Geochemical basis of tropical endomyocardial fibrosis

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Endomyocardial fibrosis (EMF) has a marked preference for the tropics and the poor socio-economic class. Tropical soil is rich in minerals such as monazite and the endomyocardial samples of patients with EMF show higher levels of cerium – a major constituent of monazite – in combination with lower concentrations of magnesium.

The geochemical hypothesis postulates that poor children are prone to develop magnesium deficiency because of insufficient intake and the higher growth needs for the element. The deficiency of magnesium promotes the absorption of cerium and enhances its toxicity which could form the basis for the initial injury in EMF.

THE tropics dominate the epidemiology of endomyocardial fibrosis (EMF). Of 779 cases reported in the last two decades, 730 originated from countries within 15° of the equator. The remaining patients (49) included no fewer than 14 who did not have EMF but the sequelae of therapy with adriamycin or methysergide or hyper-eosinophilia (Figure 1). What is common to the tropical zone is not culture, race or genetic trait but the chemistry of its terrestrial environment which is a product of erosion and weathering of rocks over vast stretches of geological time.

Given the predominantly tropical distribution, it is surprising that geographical factors received so little attention over the years in the investigation of EMF. This must be attributed to the general lack of interest in the influence of geography on man.

Distribution of EMF in Kerala

The high incidence of EMF in Kerala is similar to that in several countries in the tropical zone. Over a period of 10 years, the Sree Chitra Tirunal Institute alone has registered 306 patients whose diagnosis was established by echo as well as angiocardiography. This number does not reflect the true incidence in Kerala as smaller series are admittedly treated and followed by physicians in other parts of the state. Figure 2 maps the incidence of EMF in Kerala on the basis of the dwelling places of our patients. To rule out the possibility that the concentration of EMF cases in the coastal zone is an artefact due to the higher density of population in the coastal villages, a map of the dwelling places of 300 patients with rheumatic heart disease registered during the same period was superimposed on the distribution map of EMF (Figure 3). The superimposition showed no spatial coincidence but a distinct tilt in favour of the

