The Distribution of Glucose-6-Phosphate Dehydrogenase Deficiency in Greece

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STUDIES IN Greece have revealed several hereditary red cell abnormalities in the population of that country. Thalassemia is most common, while the sickling trait is found only in areas with a history of widespread malaria (Malamos, Fessas, and Stamatoyannopoulos, 1962; Barnicot *et al.*, 1963; Stamatoyannopoulos and Fessas, 1964). The X-linked enzymatic abnormality glucose-6-phosphate dehydrogenase (G6PD) deficiency may occur in Greece as commonly as thalassemia. This impression has been gained from the number of cases of favism admitted to hospitals (Zannos-Mariolea and Kattamis, 1961), from the study of random samples of newborns (Fessas, Doxiadis, and Valaes, 1962), as well as from the study of areas selected mainly according to their past malarial endemicity (Choremis, Zannos-Mariolea and Kattamis, 1962; Allison *et al.*, 1963; Stamatoyannopoulos and Fessas, 1964). In the present investigation, a representative sample of the Greek population was studied in order to obtain more systematic information on the distribution of G6PD deficiency in Greece.

MATERIALS AND METHODS

Conscripted airmen, aged 21 to 30 years, serving in the Greek Air Force were examined. Only individuals aware of the exact place of birth of their mother and the origin of her ancestors were selected for study. The 5,828 cases studied fell into two groups.

Series A consisted of 672 airmen whose mothers originate from metropolitan areas of Athens and Salonica; from Asia Minor, eastern Thrace, and the coast of the Black Sea; and from immigrants of the Greek communities of Egypt, Rumania, and Russia.

Series B included 5,156 airmen whose mothers and maternal ancestors came from the rest of the native Greek population. Table 1 shows the distribution of

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TABLE 1. DISTRIBUTION OF THE POPULATION OF GREECE IN THE NINE DISTRICTS COMPARED WITH THE DISTRIBUTION OF THE CASES INCLUDED IN SERIES B (NATIVE POPULATION)

District	Population size as percent of the population of Greece*	Number of persons examined	Sample size as percent of the total cases of Series B
Central Greece	15.7	827	16.0
Peloponnese	17.7	911	17.6
Ionian Islands	3.3	171	3.3
Epirus	5.7	305	5.9
Thessaly	11.2	553	10.7
Macedonia	26.5	1.418	27.5
Thrace	4.4	203	4.0
Aegean Islands	7.7	378	7.3
Crete	7.8	390	7.7
Total	100.0	5,156	100.0

*Population of Greece (census of 1951) after subtraction of the population of Athens, Pireus, and Salonica, which are not represented in series B.

the cases of Series B in the nine Greek districts. There is excellent concordance between the size of the examined samples and the size of the population of the districts.

Venous blood was taken in ACD from two-thirds of the subjects, capillary blood from one-third. When capillary blood was utilized, the tests were performed immediately after the blood was obtained. If an abnormal result was found, venous blood was drawn in ACD and the tests were repeated. When venous blood was used, the tests were performed not later than 48 hours after venesection. The samples were kept at 4° C. All abnormal findings were confirmed by testing a second sample.

The screening method was the Brilliant Cresyl Blue (BCB) decolorization test (Motulsky and Campbell-Kraut, 1961). Samples decolorizing BCB in less than 60 minutes were considered normal, while samples failing to decolorize the BCB in three hours were considered as severely deficient. In samples decolorizing BCB between 60 and 180 minutes, G6PD activity was assayed; the majority of such cases had G6PD levels between 5% and 50% of normal, suggesting presence of a "mild" type of G6PD deficiency, different from the common severe type occurring in Mediterraneans (Stamatoyannopoulos, Panayotopoulos, and Papayannopoulou, 1964).

RESULTS

Of the 672 males of Series A, only 14 were deficient for G6PD. Deficiency was more common among the 5,156 males of Series B, 287 being deficient. The detailed findings in Series A are shown in Table 2. Greeks from Asia Minor, the coast of the Black Sea, and eastern Thrace and immigrants from the communities of Egypt, Rumania, and Russia very rarely had G6PD deficiency; only seven of 478 such individuals were deficient.

