Genetic Association in Myocardial Infarction

Ethnicity; ABO, Rh, Le^a, Xg^a Blood Groups; G6PD Deficiency; and Abnormal Haemoglobins

N. SAHA,* C. C. S. TOH, and M. B. GHOSH†

Departments of Physiology and Medicine, Faculty of Medicine, University of Singapore, Singapore 3

Summary. Four hundred and eighty-six patients with myocardial infarction of both sexes comprising 213 Chinese, 53 Malays, 199 Indians, and 21 Europeans, resident in Singapore were investigated for differences in relative incidence, and for the ABO, Rh, Le^a, and Xg^a blood groups, G6PD deficiency, and haemoglobin types. Relative incidence of myocardial infarction was appreciably higher among Indians than Chinese and Malays in all age groups, more so in younger people. There was no significant difference in the distribution of the genetic markers between patient and control series in either Chinese, Malays, or Indians.

Results of twin studies are suggestive of some genetic factor involved in the causation of coronary thrombosis (Hauge, 1969) and in recent years an association with ABO blood groups, with a higher incidence among group A persons, has been demonstrated in most of the populations studied and the literature has been reviewed recently by Mourant, Kópéc, and Domaniewska-Sobczak (1971). From this it appears that there might be some epistatic genetic factor involved, though precisely how this might operate is not clear.

Several reports have shown that Chinese have a lower incidence of coronary thrombosis than do either Europeans or Indians (Danaraj *et al.*, 1959; Toh, Low, and Tan, 1970; Barnes, 1972). The multiracial population of Singapore with a population of about two million made up of approximately 76% Chinese, 15% Malays, and 7% Indians seemed to us therefore to offer special opportunities to study some of the ethnic and genetic factors involved in the development of myocardial infarction by analysing the incidence of the disorder in different ethnic groups and looking for possible association of myocardial infarction with the ABO, Rh, Le^a, Xg^a blood groups, G6PD deficiency, and abnormal haemoglobins.

Materials and Methods

Patients. Four hundred and eighty-six consecutive patients of both sexes comprising 213 Chinese, 53 Malays, 199 Indians, and 21 Europeans admitted to the Coronary Care Unit of Medical Unit II and to wards of Medical Unit I of the General Hospital, Singapore between December 1969 and December 1971, formed the sample. These were all cases of myocardial infarction as confirmed by clinical, electrocardiographic, and biochemical investigations.

Controls. For ABO blood groups the published data for blood donors of the Singapore Blood Transfusion Service was taken as control (Chan, 1962). For control series for abnormal haemoglobins, G6PD deficiency, and Xg^a blood group our data, previously published for healthy individuals (matched for race and sex) attending the Singapore Anti-Tuberculosis Association for Employees Health Insurance Scheme were used (Saha and Banerjee, 1971a and b; 1973). Another series of healthy individuals (matched for race and sex) from the same source was investigated for Rh and Le^a blood groups.

Methods. Blood was collected in fasting condition from each patient between the third and fifth day after the infarction using heparin as an anticoagulant. Blood was stored at 4°C and was tested within 48 hours of collection. Routine blood grouping was carried out by slide test using commercial antisera.* The details of Xg^a blood grouping, G6PD deficiency, and haemoglobin typing were the same as published previously (Saha, 1969 and 1970; Saha and Banerjee, 1973).

Received 30 May 1973.

* Present address: Department of Human Biology, The John Curtin School of Medical Research, The Australian National University, P.O. Box 334, Canberra City, ACT 2601, Australia.

† Dr M. B. Ghosh died on 25 February 1972 before this work was completed.

* Biotest, USA.

TABLE I
DISTRIBUTION OF MYOCARDIAL INFARCTION

Group	Population of Singapore (1970 Census)		Patients	
	No. (in thousands)	%	No.*	%
Chinese	1579.8	76.15	213 (175m + 38f)	43.83
Malays	311.4	15.01	53 (49m + 4f)	10.91
Indians	145.2	7.00	199 (194 + 5f)	40.94
Others	38.1	1.84	21 (19m + 2f)	4.32
Total	2074.5	100.00	486 (437m + 49f)	100.00

* m = male; f = female.

