Sickling phenomenon can be regarded as a particular characteristic of any race which shows it in the absence of admixture with another race in which it exists. Its higher incidence around the Mediterranean could be accounted for by the suggestion that some races of the Mediterranean basin, with a few exceptions in other parts of the world, appear to be more prone to develop a mutation affecting their blood-forming tissue. At the same time some unknown geophysical and other factors, one of which may possibly be malaria, favour the high frequency of this mutation in these areas of the globe.

Conclusions

The sickling trait exists in Northern Greece, particularly in Chalkidiki, where in the Sithonia Peninsula the rate is 32%, in the neck of the same peninsula the rate is 18–24%, in the Kassandra Peninsula and in the plain of Salonika it reaches 14%, and at the foot of Pangaion Mountain it is 6%.

The sickling phenomenon is mainly observed among highly inbred groups of natives; it is an indigenous, local, and static condition of this area.

The sickling is due to a mutated gene. Its high frequency and manifestation in a given area can be accounted for by inter-marriage and the elimination of the influence of counter-selection by malaria.

Mediterranean and sickle-cell anaemias must not be regarded as exclusively racial diseases, since many cases have been observed (a) of Mediterranean anaemia among coloured people (negroes, Chinese, Thais, Egyptians, Indians, and American Indians), (b) of sickle-cell anaemia among white people in whom any admixture with negro blood must definitely be excluded.

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COMPATIBILITY OF SICKLING WITH MALARIA

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The appearance of severe hereditary anaemias in areas where malaria has been endemic for many centuries raises the question of how far malaria can be considered to be connected with the aetiology of these anaemias. We rejected such a connexion for Mediterranean anaemia¹⁻³ because we had never found malaria in our patients or their relatives. On the other hand, according to some authors the tentative treatment of this disease caused no improvement of the anaemia or any decline in the fever when this was present. Some trials of experimental transmission of malaria from patients suffering from Mediterranean anaemia into animals (*Macacus rhesus*, etc.) were unsuccessful.

Several writers have tried to correlate sickle-cell anaemia and trait with malaria. But recent clinical observations and experimental findings show little compatibility between these two morbid entities. Many workers in Africa, observing the low frequency of malaria in sicklers in contrast to non-sicklers, have concluded that sicklers are more resistant than non-sicklers because they are possibly protected by some unknown factor against attack by malaria parasites. They also think that abnormal red cells are less subject to parasitism than normal cells, and so children bearing the trait and living in malaria-stricken areas have a better chance of reaching adult life than children with normal blood.⁴⁻⁸

On the other hand, a different opinion was given by Edington⁹ and Moore *et al.*,¹⁰ who found in Africa (Gold Coast and Nairobi) the same incidence of malaria in sicklers as in non-sicklers. It is worth pointing out, however, that Edington counted 500 malarial parasites

per c.mm. in sicklers and 1,000 per c.mm. in non-sicklers. Perhaps these findings, obtained in hyperendemic areas, are due to local conditions—that is, to mass infection, diminution of the resistance of the body for different reasons, etc.

Investigation in Greece

We had an opportunity of investigating this subject in Chalkidiki, where malaria is endemic and the population shows the highest rate of sickling known in Greece.

Making use of lists supplied by the Department of Malaria in Northern Greece, we examined 136 out of 174 cases of malaria confirmed by microscopical examination and reported during the three years (1952–4). These patients came from four villages with the highest rate of sickling known in Greece (32%, 24%, 19%, 18%). The mean rate of sickling in persons suffering from malaria in this area was only 5.8%. On the other hand, the mean sickling rate in 500 unselected individuals examined in this area was 23.6%. It is noteworthy that the number of sicklers with malaria is extremely low, whereas one would expect it to be similar to that of non-sicklers, because the existing conditions of infection and sensitiveness are the same (Table I).

TABLE I.—Percentage of Sickling and Malaria in Examined Cases

Villages	Unselected Sickling			Malaria		
	No. Exam.	Positive	%	No. Exam.	Sickling Positive	%
Parthenon ..	153	49	32	28	1	3.6
St. Nicholas ..	101	24	24	40	2	5.0
Nikiti ..	143	27	19	31	3	9.6
Ormylia ..	103	18	18	37	2	5.4
Total ..	500	118	23.6	136	8	5.8

Blood investigations for sickling were made on siblings of families affected by malaria. This was done in order to secure, so far as possible, the same conditions of living and sensitivity to malaria infection. Only the siblings of the children infected by malaria were examined. It seemed to us that the results could give us a better picture of the relationship between malaria and sickling as well as the frequency of the former in persons with or without the latter condition. In fact, we noted that, in the families of sicklers, the members who were not infected by malaria parasites were mostly positive for sickling, whereas those who were negative for sickling were infected more often by malaria (Table II).