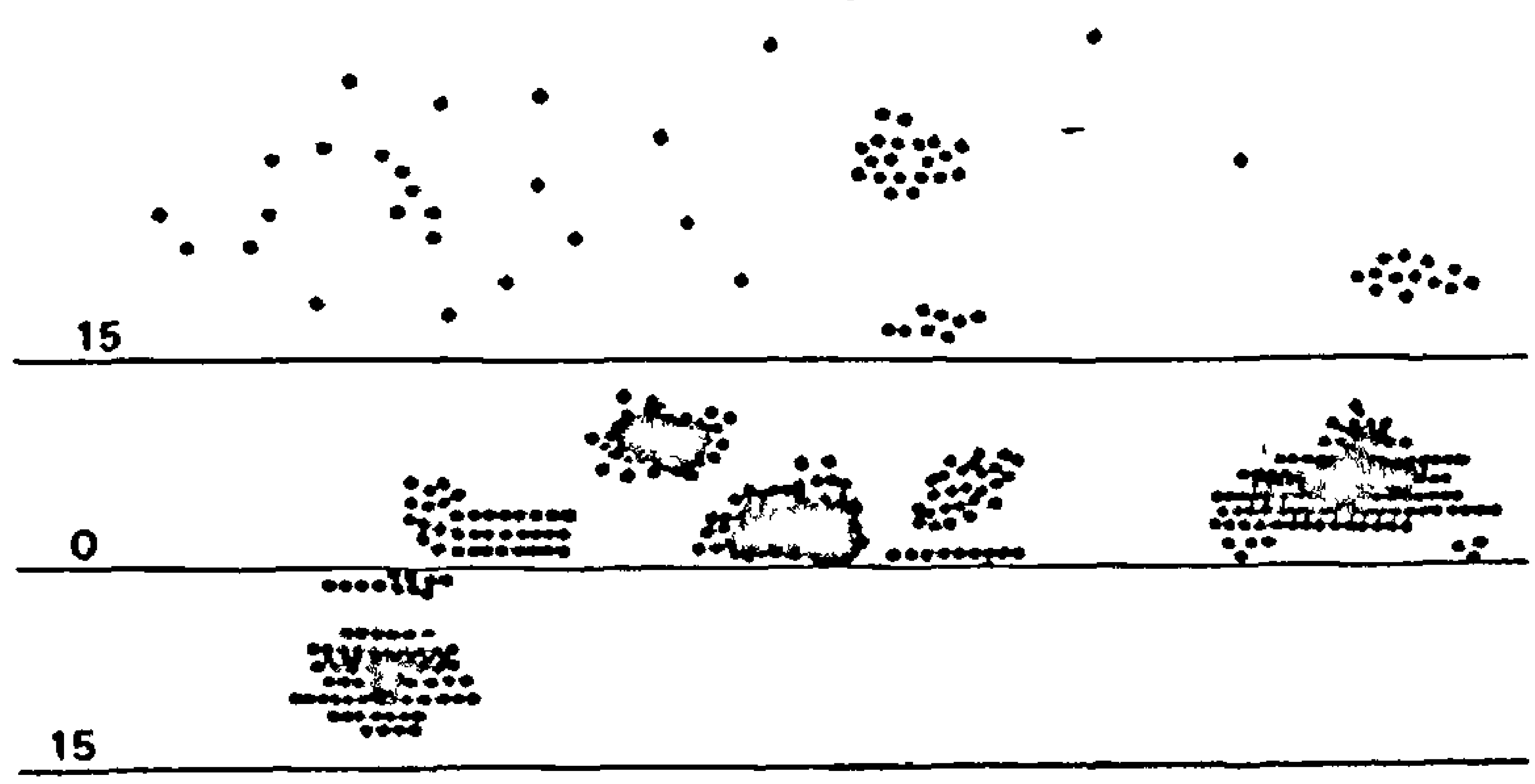

Figure 1. Global prevalence of endomyocardial fibrosis Note the cluster of cases around the equator.

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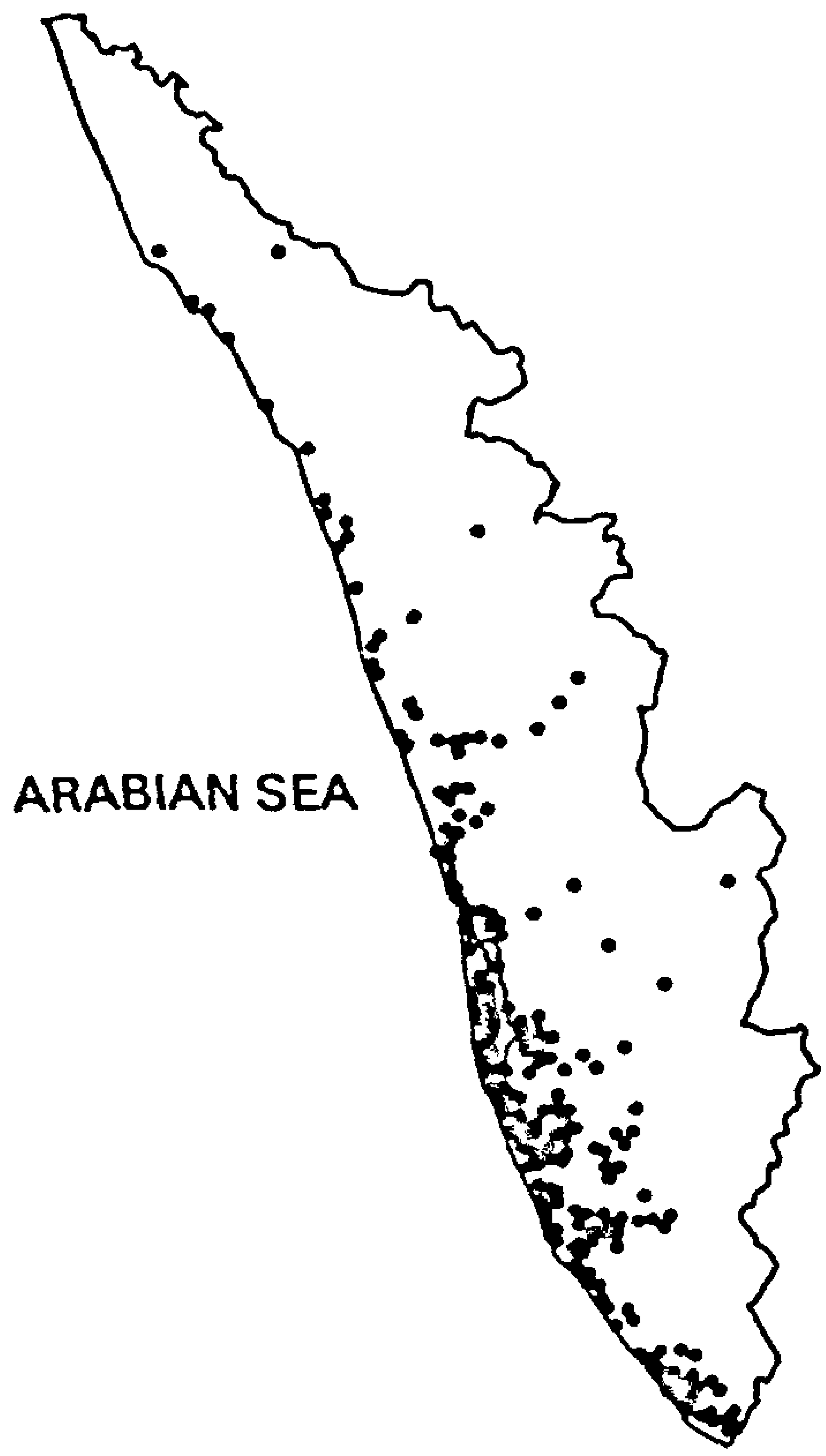

