MEDICAL PRACTICE

Contemporary Themes

Cardiovascular Disease in the Tropics*—II, Endomyocardial Fibrosis

A. G. SHAPER

British Medical Journal, 1972, 3, 743-746

A large variety of processes may lead to lesions in the endocardium and in the subendocardial myocardium. Irrespective of the initiating factors fibrin deposition and thrombus formation take place on the damaged endocardium. The healing process is associated with the incorporation of the thrombus into the endocardium, producing an area of scarring which sometimes calcifies. The heart has a limited range of response to injury, and this is a non-specific lesion. Nevertheless, there are situations in which a particular group of cases with endomyocardial fibrosis share common characteristics and may have the same aetiology and pathogenesis. My presentation predominantly concerns the tropical endemic form of endomyocardial fibrosis. It will be necessary to discuss endomyocardial lesions in conditions which are neither tropical nor endemic, and these will be referred to by the general term endomyocardial fibrosis.

Endomyocardial fibrosis is a form of heart disease endemic in several tropical countries and characterized in the established condition by fibrosis in the ventricular cavities. In all the endemic areas it is as common a disorder clinically and at necropsy as rheumatic heart disease. It is not a tropical rarity; it is a disease of equal importance to rheumatic heart disease. The macroscopic appearances of established endomyocardial fibrosis are distinctive, and on these features the diagnosis is usually made and not on isolated microscopical sections. It is essential to regard the disease not merely as a problem of "scarring in the heart" but as an active disorder, sometimes progressive and possibly recurrent. Without prejudice towards the various concepts of aetiology and pathogenesis it can best be considered in the same pattern of natural history as rheumatic fever and

rheumatic heart disease. Throughout this discussion of endomyocardial fibrosis I will use rheumatic heart disease as a model, and I will try to support the use of this model by the available evidence concerning these two disease processes.

Like rheumatic heart disease, endomyocardial fibrosis is a disorder predominantly affecting children and young adults. In a necropsy series in Uganda covering a 16-year period, more than two-thirds of the subjects with the disease were below 35 years of age (Fig. 1).⁹

FIG. 1—Age distribution of subjects with rheumatic heart disease and endomyocardial fibrosis at necropsy in Kampala, Uganda, 1950-65 (Shaper, *et al.*).⁹

Natural History

In Nigeria an acute febrile episode has been described as the earliest stage in the natural history.¹⁸ The symptoms were very non-specific; malaise, anorexia, and a fever which on occasions persisted for weeks or months, and then these symptoms merged gradually with those of heart failure. However, when first seen these patients in the acute episode already had the

* The Milroy lectures delivered at the Royal College of Physicians of London on 9 March 1972.

features of an established heart lesion in addition to all the signs of acute carditis. Endomyocardial fibrosis seems to be a disease with recurrent inflammatory episodes, each accompanied by myocarditis and fresh necrosis, rather than a single-episode disease.¹⁹ It is a pancarditis, and the analogy with rheumatic fever seems apparent.

Morphology

The characteristic involvement in endomyocardial fibrosis is fibrosis in the inflow tract and at the apex of one or both ventricles, the major lesion affecting the endocardium and the inner-third of the myocardium. The fibrosis may be localized to the apex or may be sufficiently extensive to involve the papillary muscles and chordae tendineae, and this may lead to the atrio-ventricular valves being held open. Pericarditis is an important feature of the disorder, more apparent in clinical than in pathological series of cases. It occurs in perhaps two-thirds of cases, may sometimes be the presenting feature, and does not produce constrictive pericarditis.

In the left ventricle a characteristic lesion affects the posterior mitral cusp, the chordae attached to this cusp, and the adjacent endocardium of the ventricle. The anterior cusp has a normal tethering system and a normal function. This posterior cusp lesion may occur without other evidence in the heart of endomyocardial fibrosis, it may be continuous with a lesion in the apex, or there may be a clear, uninvolved ("skip") area of endocardium between mitral and apical lesions.

