Microvascular study of hearts with endomyocardial fibrosis

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The vascularity of 11 hearts with endomyocardial fibrosis, which were part of a larger series of 147 hearts from patients dying at the Mulago Hospital, Kampala, Uganda, have been studied by injection, microradiographic, and histological techniques. A complete range of pathological types of endomyocardial fibrotic hearts were studied. Every heart showed some pericarditis and small scars scattered within the myocardium, while three hearts contained small foci of active myocarditis, but without eosinophil infiltration. No constant relation was seen between the distribution of endocardial and myocardial damage, but in general the more extensive the endocardial damage the more extensive the myocardial damage, particularly in the subendocardial zone. Endocardial thrombus became organized by numerous small vessels extending out from the subendocardial zone while the resulting fibrous tissue was relatively avascular. The valves were not primarily diseased but were secondarily involved by encroaching organizing thrombus.

The findings show that a small vessel pathology is unlikely and that endomyocardial fibrosis should be considered a pancarditis. It is suggested that more attention should be directed at establishing whether a toxic or infective agent acting directly on the endocardium and myocardium is of importance and whether there is an abnormal individual response.

Endomyocardial fibrosis first described independently by Bedford and Konstam (1946) and by Davies (1948) has a well-defined geographical distribution (Shaper, 1970). Characteristic clinical syndromes relate closely to the pathological lesions in this condition (Ball, Williams, and Davies, 1954; Somers *et al.*, 1968a; Somers, Brenton, and Sood, 1968b; Fowler and Somers, 1968), but the aetiology is unknown, though nutritional, toxic, and infective factors as well as hypersensitivity or an abnormal immunological reaction have all been postulated on clinical, pathological, or epidemiological grounds. In addition Patel *et al.* (1971) have recently discussed possible familial factors. The pathology of the established lesions in endomyocardial fibrosis is well defined, and all authors support the view

that organization of thrombus overlying an abnormal endocardium gives rise to the eventual scar (Davies and Ball, 1955; Connor *et al.*, 1967, 1968). There is, however, still controversy as to the pathogenesis of the initial lesion. Connor *et al.* (1968) postulate that endomyocardial fibrosis is a hypersensitivity disease affecting the cardiac connective tissues, resulting in an accumulation of acid mucopolysaccharides and necrosis of collagen. They suggest that these lesions, which may be widespread, initiate the subsequent processes. Small vessel disease in the myocardium has also been considered, and in view of this possibility a research project was initiated in August 1969 to study by injection, microradiographic, and histological techniques the pattern of the microvasculature, in relation to the overall pathology of the hearts, of patients dying of this condition in the Mulago Hospital, Kampala, Uganda.

Methods and subjects

Examinations were made of 11 hearts with endomyocardial fibrosis, which were part of a large series of 147 'normal' and 'abnormal' hearts

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obtained at random at necropsy from patients who had died at the Mulago Hospital, Kampala, Uganda. Hearts were considered to show endomyocardial fibrosis only if they fulfilled the pattern of pathology for this disease described by Shaper, Hutt, and Coles (1968). Three hearts with some features of endomyocardial fibrosis were excluded as one had more widespread myocarditis than is generally accepted, while the appearances of the other two hearts could not be distinguished from idiopathic cardiomegaly with thrombosis formation. These hearts are described in a separate publication (Farrer-Brown and Tarbit, 1972a).

The basic technique used for this investigation has been described previously (Farrer-Brown, 1968a), but a few minor modifications were used in this study and briefly it is as follows. Radio-opaque medium (Colorpaque, Pilot Chemical Ltd), with 4 per cent added gelatin, was injected simultaneously into both coronary arteries at a pressure equivalent to the patient's systolic blood pressure or, if this was unknown, at a pressure of 120 mmHg. After fixation the hearts were sectioned on a bacon slicer into uniform 5 mm thick slices from the apex up to just below the mitral valve. The overall vascular pattern of these slices was visualized by x-raying onto fine grain film (Microtex, Kodak), using a water-cooled low voltage Machlett x-ray tube: 25 kV and 20 mA exposures were used for 10 seconds, with a tube distance of 64 cm. A similar exposure, but for 20 minutes, was used to x-ray the atrial portions of the hearts, submerged under water, on to Crystalex film (Kodak). To demonstrate the finest vessels, selected ventricular slices were radiographed on Kodak Maximum Resolution plates using the same x-ray tube and exposures of 25 kV and 10–20 mA for 15 to 30 minutes according to the thickness of the slice. The plates were developed for 4 minutes at 68°C in high contrast developer (Kodak D178) and then fixed and washed using the recommended procedure. Initial photographic enlargements of the plates were made using a Durst 1000 condenser enlarger and 20–25 cm rapidoprint paper which was processed on an Agfa Gevaert rapid print processor. Areas of interest were then magnified either on the Durst enlarger or under the microscope.