The distribution of G6PD deficiency in the native population (Series B) is shown in Table 3. The frequency in series B differs from the frequency in

TABLE 2. G6PD DEFICIENCY IN ATHENS, SALONICA, AND THE NON-NATIVE GREEK POPULATION (SERIES A)

Origin	Number examined	Number normal	Number deficient	Prevalence of G6PD deficiency %
Athens	120	117	3	2.5
Salonica	74	70	4	5.4
Eastern Thrace	127	124	3	2.3
Coast of Black Sea	72	72	0	0
Asia Minor	225	221	4	1.7
Immigrants	54	54	0	0
Total	672	658	14	2.1

TABLE 3. G6PD DEFICIENCY IN THE NINE MAJOR DISTRICTS OF GREECE (SERIES B)

Area	Number examined	Number normal	Number deficient	Prevalence of G6PD deficiency %
Peloponnese	911	857	54	5.9
Central Greece	827	781	46	5.5
Thessaly	553	503	50	9.0
Epirus	305	294	11	3 6
Macedonia	1,418	1,328	90	6.3
Thrace	203	198	5	2.4
Aegean Islands	378	367	11	2.9
Ionian Islands	171	166	5	2.9
Crete	390	375	15	3.8
Total	5,156	4,869	287	5.6

series A ($\chi^2 = 14.8$, 1 df, $P < 0.001$). The anomaly was present in all districts but was apparently more common in Thessaly ($\chi^2 = 14.2$, 1 df, $P < 0.001$). G6PD deficiency was more common in the population of continental Greece (6.1%) than in the islands (3.3%: $\chi^2 = 5.44$, 1 df, $P < 0.02$). The frequency of the mild type of G6PD deficiency among the 287 deficient individuals of Series B is shown in Table 4. In further analysis of these data, the two types of G6PD deficiency were not differentiated.

The frequency of G6PD deficiency in the prefectures of the Peloponnese is shown in Table 5 and Fig. 1. A peculiar clockwise decrease in the frequencies was observed: The higher frequencies were found in the western and northwestern coast prefectures (Fig. 1: Messenia, 1; Ileia, 2; and Achaia, 3); they decreased in the north (Corinthia, 4) and became low in the eastern (Argolis, 5), central (Arkadia, 6), and southern (Laconia, 7) prefectures. The differences were statistically significant ($\chi^2 = 18.2$, 6 df, $P < 0.01$). In central Greece (Table 5), the G6PD frequencies increased from 2.3% in the eastern prefectures (Euboea, 8; Attica, 9) to 6.8% in the central prefectures (Boeotia, 10; Phthiotis, 11; Phocis, 12) and 9.6% in the western prefecture (Aetoloacarnania, 14). G6PD deficiency was absent among 34 males from the mountainous prefec-

TABLE 4. DISTRIBUTION OF CASES WITH MILD G6PD DEFICIENCY

Area	G6PD deficient cases, total	Cases with severe G6PD deficiency	Cases with mild G6PD deficiency
Peloponnese	54	49	5
Central Greece	46	38	8
Thessaly	50	43	7
Epirus	11	11	0
Macedonia	90	79	11
Thrace	5	4	1
Aegean Islands	11	9	2
Ionian Islands	5	5	0
Crete	15	4	11
Total	287	242	45

ture of Eurytania (13). The differences among the prefectures were statistically significant ($\chi^2 = 15.86$, 6 df, $P < 0.02$). In Thessaly (Table 5), with the sole exception of the eastern coast (Magnessia, 15), G6PD deficiency was very common. In Epirus (Table 5), the frequency of the gene fell significantly ($\chi^2 = 9.5$, 1 df, $P < 0.01$) from 7.1% in the southern lowland prefectures (Arta, 19; Preveza, 20) to 0.6% in the mountainous prefectures of the north (Thesprotia, 21; Ioannina, 22). G6PD deficiency was similarly rare in the neighboring mountainous prefectures (23–25) of western Macedonia (Table 6); the mean G6PD deficiency there (1.2%) is significantly lower than in the remaining Macedonian population (Prefectures 26–34, $\chi^2 = 12.7$, 1 df, $P < 0.001$). Higher frequencies (mean 7.8%) were found in central Macedonia (Prefectures 26–32); they fell slightly (mean 6.1%) in eastern Macedonia (Prefectures 33–34) and became very low in Thrace (Prefectures 35–37). (See Table 6.) In the Greek islands, frequencies of G6PD deficiency higher than 5% were found only in the Dodecanese (Prefecture 38) and in one prefecture of Crete (50).

