DISTRIBUTION OF THE SICKLE CELL GENE*

A NEW LIGHT ON THE ORIGIN OF THE EAST AFRICANS

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PROFESSOR JAMES HERRICK of Chicago, whose place in medical history is secure for his work on .coronary sclerosis, reported in 1910 a curious finding in a Negro student with chronic anæmia. Whereas normally the red cells of the blood seen under the microscope have the appearance of round discs, in this patient numerous elongated " sickle " shaped forms could be seen. These Professor Herrick called sickle cells. The anæmia associated with these cells was called sickle cell anæmia. It was soon found that many other Negroes harboured these abnormal cells, and that more often than not there was no association with an anæmia. They could be produced *in vitro* by incubating blood anærobically and it was found that blood cells from many Negroes might look perfectly normal when fresh but would take on the sickle cell shape on incubation. Individuals in whom the sickle cells could thus only be demonstrated by artificial measures in the laboratory were called sickle cell trait carriers. It was demonstrated only recently by Professor Linus Pauling in the California Institute of Technology (1950) that sickle cells contain a hæmoglobin which differs in its physical properties from normal adult hæmoglobin and Pauling and his colleagues separated the two by electrophoresis.

In 1923 Huck showed in Baltimore that the sickling phenomenon was inherited as a Mendelian dominant. Numerous investigations were made in the U.S.A. to define the incidence and racial distribution of the sickle cell hæmoglobin. About 10 per cent of American Negroes were found to be " sicklæmic " but other races did not seem to harbour the gene. Occasionally findings were made in people of European descent, but a Negro ancestry could never be ruled out to everyone's satisfaction.

In Africa there were occasional reports of sicklæmia from the Sudan and West Africa but not until the second world war were large-scale surveys undertaken. R. W. Evans published his results in 1944 and 1945 and reported a 20 per cent incidence of sicklæmia in 561 Africans from Nigeria, the Cameroons, the Gold Coast and Gambia. G. M. Findley and his collaborators, also from West Africa, published in 1946 a survey of several thousand individuals and found a similar frequency of the gene; an analysis of their material according to tribal origin did not suggest that the trait was of ethnological significance. H. C. Trowell found sickle cells in East Africa in 1945 and Altmann reported in 1945 their absence in South African Negroes. Beet in 1946 found an incidence of about 12 per cent in Northern Rhodesia and he reported that there were less sickle cells in the Balovale south of the River Zambezi than in those on its north bank; he suggested that this might indicate that the trait had come from the North and that the river had acted as a barrier against its spread southwards.

There were reports that sickle cells had been found in a number of non-Negro populations and even in certain species of deer. These were usually shown to be based on artefacts. The sickling phenomenon was shown in 1950-51 by M. F. Perutz and his colleagues to be due to a peculiar physical property of the sickle cell (S) hæmoglobin. Whereas normal adult (A) hæmoglobin is equally soluble whether oxygenated or reduced, S hæmoglobin is quite insoluble in its reduced form. When S hæmoglobin containing cells is reduced either by incubation without access of air—when the oxygen is used up by the leucocytes of the blood—or by addition of reducing agents, the hæmoglobin crystallizes inside the cells and the resulting " tactoids " distort the cell and give it the bizarre shape of the " sickle cell." It is obvious that other external stresses such as

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the drying of a blood film can produce very similar distortions and some experience in the recognition of sickle cells is required to differentiate between " true " and " false " sickling (Fig. 1). However the development of the technique of paper electrophoresis enables us nowadays to make a clear-cut definite distinction between normal and S hæmoglobin containing cells (Fig. 2).

Uganda.

The writer investigated the sickle cell trait in Uganda and Tanganyika together with Mr. A. H. Milne in 1949. To our surprise we found a very much higher incidence than had up to then been reported in East Africa. Dr. A. B. Raper, working in Kampala, Uganda, had found it to be 11 per cent, whereas we found it to be at least twice as high in Uganda, and in Tanganyika the incidence was 35 per cent. When we compared our results with those of Raper more closely it struck us that we had examined different tribes. Raper's figures were derived from hospital post-mortems at Kampala and ours in Uganda from a survey of local schools. The post-mortem material in the Kampala Government hospital deals predominantly with immigrant labourers who come from Ruanda Urundi and who are quite different from the local Baganda, who tend to remove their relations from hospital before they die (Fig. 3). The Banyaruanda, though Bantu speaking, are in appearance much more Europoid. We therefore decided to examine Baganda and Banyaruanda separately and found that there were considerable differences, the percentage of sicklæmia in the Baganda was 19 and in the Banyaruanda 8. We then decided to make a tribal survey of sicklæmia of Uganda. This country lies at the point of contact of several ethnological groups, in particular the Nilotes, Half Hamites and Bantu. Thus widely differing tribes could be studied within a comparatively small area. Nearly 5,000 persons belonging to twenty-four tribes about one in 1,000 of the population of the Uganda protectorate were examined (H. Lehmann and A. B. Raper, 1949). Every possible precaution was taken to obtain true random samples as it was realized that the African way of life tends to create genetic " isolates " within the same tribe. (Lehmann, 1951.)

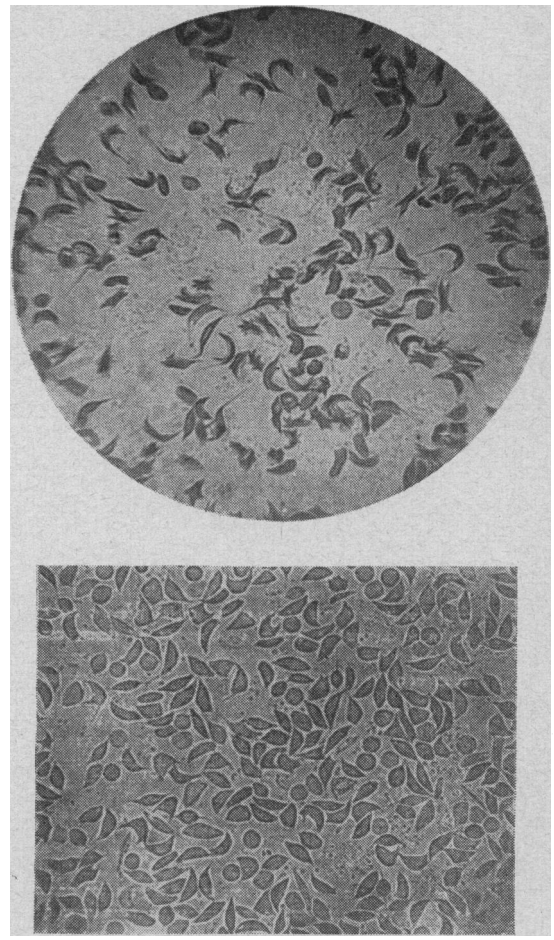


FIG. 1. Comparison of " true " and " false " sickle cells. *Above*, true sickle cells in an American Negro (Huck, 1923). *Below*, distorted cells mimicking the sickling phenomenon seen in a blood slide from a Yemenite Jew (Dreyfuss *et al.*, 1951) (from Dreyfuss *et al.*, 1953).

TABLE 1

Nilotic speaking tribes	Number examined	Percentage of sicklæmia
Lango	... 278	27
Acholi	... 141	27
Jaluo	... 130	28
Lugbara	... 120	21
Kakwa	... 101	25
Alur	... 114	25
Jonam	... 109	26
Madi	... 109	3

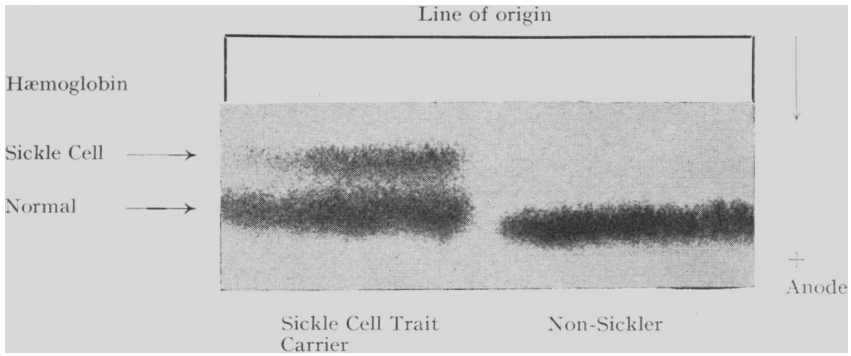


FIG. 2. Separation by filter-paper-electrophoresis of normal and sickle cell hæmoglobins. In an electric field and in an alkaline buffer hæmoglobin will move towards the positive pole. Sickle cell hæmoglobin will move more slowly than normal hæmoglobin.

It will be seen that in the Nilotic speaking group there was a remarkably homogeneous sicklæmia incidence. The exception were the Madi who are found in the most northerly corner of Uganda and who extend from there into the Southern Sudan. Recently Dr. A. C. Allison has re-examined the Madi and has told the writer that he has found a much higher incidence of sicklæmia than we discovered in 1948-49. On the other hand Dr. H. Foy and his colleagues (1954) have surveyed the Southern Sudanese and found that the Nilotics fall into two groups, those which are allied to the Uganda Nilotics showing a high incidence whereas others like the Dinka, Nuer and Shilluk do not. These latter Nilotics resemble in their pastoral and dietetic habits the Half Hamitic tribes such as the Masai, Turkhana, Karamajong.