The atrial portions of the hearts, which included the mitral and tricuspid valves, were examined macroscopically by cutting across and opening out each valve. The main portions of the coronary arteries were sectioned with a fine scalpel at right angles to their lumen every 1 to 2 mm in order to assess the presence of disease. Diseased valves were excised for microradiography, after which sections across each valve and the apex of the heart were examined by conventional histological techniques. The whole transverse ventricular slices which had been microradiographed were then processed for histology, with slices up to 10 cm in width being cut on a sledge microtome after embedding in a mixture of paraffin, dental, and beeswax. Sections were stained with haematoxylin and eosin, elastic van Gieson, Mallory's

FIG. 1 Midventricular slice showing fibrous tissue obliterating the right ventricular chamber and a thick layer of fibrous tissue lining the cavity of the left ventricle. ($\times 1.5$.)

FIG. 2 The posterior cusp of a mitral valve on the left of the photograph shows gross contraction and binding down so that it appears to be merely a rim of fibrous tissue. ($\times 2$.)

TABLE Details of patients

Case No.	Patient		Tribe	Heart weight (g)
	Age (yr)	Sex		
K6	18	M	Rwanda	360
K27	16	M	Rwanda	520
K31	60	M	Luhya	360
K48	50	M	Rwanda	300
K73	18	F	Ganda	520
K102	22	F	Ganda	320
K104	20	M	Hangaza	450
K140	8	M	Ha	390
K155	5	M	Rwanda	220
K166	38	F	Ganda	310
K171	30	F	Rwanda	360

trichrome, and alcian blue. When necessary all the radiopaque medium in the vessels was removed by immersing the cut section in 10 per cent sequestrene solution at room temperature for about 20 minutes.

Results

The details of the patients in this study are shown in Table 1. The 7 male and 4 female patients had an age range of 5 to 60 years, with a median of 20 years. The weight of the hearts varied from 220 to 520 g. When related

FIG. 3 A midventricular slice with organizing thrombus almost obliterating the chamber of the left ventricle. Mature fibrous tissue lines the posterior wall of the right ventricle and surrounds the posterior papillary (p) muscles. ($\times 1.1$.)

FIG. 4 The radiograph of the atrial portion viewed from above, of a 5-year-old child with the portions of coronary arteries present being normal.

to the body weight of the patient (Coles and Davies, 1959), 7 of these hearts were considered overweight; 4 were within the normal range, though 3 of these were at the upper limit. The tribal origin of the patients varied and consisted of 3 Ganda and 8 'immigrants' who came from Rwanda or its vicinity.

Macroscopical pathological features

A complete range of pathological types of endomyocardial fibrosis were encountered in this study. One of the hearts (K102), from a 22-year-old Ganda, had extensive fibrosis involving both the right and left ventricles (Fig. 1), which obliterated the apices of these chambers; this was considered to illustrate a late stage of the disease. On the left side, the residual cavity began just above the base of the papillary muscles, while on the right it was near the top of the muscle columns. In each ventricle the remainder of the chamber was lined by fibrous tissue, about 2 to 3 mm thick, which also involved both atrioventricular valves.

FIG. 5 Thrombus fills the right ventricle and lines part of the cavity of the left ventricle in this midventricular slice. ($\times 1.8$.)

FIG. 6 Microradiograph of the ventricular slice superior to the one shown in Fig. 5. The vascular pattern is normal except in the areas of thrombus lining both ventricles. Magnified photographs of the arrowed areas are seen in Fig. 7-8. ($\times 1.5$.)