Since G6PD deficiency has been related to the previous endemicity of falciparum malaria, which occurred less frequently with increasing altitude in Greece, the individuals of Series B were also considered according to their origin from highland, semimountainous, or lowland areas (Table 7). The frequency of G6PD deficiency decreased as the altitude increased; thus, from 6.4% in the lowlands, it fell to 4.3% in the semimountainous and 3.6% in the mountainous areas ($\chi^2 = 12.7$, 2 df, $P < 0.01$).

The frequencies of G6PD deficiency were also plotted by three isoaltitude lines (0, 300 and 700 meters) to construct the map of Fig. 2. In this figure, political borders of prefectures were disregarded; for example, western Peloponnese, western Thessaly, eastern Macedonia, etc. have been treated as geographical regions. With this approach, foci of G6PD deficiency over 10% were revealed in many areas, such as the lowlands of Messenia and Ileia (Prefectures 1 and 2, Peloponnese), highlands of Achia (Prefecture 3, Peloponnese), lowlands of Phocis and Aetoloacarnania (Prefectures 12 and 14, central Greece), lowlands of Arta (Prefecture 19, Epirus), lowlands of Karditsa and Trikkala (Prefectures 17 and 18, Thessaly), lowlands and semimountainous

TABLE 5. G6PD DEFICIENCY IN GREECE. DISTRIBUTION IN PELOPONNESE, CENTRAL GREECE, THESSALY, AND EPIRUS

Prefectures	Population of the prefecture as percent of the district population	Number of individuals examined	Size of the prefecture sample as percent of the district sample	Number of normal persons	Number of G6PD deficient persons	Prevalence of G6PD deficiency %
A. *Peloponnese*						
1. Messenia	19.3	180	19.7	164	16	8.8
2. Ileia	17.2	144	15.8	132	12	8.3
3. Achaia	21.8	186	20.4	170	16	8.6
4. Corinthia	10.3	90	9.9	85	5	5.5
5. Argolis	8.2	71	7.8	69	2	2.8
6. Arcadia	12.3	128	14.1	126	2	1.5
7. Laconia	10.9	112	12.3	111	1	0.9
TOTAL	100.0	911	100.0	857	54	5.9
B. *Central Greece*						
8. Euboea	17.1	140	16.9	136	4	2.8
9. Attica	21.1	160	19.4	157	3	1.8
10. Boeotia	11.7	103	12.4	97	6	5.8
11. Phthiotis	16.6	137	16.5	126	11	8.0
12. Phocis	4.9	67	8.1	63	4	5.9
13. Eurytania	4.1	34	4.1	34	0	0
14. Aetoloacarnania	24.5	186	22.6	168	18	9.6
TOTAL	100.0	827	100.0	781	46	5.5
C. *Thessaly*						
15. Magnessia	23.3	128	23.1	123	5	3.9
16. Larissa	34.2	189	34.2	168	21	11.1
17. Karditsa	22.0	124	22.4	109	15	12.1
18. Trikkala	20.5	112	20.3	103	9	8.0
TOTAL	100.0	553	100.0	503	50	9.0
D. *Epirus*						
19. Arta	23.6	86	28.4	80	6	7.0
20. Preveza	17.8	54	17.7	50	4	7.4
21. Thesprotia	14.7	41	13.4	41	0	0
22. Ioannina	43.9	124	40.5	123	1	0.8
TOTAL	100.0	305	100.0	294	11	3.6

areas of Larissa (Prefecture 16, Thessaly), and lowlands of Emathia and Thessaloniki (Prefectures 27 and 30, Macedonia). In both Figs. 1 and 2, the G6PD deficiency focus detected by Fraser *et al.* (1964) in Lemnos (Prefecture 42, Aegean Islands) is included.

