathology; indeed, it is just the sort of problem which falls squarely into the ambit of the Epidemiological Club.

Aetiology

So far I have said little about the aetiology of myocarditis of the E.M.F. type except to imply that it is virtually unknown. As regards its geographical distribution, the only certain thing is that it is common in Africa, very rare in Europe and America, and not reported from Asia. Owing to the lack of vital statistics and the inadequate clinical and pathological services there is no definite information about its distribution within Africa. It is certainly common in Uganda and apparently common in West Africa. Ethnically the disease is not exclusive.

Williams *et al.* (1954) and Davies (1956) give excellent accounts of the disease in Uganda and penetrating discussions of its possible aetiology. As regards the mechanism of the lesion, they suggest that the initial injury is to the ventricular myocardium in its inner third. The resulting necrosis causes thrombus formation on the endocardial surface; this becomes fibrosed and covered by endothelium, but there is a recurring cycle of necrosis, thrombosis, and fibrosis. Surviving muscle fibres hypertrophy. The injurious factor which damages the myocardium could be nutritional, direct infection by a micro-organism probably viral, allergic in nature of the type such as is regarded as the basis of rheumatic heart disease, an effect of one of the forms of parasitism so common in Africa, the breakdown of some enzyme system consequent upon an inborn error of metabolism, or the action of some blood-borne poison.

As regards a possible nutritional basis, there is, of course, much popular support for this. It is an undoubted fact that by European standards the diet of Africans is deficient, particularly in proteins; however, if this were an important factor one would expect the disease to be present in Asia and to have appeared to some extent in Europe during the famines which have occurred as the result of modern wars. With the exception of Gillanders's (1951) report from Johannesburg, there is no evidence that the disease can be favourably influenced by dietetic means. Deficiency of a trace element may play a part, as copper deficiency is known to contribute to myocardial fibrosis in cattle (Arnold, 1954).

The infective hypothesis is worth considering. While there is little evidence pointing to an infective origin, the existence of viruses capable of causing myocardial injury is known. The virus of encephalomyocarditis (E.M.C.) isolated from monkeys can cause experimental lesions resembling E.M.F. in man. The Mengo encephalomyelitis virus isolated by Dick, Haddow, Best, and Smithburn (1948) from the Mengo district of Uganda is closely akin to the E.M.C. virus. It is clearly impossible to dismiss the virus hypothesis, but if, as

Williams *et al.* point out, such is the case, the early lesion may well be found among the minor physical illnesses of obscure aetiology rather than among those with manifest heart disease.

The allergic hypothesis has really very little to support it. Eosinophilia, on which much emphasis has been placed, is inconstant and often more readily explicable on the basis of parasitism. Though advanced E.M.F. in some ways resembles chronic rheumatic carditis in its capacity to distort—but not stenose—valves, the resemblance is not close, and if it be eventually shown to have a causal affinity with cardiac rheumatism then the current concept of that disease will have to be radically revised.

That the disease is due to an effect of one or more of the many forms of parasitic infections in Africa must clearly be considered. Long-standing severe anaemia is unlikely to be a cause, as anaemia is just as severe in India and China. Schistosomiasis is widespread in Africa, but so it is, and of greater severity, in South-east Asia; furthermore, it is very severe in Egypt, where apparently E.M.F. is not prominent. There seems to be grave objection to regarding any of the known parasites as playing a part, but then not all parasites, or the life-cycles of all parasites, are yet known.

Though there is really no evidence whatsoever for incriminating an inborn metabolic error such as causes sicklaemia, etc., our knowledge of this type of biochemical abnormality is so rudimentary that an open mind must be preserved. In any case, the disease seems too widespread throughout Africa to make this likely. African peoples are so diverse and their migratory movements so relatively slight compared with other continents that community of genetic structure cannot be great. A dark skin, which is a merciful provision for the climate, seems to be about all the peoples of Africa have in common.

That the condition could be due to some specific poison present either in food or taken for medicinal purposes has hardly received consideration, though I think it is not altogether fanciful. That chemical factors can cause pathological changes in vascular tissues is now established. The veno-occlusive disease of the West Indies seems to be due to specific toxins of the *Crotalaria* group present in the bush teas which are widely used in the mistaken belief that they are medicinally beneficial (Bras, Berry, and György, 1957). Hepatic venous occlusions are also known to result from the toxic alkaloid retrorsine from one of the *Senecio* group (Davidson, 1935; Selzer, Parker, and Sapeika, 1951). It may well be that among the innumerable vegetable products eaten throughout Africa there are substances present, perhaps only at certain phases of the plant's life-cycle, which can cause specific myocardial damage. That a substance normally present in the body when produced to excess can cause organic changes in the heart is shown by the thickening of the cusps of the pulmonary valves and the narrowing of the right ventricular outflow tract which is sometimes seen in patients with massive hepatic metastases from a carcinoid tumour. The cardiac changes are thought to be due to the large amounts of 5-hydroxytryptamine (serotonin) which the tumour produces.