Two cases (K140 and 155) showed characteristic late stage involvement of the mitral valves combined with milder endocardial fibrosis in the ventricles. In both these hearts, which were from male children aged 5 and 8 years, the posterior cusp of the mitral valve was grossly contracted and folded back on itself (Fig. 2) so that it measured approximately 3 mm from the free to the attached edge. The chordae tendineae were bound down by fibrous tissue to the myocardial endocardium, with the normal sharp junction between the valve and the myocardial wall obliterated. The anterior cusps of these valves were normal.

Five hearts in this series (K6, 27, 31, 73 and 104) showed less extensive disease with scattered areas of ventricular, endocardial fibrosis. In 4, the distribution of the lesions corresponded with Type 4 as described by Shaper *et al.* (1968), with the apex and atrio-ventricular valvular regions involved. In the fifth heart the pattern was Type 1 with the apex only involved, though the atrioventricular valves were affected by rheumatic heart disease.

The remaining 3 hearts (K48, K166, and

K171), all from adult patients, showed features considered to be a stage earlier in the development of endomyocardial fibrosis. Extensive organizing thrombus filled both or predominantly one of the ventricles (Fig. 3) and was beginning in each case to involve the heart valves. The apices of these hearts were obliterated by fibrous tissue on which there was superimposed organizing thrombus. Superior to this, the thrombus was more recent and showed no evidence of organization. In each case the ventricular cavities were almost completely obliterated up to the top of the papillary muscles, which were bound down either by mature fibrous tissue or by organizing thrombus. Above this level there was a residual cavity, with the thrombus not only lining the endocardial surface but also encroaching onto the atrioventricular valves and, in 2 instances, the pulmonary valve. In 2 of these hearts thrombus was also present in one of the atria.

Abnormal vascular patterns The lumen diameters, dominance, and patterns of the main coronary arteries of these hearts were

FIG. 7 High magnification from Fig. 6 of the vascular pattern of the subendocardial area and endocardial thrombus in the lateral wall of the left ventricle with appearances as described in the text. ($\times 8.5$.)

similar to those seen in 'normal' East African hearts studied by the present authors. Fig. 4 illustrates the radiograph of the atrial portion of the heart of the youngest patient in this series, a child of 5 years, with characteristic late stage endomyocardial fibrosis involvement of the mitral valve and both ventricles. The portions of the main coronary arteries seen in this x-ray are entirely normal, and in none of the other hearts was any significant disease found in the extramyocardial portions of the main coronary arteries. The basic pattern of the 'branching' and 'straight' type arteries (Farrer-Brown, 1968b) in the left and right ventricular free walls and the interventricular septum (Farrer-Brown and Rowles, 1969) in all 11 hearts was also normal, as illustrated in subsequent figures. The most striking abnormal vascular patterns were seen in the endocardium of the three hearts considered to show the earlier stages of the disease with the ventricular cavities filled with organizing thrombus. This is illustrated in Fig. 5 which shows thrombus completely filling the right ventricle and lining the left ventricular cavity.

Particular attention was paid to the endocardial-subendocardial junctional zone in these hearts, as this is the area predominantly affected by endomyocardial fibrosis, and it is less likely that any vascular abnormalities present in this region of these hearts are secondary to the disease process, as compared with the hearts with late stage disease where resulting fibrosis may have affected the blood supply. To show the manner in which the vascular patterns were studied the subsequent five figures, illustrating the appearances seen at different levels of the ventricular cavity, have been selected from a single heart, but the abnormal patterns present in the other two hearts were similar. Fig. 6 shows the vasculature of a midtransventricular 5 mm slice, superior to the slice shown in Fig. 5. Thrombus is no longer completely filling the right ventricular cavity, but is confined to the edges of both ventricular chambers. The pattern of the 'branching' and 'straight' type arteries in the right and left ventricular walls is normal and it is not until the subendocardial zone is reached that there is any abnormality. This

FIG. 8 *High magnification of the microradiograph of the interventricular septum at the junction of the left and right coronary trees. The overall pattern is normal but on the left of the photograph small vessels are seen extending out into the endocardial thrombus lining the right ventricular side of the septum. ($\times 6.8$)*

is well illustrated in the high power view of this area in the lateral wall of the left ventricle (Fig. 7). On the right side of the microradiograph the normal fan-like termination of the 'branching' type arteries can be seen. In addition, two straight type arteries are present converging in the subendocardial zone, while the termination of another of these arteries is seen communicating with a slightly tortuous collateral type vessel running more circumferentially. On the left of this collateral vessel the microvasculature is abnormal with small arteries, without any particular pattern, passing out from the subendocardial area into the organizing thrombus. Background capillary filling is also present.