In the more acute cases the endocardial lesions are covered with a soft, spongy, greyish-green layer of thrombus; in chronic cases the endocardial lesions are hard and white, sometimes calcified. It requires little imagination to visualize the pathogenesis, starting with the acute endomyocardial lesion and ending with a fibrosed and contracted ventricle.

Vascular Aspects

Let me turn now to some very recent studies by Farrer-Brown and Tarbett of the vascular pattern in diseased hearts from Uganda which throw considerable light on the nature of endomyocardial fibrosis compared with rheumatic heart disease.^{20, 21}

In the endomyocardial fibrosis hearts there were no abnormalities in the medium or large coronary arteries, and only very occasionally were abnormal small vessels seen, usually within fibrosed myocardial areas. The valves contained no vessels and showed no evidence of inflammation—that is, the disease did not primarily affect the heart valves. Thrombus was laid down on an abnormal endocardial surface below the valves and this became vascular and organized, so that the valves were bound down by fibrous tissue, finally leaving only a rim of valve. By contrast, the rheumatic hearts in this study showed considerable vascularity, the abnormal arteries arising in the subendocardial zone and passing into the valve, where they formed a dense network without any pattern. We can now understand why bacterial endocarditis is a common complication in rheumatic heart disease and is very unusual in pure endomyocardial fibrosis.

This vascularity of the valves is of value in distinguishing rheumatic heart disease and endomyocardial fibrosis and in confirming the concurrence of both disorders in a single heart. Indeed, using this microvascular technique Farrer-Brown and Tarbett²⁰ described a mitral valve which showed the posterior cusp affected by endomyocardial fibrosis and the anterior cusp by rheumatic heart disease. They also commented on the myocardial scarring present in the endomyocardial fibrosis hearts. Myocardial fibrosis was found throughout the width of the myocardium in all parts of the heart, and the distribution resembled that seen in healed cases of myocarditis rather than the pattern associated with ischaemia.

Hypersensitivity

Connor *et al.*^{22, 23} made detailed studies of endomyocardial fibrosis in Uganda using a wide variety of histological staining methods. They concluded that in the early stages the cardiac connective tissues, especially those of the endocardium, are swollen with acid mucopolysaccharide and the endocardium is covered by a layer of fibrin. Increased acid mucopolysaccharide is also present in the mitral and tricuspid leaflets, and they reported peculiar foci of collagen necrosis in the scar tissue at the endomyocardial junction. They regarded the consistent mucinous swelling of the cardiac "ground substance" plus the collagen necrosis as strongly suggestive of a hypersensitivity mechanism in endomyocardial fibrosis.

Immunological Basis

Several studies have been carried out in Kampala in the search for immunological factors in the aetiology or pathogenesis of endomyocardial fibrosis.²⁴ The search began with heart antibodies, but it soon became evident that not only heart antibodies but other tissue autoantibodies were very frequent in the patients being studied, and this led to more detailed investigations into the reasons for this phenomenon.

In a study of sera from patients with endomyocardial fibrosis, rheumatic heart disease, "cardiomyopathy," other cardiovascular diseases, and pulmonary tuberculosis, heart antibodies were present more frequently in the patients with endomyocardial fibrosis than in any of the other groups.²⁵ This increased frequency was not statistically significant for all grades of heart antibody reactions. However, intensely positive reactions for autoantibodies to heart were significantly more frequent in endomyocardial fibrosis (29%) than in any other group studied or in all of the other groups combined (3%) (Table I).