In this connexion let me introduce a fanciful note. Late one night recently, with the problem of E.M.F. not far below the surface of the conscious, I was reading

a review of serotonin in relation to disease and came across the information that bananas contain considerable amounts of serotonin—so much so that after their consumption the urine gives a positive reaction for the presence of 5-hydroxy-indole-acetic acid. There suddenly flashed into my mind a picture of Uganda with its universal banana-trees. In fact, the banana is at one and the same time the blessing and the curse of that country, as so many of the population eat it to the almost complete exclusion of other things. This sudden rosy dream faded, however, when I realized that the quantities of serotonin in the blood-stream due to eating bananas could hardly compete with those in carcinoid tumour; furthermore, the changes in E.M.F. are present in both the right and left heart, whereas the heart changes in carcinoid are limited to the right ventricle. Indeed, the lungs have the property of destroying serotonin. Yet the possibility of harmful substances in food cannot lightly be dismissed.

Though we have identified most of the agents causing immediate severe damage, the possibly harmful long-term effects of slow-acting poisons are almost unexplored. Who would have thought a few years ago that any possible hurt could lurk in much-prized "protective" foods such as cream, butter, and eggs.

E.M.F. has been produced experimentally in rats by Selye (1958) by subjecting them for 30 days to daily injections of 50 μ g. of the corticoid 2 α -methyl-9 α -chlorocortisol along with $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$, which constituted 1% of their drinking-water. This results in myocardial necrosis localized predominantly in the subendocardial layers. After the corticoid and sodium were stopped the necrosis healed, with the formation of thick scar tissue, producing a condition resembling E.M.F. The development of myocardial necrosis could be prevented by giving magnesium salts (1 mM. of $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ twice daily by stomach-tube). These observations are of great interest, but their relevance, if any, to the lesion in man is not clear. Selye suggests that it may be a "stressor" reaction.

Possible Investigations

The many possible approaches to the problem of E.M.F. fall broadly into two groups, those which consist of the intensive study of the individual case using all the resources of medical science. Not only must the patient be assessed clinically by physical examination, but electrocardiographic and haemodynamic studies are essential. His general physical state with reference to the pattern of his blood proteins, his immunological responses as measured by anti-streptolysin titres, C-reactive proteins, etc., the amino-acids excreted in the urine, and the possible presence of 5-hydroxy-indole-acetic acid and much else, must all be studied. As much as possible of his history and the nature of his environment, particularly in respect of his diet, "medicine," etc., and the health of his relatives, must be ascertained. The parasites he harbours should be known and the antiviral pattern of his blood studied. When death claims him the necropsy should be as complete as possible. There are formidable difficulties in the way of all this, not the least of which is the necessary co-operation of the patient. In fact, a real insight into his environment can be gained only by an investigation by his own people, speaking his own tongue.

This is particularly important in a search for possible toxins present in native medicine. In fact, this problem

could be studied very satisfactorily by an African who was "doubly" qualified—that is, had first of all been trained as a "native" doctor and then as an orthodox doctor with special training in pharmacology and toxicology. Lastly in this respect, examples of the syndrome must be followed throughout the whole course of the disease.

Very promising work on these lines is already in progress at Makerere College in Uganda under Professors Williams and Davies and their colleagues, and at Ibadan in Nigeria, where Dr. Abrahams is deeply engaged in such a study. Dr. Wallace Brigden, of the National Heart Hospital, London, is shortly going to Ibadan to spend some months working in collaboration with Dr. Abrahams.

The other approach is "horizontal" in the sense that the incidence of the syndrome is studied in relation to location in time and space. The time factor of incidence must be related to cyclical and random events in the environment such as climate. Seasonal changes in food-stuffs, particularly those of vegetable origin, might reveal the presence at certain times of some vegetable toxin. Climate has obvious relationships to infections. The religious and ceremonial life must be studied, as this might involve the ingestion of toxins, though we already know that the condition is so widespread and tribal beliefs and rituals vary so much that a common causal denominator in this field seems unlikely. All this work is immensely difficult in a vast underdeveloped continent like Africa. It is a continent of numerators with very few denominators. In the absence of comprehensive registration of births and deaths one never knows the "number at risk." Ages are unreliable; indeed, a patient can easily be admitted on several occasions to the same hospital and registered under a different name each time, not because of any deliberate deceit but to the inability of an alien alphabet to express adequately the subtleties of a purely spoken language.

What a rich harvest of valuable information awaits the development in Africa of a way of life in which a stable community has a modern comprehensive medical service which observes individuals from birth to death. This demands doctors who spend their active working lives in the community, a circumstance which it is almost impossible to secure with an expatriate medical staff. It can be achieved only by doctors derived from the community itself. The attainment of such a state of affairs will inevitably be accompanied by profound changes in the environment of the people, especially in respect of hygiene and nutrition, so that the results of study will not be closely comparable to the state as it exists now. One cannot treat man as an experimental animal by changing nothing except the standard of his medical care. From the point of view of scientific knowledge one must face the risk that modernization may banish a disease before its aetiology is uncovered.