As the microvascular pattern of the interventricular septum is distinctive, particular attention was also directed to the blood supply of this area. The normal arrangement of the main supplying branches from the anterior and posterior descending coronary arteries

lying in the middle section of the septum is seen in Fig. 6. The pattern of the smaller branches to the left half of the septum resembles the pattern seen in the left free ventricular wall, while that to the right half of the septum resembles the pattern in the right ventricular free wall. High power magnification of the area of this septum with organizing thrombus present on the right ventricular side (Fig. 8) shows that the overall pattern of the vessels is similar to that seen in normal East African hearts studied by the authors, and it is not until the subendocardial area that there is any abnormality. In this zone small arteries are seen extending out into the organizing thrombus in a similar manner to the left ventricle. In order to understand the sequence of events of this disease, a detailed study was made of the microvasculature of the slices nearer the apex (Fig. 9) where the endocardial thrombus was of earlier origin, but the basic pattern of the myocardial arteries was again

FIG. 9 *Microradiograph of ventricular slice nearer the apex than Fig. 6. There is abnormal vascularity of the thrombus lining the left ventricle and obliterating the cavity of the right ventricle, but the basic pattern of the branching and straight type arteries of the myocardium is normal. ($\times 2.3$.)*

normal. In the right ventricle, where the cavity has been completely obliterated, a high power magnification (Fig. 10) shows complete vascular filling in the subendocardial area which contains moderate sized circumferentially running collateral vessels, while internal to these vessels small arteries are seen coursing throughout the endocardial fibrous tissue and organizing thrombus.

As expected the endocardial thrombus became less vascular as organization with replacement fibrosis progressed and finally few vessels remained in the endocardium. The appearances of the vascularity of the inner myocardium and endocardium of the 8 hearts with mature fibrous tissue lining either the majority or small portions of the ventricular cavities were similar, and the typical features are shown in Fig. 11. The inner myocardial vasculature shows complete filling and a normal pattern with the terminal branches of both the 'branching' and 'straight' type arteries being well demonstrated, but in the subendocardial zone, particularly on the right of the photograph, a few small focal areas of less dense vascular filling are seen

which correspond to the small areas of fibrosis in the inner myocardium. The small arteries supplying these areas, however, show normal filling.

Heart valves In this series of hearts, 7 mitral valves, 7 tricuspid valves, and 2 pulmonary valves were secondarily affected by the endomyocardial fibrosis disease process, but in all instances the valves were avascular and not primarily diseased. The details of the appearances of these valves and the process of involvement by endomyocardial fibrosis are described elsewhere (Farrer-Brown and Tarbit, 1972b).

Myocardial lesions The degree of myocardial disease in these hearts varied, but in every case scars of varying size and number were present in the myocardium. These were seen anywhere within the wall of the heart, and were most readily appreciated on study of the whole transventricular slices. In general, the more extensive the endocardial lesions the more extensive was myocardial damage, particularly in the subendocardial zone (Fig. 12).

FIG. 10 High power from Fig. 9 showing small capillary like vessels extending throughout the thrombus obliterating the cavity of the right ventricle. Medium sized collateral type vessels are present in the subendocardial zone. ($\times 10$.)

Even with this degree of myocardial fibrosis, however, the small arteries present in the inner myocardium appeared normal though there had obviously been some loss of arterioles and capillaries in the areas of scarring. The medium sized arteries seen supplying these areas of myocardial fibrosis also showed a normal lumen (Fig. 13). In the microscopical study of the whole transventricular slices, of which there were often more than one from each heart, only two areas were found with one or two arteries showing disease. One of these areas was a fibrotic subendocardial zone and the other a fibrotic papillary muscle. There were no histological features within these vessels to distinguish them from similar vessels seen in hearts without endomyocardial fibrosis.

No constant relation was found between areas showing myocardial fibrosis and involvement of the overlying endocardium by endomyocardial fibrosis. Frequently both showed disease, with merging of the myocardial and endocardial fibrous tissues, but the myocardium was often involved without overlying

endocardial disease (Fig. 13), and similarly the endocardium often showed disease with normal underlying myocardium (Fig. 14).

