Glucose-6-Phosphate Dehydrogenase Deficiency in Saudi Arabia: A Survey

By A. P. Gelpi

Within the past 10 years the pathogenesis of certain drug-induced hemolytic anemias and favism has been clarified by a number of investigators. Primaquine sensitivity, among others, is now known to be associated with a deficiency of erythrocyte glucose-6-phosphate dehydrogenase (G-6-PD). The incidence of this defect has been estimated at approximately 10 per cent among American negroes and is found in variable frequency among a number of ethnic groups in the Mediterranean littoral, Middle East, and Africa. A survey of the incidence of G-6-PD deficiency has not previously been made on the Arabian peninsula and it is the purpose of this communication to provide some preliminary data relating to the incidence of G-6-PD deficiency in Saudi Arabia.

Materials and Methods

Blood samples were collected by two technics: In part I (pilot study) 5 cc. of venous blood were collected in a dry syringe and immediately released into a clean test tube containing 1 cc. of ACD solution. These samples were stored at 4 C. prior to assay. In parts II and III of the survey, blood samples were taken by finger puncture and collected in capillary tubes. Each sample was mixed with approximately one-fourth its volume of ACD solution and tubes were sealed with Plasticine clay. The tubes were stored in a vertical position in a suitably drilled wooden block at 4 C. Samples were assayed usually within 48 to 72 hours of collection. However, with the screening method employed, G-6-PD activity did not change appreciably for a period of at least 10 days. Two-hundredths ml. of red cell sediment from test tube, or capillary tube, was mixed with 1 cc. of distilled water immediately prior to assay. The dye* test of Motulsky, was used exclusively for the entire survey. After addition of dye-substrate solution to hemolysates, the mixtures were incubated at 37 C. A decolorization time of 120 minutes or less was arbitrarily selected as normal, based upon the experience of other investigators, and on preliminary observations in the course of this study.

Results

The survey was divided into three parts, determined by the results of the pilot study conducted simply to find out if G-6-PD deficiency occurred in Saudi Arabia. The pilot study (part I) consisted of a survey among 229 randomly selected Saudi males and 14 females drawn from the hospital and clinic population. Most of these were Arabian American Oil Company (ARAMCO) employees. In this group 31 males, or 13.5 per cent, had decolorization times greater than 120 minutes. None of the females had decolorization times greater than 120 minutes.

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*Brilliant cresyl blue, manufactured by the National Aniline Division of the Allied Chemical and Dye Corporation, New York, N. Y.
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Fig. 1.—Frequency distribution of decolorization times using the Motulsky dye test among Saudi females.

The survey was extended to include an additional 202 Saudi males and 500 Saudi females (part II). In this group decolorization was observed at 60, 90, 120, 150, 180, 360 minutes and 24 hours. In the pilot study, it had been noted that almost all of the subjects with decolorization greater than 120 minutes showed none at 24 hours, and it was thought that female heterozygotes might be detected with decolorization times between 120 minutes and 24 hours. Twelve females were found to have decolorization times greater than 120 minutes (fig. 1), instead of an expected 113 \(2pq+q^2\). One female had a decolorization time greater than 24 hours. The frequency distribution of decolorization times revealed no modal difference from that of the males (fig. 2) which would select female heterozygotes. Twenty-five Saudi males (12 per cent) were found to have decolorization times greater than 120 minutes; this was not a significant difference from the incidence in the pilot study.

Among the males from both study groups (part I and II) geographic data (village of birth) was available in 306. Forty-six of these subjects were G-6-PD deficient; 42 (91 per cent) were from the oasis area of the Eastern province (table 1). A total of 111 subjects were from the Qatif oasis, of whom 38 (34.2 per cent) were deficient. The difference in incidence of G-6-PD between subjects from the Eastern province and elsewhere in Saudi Arabia is highly significant (table 1), but this difference is due to the concentration of G-6-PD deficient subjects in the Qatif area. \(P < 0.001\).
The peculiar geographic localization of G-6-PD deficiency in Saudi Arabia (fig. 3) encouraged us to include in the survey a smaller study among subjects from representative oases villages (part III). In order to modify the factor of selective bias (clinic population), sampling was done in the villages among a group of 351 male children in conjunction with an annual malaria survey undertaken by Aramco. The incidence of G-6-PD deficiency varied from 24 per cent in one Al-Hasa oasis village to an unexpected 65 per cent in one Qatif oasis village. The ages of the children varied from 4 months to 16 years; 84.5 per cent of those tested were in the 2 to 13-year-old group. Because of the comparatively small number of subjects in consecutive age groups (by years), it was apparent that reliable statistics could not be developed concerning age group differences in G-6-PD deficiency. The incidence of G-6-PD deficiency in each village of Al-Hasa and Qatif oases was compared with that of the group (table 2). With the exception of Qarah, an Al-Hasa village, the differences were not statistically significant.

Of special significance in this study is the fact that until recent years, the two large Eastern province oases were hyperendemic malaria foci. Because of the effective eradication program carried out over the past 10 years, only a very small proportion of village children tested in the G-6-PD survey were found to be infected with malaria. Within this subgroup equal numbers were
normal and deficient in G-6-PD. However, of surpassing importance is the fact that the Qatif oasis is populated almost exclusively by members of the Shiite Muslim sect which is a highly inbred minority group in Saudi Arabia. Among these people marriage practically always involves partners from the same village, and second- and third-cousin marriages are very common. The two Al-Hasa villages included in this survey also happen to be Shiite, which may in part account for the relatively high incidence of G-6-PD deficiency among the children tested as compared with the small group of randomly selected adult employees from the same general area which was composed of both Shia and Sunni Arabs (table 1). Al-Hasa oasis has a number of predominantly Sunni villages, and the majority of the nonoasis Eastern province population belongs to the Sunni sect. The difference between adults and children from the Qatif oasis in the incidence of G-6-PD deficiency cannot be explained. Here again there is a distinct possibility that a proportion of Sunni Arabs from the Qatif oasis were included in the clinic survey. Another possibility is that a significant sampling error was introduced by surveying children from only two villages.