Results and Discussion

Table I shows that Indians* represent 40.9% of all myocardial infarction cases though they contribute to only 7.0% of the population. On the other hand, Chinese constitute only 43.8% of the patients though they represent 76.1% of the population and Malays represent 10.9% of the patient series against a population contribution of 15.0%. Patients of European descent form 4.3% of the patient series (in the total population Europeans are included in other ethnic groups which make up only 1.8%) but because of the small absolute number they have been excluded from further considerations. From the figures for the three main ethnic groups in the Singapore population it is very suggestive that the relative incidence of myocardial infarction is low among Chinese and Malays com-

* Indians also include Pakistanis and Ceylonese.

pared to that for Indians being 0.1 and 0.125, respectively.

The male/female ratio for myocardial infarction in the present series is 4.6 in Chinese, 12.2 in Malays, and 38.8 in Indians. Toh *et al* (1970) reported a lower male/female ratio for all three ethnic groups. However it may be noted that male/female ratio of Indians in the general population is disproportionately high in higher age groups, which may partly explain the high sex ratio in Indians.

Table II shows the relative age-specific incidence of myocardial infarction in different ethnic groups in males only. Females have been excluded as the number is too small. Relative incidences have been presented per thousand population in 10-year age groups. It is seen that in all age groups the relative incidence of myocardial infarction is higher in Indians than in Chinese and Malays. Another interesting aspect revealed is that there is a higher relative incidence of the disease in younger people among Indians than in Chinese and Malays. The significance of the higher relative incidence of myocardial infarction among Indians is not apparent at the moment, but is in agreement with previous reports (Danaraj *et al*, 1959; Toh *et al*, 1970; Barnes, 1972).

Plasma-cholesterol and plasma-triglycerides are known to be important risk factors for myocardial infarctions (Kannel, Gastelli, and McNamara, 1967; Carlson and Böttiger, 1972). It would be expected that Indians with higher relative incidence of myocardial infarction will have higher levels of those plasma lipids. However, in previous studies in Singapore and Malaya no significant differences of serum total cholesterol levels, lipid phosphorus, triglycerides, and lipoprotein levels were found between Chinese, Malay, and Indians either in healthy

TABLE II
AGE-SPECIFIC INCIDENCE OF MYOCARDIAL INFARCTION (MALES ONLY)

Age (yr)	Chinese			Malays			Indians		
	Population* (in thousands)	Patients		Population* (in thousands)	Patients		Population* (in thousands)	Patients	
		No.	No./Thousand		No.	No./Thousand		No.	No./Thousand
20-29	135.2	1	0.007	21.3	0	0	10.4	6	0.577
30-39	95.1	16	0.168	17.0	10	0.588	11.4	31	2.719
40-49	68.0	37	0.544	15.8	23	1.456	16.4	77	4.695
50-59	51.9	64	1.233	8.3	8	0.964	10.0	59	5.900
60-69	33.9	47	1.386	3.8	7	1.842	3.1	15	4.839
70 and over	11.8	10	0.847	1.3	1	0.769	0.7	6	8.571
Total	395.9	175	0.442	67.5	49	0.726	52.0	194	3.731

* 1970 Census.