Fibrosis within the papillary muscles varied. In hearts which were considered to be at an early stage of the disease, the papillary muscles and vessels within them appeared entirely normal, though these muscle columns were surrounded by either organizing thrombus or dense fibrous tissue (Fig. 15). Other hearts showed fibrosis within the papillary muscles associated with subendocardial scarring. As the degree of endocardial fibrosis increased so the muscle fibres within the bound down papillary muscles showed degenerative changes and final replacement by fibrous tissue.

In three hearts, in addition to small fibrous scars, foci of chronic inflammatory cells associated with small areas of muscle degeneration were seen. The histological appearances of these areas were nonspecific and might be seen in any type of myocarditis (Fig. 16 and 17) and the adjacent small vessels all appeared normal.

FIG. 11 *A less dense vascular pattern is seen as organization of the endocardium (E) proceeds and it becomes fibrotic. The arterial filling of the supplying arteries of the myocardium is normal but a few focal areas of less dense vascularity are seen in subendocardial area which correspond with focal scars. ($\times 7$.)*

FIG. 12 Extensive subendocardial fibrosis associated with overlying endocardial fibrosis (E). The small arteries in the inner myocardium are normal. (H. and E. $\times 7$.)

Pericardium In all hearts evidence of pericarditis was present though the severity of the inflammation varied considerably and was usually mild.

Discussion

The aim of this study was to investigate the role of vascular lesions in the pathogenesis of endomyocardial fibrosis. The findings suggest that a vascular pathology is unlikely. No significant abnormality was seen in the medium-sized or large portions of the coronary arteries. Only occasionally were abnormal small vessels present and these were within fibrous tissue in the subendocardial zone or in papillary muscle, where the 'straight' (Farrer-Brown, 1968b) type arteries entering the base of the papillary muscles might have been constricted by surrounding endocardial fibrosis. The majority of areas with myocardial scarring showed vessels with a normal-sized lumen and wall. The histological areas of myocardial fibrosis resembled the distribution seen in healed cases of myocarditis rather than the pattern associated with ischaemia resulting from coronary artery atheroma.

The vascular patterns within the myocar-

dium which occur following ischaemia were not present in these hearts with endomyocardial fibrosis, and the 'plexus' formation (Farrer-Brown, 1968c) associated with subendocardial fibrosis occurring with large coronary artery disease was not seen. It seems unlikely that the majority of small scars within the myocardium in endomyocardial fibrosis hearts are microinfarcts as suggested by Connor *et al.* (1968), though it is possible that constriction of arteries supplying the papillary muscles and the lack of diffusion of blood from the ventricular cavities does result in some superadded muscle degeneration and scarring. This may also explain the presence of large collateral vessels in the subendocardial areas of some of the hearts, though these arteries were also found in 70 per cent of the normal East African hearts in this study. The findings suggest that endomyocardial fibrosis is more likely to be a pancarditis with, for some unknown reason, the endocardium being more severely involved than the myocardium. Small lesions within the myocardium, indistinguishable from those seen in active myocarditis, were present in three

FIG. 13 A subendocardial scar supplied by a normal sized artery (A) containing radio-opaque medium. A small rim of myocardium (M) separates the scar from the normal overlying endocardium (E). (Elastic van Gieson. $\times 9.5$.)

hearts. As the muscle fibres degenerated and disappeared the chronic inflammatory cell infiltrate was no longer apparent, but the capillary vascular network was still visible. These areas of myocardial damage presumably heal with resulting fibrous scars. Though mainly subendocardial in distribution they were found throughout the width of the myocardium and in all parts of the heart. The fact that only a minority of the hearts showed active myocardial lesions raises the possibility that endomyocardial fibrosis in many instances might be a one-insult disease. It would not be necessary to have repeated insults to explain the development of the endocardial lesions. Continued superimposition of thrombus on the endocardium can be self-perpetuating once the process has started. On the other hand the hearts with active myocardial inflammation may indicate either a smouldering disease or repeated small damage. In general it is rare to see extensive inflammatory cell infiltrates in the endocardium, possibly due to the fact that few vessels from the myocardial side extend into the endocardium and that this area remains viable from perfusion of blood from the ventricular cavities. In this event it is unlikely that lymphocytes will marginate along the endocardium and gain access to the underlying connective tissue. Therefore, if one is postulating a pancarditis, it is not surprising that the initial inflammation within the endocardium never appears severe. It is not known whether endocardial inflammation takes place over a small or wide area but overlying endocardial thrombosis starts usually in the apex. Then thrombus gradually obliterates the middle of the myocardial cavity and may involve the valves in continuity or as an isolated process. Similar to the healing process elsewhere in the body, organization of this thrombus takes place with the formation of granulation tissue and eventually fibrous tissue. Initially the endocardial vascularization is dense with an irregular network of capillary-like vessels, but at a later stage the fibrous tissue becomes devascularized and relatively few vessels remain. These findings have been confirmed recently in life by the use of a cardiac biopsy technique (Somers *et al.*, 1971).