TABLE I—Heart Antibodies in Subjects with Cardiovascular Disease and Pulmonary Tuberculosis (Shaper *et al.*²⁵)

Group	No. of Patients	No. with Heart Antibodies	No. with Intensely Positive Heart Antibodies
Endomyocardial fibrosis	14	10 (71%)	4 (29%)
Rheumatic heart disease	27	12 (44%)	1 (4%)
"Cardiomyopathy" ..	17	8 (47%)	0 (0%)
Hypertension ..	33	9 (27%)	1 (3%)
Other cardiovascular diseases	14	4 (29%)	0 (0%)
Pulmonary tuberculosis	33	6 (18%)	1 (3%)

Because of the unexpected frequency of heart antibodies in pulmonary tuberculosis and hypertension it was considered whether positive reactions to heart were being produced by cross-reaction with other antibodies present in the serum. There was no relation between antistreptolysin O titres and the presence of heart antibodies but there was a clear relation between the titre of malarial antibody and the frequency of heart antibodies. This relation was again most evident for intensely positive heart antibody reactions (Table II).

TABLE II—Relation between Titre of Malarial Antibody and Presence and Intensity of Heart Antibodies (Shaper *et al.*²⁵)

	Malarial Antibody Titre	
	1/200 or Less	1/400 or More
No. ..	82	15
Heart antibodies present ..	28 (34%)	12 (80%)
Heart antibodies > ++ ..	2 (2%)	4 (26%)

We then examined further the relation between malarial antibody, heart antibodies, and other immunological factors in subjects without heart disease in Kampala (Table III). Again there was a progressive increase in frequency of heart antibody with increasing titres of malarial antibody. Furthermore, there was a significant relation between high titres of malarial

TABLE III—Malarial Antibody Titres and Heart Antibodies in Subjects without Heart Disease (Shaper *et al.*)²⁵

Malarial Antibody Titres								Presence of Heart Antibody
1/200 or less	..	..	..	..	..	..	..	10%
1/400	..	..	..	..	..	..	..	17%
1/800	..	..	..	..	..	..	..	43%
1/1,600 or more	..	..	..	..	..	..	..	62%

antibody and high levels of immunoglobulin M. In addition those with high titres of malarial antibody and high levels of immunoglobulin M had a high frequency of heart antibodies, thyroid antibodies, gastric parietal cell antibodies, and rheumatoid factor.²⁶ For convenience this phenomenon will be referred to as the tropical immunological syndrome, and it is important to consider that this syndrome can be present in persons who are perfectly healthy by any ordinary clinical standards.

Geographical Aspects

The earliest reports on endomyocardial fibrosis from Uganda²⁷ noted that most of the subjects were poor migrant labourers from Ruanda-Urundi (now Rwanda and Burundi). Detailed studies of subjects coming to necropsy in Kampala with endomyocardial fibrosis established a conspicuous preponderance of the disease among these Rwandans.⁹ The Ganda people indigenous to the Kampala region showed a much lower frequency of endomyocardial fibrosis than expected. Rheumatic heart disease behaved in the converse manner, affecting the Ganda group more and the Rwandan people less than expected (Table IV). In addition, characteristic lesions of both diseases occurred in the same heart five times more frequently in the necropsy series than would be expected if the two disorders were not in some way associated.⁹ This significant concurrence of endomyocardial fibrosis and rheumatic heart disease has now been independently confirmed by Farrer-Brown and Tarbett.²⁰

TABLE IV—Observed (O.) and Expected (E.) Cases of Endomyocardial Fibrosis and Rheumatic Heart Disease in Ganda and Rwandan Subjects at Necropsy during 1950-65 in Kampala, Uganda (Shaper *et al.*)⁹

	Ganda				Rwandans			
	Males		Females		Males		Females	
	O.	E.	O.	E.	O.	E.	O.	E.
Endomyocardial fibrosis	10	32	9	26	76	30	33	13
Rheumatic heart disease	60	41	50	39	24	32	7	16