Figure 2. Distribution of places of origin of 300 patients with endomyocardial fibrosis in Kerala.

coastal zone for the distribution of EMF. Apart from this intraregional difference in incidence, EMF also showed a clear preference for the young from the poorer strata of society in Kerala. In our series, 46% of patients were below the age of 20 years and the annual income amounted to less than Rs 3600 for 85% of patients.

The geographical and socio-economic selectivity in the distribution of EMF is important in understanding its pathogenesis.

Table 1. Rare earth element data – monazite (from two sites of coastal Kerala)

Sample	[1]Th%	[2]La%	[2]Ce%	[2]Pr%	[2]Nd%	[2]Sm%
*Manavalakurichi	8 6	4.907	37.321	4.574	8.89	0.772
**Chavara	8 6	5 83	34 417	3.941	10 167	0 684

*Average of 12 samples.
**Average of 3 samples
Source: [1]Bhabha Atomic Research Centre, Bombay, [2]Centre for Earth Science Studies, Trivandrum
Th Thorium; La Lanthanum, Ce Cerium; Nd Neodymium; Pr Presedymium; Sm Samarium

Geomorphology and soil profile in Kerala

Located within 8° to 12° of the equator at the south-western tip of peninsular India, Kerala is sandwiched between the Arabian sea and the Western ghats. With a coastline of 580 km, its width varies from 11 to 121 km. The rainfall exceeds 3000 mm over two monsoons and the temperature ranges from 80°F to 90°F throughout the year. Its land area measures less than 40 000 km^2 and the natural terrain falls into lowland, midland and highland as one moves from the coastal strip to the ghats. It has the highest density of population in India, 654 persons per km^2 as against the national average of 221.

The coastal belt of Kerala is broken up by as many as 47 west-flowing streams which flow into the sea through numerous lagoons and backwaters. The hinterland consists of crystalline rocks and the products of their weathering such as laterites. Minerals for which Kerala is famous are derived from the crystalline rocks of the Western ghats and the mineral deposits in river beds and beaches merely indicate their course and destination.