TABLE III
DISTRIBUTION OF ABO BLOOD GROUPS IN 463 PATIENTS WITH MYOCARDIAL INFARCTION

Blood Groups	Chinese		Malays		Indians	
	No. of Controls*	No. of Patients	No. of Controls*	No. of Patients	No. of Controls*	No. of Patients
O	6644 (43.53%)	91 (42.72%)	2098 (38.42%)	20 (39.22%)	1951 (39.02%)	68 (34.17%)
A	3967 (25.99%)	54 (25.35%)	1369 (25.07%)	13 (25.49%)	1051 (21.02%)	52 (26.13%)
B	3814 (24.99%)	50 (23.48%)	1596 (29.22%)	13 (25.49%)	1680 (33.60%)	57 (28.64%)
AB	837 (5.49%)	18 (8.45%)	398 (7.29%)	5 (9.80%)	318 (6.36%)	22 (11.06%)
Total	15,262	213	5461	51	5000	199

* Chan (1962).

individuals or patients with myocardial infarction (Chong, 1961/1962; Davies and Willsher, 1961/1962; Lau, Lopez, and Gan, 1961/1962; Chong *et al.*, 1971).

Table III shows the distribution of ABO blood groups in Chinese, Malay, and Indian patients compared to normal controls. There is no significant difference in the distribution of ABO blood groups between patient and control series in any of the ethnic groups. Most of the populations studied, including two Indian series (Bronte-Stewart, Botha, and Krut, 1962; Srivastava, Thakur, and Das, 1966) had a higher incidence of myocardial infarction among those with blood group A. There is no published data for Chinese and Malays. However, there is a higher incidence of myocardial infarction among Indians with blood group A, but the association is only significant at the 5% level if half of AB is taken into account ($A:O = 1.42$ [$p > 0.05$]; $A + \frac{1}{2}AB:O = 1.49$ [$p < 0.05$]). However the possibility remains that there is higher mortality among A-group individuals compared to those who survived the attack of myocardial infarction. Furthermore, preliminary studies of prehospital deaths from acute myocardial infarction suggest that as many patients die outside the hospital as in hospital.

It has been reported that Le(a+) individuals have higher serum cholesterol than Le(a-) persons (Langman *et al.*, 1969) and one would expect therefore higher incidences of Le(a+) persons amongst myocardial infarction patients. However, Table IV shows the distribution of Le^a blood group in 184 patients with myocardial infarction and 425 healthy individuals of three ethnic groups with no significant differences in any of the ethnic groups between the disease and control series. Further work with larger series is needed for a valid conclusion.

Table V shows the distribution of the Rh(D) blood group of 354 patients with myocardial infarction and 615 healthy individuals. There was again no significant difference in the frequency of Rh(D) between patient and control series. Out of these, 64 patients and 165 controls were tested with five anti-sera (D, C, E, c, and e): there was no significant difference in the frequency distribution of the Rh subtypes.

Tables VI, VII, and VIII show the distribution in patients and controls of abnormal haemoglobins, G6PD deficiency, and Xg^a blood groups, respectively. There was also no significant difference in the frequency distribution of these genetic parameters between myocardial infarction and control series in any of the three ethnic groups.

TABLE IV
DISTRIBUTION OF Le^a BLOOD GROUP IN 184 PATIENTS WITH MYOCARDIAL INFARCTION

Group	Controls			Patients		
	No.	Le(a+) No.	Le(a-) No.	No.	Le(a+) No.	Le(a-) No.
Chinese	214	33 (15.42%)	181 (84.58%)	87	19 (21.84%)	68 (78.16%)
Malays	93	23 (24.73%)	70 (75.27%)	24	4 (16.67%)	20 (83.33%)
Indians	118	25 (21.19%)	93 (78.81%)	73	18 (24.66%)	55 (75.34%)
Total	425	81 (19.06%)	344 (80.94%)	184	41 (22.28%)	143 (77.72%)

TABLE V
DISTRIBUTION OF Rh(D) BLOOD GROUP IN 354 PATIENTS WITH MYOCARDIAL INFARCTION

Group	Controls			Patients		
	No.	Rh +	Rh -	No.	Rh +	Rh -
		No.	No.		No.	No.
Chinese	237	235 (99.16%)	2 (0.84%)	169	169 (100.00%)	0
Malays	148	148 (100.00%)	0	42	42 (100.00%)	0
Indians	230	220 (95.65%)	10 (4.35%)	143	136 (95.10%)	7 (4.90%)
Total	615	603 (98.05%)	12 (1.95%)	354	347 (98.02%)	7 (1.98%)