It seemed reasonable to ask how the differences in geographical and tribal origin between the Rwandans and the Ganda might render the one group more susceptible to endomyocardial fibrosis than the other. One obvious factor is that all the areas inhabited by the indigenous Ganda and by the Rwandans when they settle in Buganda are subject to malarial transmission at all seasons. In contrast malaria is absent or seasonal in Rwanda and Burundi. This migration between zones differing in malarial endemicity appears to be reflected in certain features seen in migrants. Firstly, they have significantly heavier spleens than the Ganda people from the age of 15 years onwards.²⁸ Secondly, apparently healthy Rwandans in Kampala manifest the tropical immunological syndrome far more frequently than the local Ganda people. We have assumed that the large spleen and the tropical immunological syndrome are related to the fact that the migrants originate in an area of low malaria endemicity and that when exposed to hyperendemic malarial in early adult life they respond in an exaggerated way. This tropical immunological syndrome may possibly determine the undue susceptibility of these migrants to endomyocardial fibrosis and possibly to other disorders.²⁹

Endomyocardial fibrosis and rheumatic heart disease

The possibility of endomyocardial fibrosis being an expression of the rheumatic process was first proposed by Abrahams³⁰ from Nigeria, who found that antistreptolysin O titres were raised during the acute carditis in some of his cases, and collections of cells resembling Aschoff nodes were found in two-thirds of the cases coming to necropsy. Subsequently he and Brigden³¹ modified this view to suggest that "endomyocardial fibrosis is the final common path resulting from many different forms of myocardial damage" and suggested that in Southern Nigeria rheumatic carditis might be concerned in some cases. It is of interest that they observed that "in several hearts both [endomyocardial fibrosis of the left ventricle and rheumatic mitral incompetence] coexisted in the same heart."

Another link between rheumatic heart disease and endomyocardial fibrosis is the close similarity in age and sex distribution. In our own survey of necropsies over a 16-year period both disorders showed a marked predilection for the younger age groups. And in both disorders the female predominance in the under-15 age group was striking.⁹ (Fig. 2).

FIG. 2—Age and sex distribution of subjects with rheumatic heart disease and endomyocardial fibrosis at necropsy during 1950-65 in Kampala, Uganda (Shaper *et al.*)⁹.

A hypothesis has been put forward that endomyocardial fibrosis is a disorder similar to rheumatic heart disease³² because of the following observations: (1) the peculiar tribal/geographical relation between the two disorders; (2) the significant concurrence of the two disorders; (3) the pronounced similarity in age and sex distribution; (4) the clinical similarity—that is, a pancarditis in both conditions and possibly an initial acute episode (possibly recurrent)—and familial occurrence in both disorders;^{33 34} and (5) the fact that both appear to be disorders of cardiac connective tissue based on a hypersensitivity mechanism. The hypothesis also suggests that endomyocardial fibrosis represents another form of hypersensitivity response to infection with the streptococcus. The reason suggested for an individual developing endomyocardial fibrosis rather than rheumatic heart disease would be the presence of the tropical immunological syndrome.

Endomyocardial Fibrosis in Europeans Resident in Africa

Having given free rein to my own hobby horse I must now explore other major hypotheses in the endomyocardial fibrosis story. Brockington *et al.*³⁵ reviewed 23 cases of endomyocardial fibrosis in Europeans, all of whom had been resident in West Africa or the Congo. In most of them there was some evidence of filariasis, and a severe eosinophilia was usually present.

Nigerian Studies

Workers in Nigeria followed up these clues of filariasis and eosinophilia and defined the geographical distribution of the disease in relation to filariasis as seen in patients presenting in Ibadan.³⁶ They discovered that patients with endomyocardial fibrosis rarely came from Ibadan itself or the savannah region to the north and west. They came predominantly from the rain-forest area where infestation with *Loa loa* (a form of filariasis) was endemic. In a study using a filarial antigen for skin testing they found that patients with endomyocardial fibrosis reacted more frequently than the controls. They concluded that loiasis was the main form of filariasis associated with endomyocardial fibrosis but not the only form. The filarial hypothesis, which was fundamentally concerned with a sensitizing parasitic infestation, has not worn well in the light of conflicting geographical evidence and has been replaced by a more embracing concept.

