Treponemal serology and blood groups on Bali island, Indonesia

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SUMMARY As part of a multidisciplinary study of the population of Bali, Indonesia,¹ 2452 blood samples from people of both sexes were tested for treponemal infection and blood groups. Analysis of blood groups of the 81 patients reactive to the *Treponema pallidum* immobilisation (TPI) test, who were considered to have latent or inactive yaws, compared with a control group of 552 healthy Balinese, showed that the ratio of MM to MN and NN phenotypes was 2.25 times higher in the patients than in the controls ($\chi^2_1 = 10.2$, $p < 0.005$). A speculative hypothesis is that yaws infection gives people with the MM phenotype a lower selective fitness. This hypothesis could explain the low prevalence of the M gene in the Australo-Melanesian populations.

Introduction

There is great genetic polymorphism of red cell antigens and red cell enzymes in human populations. In many cases, however, we understand incompletely the difference in prevalence of genes between one population and another. Some diseases are clearly known to act as selective agents for such differences — for example *Plasmodium falciparum* malaria may increase the prevalence of haemoglobin S.²

Yaws is a non-venereal treponemal disease caused by *Treponema pertenue* and, until eradication campaigns, it was found in all the humid tropical countries of Africa and Asia. Steinbock reviewed the evidence of yaws infection in human bones from Australia, Melanesia and Polynesia.³ Whether the present four human treponematoses are different ecological variants of the same disease or have arisen by mutation from one another is still not known.^{4,5} Hackett suggested that pinta was the earliest human trepanomatos, which spread throughout the world before 15 000 BC, and was subsequently isolated in the Americas when the Behring Strait was flooded.⁵ Around 10 000 BC, in the Afro-Asian land mass, environmental conditions might have favoured muta-

tions of treponemes, which caused yaws. According to Hackett, around 7000 BC endemic syphilis developed, which gave rise to venereal syphilis around 3000 BC in south west Asia as large cities developed there.⁵ Figure 1 shows the probable extent of yaws around 7000 BC.

Has trepanematos acted as a selective agent on blood groups? Vogel and Motulsky tried to find evidence of the role of syphilis as a selective agent on the ABO blood group system.² They concluded that data suggested that people with blood group O had a more efficient immune response to the disease. Mourant *et al* reviewed the data about associations between yaws and the ABO system: none was significant.⁶ Though data for the MN system were not available for yaws, its association with syphilis was not appreciable.

The polymorphism of the MN system in the tropics is shown by two zones where the N gene is more common than the M gene.⁷ One zone includes the eastern islands of Indonesia, New Guinea, insular Melanesia, and Australia; the other includes western and equatorial Africa (fig 2).

Patients and methods

The blood sampling was undertaken in Bali between 1978 and 1981. The technical methods used were those of Race and Sanger for blood groups,⁸ and of Ney *et al* for treponemal serology.¹

The Balinese population consists of more than 2 500 000 inhabitants, who can be roughly divided into

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FIG 1 World map showing, in black, probable extent of yaws around 7000 BC (after Hackett⁵).

FIG 2 World map showing, in black, where *N* gene is more common than *M* gene in indigenous populations (after Mourant *et al*⁷).

peasants and high caste groups. The peasants, who form more than 95% of the population, live in villages. We tested 1118 students of both sexes, aged 16 to 29, in the 10 main towns of the island. From this popula-

tion we selected a sample of 552 peasant students, who were representative of the village population of the various regencies (administrative and geographical areas) of Bali. This sample can be considered to be a

fair representation of the prevalence of the blood groups in the rural population of Bali. We also tested 1334 villagers of both sexes (mean age 40.8 years for men and 40.7 years for women) from different locations in all the regencies of the island.

Results

The 552 peasant students were used as the control group. None gave positive result to the *T pallidum* immobilisation (TPI) test. Of the 1334 villagers tested, 81 gave positive results and 92 were considered as having false positive results. Our previous paper concluded that these positive patients were probably infected by old inactive or latent yaws.¹

Table I shows the blood groups of patients with posi-

tive or biological false positive results and of controls. Most striking was the high incidence of the MM phenotype in patients with positive results to the TPI test (6.7%), compared with that of the control group (47%), a difference of 20%.