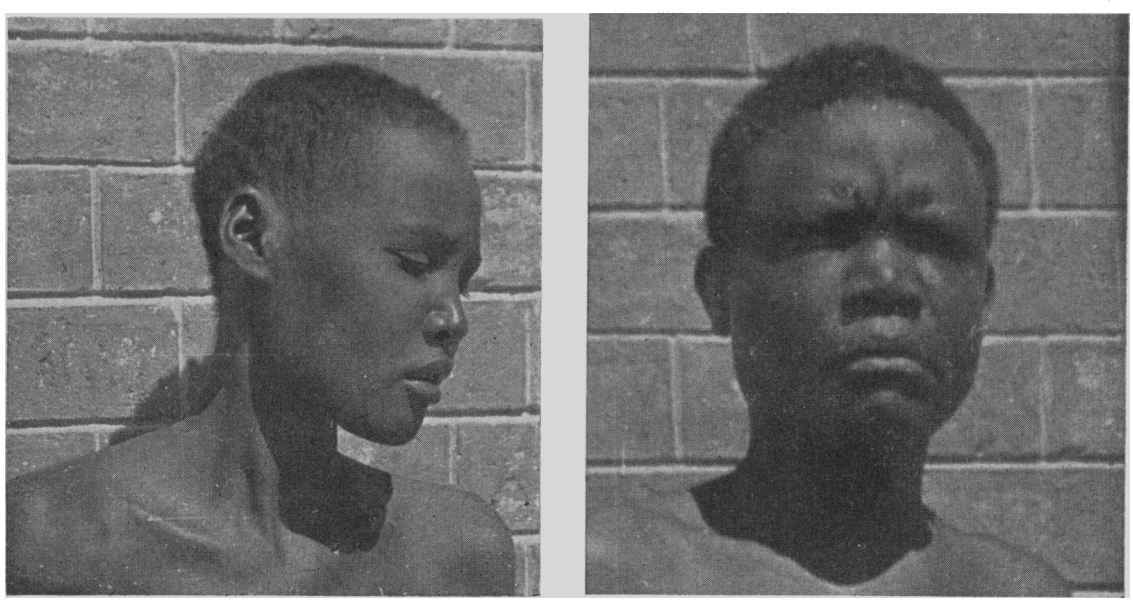


FIG. 3. A patient from Ruanda Urundi (left) and a local Muganda (right) at Kampala Hospital. The immigrant Banyaruanda differ from the Baganda by their more Europoid appearance.

TABLE 2

Half Hamitic speaking tribes	Number examined	Percentage of sicklæmia
Bahima*	166	2·4
Sebei	124	0·8
Suk	128	3·9
Karamajong	156	3·2
Teso	416	17·8

The Half Hamitic speaking tribes are pastoral and have arrived from the North together with their famous cattle which resembles that of old Egypt. They have settled in the grazing lands of Uganda along the rift valleys and have kept themselves fairly separate from their Bantu neighbours. They differ from them in their Europoid features (Fig. 4). It will be seen that they have very few sickle cells. The single exception is the Teso. They however have not the Caucasian features of the Hamite stock, they are a largely agricultural group settled among Nilotic and Bantu speaking tribes. Agricultural work in Central Africa is mostly carried out by women and the best way to recruit labourers is to marry them. The Teso have thus freely intermingled with their neighbours and the possession of the sickle cell trait is an additional physical character distinguishing them from the Hamitic group with which they have been classed on a linguistic basis.

Whereas there was a fairly uniform picture of high sicklæmia incidence among the Nilotics and low frequency of the gene among the Half Hamites a wide variation was seen among the Bantu tribes.

TABLE 3

Bantu speaking tribes	Number examined	Percentage of sicklæmia
Bairu	139	2
Banyaruanda	496	8
Banyoro	91	12
Batoro	120	12·5
Baganda	740	19
Bakonjo	102	18
Barundi	108	19
Bakenyi	88	26
Basoga	241	29
Bagishu	207	30
Baamba	140	45

* Although the Bahima now speak the Bantu language of their subjects, they have—for obvious reasons—been included by Dr. Raper and myself in this group.

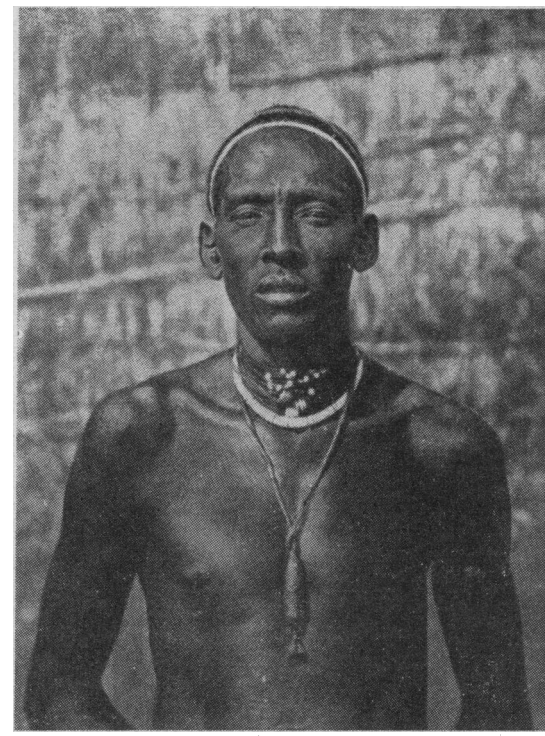


FIG. 4. A member of the Bahima tribe showing the Mediterranean features of the Half Hamites (from Johnston, 1904).

Here the sicklæmia appears to be inversely proportional to the contact the various tribes have had with their most recent Half Hamitic invaders. Thus the trait is least common among the Bairu, who have lived for generations as helots to the ruling class of Half Hamitic conquerors, the Bahima, on the best pastoral land in Uganda (Fig. 5). Next come the Banyaruanda, Banyoro and Batoro, whose traditions and customs testify to prolonged contact with the Bahima, and whose aristocracy possesses Hamitic features. The contact of the Baganda, Bakonjo and Barundi with the Half Hamitic peoples has until recent times been less direct and has been by way of their neighbours, the Banyoro, Batoro and Banyaruanda (Fig. 7).

The Basoga and Bagishu, two closely related tribes, live remote from the track of the cattle grazing peoples. The South-Basoga to whom the table refers live in the swampy country of the upper Nile, north of

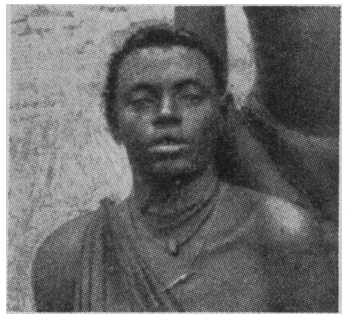


FIG. 5. A member of the Bairu group, a Bantu tribe showing Europoid features (from Johnston 1904).

Lake Victoria. The Bagishu live on the western slopes of Mount Elgon.

The Baamba are a secluded pygmoid tribe in the forests of the Mountains of the Moon. They claim to be autochthonous and of all the tribes we investigated these people with their prominent ridges of the eyebrows, the broad base of the nose, the wide mouth and the weak chin are furthest removed from the Bahima and come nearest to the "arch type" of the forest Negro which Sir Harry Johnston, the first Governor of Uganda, pictured in 1904 in his book on the Protectorate (Figs. 6 and 12).

A map of Uganda with the invasion route of the cattle-owning Half Hamites will show how the sickle cell trait incidence is lowest among the Bantu living in the path of their movement and is highest the farther away they live in the less accessible swamps, jungles and mountain forests (Fig. 8).

Dr. C. A. Allison (1954) has recently pointed out that there is an alternative to this ethnological explanation of differences in the incidence of sicklæmia among the Bantu of Uganda. The conquerors took for themselves the healthiest and least malarious areas of the country. If the sickling gene has a selective advantage and S hæmoglobin is less desirable to the malarial parasite than A hæmoglobin, sickling will be at a higher frequency the more malarious the surroundings of a tribe. There is no doubt that the Half Hamitic tribes all live in the least malarious areas of Uganda, and that the more closely the contact between a Bantu tribe and the Half Hamites the less malarious will be their surroundings. This attractive theory will have to be carefully examined, but the fact remains that the higher the sickling rate the lower will be the admixture of physical Hamitic features in any one Bantu tribe.