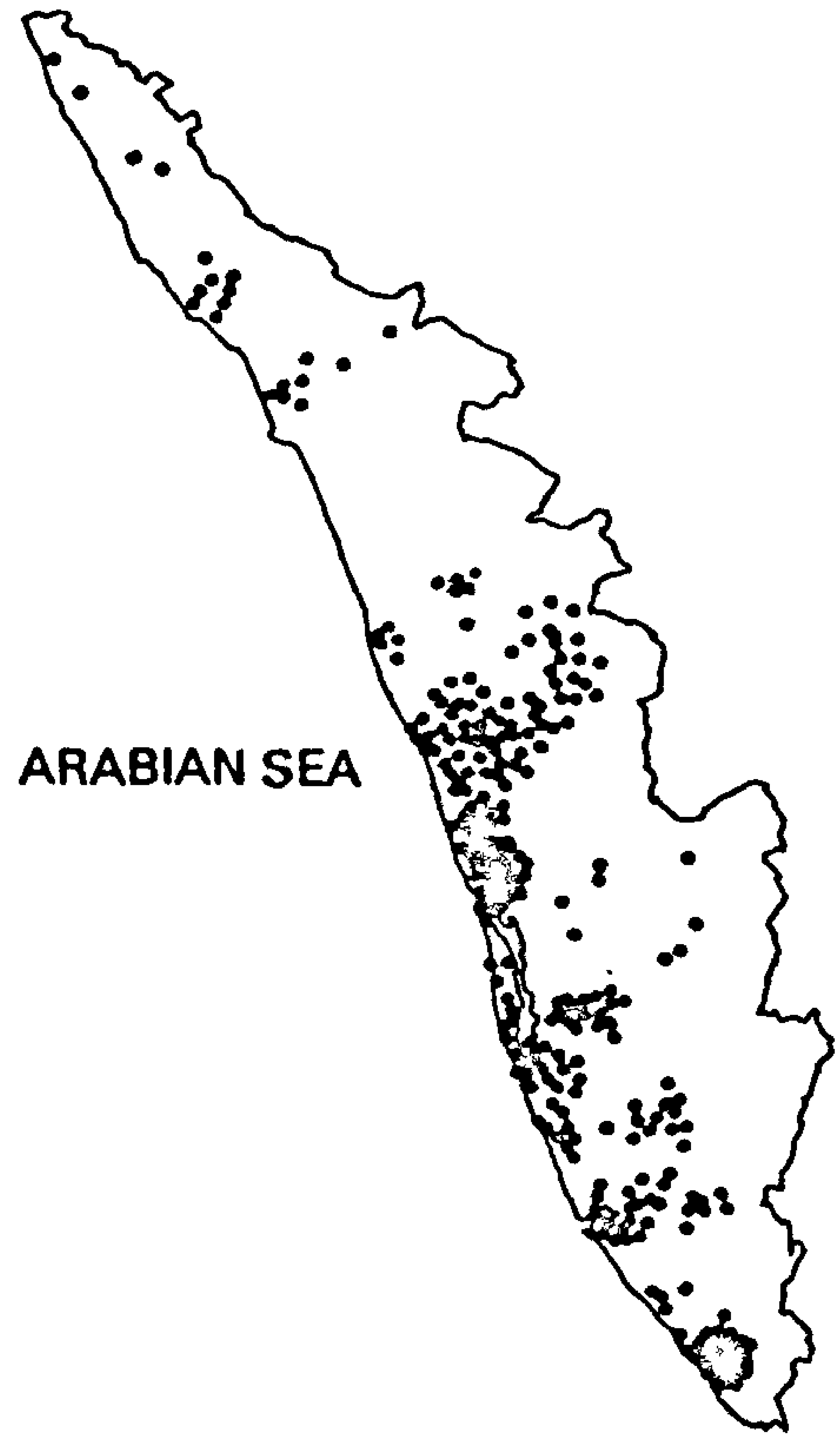

Figure 3. Distribution of places of origin of 300 patients with rheumatic heart disease in Kerala.

The mineral deposits are heaviest in the Chavara and Manavalakurichi sectors of the Kerala coast even though smaller deposits occur in several other places (Figure 4). Among the minerals, monazite is of major economic importance insofar as it provides a rich source of rare earth metals (Table 1). The concentration of monazite in the soil, its percentage composition of elements, grain size and other physicochemical characteristics vary from region to region and determine not only its viability for mining but also its potential for transfer to biosystems.

Cerium among rare earths

Cerium is the most abundant rare earth metal of monazite and exhibits most of the properties of this group of elements known as lanthanides. It is normally trivalent and has the highest solubility among all rare earth metals. It resembles aluminium in chemical properties and pharmacological action and is concentrated 2000 to 4000 times by planktonic algae from sea water[1]. Tubers which grow under the soil concentrate rare earth metals significantly even though the data available relate largely to thorium[2].

Rare earth metals like neodymium and cerium were used therapeutically long ago for their anticoagulant and anti-emetic properties, till their toxicity became known. The toxicity studies carried out on cerium so far involved acute tests of intravenous, intramuscular, intragastric and intracutaneous administration of large doses and the determination of toxicity and cerium levels in the viscera after intervals of as short as four days[3]. Reports are also available on the production of cardiac injury and polycythaemia in small animals by cerium tartrate. However, no investigations seem to have been carried out to assess the toxic effects of the chronic ingestion of low doses of cerium.