TABLE VI
INCIDENCE OF ABNORMAL HAEMOGLOBINS IN 463 PATIENTS WITH MYOCARDIAL INFARCTION

Group	Controls			Patients		
	No.	Abnormal Haemoglobin		No.	Abnormal Haemoglobin	
		No.	Type		No.	Type
Chinese	1102	7 (0.64%)	AE-7	213	1 (0.47%)	AE
Malays	308	17 (5.52%)	AE-16; AH-1	51	1 (1.96%)	AE
Indians	2455*	27 (1.10%)	AD-8; DD-1; AE-11; EE-2; AH-4; AF-1	199	0	—
Total	3865	51 (1.32%)		463	2 (0.43%)	

* Saha and Banerjee (1971b).

TABLE VII
INCIDENCE OF G6PD DEFICIENCY IN 364 MALE PATIENTS WITH MYOCARDIAL INFARCTION

Group	Controls		Patients	
	No. Tested	No. Deficient	No. Tested	No. Deficient
Chinese	577	21 (3.64%)	167	5 (3.00%)
Malays	232	8 (3.45%)	39	0
Indians	362	6 (1.66%)	158	4 (2.53%)
Total	1171	35 (2.99%)	364	9 (2.47%)

Two aspects of the results emerging from the present study require clarification. The first concerns the striking difference in the relative incidence of myocardial infarction among Indians when compared with Chinese and Malays living in the same urbanized environment; the second concerns the failure to demonstrate the excess of blood group A among myocardial infarcted patients in any of the three ethnic groups studied here. High incidence of myocardial infarction has been reported in Indians in India also (Padmavati, Gupta, and Pantulu, 1959; Sarvotham and Berry, 1968).

The increased incidence of myocardial infarction amongst Indians confirms reports by other investigators, but it does not elucidate the reasons for this striking difference in the present report and other instances between the Indians on the one hand and Malay and Chinese on the other (Danaraj *et al*, 1959; Toh *et al*, 1970; Barnes, 1972). Though genetic factors predisposing to myocardial infarction may be involved the fact that many investigations have attempted to implicate dietary difference as the main aetiological factor explaining susceptibility to myocardial infarction does suggest that this may be a factor in the Singapore situation (Keys and White, 1958).

Superficially there are similarities in the dietary patterns of Indians and Chinese in Singapore. Both are rice eaters and both use more or less the same basic ingredients of food. There is, however, a striking difference in the manner in which food is prepared by the Indian and Chinese communities; the former use mostly food fried in cooking oil such as coconut oil, ghee, etc, which are high in saturated fats, whereas the latter use mostly boiled or steamed food and such oil used (ground nut oil, soya bean oil, linseed oil, and lard) is high in polyunsaturated fats.

TABLE VIII
DISTRIBUTION OF THE Xg^a BLOOD GROUP IN 145 MALE PATIENTS
WITH MYOCARDIAL INFARCTION

Group	Controls*			Patients		
	No.	No. with Xg(a+)	No. with Xg(a-)	No.	No. with Xg(a+)	No. with Xg(a-)
Chinese	87	41 (47.13%)	46 (52.87%)	63	28 (44.44%)	35 (55.56%)
Malays	49	28 (57.14%)	21 (42.86%)	17	10 (58.82%)	7 (42.18%)
Indians	85	48 (56.47%)	37 (43.53%)	65	32 (49.23%)	33 (50.77%)
Total	221	117 (52.94%)	104 (47.06%)	145	70 (48.28%)	75 (51.72%)

* Saha and Banerjee (1973).