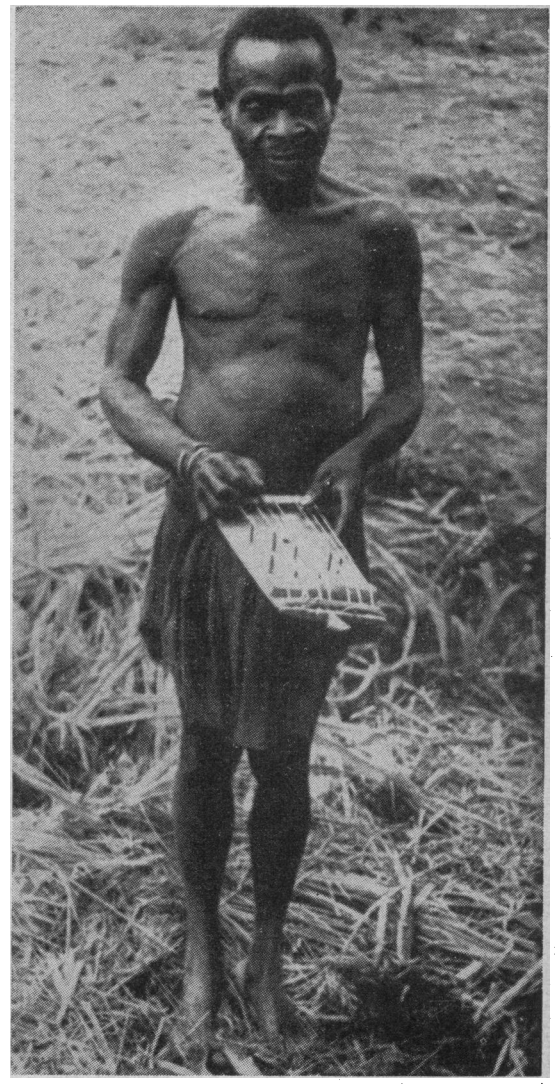


FIG. 6. A member of the Baamba tribe, playing the board zither. Note the pygmoid stature, the ridges of the eyebrows, the broad base of the nose, the wide mouth and the weak chin (from Trowell and Wachsmann, 1953).

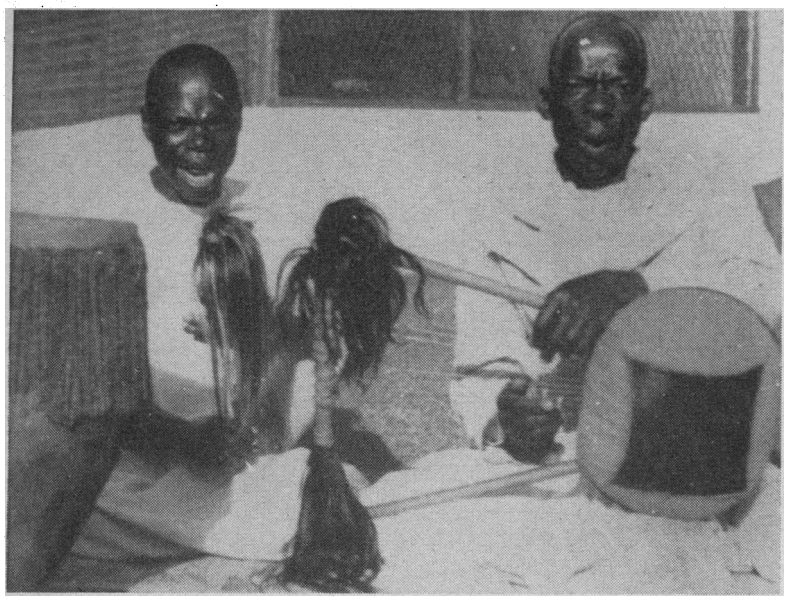


FIG. 7
Two Baganda, Court Musicians to H.H. the Kabaka of Buganda. Note the Uganda harp which shows features similar to those used in ancient Egypt.

Sickle cell trait and blood groups as " markers " for links with Africa

The late Dr. A. C. Haddon of Christ's College, Cambridge, often discussed—though never published—a theory of the invasion of Africa by an Asiatic population in Neolithic times. The East African cattle (unlike the Egyptian type Bahima cattle) and the East African poultry are closely allied to those of India. Some time in the Neolithic period a profound change took place in the skeletal type of the East African. Whereas previously the configuration was elegant and small, there appeared all at once coarser and bigger structures. The fact that they turned up in considerable numbers led Dr. Haddon to think that the people to whom they had belonged could not have gradually risen in Africa, but had arrived there as a group from elsewhere, possibly from India.

The fact that the sickling trait was more closely associated with the " arch type " of East African Negro made it possible that it could be used as a marker to trace the

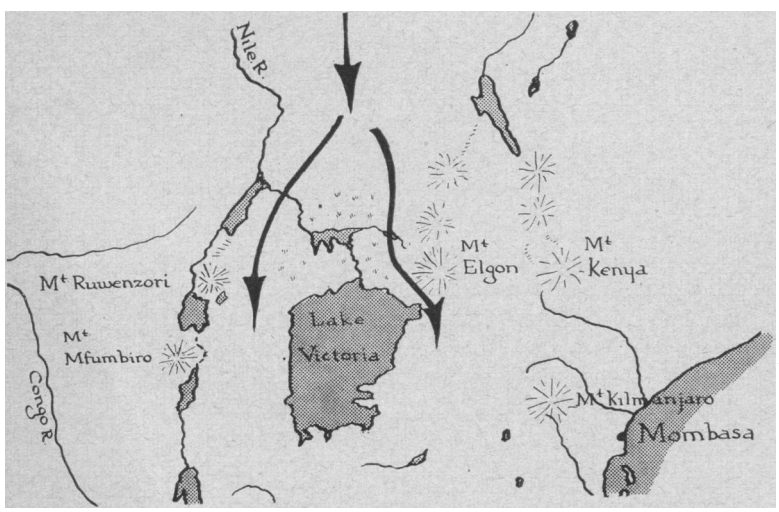


FIG. 8. The route of the migration taken by the cattle-owning Half Hamites in Uganda. The pastoral tribes followed the rift valleys avoiding the swamps of the Upper Nile and the mountain forests east and west of Uganda. The Bantu speaking tribes living along this route have a lower sickle cell trait incidence than those who live farther away.

origins of the East African. The writer would like to pay tribute to Dr. J. C. Trevor of Cambridge University and to Dr. A. E. Mourant of the Medical Research Council Blood Group Reference Laboratory for supporting what must have then seemed a wild scheme of visiting India in search of the sickle cell trait.

Dr. Mourant did not give his help unreservedly. He made the writer promise to combine the search for the sickling gene with the investigation of the blood groups of any aboriginal Indian tribe he visited. It may therefore be appropriate here to describe briefly the help which can be given to such a task by a blood group survey. There are a number of human blood group systems, the best known is the ABO system. The ABO chromosome has one locus which is either A, B or O. As we have two chromosomes of each type, one from each parent, every man has two ABO chromosomes which confer on him the blood groups A, B or O respectively. As O is a recessive, we can have the following

TABLE 4

EACH BLOOD GROUP SYSTEM REFERS TO A CHROMOSOME

ABO chromosome	A or B or O				
MNS chromosome	M or N				S or s
Rhesus (CDE) chromosome	C or c	D or d	E or e	F or f	

phenotypes A (AA or AO), B (BB or BO), AB and OO. Another system is the MNS system. Here two loci are known, one can be occupied either by the M or by the N gene, the other by S or s. This results in the following possible combinations for two

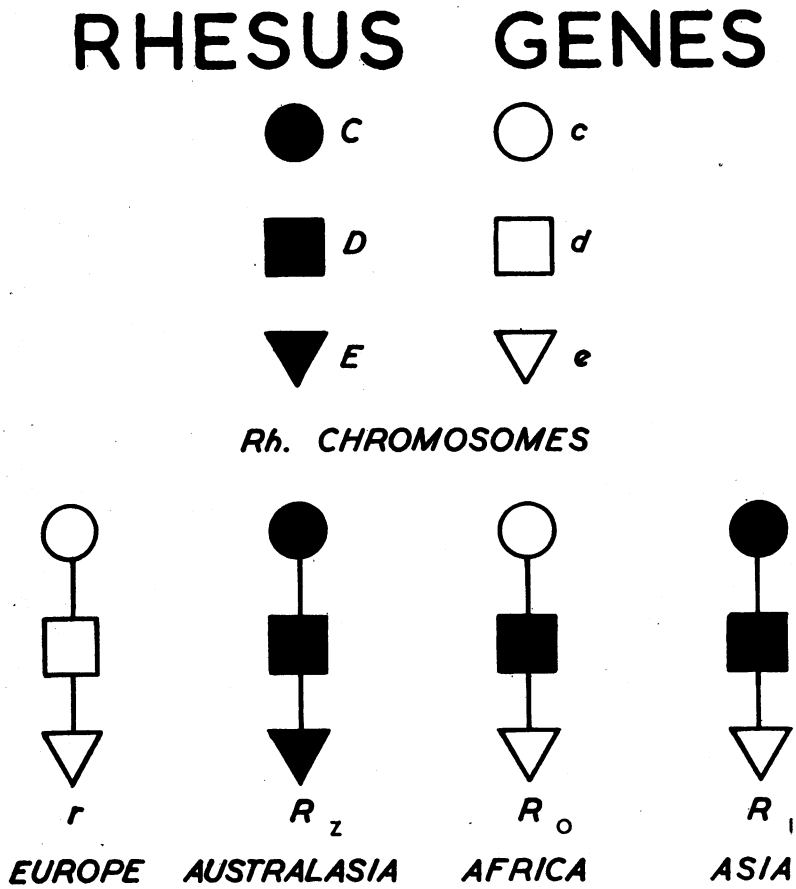


Fig. 9. The Rhesus Chromosomes.