DISCUSSION

The method of sample selection is important for population studies in Greece, since recent historical events have altered the constitution of the population in many areas of the country. The most extensive population movement took place in 1922: More than one million Greeks, driven out from Asia

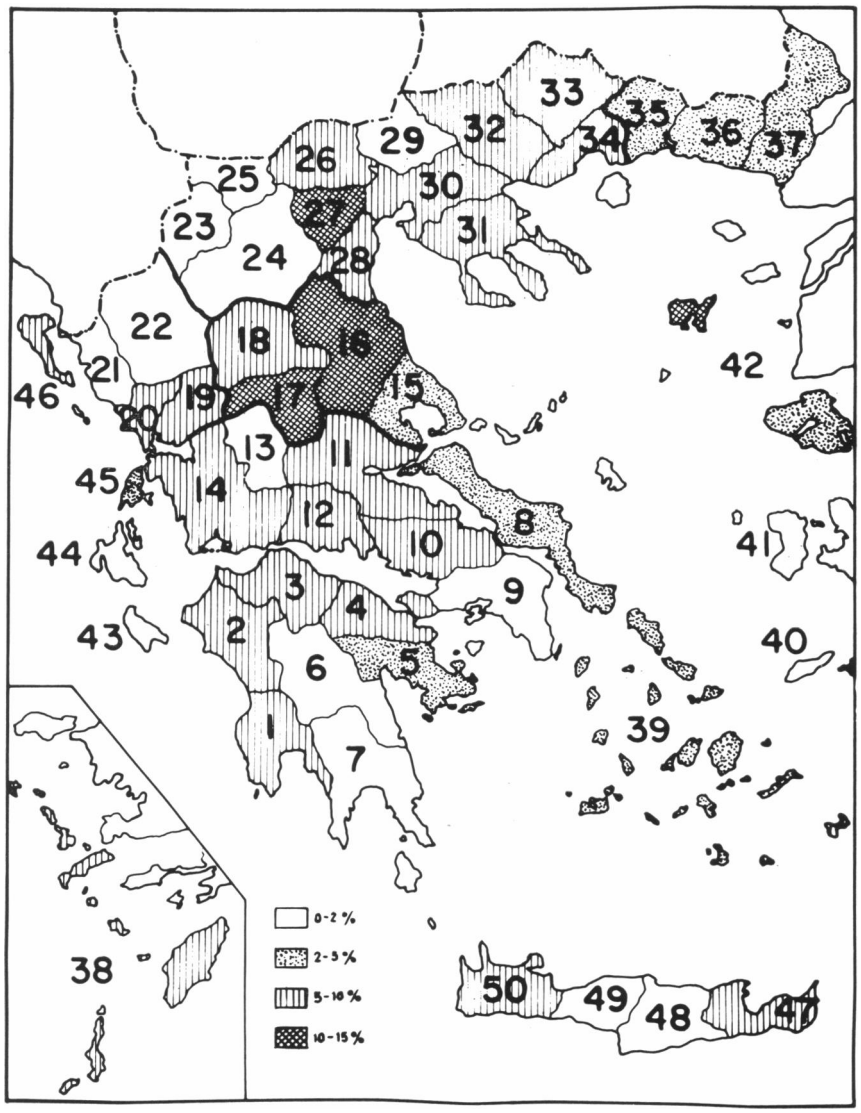

FIG. 1. G6PD deficiency in the 50 prefectures of Greece. Numbering of the prefectures corresponds to Tables 5 and 6.

Minor, the coast of the Black Sea, and eastern Thrace, settled mainly in the agricultural areas of Macedonia and Thrace but also in small communities all over the country. Less extensive movements took place during the German occupation (1941–1944) and subsequently during the guerilla war (1946–1950) when highland populations, particularly of the northern Greek borderlands, moved to towns and to safer lowlands. A careful selection of the sample was thus all the more necessary before attempting any interpretation of our data. These show that the G6PD deficiency gene was present in most of the areas of the country. The wide distribution suggests that this gene is a very old char-