As mentioned above, eosinophilia was frequently present in Europeans with endomyocardial fibrosis. Eosinophilia is also a manifestation of Löffler's endocarditis, a non-endemic, non-tropical form of endomyocardial fibrosis which bears a striking macroscopic resemblance to tropical endemic endomyocardial fibrosis. Furthermore, in eosinophilic leukaemia some 40% of the reported cases have a heart lesion which is grossly indistinguishable from endomyocardial fibrosis. In other sporadic cases of non-tropical endomyocardial fibrosis eosinophilia has frequently been an associated finding. The unitarian hypothesis arising from these observations is that "the presence of an eosinophil leucocytosis, in a susceptible person, by some unknown mechanism, causes endomyocardial damage."³⁷ Endomyocardial fibrosis, Löffler's endocarditis, the endomyocardial fibrosis of eosinophilic leukaemia, and other endomyocardial conditions with eosinophilia are thus all variants of the same cardiopathy, varying only in the acuteness of presentation and the severity of the damage.^{37 38}

It is of some interest to the hypothesis of the pathogenic eosinophil that the tropical condition associated with the most severe degree of eosinophilia is not known to produce appreciable cardiac damage.^{39 40} I refer to tropical eosinophilia, a condition of high eosinophilia associated with pulmonary symptoms and characteristic radiographic changes, almost certainly produced by a non-human filarial infestation. Tropical eosinophilia is commonly seen in India, Pakistan, and Ceylon and it occurs very rarely in tropical Africa, where endomyocardial fibrosis is endemic.

I intend no pun when I say that eosinophilia in endomyocardial fibrosis is a red herring. It is the underlying immunological status of the individual which is probably of major importance, and this may or may not be associated with an eosinophilia. A study of the immunoglobulin and tissue auto-antibody patterns in non-tropical, non-endemic cases of endomyocardial fibrosis would be of considerable interest.

Conclusion

I do not want to convince you of any particular hypothesis concerning endomyocardial fibrosis. What does seem important in the story is not only an infection but a susceptible host. I would like to think that when the final chapters in the endomyocardial saga come to be written we may, in the process of studying this disease, have made a contribution to the understanding of individual susceptibility in other diseases, including rheumatic fever. We have the unique opportunity of applying the scientific methods of the 1970s to disease situations encountered in Great Britain in the previous century and present in the tropical world of today.

Part III of these lectures will appear in next week's issue. A list of references will be given in part IV, to be published in our issue of 7 October.

Reactions to Drugs

Evaluation of Spontaneous Reports of Adverse Reactions to Drugs

WILLIAM H. W. INMAN, DAVID A. PRICE EVANS

British Medical Journal, 1972, 3, 746-747

Summary

An adverse drug-reaction monitoring system based on spontaneous reporting to a central register of adverse reactions has been in operation for eight years. As a test of the validity of the reports and of the probability of causal relationship between drug and reaction a random sample of 82 cases were followed up in detail. The sample included 17 deaths, 26 serious reactions, and 39 reactions of moderate or only minor severity. Altogether 78% of the reactions were considered to be "probably" drug

related and 13% "possibly" drug related. It is concluded that the reports are of value in the detection and evaluation of drug safety.

Introduction

In 1964 the Committee on Safety of Drugs* established an adverse reactions reporting system managed by its Subcommittee on Adverse Reactions. Doctors, dentists, and, later, coroners were invited to submit summarized reports of suspicious events after the use of drugs to a central Register of Adverse Reactions. Since then between 3,000 and 5,000 reports have been received each year, about three-quarters of these on a business reply card (the "yellow card"). About half of the reports are from general practitioners and the remainder are from hospitals,

*Now replaced under the Medicines Act 1968 by the Committee on Safety of Medicines.

Committee on Safety of Medicines, London E.C.2

WILLIAM H. W. INMAN, M.B., M.R.C.P., Senior Medical Officer

Nuffield Unit of Medical Genetics, Department of Medicine, University of Liverpool

DAVID A. PRICE EVANS, M.D., F.R.C.P., Professor of Medicine