According to the theory of Fisher and Race the Rhesus genes combine to form different chromosomes. The frequency of these chromosomes differs in different human populations: r is more frequent in Europe, R_z in Australasia, R_0 in Africa and the highest frequencies of R_1 are seen in Asia.

chromosomes: MMSS, MNSS, NNSS, MMss, MNss, NNss, MMSs, MNSs and NNSs.

These possible blood group combinations not only help to distinguish between different individuals—which is most important in legal cases or in the establishment of paternity—but they are also differently distributed among the various races of mankind. On the Asiatic-European land mass B is most frequent in India and becomes rarer the farther away a population is from that sub-continent; M is more frequent than N west of the "Birdsell line" named after the Californian anthropologist who showed that N was more frequent than M east of a line running from north to south just west of Japan and Australia. The frequency of blood groups is a very stable feature and remains with immigrant races for a long time, although like all genes they cannot be quite neutral in the evolution of mankind by natural selection. Thus the Caucasoid Australians have of course more M than N, and very ancient aboriginal communities in the heart of India differ from all other Indians by having a high A frequency.

The Rhesus system knows of four loci on the chromosome and an even wider variation of possibilities exists. It is debatable whether the Rhesus genes are truly at different loci or whether they are all factors attached to the same locus of the chromosome. In any case the various combinations are of great anthropological interest. There are known or assumed C, c, D, d, E, e, F and f. F and f have only recently been added to our arsenal and most anthropological studies have been concerned with the CDE system (Fig. 9). The combinations are found at varying frequency in different parts of the world: cde(r) is rare everywhere except in Europe where the frequency is highest among the Basques and is the higher the more the populations coming into Europe have intermingled with the type of people of whom to-day's Basques are a remnant; CDe(R_1) is found everywhere, but it is highest in Asia where it may have a frequency of well over 80 per cent in many populations; CDE(R_z) is very rare everywhere but up to recently has been found at a frequency of several per cent only in people associated with Australasia; cDe (R_o) is not a frequent blood group except in Negroes where A. S. Wiener discovered a high incidence in 1946. Since then it has been found at a very high frequency all over Africa by many workers, particularly by Dr. A. E. Mourant who has been associated with numerous studies in all parts of that continent. Regardless of the Negroid group to which the people belong, whether Bantu, Nilotic, Half Hamitic or Pygmie, no tribe has yet been found south of the Sahara in whom the R_o frequency is not above 50 per cent. The highest frequency so far has been seen in the Bushmen of South Africa where A. Zoutendyk and his colleagues (1953) found it to be above 80 per cent.

It was thus clear that in the search for links with Africa among Indian aboriginals an investigation of blood groups was most important—particularly one of the Rhesus system which might show a high R_o frequency.

The Nuffield Foundation generously financed an expedition to South India in 1952 and I was lucky enough to be joined on it by Marie Cutbush, an authority in work on blood groups.

India

India has been invaded by successive waves of populations, each wave penetrating less far south than the one before it. Thus the Aryans are in the North, and the older Dravidians in the South of India. Still older aboriginal tribes have either been absorbed into the modern Indian society as low castes or have been driven into less accessible jungles or hills. In the South of India the Nilgiri hills are populated by a variety of such old communities widely differing in culture and appearance.

The upper regions of the Nilgiris, the "blue mountains," are a rolling country where the Todas graze their buffaloes. Their men are magnificent-looking bearded individuals of proud bearing. They resemble in appearance the Eastern Mediterraneans, and connections have been traced between their cattle culture and milking ritual and customs

discovered in ancient Assyria. A rather less magnificent but otherwise similar looking tribe are the Kotas who are the craftsmen of the Nilgiris.

TABLE 5

INCIDENCE OF THE SICKLE CELL TRAIT IN THE NILGIRI HILLS

(All individuals except the Todas are unrelated).

Community	Number of persons tested	Number of persons with sickle cells	Percentage incidence
Paniyans	61	21	34
Irulas	124	39	31
Kurumbas	16	3	—
Badagas	191	16	8.4
Todas	84	3	4
Kotas	86	0	0
Canarese	95	0	0
Telegus	109	0	0
Malayalees	111	0	0
Tamils	128	0	0

The fertile slopes of the mountains are intensely cultivated by an agricultural community, the Badagas, who are related to the Dravidian Canarese. In jungles, or employed as near-slaves on the land by the other tribes live the Veddoids; Irula, Kurumba, Paniyans. They belong to some of the most primitive races of mankind, and up to recently were still food gatherers without any knowledge of agriculture. We received the generous hospitality of the Pasteur Institute and the Nutrition Research Institute at Coonoor and from there examined the various populations. The sickle cell trait was soon discovered and it was seen to be primarily a feature of the Veddoids.

We were less successful in our search for the R_o blood group. In fact the Veddoids, who had the sickle cell trait at a frequency up to then only seen in Africa, failed to produce a single R_o individual. Nevertheless it was the Veddoids who differed most markedly from all the other Indians of the Nilgiris (Fig. 10). The others had in common the Europoid features of what the anthropologists call the Mediterranean race, while the Veddoids showed the ridges of the eyebrows, the broad base of the nose, the wide

FIG. 10. The difference between the Veddoids and other Indian aboriginals. Left, a Paniyan woman (Veddoid); right, a Toda with typically Mediterranean features (from v. Eickstedt, 1935).

mouth and the weak chin we had seen in the arch type of the forest Negro in East Africa. Unlike their neighbours, the Veddoids showed more blood group A than B and what was more surprising still, Miss Cutbush discovered a frequency of R_z of 4·4 per cent, higher than had been seen up to then anywhere outside Australia. The Veddoids had actually been called Australo-veddoids by the eminent Indian anthropologist B. S. Guha (1937) because of similarities in skull figuration between them and the Australian aborigines. They thus showed a link with Africa as regards their sickling gene and with Australia in their Rhesus blood groups. The fact that some sickle cells were also found among the Todas and Badagas may be due to occasional miscegenation. Professor C. von Fürer-Heimendorf has told me that he has recently discovered a ritual involving exchange of wives between the Todas and the Kurumbas.

TABLE 6

BLOOD GROUP FREQUENCIES IN THE NILGIRIS

System	*Dravidians* Canarese Telegus Tamils	Badagas	Kotas and Todas	*Veddoids* Irulas Kurumbas Paniyans
ABO				
Number tested ...	77	64	168	194
A_1	11·87	12·35	7·00	21·36
A_2	3·03	0	1·27	4·38
A	14·90	12·35	8·27	25·74
B	23·85	15·26	33·17	18·15
O	61·23	72·21	58·54	56·11
MNS				
Number tested ...	67	57	141	161
MS	19·61	23·91	23·20	31·29
Ms	40·84	41·00	56·58	42·31
NS	14·60	0	11·56	0
Ns	24·95	35·09	8·65	26·40
Rhesus				
Number tested ...	61	64	152	156
CDe (R_1)	60·98	62·27	69·29	66·72
CDue (R^u_1)	6·40	16·63	8·02	—
CDE (R_2)	0·65	—	—	4·43
cDE (R_z)	11·65	14·06	—	15·76
cDe (R_0)	—	7·03	3·71	—
cde (r)	20·32	—	18·99	13·09

An interesting observation was that the Todas and Kotas showed in their blood groups to an extreme what is considered typical of the modern Indian generally. The Indians are noteworthy for a high frequency of blood group B and a low frequency of R_2 (cDE). The Todas and Kotas had no gene E at all and a very high frequency of B, in fact the 86 Kotas had not a single A blood group (52 O and 34 B) and the 82 Todas had the highest B frequency ever found (27 A, 45 B, 10 O). The Badagas and modern South Indian Dravidians seem to be the result of a mixture of the two extremes, the Toda-Kota element, an " arch Indian " prototype and the Veddoids. I should like to acknowledge my indebtedness to Dr. Ada Kopeć of the Nuffield Blood Group Centre for calculating the blood group frequencies reported in this paper. The methods of calculation are those of Dr. A. E. Mourant (1954).

The absence of R_0 and the high sicklæmia rate in the Veddoids precludes the theory that the sickle cell gene can have been imported from Africa. Not only would such a movement of African stock into India have brought with it a higher frequency of R_0, but also any known contacts of Negroes with India were with Aryan and Dravidian elements and would scarcely have penetrated and singled out the isolated groups of Veddoids.

It is of course possible for the sickling gene to have arisen in India independently by mutation, but there again it is unlikely that this would have been restricted to the Veddoid aborigines. Shortly after we made our observations in South India K. J. Dunlop and U. K. Mozumdar reported the finding of sickle cells among some tea plantation coolies in Assam who were aborigines of Bihar: Tanti. Miss E. W. Ikin and the writer examined 100 Oraons and 23 Kharias, Bihar aborigines working as forest labourers in the Andaman Islands, but we could find no sickle cells.

If one assumes a connection between the sickling phenomenon in India and in Africa, the absence of R_0 among Indian Veddoids suggests that the trait was carried from Asia to Africa, presumably by the same kind of people from whom the Veddoids of South India have derived.

It is noteworthy that Veddoid remains have been reported in Persia and in South Arabia; in Arabia they have been largely studied by C. S. Coon (1943).