TABLE 6. G6PD DEFICIENCY IN GREECE. DISTRIBUTION IN MACEDONIA, THRACE, AEGEAN ISLANDS, IONIAN ISLANDS, AND CRETE

Prefectures	Population of the prefecture as percent of the district population	Number of individuals examined	Size of the prefecture sample as percent of the district sample	Number of normal persons	Number of G6PD deficient persons	Prevalence of G6PD deficiency %
E. *Macedonia*						
Western						
23. Kastoria	2.9	39	2.8	39	0	0
24. Kozani	11.7	151	10.6	148	3	2.0
25. Florina	4.1	51	3.6	51	0	0
Central						
26. Pella	8.1	121	8.6	114	7	5.7
27. Emathia	7.2	103	7.2	89	14	13.5
28. Pierria	6.0	63	4.4	59	4	6.3
29. Kilkis	6.3	101	7.1	99	2	1.9
30. Thessaloniki	17.8	262	18.5	237	25	9.5
31. Chalkidiki	4.9	72	5.1	66	6	8.3
32. Serrae	15.0	225	15.9	210	15	6.7
Eastern						
33. Drama	7.4	101	7.1	95	6	5.9
34. Kavalla	8.6	129	9.1	121	8	6.2
TOTAL	100.0	1,418	100.0	1,328	90	6.3
F. *Thrace*						
35. Xanthi	25.1	41	20.2	40	1	2.4
36. Rodhopi	30.7	40	19.7	39	1	2.5
37. Evros	44.2	122	60.1	119	3	2.4
TOTAL	100.0	203	100.0	198	5	2.4
G. *Aegean Sea Islands*						
38. Dodecanese	25.8	97	25.7	91	6	6.2
39. Cyclades	20.9	92	24.4	90	2	2.1
40. Samos	10.9	42	11.1	42	0	0
41. Chios	13.0	50	13.2	50	0	0
42. Lesbos	29.4	97	25.6	94	3	3.1
TOTAL	100.0	378	100.0	367	11	2.9
H. *Ionian Sea Islands*						
43. Zakynthos	16.9	30	17.5	30	0	0
44. Cephalonia	21.6	37	21.7	37	0	0
45. Leukada	13.6	25	14.6	24	1	4.0
46. Corfu	47.9	79	46.2	75	4	5.0
TOTAL	100.0	171	100.0	166	5	2.9
I. *Crete*						
47. Lassithi	15.3	59	15.1	56	3	5.0
48. Heraclion	43.1	163	41.8	160	3	1.8
49. Rethymnon	14.5	61	15.7	60	1	1.6
50. Chanea	27.1	107	27.4	99	8	7.5
TOTAL	100.0	390	100.0	375	15	3.8

TABLE 7. G6PD DEFICIENCY IN GREECE. DISTRIBUTION IN HIGHLAND, SEMIMOUNTAINOUS, AND LOWLAND AREAS

	Percentage distribution of the population	Percentage distribution of the examined sample	Number of individuals examined	Number of G6PD deficient individuals	Prevalence of G6PD deficiency %
Peloponnese					
0–300 m	63.6	60.6	552	35	6.3
300–700 m	24.2	20.9	190	9	4.7
700–	12.2	18.5	169	10	5.9
Central Greece					
0–300 m	70.4	62.4	516	29	5.6
300–700 m	20.1	24.8	205	12	5.8
700–	9.5	12.8	106	5	4.7
Thessaly					
0–300 m	75.5	71.6	396	37	9.3
300–700 m	13.7	18.8	104	10	9.6
700–	10.8	9.6	53	3	5.6
Epirus					
0–300 m	35.7	35.4	108	8	7.4
300–700 m	45.6	37.8	115	2	1.7
700–	18.7	26.8	82	1	1.2
Macedonia					
0–300 m	65.4	64.0	908	73	8.0
300–700 m	23.0	22.1	313	14	4.4
700–	11.6	13.9	197	3	1.5
Thrace					
0–300 m	91.4	98.5	200	5	2.5
300–700 m	7.1	1.0	2	0	—
700–	1.5	0.5	1	0	—
Aegean Islands					
0–300 m	86.2	87.6	331	11	3.3
300–700 m	13.8	12.4	47	0	0
700–	—	—	—	—	—
Ionian Islands					
0–300 m	85.6	82.4	141	5	3.5
300–700 m	14.4	17.6	30	0	0
700–	—	—	—	—	—
Crete					
0–300 m	61.7	55.9	218	12	5.5
300–700 m	35.5	41.2	161	3	1.8
700–	2.8	2.9	11	0	—
TOTAL					
0–300 m	68.8	65.4	3370	215	6.37
300–700 m	22.1	22.6	1167	50	4.28
700–	9.1	12.0	619	22	3.55

acteristic of the Greek population, a concept supported by indirect evidence that favism possibly was known to the ancient Greeks (Veras, 1939, quoted by Sansone, Piga, and Segni, 1958).