Geochemical basis

Serious studies on EMF began at our Institute ten years ago with the regular availability of surgical biopsy material from patients[4]. We soon found that eosinophil counts in patients were no higher than those of controls

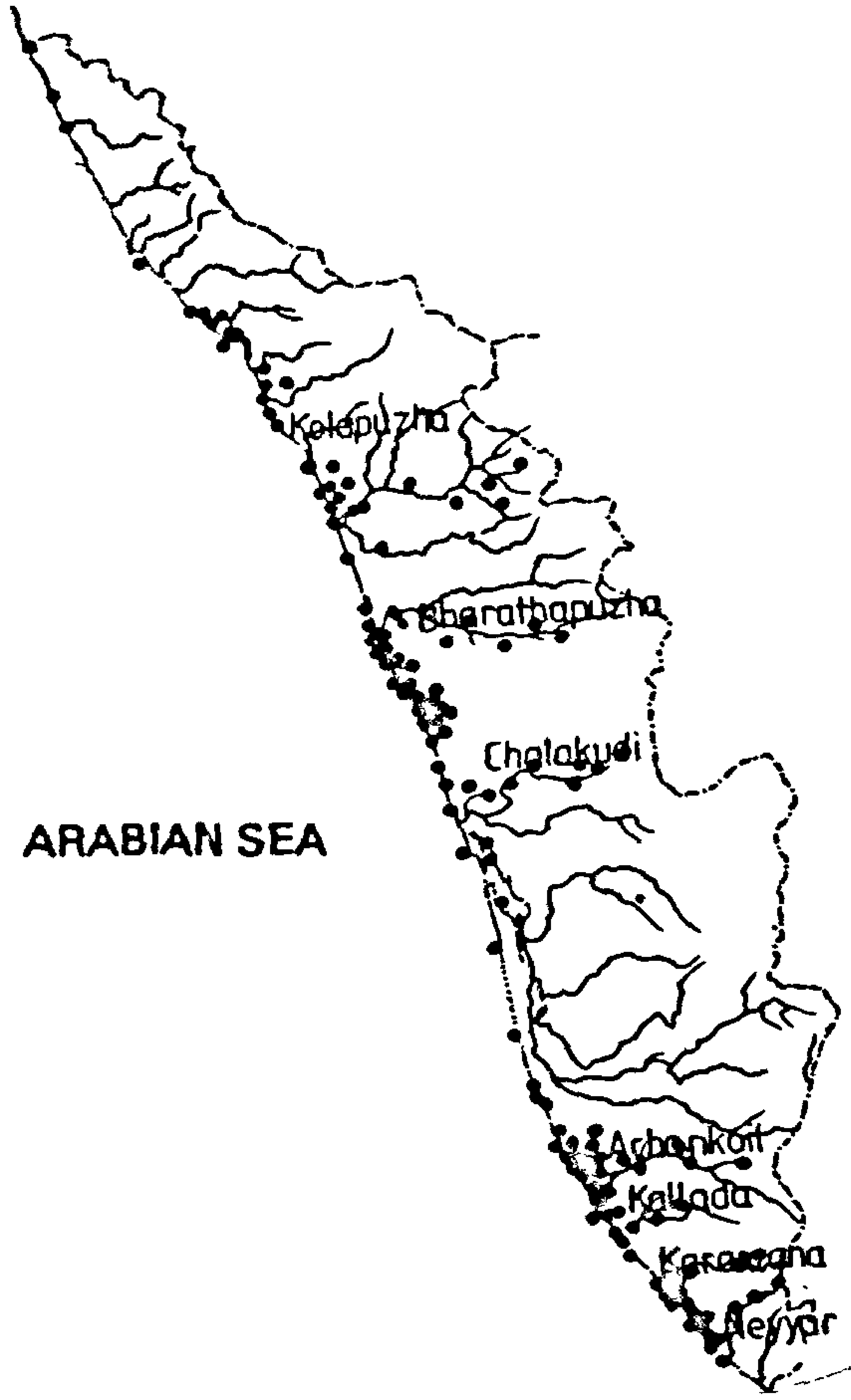

Figure 4. Distribution of monazite sand along Kerala coast

and that eosinophil granule protein could not be demonstrated in the cardiac tissues of patients[5]. It was also observed that EMF is extremely rare in India's hyper-endemic spots for filariasis such as Thanjavur, Orissa and Bihar. These observations and the clinical dissimilarity between EMF and the hyper-eosinophilic syndrome made us sceptical of the causative role of eosinophilia in EMF. On the other hand, the non-random distribution of EMF in Kerala and its spatial coincidence with latasolic soils suggested that geochemical factors could have a causal association with the disease.