Following our study of sickle cell distribution in Uganda, which had shown a possible ethnological significance of this feature, a

large number of investigations were made all over the African continent. A detailed account of this work cannot be given here ; an exhaustive table will be presented in Dr. A. E. Mourant's new book *The Distribution of the Human Blood Groups* (1954). Unlike the high R_o frequency the sickle cell trait was found to be only patchily distributed in Africa. The highest incidences have been reported from East Africa when they varied from 30 to 45 per cent in some Bantu tribes. Considering the highest incidences only, it was found that they fall towards the West, at the coast they are only 20-25 per cent. They also decline the farther one goes south, in Rhodesia they are about 10 per cent and they become practically nil in South Africa. The Bushmen, who have the highest R_o frequency recorded, have no sickle cells at all (S. B. Griffiths, 1953), similarly the " yellow" pygmies of Central Africa were found to be virtually free of sickle cells. Thus the trait is not a universal African feature and one might suggest that it entered the continent well after the African races had established themselves, and that the present East African population is a mixture of the high R_o non-sickling Bushmen type with Veddoids bringing R_2 and sicklæmia as their contribution. The fact that Veddoids are still found in Persia and in Arabia brings them to the former land bridge between Asia and Africa in the region of Aden, the trait may thus have entered Africa from the North

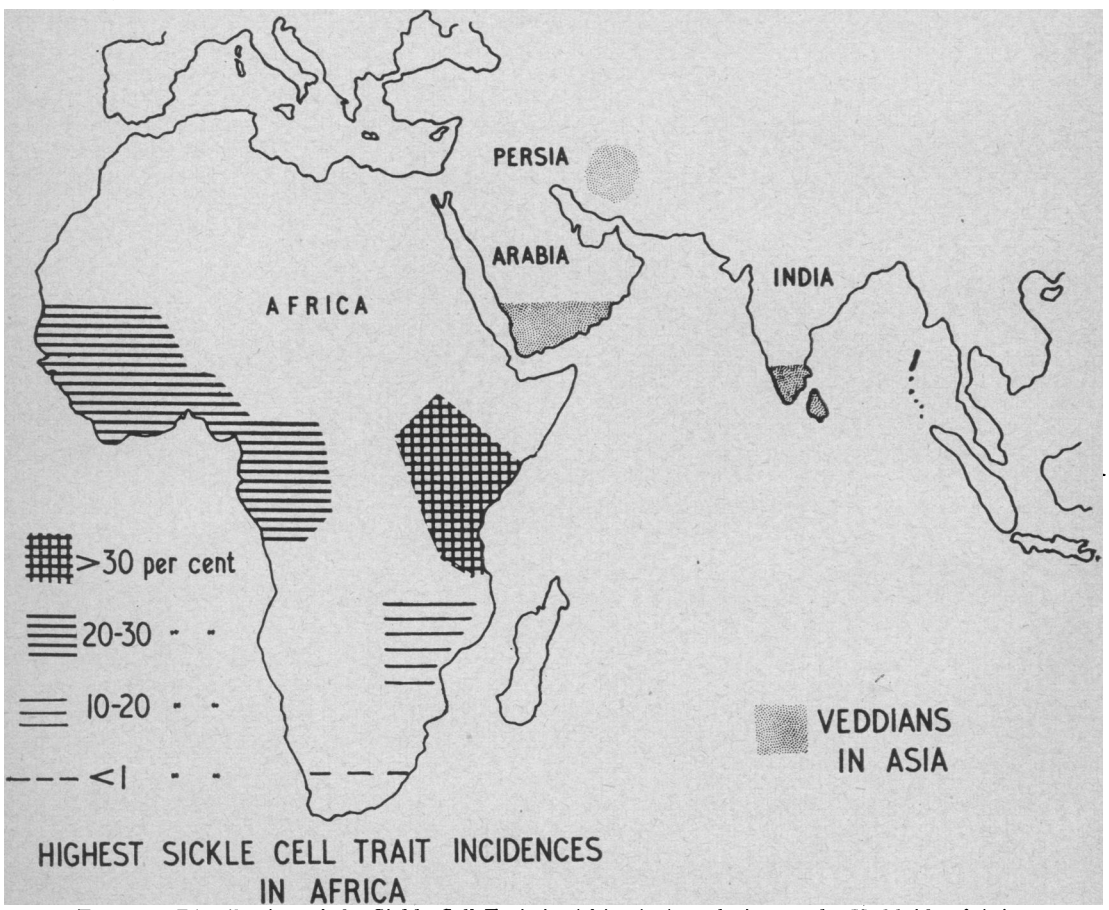


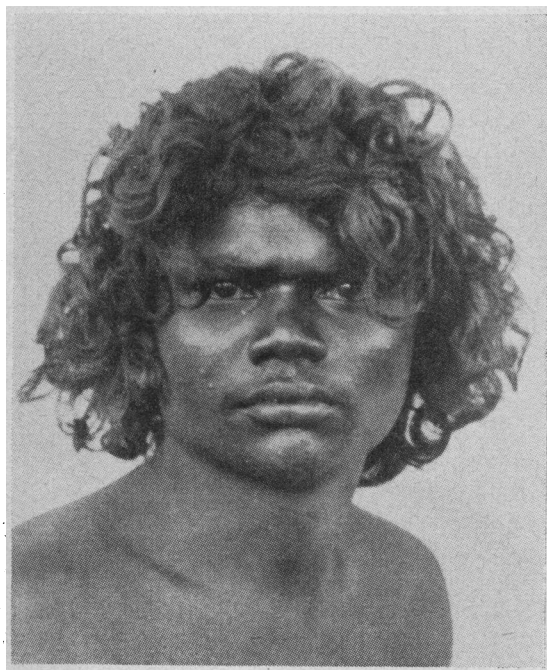
FIG. 11. Distribution of the Sickle Cell Trait in Africa in its relation to the Veddoids of Asia. Veddoids live in Arabia, Persia and South India. Some communities in the interior of the Nicobar islands and of Malaya also show Veddoid features. It is suggested that Veddoids brought the sickle cell gene to Africa entering at the southern end of the Red Sea.

East to spread southwards and westwards. Since then Hamitic and Semitic elements, Somali and Abyssinians have settled in the North East of Africa and have interrupted the continuity between the Veddoids of Arabia and the East African Negro (Fig. 11).

Dr. P. Brain (1953) has recently pointed out that this proposed migration of the sickle cell gene is much like that suggested for the shorthorn Zebu. This Asian cattle breed is thought to have entered Africa at the southern end of the Red Sea and to have spread from there along two routes: westwards to the West African coast, down the east coast as far as the Zambezi river which, it is to be noted, it did not cross. Singer asks: "Is it possible that the sickle cell gene was distributed in Africa by the custodians of the short-horn Zebu?" My own guess is that the Veddoids preceded the cattle-owning people, and that the fact that the two distributed themselves alike only shows the typical invasion routes into Africa from Asia; both Romans and Normans came across the Channel but at different times.

Arabia

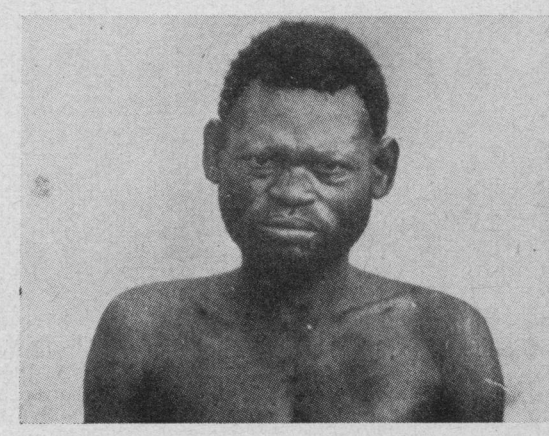
To test this theory of a connection between the sicklæmia of the Veddoids in India and of the East Africans an investigation was made of sickle cell trait incidence in South Arabia. Once again we were fortunate enough to secure the financial help of the Nuffield Foundation, who supported in 1953 an expedition to the Andaman Islands and the Wenner Gren Foundation enabled us to combine this scheme with a detour to Aden. On this occasion the writer was accompanied by another distinguished expert in the field of blood group research, Miss Elizabeth W. Ikin of Dr. Mourant's laboratory.



A Paniyan South Indian Veddoid (from Eickstedt, 1935).

FIG. 12. Resemblance between the sickle cell trait carriers of India, Arabia and East Africa.

Veddoid from South Arabia (from Coon, 1939).



"Arch type" of East African Forest Negro (from Johnston, 1904).

We examined two groups of people in Southern Arabia: the Arabs themselves (111), and the Achdam (104) and we found the sickle cell trait among the latter at a high frequency. The Achdam are a dark-skinned people with Veddoid features living near Zabid in the southern half of Yemen. Dr. C. S. Coon, who has contributed most to the knowledge of Veddoids in Southern Arabia, has, in a personal communication, confirmed that they very likely represent a Veddoid survival. The local Arabs think of them as Negroes because of their dark colour. However their social status is very different from that of the African slaves of Arabia. These slaves, or their ancestors, have indeed been imported from Africa, but their status is comparable to that of the serfs of feudal Europe, and although not free, they are valued, and often beloved, members of the household in which they have found their home. Intermarriage, though not encouraged, is practised, and at present a respected ruler in Southern Arabia is the son of such a slave woman. On the other hand, the Achdam are curiously similar in their social status to the Indian Veddoids, inasmuch as they have become a caste of untouchable sweepers. Intermarriage with them is out of the question for the Arabs. When the Administration in Aden needed sweepers, they imported the Achdam from Zabid for this purpose (Fig. 12).