In table II, we analysed these data according the χ^2 standard method,^{2,6} comparing the ratio of MM to MN and NN phenotypes in the 81 patients with that in the 552 controls. The relative incidence between the two ratios was 2.25; in other words, in the Balinese population, a MM phenotype person is 2.25 times as likely as an MN or NN phenotype person to be reactive to the TPI test. The difference of the relative incidence from the postulated unity was significant ($\chi^2 = 10.42$, $p < 0.005$). The result of the test led us to reject the hypothesis of a similarity between the two groups according to the distribution of the MM system

TABLE I Blood groups and gene prevalencies of patients giving positive and biological false positive results to the *Treponema pallidum* immobilisation (TPI) test and of controls

Blood groups by systems	Positive (n=81)		Biological false positive (n=92)		Controls (n=552)*	
	No (%)	Distribution of gene prevalence†	No (%)	Distribution of gene prevalence†	No (%)	Distribution of gene prevalence†
ABO system:						
Group O	47 (58.0)		41 (44.6)		265 (48.1)	
A ₁	13 (16.1)		12 (13.0)		73 (13.3)	
B	18 (22.2)		30 (32.6)		181 (32.8)	
A ₁ B	3 (3.7)		9 (9.8)		32 (5.8)	
Gene p ₁		0.104		0.120		0.100
q		0.139		0.237		0.216
r		0.757		0.643		0.684
MN system:						
Group MM	54 (66.7)		47 (51.1)		260 (47.1)	
MN	22 (27.2)		33 (35.9)		234 (42.4)	
NN	5 (6.2)		12 (13.0)		58 (10.5)	
Gene M		0.802		0.690		0.683
N		0.198		0.310		0.317
P system:						
Group P ₁	21 (25.9)		21 (22.8)		183 (33.2)	
Gene P ₁		0.139		0.122		0.182
Rh system:						
Group CCDEE	0 (0)		0 (0)		1 (0.2)	
CCDEe	1 (1.2)		0 (0)		5 (0.9)	
CCDee	54 (66.7)		63 (68.5)		394 (71.5)	
CcDEE	0 (0)		0 (0)		1 (0.2)	
CcDEe	12 (14.8)		15 (16.3)		79 (14.3)	
CcDee	12 (14.8)		13 (14.1)		58 (10.5)	
ccDEE	1 (1.2)		0 (0)		6 (1.1)	
ccDee	1 (1.2)		0 (0)		7 (1.3)	
Gene R ₂ (CDE)		0.007		0.003		0.008
R ₂ (CDe)		0.820		0.843		0.844
R ₂ (cDE)		0.086		0.082		0.089
R ₀ (cDe)		0.087		0.072		0.059
Duffy system:						
Group Fy (a+)	81 (100)		80 (96.7)		544 (98.6)	
Gene Fy ^a		1.000		0.819		0.880

* 551 for ABO and Rh systems.

† Derived from maximum likelihood estimations.

TABLE II Association between patients with MM phenotype and those reactive to *Treponema pallidum* immobilisation (TPI) test

	No (%) with phenotype:		Relative incidence
	MM	MN or NN	
Patients positive to TPI test (n=81)	54 (67)	27 (33)	2.25
Controls negative to TPI test (n=552)	260 (47)	292 (53)	

χ^2 test for difference from unity: 10.42; significance $p < 0.005$.

phenotypes. An association between reactivity to the TPI test and the presence of the MM phenotype therefore seems probable.

Conclusion

Our data show that, in the Balinese population, people who react to the TPI test have a higher prevalence of the MM phenotype. If this observation were to be confirmed by further studies, we suggest that yaws could act as a negative selective agent, specially for people with the MM phenotype because this group would have a higher prevalence of the disease. That could lead, after numerous generations, to a decrease in prevalence of the M gene in populations in areas where yaws is endemic. This hypothesis could explain the low prevalence of the M gene among the Australo-Melanesian populations that have lived in an area of endemic yaws for more than 10 000 years. The Indonesian populations, like the Balinese, arrived much later in this area and have therefore undergone a shorter selective mechanism.

As shown by comparing figures 1 and 2, the current division of populations in which the N gene is more common than the M gene is compatible with our hypothesis. Menozzi *et al* (unpublished observation) have also shown that the prevalence of the Ns gene correlated positively with high maximum and minimum temperatures and rainfall, the climatic conditions necessary for the appearance of yaws. Further studies will obviously be needed to corroborate this hypothesis.

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