A substantial proportion of the Indian population in Singapore is still almost exclusively vegetarian, almost none of the protein in their diet coming from animal sources. Chong (1961/1962) quoted the percentage of calories derived from fat as 11.4% to 18.3% for Malay army and police personnel, 15.8% for Indian estate labourers, and 16.7% for Chinese labourers; these are very selective, low-income groups and do not represent the populations as a whole. However, we have recorded an intake of about 30% of calories from fat in medical students and police forces, mostly of Chinese origin, of both sexes and in pregnant and non-pregnant women during our study of energy metabolism in Singapore (Banerjee and Saha, 1970; Banerjee, Tan, and Saha, 1972). Wysham, Kohli, and Mulholland (1970) reported an intake of 29.5% of calories as fat in a Punjabi population; about 90% of which was saturated fat. In an early study of diet (by chemical analysis) in India a similar fat intake was observed (Banerjee, Lal, and Saha, 1965). Furthermore, Malmros and Wigand (1957) and Bronte-Stewart (1958) have reported the serum cholesterol raising effect of coconut oil in man when fed on fat levels of about 40% of total calories. It will be of interest to investigate further, in more detailed studies, the serum lipids in cases of myocardial infarction and in matched healthy controls from the three ethnic groups in Singapore. Such a study should include persons in all age groups and involve a simultaneous search for association of serum lipid levels with genetic markers.

The present study has failed to reveal any significant association between myocardial infarction and any of the genetic markers investigated, with the exception of the A factor of the ABO blood group system when this is considered together with AB group individuals among Indians. By itself a single significant association of this kind would not be noteworthy, since a large number of comparisons were carried out and it would be expected that some

at least of these would show a significant difference at the 5% level. However it is of interest that the deviation between the myocardial infarction patients and controls is in the direction of an excess of group A among Indian patients as recorded in a number of other independent investigations (Mourant *et al*, 1971). It is possible that a larger series in Singapore would make the association between group A and myocardial infarction statistically significant, at least in Indians.

The authors are grateful to the Medical Superintendent of the General Hospital, Singapore for permission to carry out this study and to Dr R. L. Kirk and Professor H. M. Whyte for their help in the preparation of this manuscript. Thanks are also due to Miss B. Lowrie for secretarial assistance.

REFERENCES

- Banerjee, B., Lal, D. C., and Saha, N. (1965). Calorie intake of male and female adult healthy middle-class Indians in summer and winter months. *Calcutta Medical Journal*, **62**, 119-122.
- Banerjee, B. and Saha, N. (1970). Energy cost of some common daily activities of active tropical male and female subjects. *Journal of Applied Physiology*, **29**, 200-203.
- Banerjee, B., Tan, P. Y., and Saha, N. (1972). Calorie and nutrient intake of pregnant Asian women. *Tropical and Geographical Medicine*, **24**, 249-252.
- Barnes, R. J. (1972). Associated factors in coronary artery disease in the Chinese. *Asian Journal of Medicine*, **8**, 419-424.
- Bronte-Stewart, B. (1958). The effect of dietary fats on the blood lipids and their relation to ischaemic heart disease. *British Medical Bulletin*, **14**, 243-252.
- Bronte-Stewart, B., Botha, M. C., and Krut, L. H. (1962). ABO blood groups in relation to ischaemic heart disease. *British Medical Journal*, **1**, 1646-1650.
- Carlson, L. A. and Böttiger, L. E. (1972). Ischaemic heart disease in relation to fasting values of plasma triglycerides and cholesterol. *Lancet*, **1**, 865-868.
- Chan, K. T. (1962). The ABO blood group frequency distribution of Singapore based on a blood donor sample. *Singapore Medical Journal*, **3**, 3-15.
- Chong, Y. H. (1961/1962). Serum lipids and lipoproteins in healthy Malaysians. *Medical Journal of Malaya*, **16**, 136-143.
- Chong, Y. H., Soh, C. C., Ho, G. S., Rajaratnam, R., and Nonis, P. (1971). Serum low density lipoproteins, triglycerides and cholesterol levels in Malaysia. *Clinica Chimica Acta*, **34**, 85-92.
- Danaraj, T. J., Acker, M. S., Danaraj, W., Wong, H. O., and Tan, B. Y. (1959). Ethnic group differences in coronary heart disease in Singapore—an analysis of necropsy records. *American Heart Journal*, **58**, 516-526.