The Africans who live nearest to Arabia are the Somali. They are a very proud people who regard themselves as of Arab origin, and it is inconceivable that any of them, or their descendants, should have fallen to the low social level of the Achdam. They have no sickle cells (we examined fifty of them and found none) as one would expect from an African population of the Hamitic type. Thus the Achdam are unlikely to have descended either from imported African slaves or from the Somali. There is a possibility that they are the last remains of pre-Mohammedan Abyssinian camp-followers. The armies of Abyssinia finally expelled in the early days of Mohammedan rule, had with them Sudanese and it is just possible that some of these might have been left behind. If the Achdam were derived and had inherited their sickling gene from such Sudanese Africans, they might be expected to resemble the Nilotic speaking tribes with high sickling frequency. Some such Sudanese of the Western Nile, the Jonam, have, within living memory, wandered southward to Kenya where they are now called Jaluo. Their blood groups were examined in 1952 by A. C. Allison, Elizabeth W. Ikin and A. E. Mourant. Like all other Africans so far investigated they show a high frequency of the R_o chromosome (82 per cent).

If we compare the Achdam as regards their sickle cell trait incidence and their blood groups with the Veddoids of Southern India and the Jaluos of Africa it will be seen that they have a high sicklæmia incidence similar to that found in the Veddoids and the Jaluos, but that the R_o chromosome has a frequency of only 28 per cent.

A link between the Asiatic Veddoids and the African sickle cell trait carriers would be expected to show a high incidence of the sickling gene together with an R_o frequency

TABLE 7

SICKLE CELL TRAIT CARRIERS IN INDIA, ARABIA AND EAST AFRICA

	Blood Group Frequencies													
	Sicklæmia percentage	O	A_1	A_2	B	M	N	R_o cDe	$R^u{}_o$ cD^{u}e	R_1 CDe	R_2 cDE	r cde	R_z CDE	R′ or R″ Cde or cdE
South Indian Veddoids See Table 6	30	56	22	4	18	74	26	0	0	67	15	13	5	0
Zabidis 114 individuals	23	76	9	5	9	66	34	28	5	33	13	20	0	0
Jaluos 128 individuals	28	69	11	4	16	52	38	82	5	0	0	4	0	9

TABLE 8

COMPARISON BETWEEN YEMENITE JEWS, YEMENITE ARABS AND EAST AFRICANS

	Blood Group Frequencies													
	Sicklæmia percentage	O	A_1	A_2	B	M	N	R_0 cDe	R^u_0 cD^{u}e	R_1 CDe	R^u_1 CD^{u}e	R_2 cDE	r cde	R′ or R″ Cde or cdE
Jews 102 individuals	0	67	19	7	6	76	24	1	20	46	7	22	3	0
Arabs 111 individuals	2	76	10	6	7	75	25	15	9	53	9	13	0	0
Jaluos 128 individuals	28	69	11	4	16	52	38	82	5	0	0	4	0	9

higher than that found in the Veddoids and lower than that seen in the Africans, and this is indeed the case in the Achdam. Had these Zabidis come by their sickle cells from Africa, in view of the high incidence found a very much higher frequency of R_0 than 28 would have been expected to accompany the sickle cell genes.

An indication as to what extent an inheritance of the sickling gene from Africans is accompanied by a rise in the R_0 incidence can be arrived at by an analysis of the blood group data we found in the Yemenite Arabs. The Yemenite Arabs represent a mixture of pure Semites and Africans. It will be seen that a comparison with the Yemenite Jews, who are of the same stock but did not intermarry with Africans for religious reasons, shows that in the Yemenite Arabs a moderate rise in sicklæmia was accompanied by considerable increase in R_0 frequency. The data on the Yemenite Jews are taken from a survey by F. Dreyfuss, Elizabeth W. Ikin, H. Lehmann and A. E. Mourant carried out in 1952.

Australia

The finding of a high R_z (CDE) frequency in the Indian Veddoids which they shared with the aborigines of Australia but did not have in common with the sickle cell trait carrying Veddoids of Arabia made it unlikely that sickle cells would also be a connecting link with "Australo-Veddoids" of India and other populations with a high R_z frequency. Nevertheless it was thought important to examine a representative group of Australians for the sickle cell trait. J. B. Birdsell (1950) divides the Australian aborigines into three groups; that in the Northern territories—the Carpentarians—is considered to have more Veddoid connections than the other two which are more intimately related to Negritos and Europoid Ainus respectively (Fig. 13). Dr. W. H. Horsfall sent the writer (1953) bloods from seventy-two Australian aborigines from a part of Queensland in which, according to Birdsell, a strong Carpentarian component prevails. Fifty-seven of these Australians were of unmixed native ancestry according to their own accounts and also to their appearance. No sickling was discovered in any of the samples.

Andamanese Negritos

Apart from the Veddoids the most important non-Mongoloid group of aborigines in Asia, and one for which connections with Africa have most frequently been claimed, are the Negritos. Impure traces of them are to be found in South India itself, in the Malayan jungle, in the interior of Java and in the Philippines. The racially purest survivors are found in the Andaman Islands (Fig. 14).

It was of interest to see how these people fitted into the picture of blood group distribution seen in pre-Dravidian, pre-Aryan, and pre-Mongoloid Asiatics. Their small stature, steatopygia and peppercorn-like arrangement of hair growth have linked them in the eyes of many anthropologists either to the Bushmen of South Africa or the Pygmies of Central Africa (Figs. 15 and 16).

With the approval of the Indian Government it was decided to visit the Andaman Islands. Professor B. S. Guha, the Director of the Department of Anthropology, Government of India, offered his Department's full support in this difficult task. Professor Guha has established a substation of his Department in Port Blair of which Dr. L. Cipriani is in charge. Professor Guha's and Dr. Cipriani's invaluable help was essential to us.

A glance at the map will show that the Himalayan mountains in their sweep to the South East are continued in the Arakan hills of Burma, which end at the sea where the Irawaddy joins the Bay of Bengal. There the mountain range continues into the sea southwards in the direction of Sumatra, but only occasionally do its tops break the surface of the water to form islands of which the most important groups are the Cocos, the Andamans and the Nicobars. It is on the Andamans, situated about 800 miles south of Calcutta and 700 miles east of Madras, that pure Negritos have survived in comparatively large numbers. In the old days, the islands were raided by Chinese and Arabs, who carried off the Andamanese as slaves. This produced fear and hatred with a will to fight to the death rather than to allow a stranger to approach. Stranded crews were invariably murdered and the reputation of the Andaman Islands became such that sailors avoided them at all costs.

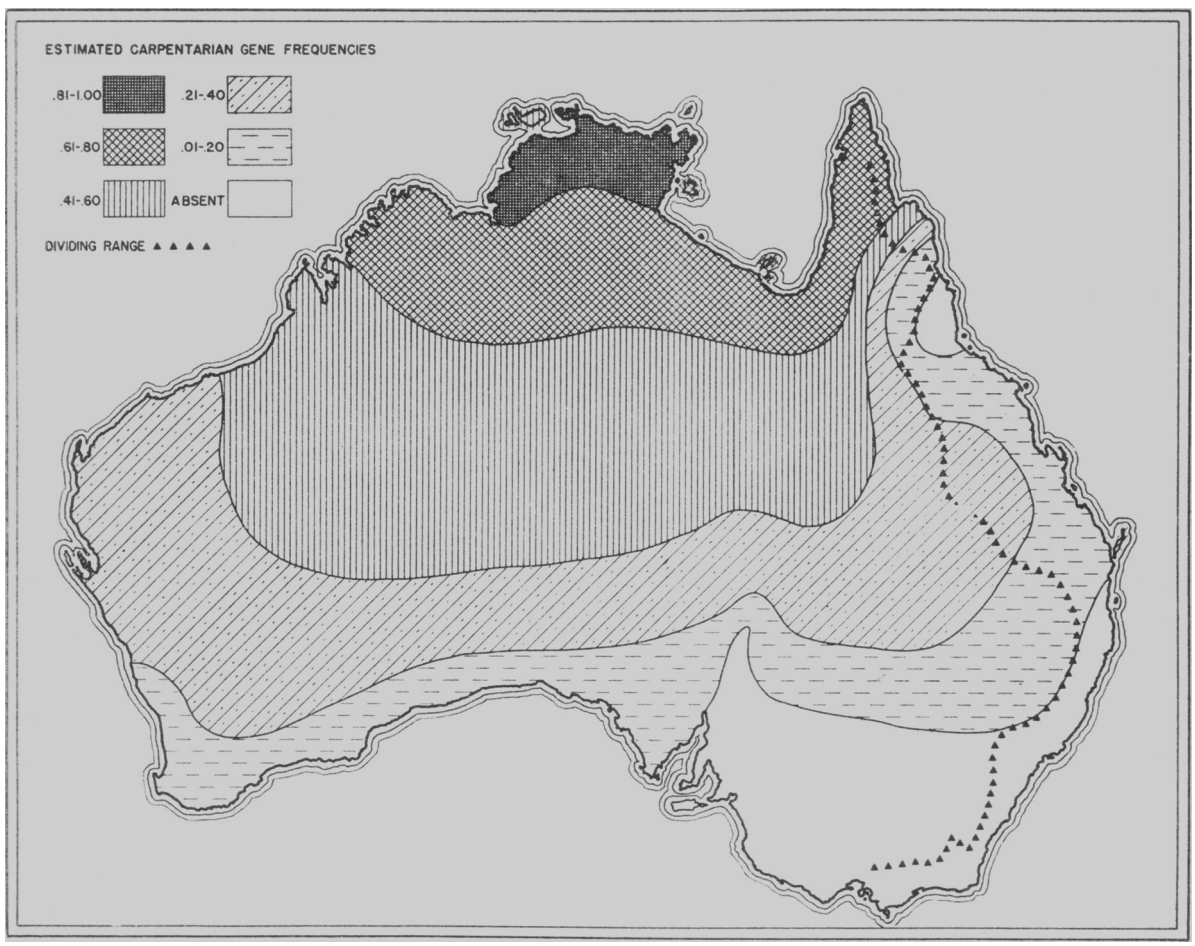


FIG. 13. The spread of the " Carpentarian " (Veddoid) type across the Continent of Australia (from Birdsell, 1950).