The distribution of the gene shows several local peculiarities and some general patterns. There was a decrease in gene frequencies from the lowlands to

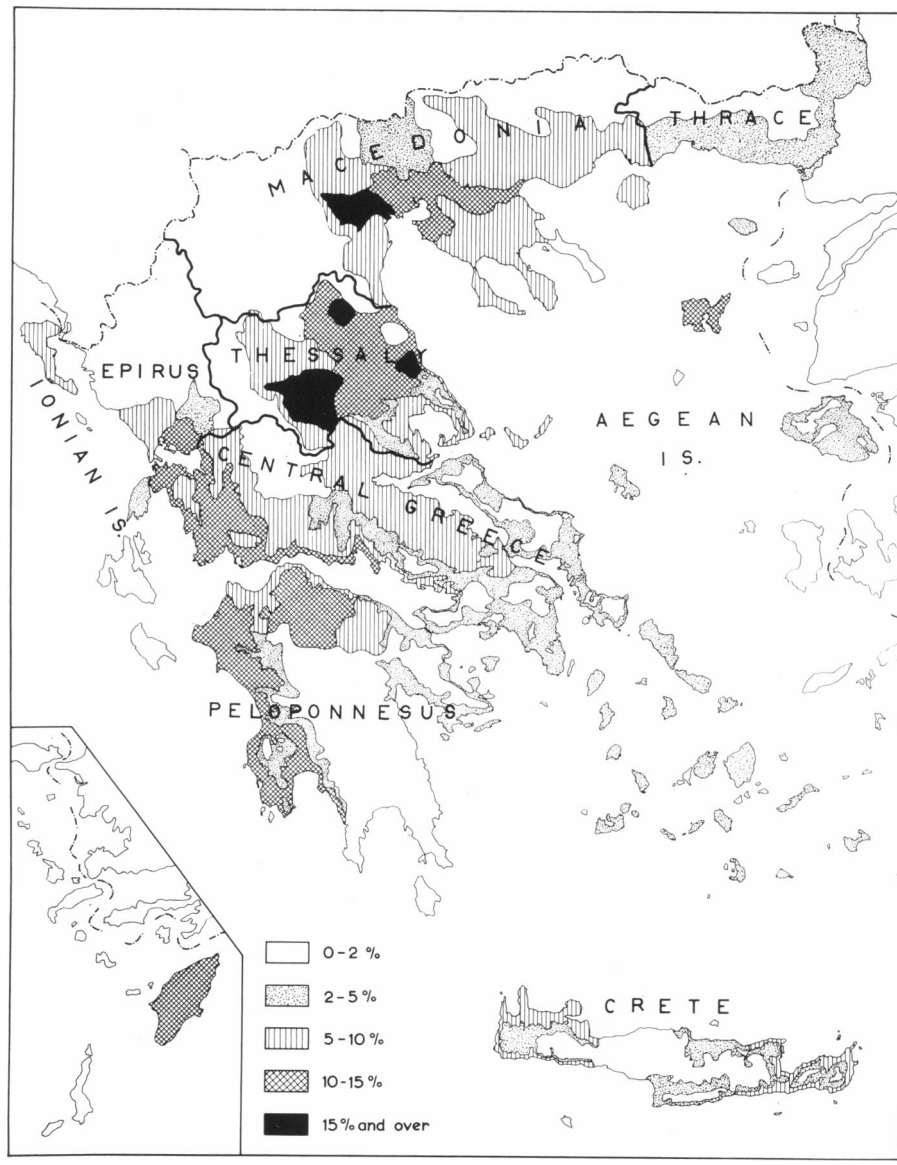

FIG. 2. The geographic distribution of G6PD deficiency in Greece.