- Davies, T. A. L. and Willsher, J. D. (1961/1962). Plasma cholesterol levels in first, second and third generation of Chinese and Tamil Indians in Singapore. *Medical Journal of Malaya*, **15**, 97-101.
- Hauge, M. (1969). Quoted by Carter, C. O. in An ABC of medical genetics: I—Genetics in the aetiology of disease. *Lancet*, **1**, 1014-1016.
- Kannel, W. B., Castelli, W. P., and McNamara, P. M. (1967). The coronary profile: 12 year follow-up in the Framingham study. *Journal of Occupational Medicine*, **9**, 611-619.
- Keys, A. and White, P. O. (1958). *Cardiovascular Epidemiology*, Hoeben-Harper, New York.
- Langman, M. J. S., Elwood, P. C., Foote, J., and Ryrle, D. R. (1969). ABO and Lewis blood groups and serum cholesterol. *Lancet*, **2**, 607-609.
- Lau, K. S., Lopez, C. G., and Gan, O. M. (1961/1962). Serum cholesterol levels in Malays, Indians and Chinese in Malaya. *Medical Journal of Malaya*, **16**, 184-192.
- Malmros, H. and Wigand, G. (1957). The effect of serum-cholesterol of diets containing different fats. *Lancet*, **2**, 1-8.
- Mourant, A. E., Képéc, A. C., and Domaniewska-Sobczak, K. (1971). Blood groups and blood clotting. *Lancet*, **1**, 233-228.
- Padmavati, S., Gupta, S., and Pantulu, G. V. (1959). Dietary fat, serum cholesterol levels and incidence of atherosclerosis in Dehli. *Circulation*, **19**, 849-855.
- Saha, N. (1969). Incidence of G-6-PD deficiency in patients of three different ethnic groups suffering from pulmonary tuberculosis. *Journal of Medical Genetics*, **6**, 292-293.
- Saha, N. (1970). Prevalence of abnormal haemoglobins in pulmonary tuberculosis in three different ethnic groups. *Journal of Medical Genetics*, **7**, 44-46.
- Saha, N. and Banerjee, B. (1971a). Erythrocyte G-6-PD deficiency among Chinese and Malays of Singapore. *Tropical and Geographical Medicine*, **23**, 141-144.
- Saha, N. and Banerjee, B. (1971b). Incidence of abnormal haemoglobins in different ethnic groups of Indians. *Humangenetik*, **11**, 300-303.
- Saha, N. and Banerjee, B. (1973). Xg^a blood groups in Chinese, Malays and Indians in Singapore. *Vox Sanguinis*, **24**, 542-544.
- Sarvotham, S. G. and Berry, J. N. (1968). Prevalence of coronary heart disease in an urban population in Northern India. *Circulation*, **37**, 939-953.
- Singapore (1971). *Census 1970*. Government Printing Office, Singapore.
- Srivastava, D. K., Thakur, C. P., and Das, M. (1966). ABO-blood groups in relation to ischaemic heart disease. *Indian Heart Journal*, **18**, 140-149.
- Toh, C. C. S., Low, L. P., and Tan, Y. T. (1970). Some aspects of the epidemiology of cardio-vascular diseases in Singapore. In *Proceedings of the Fourth Asian Pacific Congress of Cardiology, 1968*, pp. 43-47, ed. by M. Eliakim. Academic Press, London and New York.
- Wysham, D. N., Kohli, K. C., and Mulholland, S. (1970). Coronary risk factors in Northern India. *American Heart Journal*, **79**, 181-187.