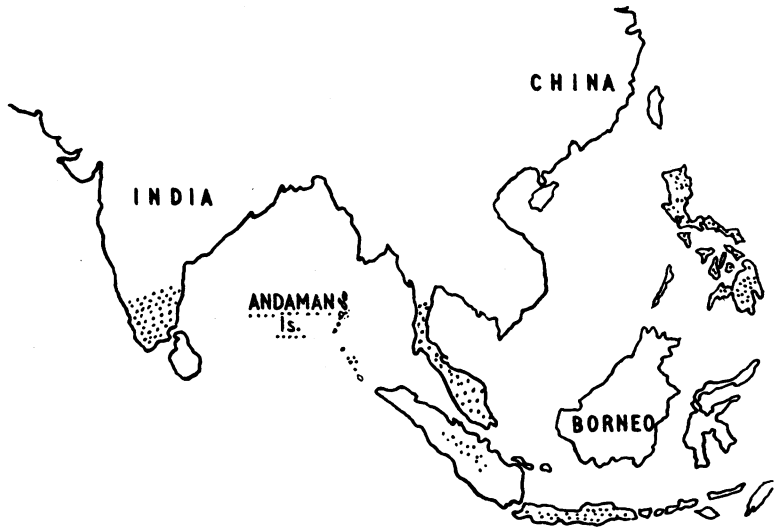


FIG. 14. The dotted areas show where Negrito influence can be found. Pure remnants of this ancient race can still be met with in the Andaman Islands.

In the eighteenth century, an attempt by the East India Company to build a harbour to safeguard shipping in these parts had to be abandoned in the face of local hostility and supervening disease. It was only after the Indian Mutiny, less than a hundred years ago, that a serious attempt was made to occupy the islands, when a penal community was founded at Port Blair.

The local inhabitants could then be divided into three groups closely related to each other in customs and appearance, but living strictly apart :

1. Jarawa 2. Andamanese 3. Onge.

1. Little is known about the *Jarawa*, who have retained their original hostility up to today. There is no man alive who has actually talked to them in the forests. It is not surprising that attempts to befriend them have so far failed, for in the past there have been wholesale shootings of surprised parties and the carrying-off of the wounded as prisoners for the purpose of " making contact." What one knows of the Jarawa is that they are virile and strong and extremely primitive ; thus, all the metal they possess is derived from old nails taken from shipwrecks. Two captured Jarawa children were brought up in Port Blair and taken to the Nicobars, where they are still living now and where Dr. Sneath, then a pathologist in the R.A.M.C. stationed at Singapore, examined their blood groups and found them both to be O and R_1R_1.

2. The *Andamanese* were friendly and submitted to religious conversion, to rehousing and to trade with the newcomers. This they did at their peril ; there were several thousands of them less than a hundred years ago, but disease and alcohol have diminished their number to between twenty and thirty today. Although the older generation looks much like Negritos, a Burmese influence is very obvious in the children. They live on the border between the mid and south Andamans, and are employed as Bush Police to warn off the Jarawa from crossing to the south Andamans, where the Indian Government is carrying out a settlement plan for East Bengal refugees. We examined sixteen of these Andamanese (excluding children), and found their blood groups to be as follows :

FIG. 15. An Onge woman from the Little Andamans. Note the small stature, the "peppercorn" arrangement of hair growth and the steatopygia. Note also, however, that though the stature is small, there is no disproportion in length of legs.

TABLE 9

ABO	MNS	P	RHESUS
O : 5	MMS : 3	P : 12	R_1R_1 CCDee : 15
A_1 : 5	MMs : 3	p : 4	R_1R_2 CcDEe : 1
B : 4	MNS : 4		
A_1B : 2	MNs : 2		
	NNS : 4		
	NNs : 0		

There were no sickle cells and these findings already suggested that there was little in common between the African Negroes and the Negritos of the Andamans. Results obtained from such a small group have to be accepted with great caution, as genetic drift becomes the more important the smaller the population. However, it was felt that, if the Onge produced similar values, it would be a strong indication that our results were applicable to the Andaman Negritos as a whole.

3. On the Little Andamans live the *Onge*, variously estimated to number from 100 to 400. They are neither as hostile as the Jarawa, nor have they been as much in contact with the modern world as their unfortunate Andamanese brethren (Figs. 17 and 18). They have been visited from time to time and a few of their men have braved the sea to paddle in outrigger canoes as far as Port Blair. It cannot be said that they are entirely tame, and the last murder was committed only in 1949, when they killed a party of shipwrecked Chinese. On the other hand, a Burmese policeman, Pado, fled to this island during the Japanese occupation, spent several years there, greatly increasing the confidence of these people towards strangers, and taught one or two of them a few words of Hindustani. This virile and, judging from the number of children, healthy community has been living isolated up to now and was considered a very suitable population to be examined for its blood groups. Fifty-two of them were investigated. This number represents an appreciable percentage of the total population. Children of parents tested were not included. The results are given in Table 10.

TABLE 10

ABO	MNS	P	RHESUS
O : 7	MMS : 5	P : 42	R_1R_1, CCDee : 45
A_1 : 37	MMs : 12	p : 10	R_1R_2, CcDEe : 6
B : 4	MNS : 5		R_2R_2, ccDEE : 1
A_1B : 4	MNs : 24		
	NNS : 0		
	NNs : 6		

The two Jarawa examined by Dr. Sneath, the 16 Andamanese and 52 Onge had a predominant frequency of the Rhesus chromosome R_1 (60 of 70 R_1R_1; 7 of 70 R_1R_2).

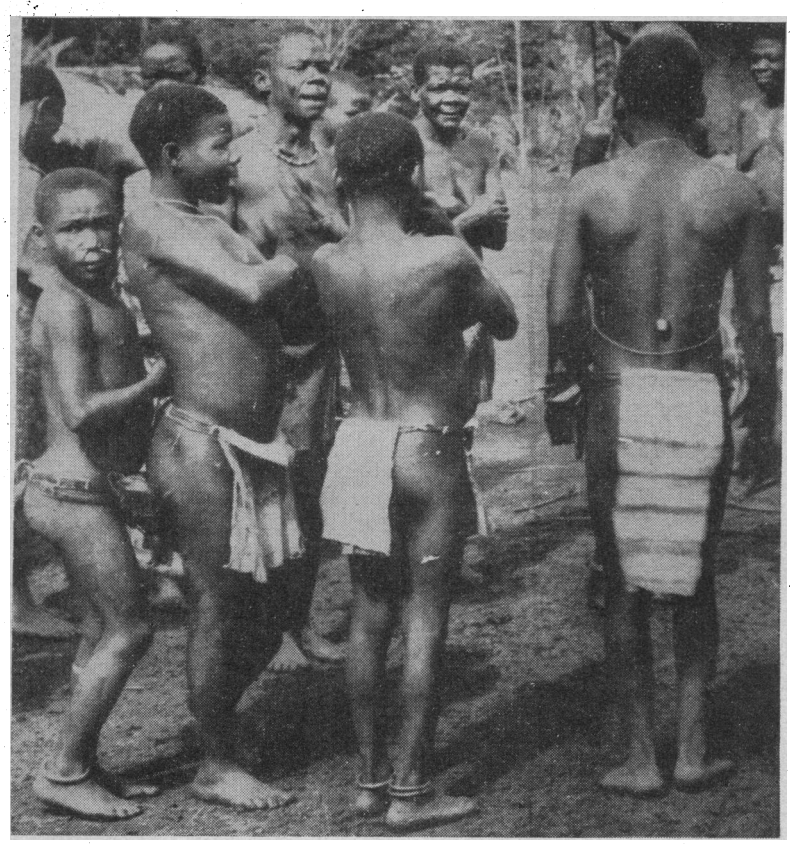


FIG. 16. African Pygmies.

Note the "peppercorn" arrangement of hair growth and the steatopygia. Whereas the Asian Negrito is well proportioned, the African pygmie's small stature is made smaller still by disproportionately short legs.