the highlands. Frequencies increased from the eastern to the western areas of Peloponnese and central Greece. Higher frequencies of the gene were observed on the mainland as compared with the islands. The low frequencies in the Greeks of Asia Minor and the Pontus and among the immigrants were also interesting. The question arises whether these patterns actually represent differences in G6PD deficiency frequencies in an otherwise homogeneous population, being thus of genetic importance, or whether they simply indicate a lack of homogeneity of the Greek population. Such heterogeneity could derive either from genetic differences in the original races which settled the Greek

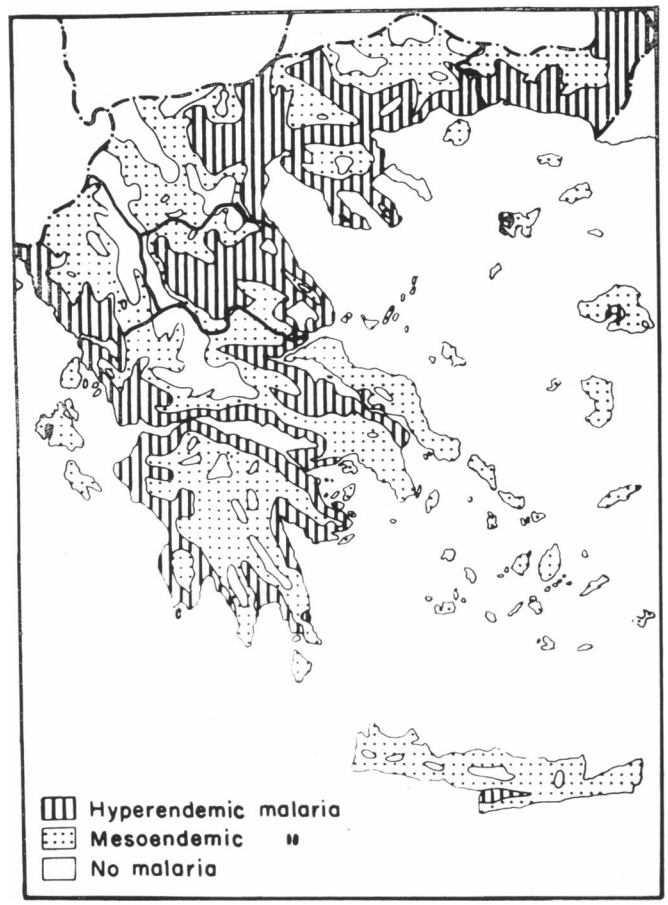

FIG. 3. The distribution of malaria in Greece. The relative proportions of *Plasmodium falciparum*, *P. vivax*, and *P. malariae* all over Greece were 49%, 27%, and 29%, respectively. The map was kindly provided by the Department of Malariology, Athens School of Hygiene.

peninsula 3,000 years ago or could result from subsequent replacement of the Greek races by other ethnic groups.

The correlation of the distribution of G6PD deficiency with the distribution of the ancient Greek races is relatively poor. It is historically documented, for instance, that the settlement of the Doric races was very extensive in the plains of Thessaly, a large part of central Greece, and the major part of the Peloponnese. The G6PD deficiency gene is now rare in most areas of Doric settlement in the Peloponnese but is frequent in those of central Greece and Thessaly. However, the similarity with respect to low frequencies of G6PD deficiency of the population of eastern central Greece and Asia Minor should be noted: Both areas were mainly settled by Ionians. The differences in G6PD deficiency frequencies observed now in lowland Macedonia and Thrace, in populations living under quite similar environmental conditions, should also be noted. The ancient Macedonians were of pure Greek origin, while the ancient Thracians were considered "barbarians" who eventually accepted the Greek

language and culture. It is also of interest that G6PD deficiency is common in the lowlands of Greek Macedonia, while only occasional cases were found by Fraser, Grünwald, and Stamatoyannopoulos (1966) in a sample from Yugoslavic Macedonia, an area in which endemic malaria was present in the past.

The second possibility, attributing the distribution patterns of G6PD deficiency to replacement of the Greek population by other nationalities, is most unlikely, since this replacement presupposes extensive settlement of other ethnic groups, covering the whole country. Many invasions of Greece took place during its long history, particularly between the 6th and the 15th centuries A.D. Extensive settlement, however, of foreign populations has not been historically documented except that of Turkish populations during the four centuries of the Turkish occupation (15th to 19th centuries). During this period, part of the Greek population was converted to Islam and intermarried freely with the new settlers from Asia. The remaining population of slaves, however, did not intermarry either with the conquerors or with those converted to Islam. The Moslems left the country after the revolution of 1821 and the wars of liberation of the early twentieth century.