To test this hypothesis, endomyocardial tissues obtained from nine patients in whom the diagnosis was established at operation or necropsy were analysed for the elemental constituents of laterite and monazite which are commonly found in the latasolic soils of Kerala. The control samples of endomyocardial tissues were obtained from healthy subjects who had undergone medicolegal necropsies after traffic accidents or homicide. While the tests showed no significant difference between the patients and controls in respect of the levels of potassium, zinc, iron, silicon, aluminium and manganese, the patient samples demonstrated a significantly lower concentration of magnesium and higher levels of sodium, calcium and thorium[6]. A subsequent study showed that the level of cerium in patient samples was higher than that of thorium which was probably no more than an indicator for monazite[7]. Unlike the elevated levels of sodium and calcium which could be explained on the basis of salt retention and the reciprocal response of calcium to magnesium deficiency, the elevation in the levels of thorium and cerium, which have no physiological role, pointed to a possible link between the disease and monazite. The presence of thorium and cerium in conjunction with magnesium deficiency suggested the possibility that EMF could be 'the cardiac expression of an elemental interaction that causes a toxic metal to replace or displace an essential element at the cellular level'. This exchange would be more likely for cerium, which constitutes over 30% by weight of monazite, than thorium which claims only 8.6%. Our investigations on the role of elemental toxicity were therefore focused on cerium.

Table 2. Radioactivity in food crops and sand in Chavara coast[3]

Source	pCi/kg
Paddy	30 0
Drumstick leaves	9 4
Tapioca	876.0
Arwi	296 0
Cucumber	86 0
Papaya	8 6
Monazite sands	277330.0

A hypothesis on the causation of EMF is useful only to the extent it fits in with the diverse observations on the disease and explains its characteristic preference for the tropical zone, for the children of the poor and for the cardiac substrate.

Tropical incidence and monazite elements

Unlike the mountainous regions of Europe, USSR and USA where monazite occurs in sparsely populated areas, the coast of Kerala which is densely populated, has abundant monazite deposits in its sandy soil. In tracing the course of monazite elements to man, tuber crops in the food chain assume importance because they form the staple food of the poor and concentrate rare earths more than other vegetables (Table 2).

In addition to tubers, monazite elements would appear to gain entry by the inadvertent ingestion of raw sand through contaminated food, unclean hands and casual food habits which are associated with small children of coastal families, who play in the sand. As monazite has lower grain size (300 μm) than other minerals in the raw sand it may stick to the skin leading to preferential intake. Moreover, children suffering from helminthiasis and anaemia are known to consume sand. The metabolization of the monazite elements of raw sand in children is shown by the observation that the radioactivity of urine measured in children in Kerala between 5 and 9 years was 21.2 ± 7.1 pCi/L against 10 pCi/L for children between 10 and 14 years which suggests incidentally that older children tend to be more scrupulous about personal hygiene[8]. While the measurement of cerium levels in tubers and urine samples has not yet been made in Kerala, a study carried out in the state of Minas Gerais, Brazil, on the human ingestion of thorium and rare earth elements based on the measurement of these elements in faeces revealed a tandem relationship between thorium and cerium[9]. It is therefore logical to assume that cerium follows the ingestion route of thorium from sand to man in gaining access to the cardiac tissues.

While the presence of monazite elements in the cardiac tissues of EMF patients suggests a basis for the tropical incidence of the disease, the geochemical hypothesis also postulates synergistic mechanisms in its pathogenesis in terms of magnesium deficiency and the replacement of magnesium by cerium[10].

The synergistic role of magnesium

Magnesium deficiency is a common accompaniment of malnutrition and hypomagnesaemia has been reported from Uganda, Brazil and, more recently, Kerala[11, 12] Children are particularly vulnerable because their growth needs of magnesium are higher and their intestinal absorption is impaired by diarrhoeal diseases. The significantly lower level of magnesium in the cardiac tissues of EMF is hardly surprising because patients are invariably poor and suffer from nutritional deficiencies.