TABLE II.—Families with Positive Sickling and Malaria

Name	Age (Yrs.)	Malaria	Sickling	Name	Age (Yrs.)	Malaria	Sickling
St. Nicholas				Parthenon			
K. N. S.	9	+	—	E. Th. K.	7	+	—
V. N. S.	7	—	+	D. Th. K.	1	—	Microcyt.
A. N. S.	6	—	+	M. Th. K.	12	—	—
H. N. S.	10	—	+	A. Th. K.	5	—	—
M. N. S.	3	—	+	T. Th. K.	38	—	+
S. N. S.	30	—	+	A. N. P.	29	+	—
A. D. P.	15	+	—	E. N. P.	2	+	—
A. D. P.	4	—	+	E. N. P.	6	—	+
G. D. P.	8	—	+	N. E. P.	35	—	+
D. A. S.	7	+	—	B. I. E.	9	+	—
M. A. S.	10	—	+	I. I. E.	7	—	+
A. Th. D.	11	+	—	A. D. H.	18	+	—
D. Th. D.	8	—	+	A. D. H.	8	—	+
A. Th. S.	6	+	—	B. K. K.	8	+	—
G. Th. S.	1	—	+	T. K. K.	4	—	+
				N. K. K.	7	—	—
Ormylia				Nikiti			
I. H. M.	12	+	—	G. I. M.	14	+	—
M. H. M.	38	—	—	A. I. M.	11	—	—
A. H. M.	11	—	—	N. I. M.	8	—	—
G. H. M.	7	—	—	G. A. K.	8	+	—
H. I. M.	46	—	+	N. A. K.	7	—	—
G. H. E.	8	+	+	M. A. K.	13	—	+
A. H. E.	10	—	—	K. M. A.	19	+	—
L. H. E.	5	—	+	G. M. A.	7	—	—
H. I. E.	47	—	+				

We must admit, with Allison,⁴ Brain,⁵ and Mackey and Vivarelli⁸ that the coexistence of malaria and sickling is of a low order. Sicklers show a stronger resistance against the infection. Their red cells are less susceptible to malarial parasitism, and this may be due to unsuitable environment because of the presence of the abnormal S-haemoglobin.

We also observed that in sicklers infected by malaria the test for sickling, using the sodium bisulphite method, was not always complete for all their red blood cells, in contrast to the cases in which only the sickle-cell trait was present.

Paper electrophoresis revealed an abnormal haemoglobin following the normal haemoglobin, like the haemoglobin of the trait.¹¹ Unfortunately it is not possible to separate the abnormal haemoglobin quantitatively by paper electrophoresis.

The infestation of some red cells with parasites in the case of sicklers could be explained by the possibly smaller amount of S-haemoglobin present in these cells, unless some special condition of the stroma favours the entrance of the parasite.

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PENICILLIN ANAPHYLACTOID SHOCK

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The clinical advent of penicillin in 1943 opened the antibiotic era. Within a decade, however, the threat of anaphylactoid reactions from this drug gradually emerged¹⁻²³ and is now a grave concern.²⁴⁻⁵⁹ Indeed, penicillin is the prime cause of drug-induced anaphylactoid reactions. It is convenient here to refer to anaphylactoid rather than anaphylactic shock, bearing in mind that some of the reported cases are hardly true examples of the latter.

Casuistic reports continue to appear, and the cautionary remark of Gilman,⁶⁰ "... One must conclude the guilt of usage rather than of the substance," merits consideration. Smith and Walker⁶¹ emphasized that the ability of penicillin "to sensitize and to cause serious and even fatal accidents should not be minimized." The continued extensive use of this valuable drug means that many patients are becoming sensitized to an anaphylactic degree. Under these circumstances the precept of Hippocrates, "Primum non nocere," is apt.

This review, while not intended as a detailed analysis of universal literature, provides a practical discussion of the extent of the problem and of suitable prophylaxis. This subject is not the sole concern of the pharmacologist or allergist, as there must be few doctors, irrespective of specialty, who are not frequent prescribers of this drug. Hence it may fall within the purview of