Since the patterns of G6PD deficiency distribution in Greece cannot be interpreted by historically documented population flows and admixtures, it would be worth while to attempt to explain the data on the basis of selection. Selection for the G6PD deficiency gene in the presence of endemic malaria was postulated by Motulsky (1960) and has been widely accepted. The population data collected so far fit this hypothesis, since high G6PD deficiency frequencies were found only in tropical and subtropical areas with hyperendemic malaria (Motulsky, 1964; Allison, 1961). Endemic and, in many instances, hyperendemic malaria was present in Greece until 1945, mainly in the lowlands, while the highlands were usually free, at least of falciparum malaria (Livadas and Sphangos, 1940; Choremis *et al.*, 1963; G. Belios, personal communication). The frequencies of G6PD deficiency, therefore, in the lowland and highland areas obtained in the present study correlate well with the past distribution of malaria in Greece (Fig. 3). In three areas, however, the data do not fit with the hypothesis (Table 7): In the sample from the Peloponnese, almost equal frequencies of G6PD deficiency are present in the highlands and lowlands, and the findings in the sample from central Greece are similar, while in Thessaly the frequencies do not differ in the lowland and the semimountainous samples. When the samples were further subdivided, however, and the distribution of the individuals by prefecture was considered, highland foci of G6PD deficiency were localized in some areas. It was these foci which were responsible for the increased frequencies of the gene in the total highland samples. Thus in the Peloponnese, the pattern of lower frequencies in the highlands than in the lowlands is found in all areas but two: in the highlands of Corinthia where a focus of high G6PD deficiency exists around the mountainous Lake Stymphalis and in the highlands in Achaia where an isolated area was localized with G6PD deficiency frequency around 15%. In Thessaly, the high prevalence in the semimountainous areas resulted mainly from two

foci, one west of Mount Olympos and a second in the region of Mount Ossa. In central Greece, a detailed study of the distribution of the highland sample did not reveal any such foci.

Differences in malaria endemicity also could be responsible for the other abnormalities in distribution patterns. Malaria was mesoendemic in the Greek islands, and this could accord with the low G6PD deficiency there. The eastern coasts of the Peloponnese and central Greece are relatively dry, not marshy and intensively cultivated, while the western coasts have much higher rainfall and, until recently, numerous lakes and marshes. Immunity against malaria was practically absent in immigrants from Asia Minor and Pontus, who soon after their settlement in the agricultural areas of Macedonia in 1922 presented a very high mortality due to malaria (G. Belios, personal communication). However, it is difficult to assume that differences in the selective action of malaria were the only factor accounting for the distribution of G6PD deficiency in the Greek populations. In the islands and the communities of Asia Minor, isolation and resultant genetic drift could be among the reasons for the G6PD deficiency rates in these areas. In addition, factors which affect the disadvantage of G6PD deficiency carriers, such as differences in *Vicia faba* consumption among populations or the presence in some populations of additional genetic factors enhancing the susceptibility of G6PD deficiency carriers to acute hemolysis, could be of importance in explaining the present distribution of G6PD deficiency frequencies. Such genetic factors acting synergistically with G6PD deficiency have already been postulated on the basis of family material in the case of severe neonatal jaundice (Fessas, Doxiadis, and Valaes, 1962; Flatz *et al.*, 1963; Doxiadis *et al.*, 1964) as well as of favism (Stamatoyannopoulos *et al.*, 1966).

SUMMARY

The distribution of erythrocyte G6PD deficiency in Greece has been studied in a sample of 5,828 males, representative of the distribution of the Greek population. The presence of the abnormal gene in most areas of Greece has been confirmed. The highest frequencies were found in the lowland areas and the lowest frequencies among the Greeks of Asia Minor, the Pontus, eastern Thrace, and in highland populations.

An explanation of the present distribution of G6PD deficiency based on the history and demography of the Greek population does not appear satisfactory. The most clear-cut correlation appears to be that between the distribution of G6PD deficiency and past malarial endemicity.

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