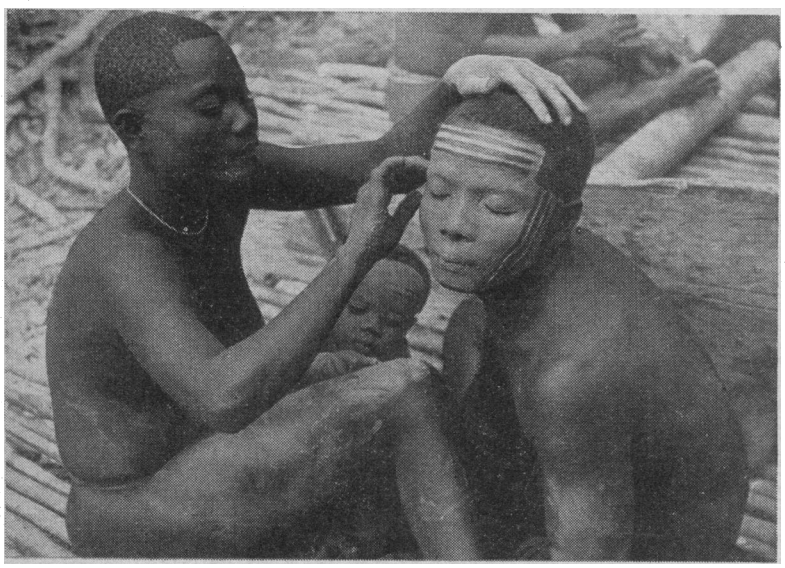


FIG. 17. A "Facial" on the Andamans.

The face is covered with a mask of mud and fat and a pattern is drawn with the fingers. Note the little son taking a lively and interfering interest in his mother's "palette." The Onge lead a happy family life.

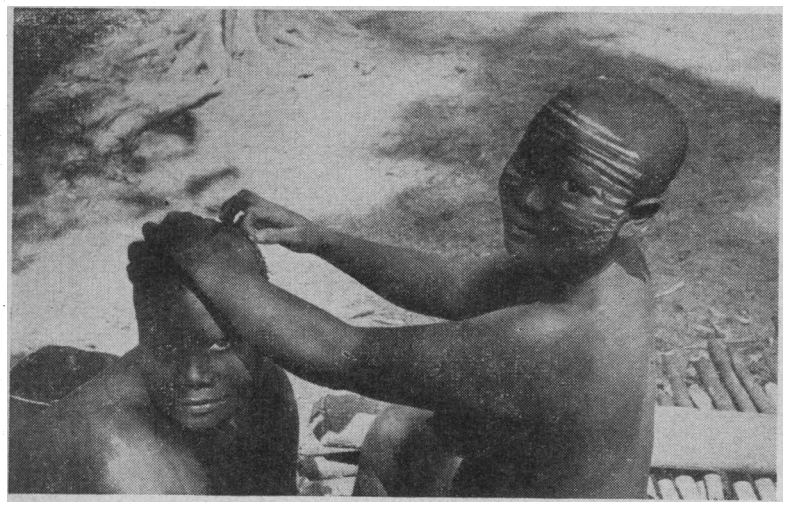


FIG. 18. The use of glass flints by the Onge.

The Onge still use flints. They are made by knocking a shell against obsidian. Here one woman shaves another, a new flint is used after every three or four strokes.

Neither the Andamanese, nor the Onge showed the blood group A_2, and none had the Rhesus chromosome R_o or R_z.

TABLE 11

GENE FREQUENCIES OF ANDAMANESE NEGRITOS

Sickle ...	A_1	B	O	R_1	R_2	M	
Ni ...	54	8	38	92	8	61	39

The African Negro shows a high incidence of R_o, he has both blood group A_1 and A_2, and particularly in East, Central and West Africa the sickle cell trait is found. The Australian aborigines show a moderate incidence of R_z which is rare elsewhere except in the Veddoids. The Veddoids have sickle cells, blood groups A_1 and A_2. Neither the African Negro nor the Australians nor the Veddoids have an incidence of R_1 higher than 80 per cent. The Oceanic Negro is the only aboriginal who, like the Andamanese Negritos, possesses no R_o, no A_2, no R_z, but the R_1 chromosome at an incidence of more than 80 per cent.

TABLE 12

WHERE DO THE ANDAMANESE NEGRITOS BELONG?

	R_o	R_z	R_1 above 80%	Sickle Cells	A_2	M>N
African Negro	+	—	—	+ —	+	+
Veddoids	—	+	—	+	+	+
Australians	—	+	—	—	—	—
Oceanic Negro	—	—	+	?	—	—
Andamanese	—	—	+	—	—	+

I have already mentioned the famous Birdsell line, which goes from north to south somewhere west of Japan. East of this line, the ratio of $\frac{\text{blood group M}}{\text{blood group N}}$ is smaller than 1; to the west of it, M is more frequent than N. Thus the African Negro and the Veddoids have more M than N, and the Australian aboriginals and the Oceanic Negroes living east of the Birdsell line have more N than M; the Onge living west of the Birdsell line have a ratio of $\frac{M}{N}$ of 3:2. However, the other findings strongly suggest that the Onge are more closely related to the Oceanic Negroes than to the African Negro and, although they are often bracketed with the Pygmies of Africa, this investigation suggests that they should be more properly classified as the Pygmies of Oceania. It is of interest that the Onge, like the Papuans, have the custom of preserving and carrying round their necks, bones, particularly the jaw bone, of near relatives who departed this life.

Greece

The sickle cell trait has been known to exist sporadically in Sicily, Southern Italy and Greece. This was thought to be due to an admixture of African blood in Roman times when liberated slaves married into the families of their former masters. A. E. Mourant (1951)

has pointed out that the R_o incidence is somewhat higher in the Europeans from the Mediterranean region than in those from others parts of Europe. Yet while measurement of R_o frequency may be used as a " tracer " of African ancestry, the sickle cell trait can obviously not be used for this purpose. Veddoid blood may have found its way into the Mediterranean peoples: L. Cipriani (1934) reported Veddoid skull features in the Sardinians of today; small, possibly Veddoid, people were discovered among the remains of pre-dynastic Egypt and Cipriani has pointed out that the piriform opening of the skulls of children found in the Grimaldi cave in Monaco has Veddoid features.

Greece is the only European country so far studied where in small areas the whole population has a high sickle cell trait incidence. Professor Choremis and his colleagues reported such a population pocket from the Lake Kopais area in 1951. The writer has recently visited Lake Kopais with Professor Choremis and a sickle cell trait incidence of 17.7 per cent was found; the true incidence is probably higher because members of families with a known sickle cell anæmia patient were not included in this survey. These people did not differ from other Greeks in their blood groups (Fig. 19) (L. Choremis, Elizabeth W. Ikin, H. Lehmann, A. E. Mourant and Leda Zannos, 1953).

The sociological factor in sickling incidence

As the sickle cell gene is potentially deleterious, causing a specific anæmia, its continued survival has been the subject of much speculation. The most notable analysis of this problem has been made by Professor T. V. Neel (1953). It has been suggested that certain races have a very high mutation rate for this gene, reproducing it with sufficient frequency to replace losses incurred by the anæmia. Alternatively it has been suggested that it confers advantages such as a resistance to malaria which balances its disadvantages in the fight for survival. Allison's correlation of high sickle cell incidence and high malarial infection rate are in support of this theory of balanced polymorphism. Some such mechanism must play a part in explaining the presence of the gene. In addition there is the anthropological factor described in this paper and lastly there must be a sociological one. The highest sickling rates were always found in the socially lowest stratum of a population. In Africa the Pygmoids of the forest, in India the Veddoids of the Nilgiri who are either living as serfs or on the lowest possible human level in the jungle; in Arabia again the Achdam,

FIG. 19. Children from the Lake Kopais area in Greece. Professor Choremis from Athens University is seen here with a group of children from the community among whom he discovered a high sickle cell trait incidence. Note that it would not be possible to point to any difference between the features of these children and any group of children from other parts of Greece, or, for that matter, from anywhere in Europe.

the lowest social community, were the carriers of the gene. Similarly the Greeks were slaves of the Turks until recently. These people are forced to live where they are, they are unable to travel and they do not intermarry with their more fortunate neighbours. Inbreeding which usually goes hand in hand with a slave-like condition in life seems to be an important factor in producing a high sickling rate.

Thus three major factors will play a part in producing a high incidence of the sickle cell gene :

1. The anthropological derivation of a population.
2. A genetic regulation such as a high mutation rate or balanced polymorphism and
3. A social situation which produces inbreeding.

ACKNOWLEDGMENTS

I should like to acknowledge gratefully permission to reproduce:

Fig. 1A : *Bulletin of the Johns Hopkins Hospital*, **34,** 335 (1923).

Fig. 1B: *Harefuah*, **41,** 168 (1951).

Fig. 4, 5, 12C : H. Johnston, *The Uganda Protectorate*, London, Hutchinson, 1904.

Fig. 7 : M. Trowell and K. Wachsmann, *Tribal Crafts of Uganda*, Oxford University Press, 1953.

Figs. 10, 12A : E. von Eickstedt, *The Mysore Tribes and Castes*, Mysore University Press, 1935.

Fig. 12B : C. S. Coon, *The Races of Europe*, New York, Macmillan, 1939.

Fig. 13 : *Cold Spring Harbor Symposia on Quantitative Biology*, **15,** 259 (1950).

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