Magnesium deficiency produces a variety of pathophysiological changes which spare practically no organ system. The tissue changes reported include perivascular inflammatory cell infiltration, multifocal necrosis or degeneration in skeletal muscles, focal necrosis progressing to scarring in the subendocardium, and calcification in the viscera[13]. However, these generalized changes are absent in EMF which is cardioselective in morphology. The role of magnesium deficiency may therefore be synergistic insofar as it enhances the absorption of cerium and provides binding sites for the toxic element in the myocardium. A similar role has been suggested for magnesium deficiency in amyotrophic lateral sclerosis as well as Alzheimer's disease where it is believed to enhance the toxicity of aluminium[14, 15].

The enhancement of the levels of toxic elements in the presence of magnesium deficiency has been the subject of several studies. Cerklewski showed that experimental magnesium deficiency in gestant rats enhanced the accumulation of tissue lead in both dams and offspring[16]. In monkeys made hypomagnesaemic by the long-term intake of a magnesium-deficient diet, Shivakumar and colleagues demonstrated enhanced levels of cerium in cardiac tissues[17]. Nair and colleagues corroborated these findings by the observation that a plant tuber, *Coleus parviflorus*, grown in a magnesium-deficient medium, increased the concentration of cerium[18].

Interactions of magnesium and cerium

The physico-chemical dissimilarity between the elements raises the question whether the replacement of magnesium by cerium is feasible and whether their observed levels in EMF tissues are coupled functionally. As the two elements differ in physical characteristics such as atomic number, charge, radius and electronic configuration, the possibility of the replacement of magnesium by cerium needs to be critically examined. Toxic elements combine with normal physiological elements by several mechanisms[19] and the likely mechanism for the toxic action of cerium is its substitution of magnesium in the active sites of enzymes. Other examples of this mechanism are the replacement of iron by mercury or lead and magnesium by aluminium. It would appear that physico-chemical differences between magnesium and cerium are less important than their charge radius ratio in determining the replacement of magnesium by cerium. This is because the charge radius ratios of magnesium and cerium are similar (3.03 and 2.09) and the ratio exerts stronger force on the charged sites of biological macromolecules than any single physico-chemical property[20].

Theoretical considerations apart, experimental evidence is available to suggest that magnesium is replaced by cerium under given conditions. Shivakumar and colleagues demonstrated that cerium promoted the binding of creatine-kinase to Cibacron blue F_3GA, the substrate analogue of the enzyme even in the absence of Mg^{2+}, the physiological co-factor[21]. The lower level of magnesium and high concentration of cerium in the cardiac tissues in EMF would appear to be functionally related.

Restriction of lesions to the heart in EMF

Other than the equatorial incidence and the poor nutritional status of patients, the third major feature of EMF is the restriction of histopathological lesions to the heart. The sensitivity and response of tissues to physico-chemical stimuli vary widely and cardiac tissue is no exception. In the study of the differential response of cardiac and skeletal muscle to doxorubicin, which is cardiotoxic, it was shown that the drug selectively and dramatically decreased the levels of mRNA for the sarcomeric genes of cardiac muscle whereas cultured skeletal myocytes were resistant to the effects of doxorubicin at hundred-fold greater doses. The differential response was also reproduced *in vivo* in the study[22]. Therefore, the restriction of tissue changes to the heart in response to a combination of magnesium deficiency and concentration of cerium is not exceptional. Nor does the initial localization of lesions to the subendocardium, inflow or apex of the ventricular chamber militate against a geochemical insult because such changes are among the limited range of cardiac responses to varied challenges. The cardioselectivity in EMF will be better understood with increasing knowledge on the heterogeneity of the biochemical and physiological response of the layers and zones of the myocardium to varied stimuli. This aspect of the differential function of the mural structures of the heart has received increasing attention of late[23, 24].

Whether a combination of magnesium deficiency and enhanced level of cerium will induce tissue changes analogous to those of EMF in an experimental model is the subject of an ongoing study. The geochemical hypothesis will stand only to the extent the model succeeds.

Conclusions .

The geochemical hypothesis pertains to the tropical version of EMF. It ceases to have relevance in the non-tropical world where diverse causes, including cytotoxic drugs and hyper-eosinophilia may produce a cardiac model which resembles EMF. If a combination of bio-inorganic stimuli such as deficiency of magnesium and enhanced levels of cerium can cause myocyte degeneration and enhanced collagen synthesis, which characterize EMF, there is no reason why similar changes would not be induced by other agents of chemical or biological origin. Instead of an identical cause of injury, the unifying link between tropical EMF and its non-tropical analogues may be the uniform response of the cardiac myocyte and interstitium to injury from heterogeneous agents.

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