Another important horizontal line of study of a syndrome such as E.M.F. is for the same team to study the problem in widely scattered areas. This is the only satisfactory method of ensuring that reports from divergent areas mean the same thing. Travelling widely as I did in Africa, most of the doctors I met, while they know a great deal about a particular problem in their own locality, had not had the opportunity of making comparable studies in other distant territories. In some respects the peripatetic observer sees more of the game than the players. I understand that Dr. Abrahams, of

Ibadan, is shortly to undertake such a study of E.M.F. in several widely separated parts of Africa.

In conclusion I need hardly emphasize the absolute necessity for team-work between the clinician, laboratory worker, and epidemiologist; in fact, the clinician must have a good grounding in epidemiology and the epidemiologist should be in substantial measure a clinician.

ADDENDUM.—At the Conference in Colombia it became apparent that an important cause of myocardial fibrosis is Chagas's disease (*Trypanosoma cruzi* infection), in which, while the infection is often contracted in childhood, cardiac failure may not supervene until middle life. Histologically, tissue reaction seems to differ from African E.M.F. in that it is much more cellular; indeed, it is essentially an inflammatory reaction. It is clear that a careful study is necessary of the distribution of cases of African E.M.F. in relation to exposure to *T. gambiense* and *T. rhodesiense* infection.

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Starting nearly 100 years ago with one rowboat, one medical officer, and one sanitary inspector, the City of London Corporation as Port Health Authority of the Port of London has gradually built up a comprehensive Port Health Service, whose main preoccupation is with imports—imports of food and imports of disease. By a day and night watch on shipping, including ships from the Far East, dangerous and infectious diseases are prevented from entering into the Port of London and beyond that to greater London and the United Kingdom itself—15,000 ships from foreign lands enter the Port of London every year. No case of smallpox has arrived in the port since 1951, and for at least the last 50 years there has been no outbreak of smallpox in the United Kingdom that could be attributed to any smallpox admitted through the port. There is also a regular spot check on foodstuffs entering the port, which is by far the greatest importing port in the United Kingdom—for instance, 85% of Britain's meat supplies enters the Port of London. Similarly the Corporation's elaborate system of rodent control in the port helps to prevent the spread of infectious diseases and the contamination and destruction of foodstuffs. These parts of the Corporation Port Health Service, like the Quarantine Service at the entrance to the port, are of benefit not only to greater London but to the nation as a whole. ("The Work of the Port of London Health Authority": Dr. J. Greenwood Wilson, at the Royal Institute of Public Health and Hygiene.)

AN EVALUATION OF CONTINUOUS ANTIBIOTIC THERAPY IN CHRONIC BRONCHITIS

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Chronic bronchitis is a major cause of industrial invalidism in the United Kingdom resulting, for example, in the loss of 22 million male working-days between June, 1955, and June, 1956, or about 25% of all male sickness incapacity. Therefore any measures which can be adopted to reduce this enormous morbidity, with its consequent drain on the national economy, must be assessed as accurately as possible.

In addition to infection, many complex factors, such as climate, atmospheric pollution, heredity, and social and occupational habits, operate in the causation of chronic bronchitis. These have been reviewed in three recent books (Stuart-Harris and Hanley, 1957; Ogilvie and Newell, 1957; Oswald, 1958) and require no further comment here. The infective element is most obvious in acute exacerbations which are responsible for much of the invalidism. The association of *Haemophilus influenzae* and the pneumococcus with these exacerbations is now well recognized (May, 1953; Stewart, 1959). Eradication of these pathogens from the bronchi might prevent further destruction of already damaged broncho-pulmonary tissue, thus reducing recurrent winter ill-health and ultimately prolonging life (L. M. Reid, 1955, 1956). For this reason much attention in recent years has been paid to the treatment of patients suffering from chronic bronchitis with various forms of long-term chemotherapy.

Continuous administration of tetracyclines during the winter months has given good results (Helm *et al.*, 1956; May and Oswald, 1956; Moyes and Kershaw, 1957; Buchanan *et al.*, 1958; Edwards and Fear, 1958; Moyes and Kalinowski, 1959). But there is still uncertainty about the selection of patients, the optimal dosage, and the justification of the expense involved (Elmes *et al.* 1957; Stuart-Harris, 1959). Further, the administration of broad-spectrum antibiotics for long periods may lead to the overgrowth of resistant micro-organisms within the host (Williams, 1954), and their dissemination among patients outside hospitals, especially in the case of *Staphylococcus aureus*, is a potential hazard.

The epidemiological significance of such a spread of staphylococci in the community is not known and