It is difficult to explain first why in endomyocardial fibrosis thrombus encroaches on to the valves, a feature not generally seen with mural thrombus associated with other conditions, or second why the disease can be localized to the area inferior to the atrio-ventricular valves without apical disease. Stasis and turbulence almost certainly play a major part, possibly associated with poor myo-

FIG. 14 Thickened fibrotic endocardium (E) with adjacent normal myocardium. (H. and E. $\times 15$.)

FIG. 15 A normal papillary muscle (P) surrounded by moderately vascular fibrous tissue. (H. and E. $\times 8$.)

FIG. 16 Area of myocardial degeneration with replacement fibrosis adjacent to a normal small artery. (H. and E. $\times 39$.)

due to merging of endocardial and myocardial fibrosis.

The importance of an initiating mucopolysaccharide change in the connective tissue of the heart is difficult to assess. Connor *et al.* (1968) have postulated that endomyocardial fibrosis is a hypersensitivity disorder affecting the cardiac connective tissues and that the initial lesion is associated with an accumulation of acid mucopolysaccharide. Undoubtedly this substance is present in these hearts but Becker, Chatgidakis, and Van Lingen (1953) have described its presence in the myocardium of hearts from Bantu in South Africa with a cardiomyopathy now thought by the majority to be different from endomyocardial fibrosis. In view of the fact that acid mucopolysaccharide may also be present in myocardial infarction (McKinney, 1970), it is possible that this substance appears as a stage in the disease process rather than as the initial lesion.

Pancarditis has been described in previous endomyocardial fibrosis hearts and the possibility of a toxic or infective aetiology or streptococcal hypersensitivity has been considered by many workers since this condition was first

FIG. 17 A focal area of myocarditis with chronic inflammatory cells surrounding degenerate muscle fibres. (H. and E. $\times 96$.)

cardiac contractility. Another factor to be considered is whether a causative agent is present in the blood directly affecting the endocardium and areas of the myocardium where there may be a certain degree of ebbing and flowing of blood, such as in the arterioluminal or venoluminal vessels in the subendocardial area. Selye (1958) has shown that cardiac toxic agents produce the greatest damage in the subendocardial zone. The extent by which the subendocardial area is nourished by perfusion of blood from the heart chambers is unknown, but it appears unlikely that obstruction to this flow in endomyocardial fibrosis plays a major role in producing subendocardial fibrosis, particularly as, on occasion, dense endocardial fibrosis may overlie completely normal myocardium. This latter appearance also suggests that it is very unlikely that ischaemia is important in producing these endocardial lesions as the adjacent myocardium would also be expected to show disease. Active invasion of the myocardium by endocardial fibrous tissue has been described (Davies and Ball, 1955) but this present study suggests that this appearance is

described, but at the present time there is no proof that any of these are causative agents. No extensive infiltration by eosinophils or evidence of parasitic involvement was seen in these hearts. Pathologically there is little similarity in the manner in which the heart is affected in rheumatic heart disease and endomyocardial fibrosis. The former, though a pancarditis, primarily affects heart valves with minimal endocardial disease while endomyocardial fibrosis, probably also a pancarditis, primarily affects the endocardium and not the valves though they may become involved secondarily.

The findings of this present study suggest that more attention should be directed at establishing whether the initial lesion is due to an agent acting directly on the endocardium and myocardium, and whether the lesions are partly dependent upon an abnormal individual response associated with hereditary factors (Patel *et al.*, 1971) and exposure to malaria (Shaper, 1970).

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