During this investigation several Saudi males were hospitalized in Aramco facilities suffering from an acute hemolytic anemia. In every case it was possible to elicit a history of ingestion of cooked beans within 24-48 hours preceding the development of symptoms. On request we were furnished with samples of the beans and these all proved to be “broad beans,” or Vicia fava. Further investigation revealed that the fava bean has become a staple commodity in Saudi Arabia within recent years and is being imported in considerable quantity from Egypt and elsewhere in the Middle East.

Several of our G-6-PD deficient male subjects were challenged with Primaquine under hospital surveillance, primarily as a check in the accuracy of the screening test. In every instance, with a challenge dose of 60 mg. of Primaquine base daily, there was a well-defined hemolytic episode, although of variable severity among the subjects tested.

**DISCUSSION**

A number of reviews have attested to the extensive distribution of G-6-PD deficiency from Equatorial Africa, through the Mediterranean littoral, the Middle East, and the Far East. The pattern of distribution roughly corresponds to that of the sickle cell and thalassemia traits, and falciparum ma-
laria. The hypothesis,\textsuperscript{7} that G-6-PD deficiency provides a selective advantage for populations in malarious regions, is attractive, but not as well substantiated,\textsuperscript{8-10} as the relationship between the sickle cell trait and falciparum malaria.

Malaria in Saudi Arabia is sharply localized to the Southwestern coastal area, and to the two oases complexes of the Eastern province which have been considered in this report. In a 1947 oasis malaria survey,\textsuperscript{6} parasite rates in children of the 2-14 year age group were: 71.4 per cent (24.5 per cent falciparum) in Safwa, 77.4 per cent (26.2 per cent falciparum) in Al-Ajam, and 100 per cent (39.7 per cent falciparum) in Qarah, representing 3 of the 4 communities studied in the G-6-PD survey (table 2). In the malarial survey of 1962, the parasite rates were: 0 per cent in Safwa, 0 per cent in Al-Ajam, and 0.6 per cent in Qarah. Thus within a 15-year period, malaria eradication has all but been achieved in the Eastern province. It may be possible, under these circumstances, to relate a change in incidence of G-6-PD deficiency to the endemity of malaria. Large numbers of individuals from various age groups should be studied in order to derive significant information. Information regarding the ages of Aramco employees and their dependents is reasonably accurate, less so among village children who are not employee dependents, and probably quite unreliable among adult nonemployees.

The only other genetic marker which has been studied in this locality is
the sickle cell trait. As expected, the distribution is similar to G-6-PD deficiency with the highest incidence in the Qatif oasis, 25 per cent. Interestingly, the incidence is 2½ times greater among Shiites of the Eastern province than among the Sunnis. Anthropometric investigations, on a limited scale, have been carried out on the Shiite inhabitants of Al-Hasa and Aqtif oases, and there are definite similarities between the two populations, as well as distinctive differences from the majority of the no-oasis inhabitants, who represent the Sunni Muslim sect. Religious tradition links the Shiite group in Eastern Saudi Arabia with the Arabs of Bahrain Island, and Southern Iraq. What ethnic bonds exist between these groups remains to be determined, but there is some archeologic evidence that commerce and cultural exchanges took place in the second and third millenium B.C. between Bahrain, Southern Iraq, the coastal strip of Eastern Saudi Arabia and Kuwait, 12.

A G-6-PD survey has not thus far been carried out in the Persian Gulf area, excluding Saudi Arabia, and only a small number of subjects have been tested from Iraq. A comprehensive study along the Western perimeter of the Persian Gulf may yield much valuable information regarding the relative importance of falciparum malaria in determining the incidence of G-6-PD deficiency, as the malarial regions are sharply circumscribed. However, the data presented in this report would not support the contention that malaria in the major part is responsible for the high gene frequency of G-6-PD deficiency. A more plausible explanation is that malaria some time in the past altered the genetic constitution of oasis inhabitants in the Eastern province of Saudi Arabia. With the early penetration of Islam this population became Shiite. It remained essentially isolated until enforced admixture with Sunnis from the West occurred, particularly in the last century with the punitive forays of the fundamentalist Wahabi (Sunni) group. The Shiites as an ethnic group remained inviolate although they did, and do live side by side in some villages with Sunnis.

In summary: what may have begun thousands of years ago as a gradual change in genetic composition through a number of generations, possibly influenced by the presence of malaria, became a stable genetic pattern in a population isolate. In broad terms this is the phenomenon of "genetic drift," a stable genetic composition maintained by geographic or self-imposed segregation.

Of considerable interest is whether the G-6-PD deficiency seen locally represents the "Caucasian" or "negro" type, or both. The history of the
Persian Gulf area is replete with accounts of the importation of negro slaves from East Africa, and negroid types are seen frequently among the Eastern province populations; however, they do not appear in the isolated populations of the oasis Shiites. Quantitative assay studies \((G-6-PD)\) are currently underway to provide some information on this point. Numerous cases of favism seen in the Aramco medical facilities in the past 3 years suggest that the local \(G-6-PD\) deficiency is mostly the "Caucasian type."\(^{14}\)

**SUMMARY AND CONCLUSIONS**

A survey of red cell \(G-6-PD\) deficiency has been conducted among 1296 Saudi subjects. Thirteen percent of randomly selected male subjects and 2.4 percent of the females tested were found to be \(G-6-PD\) deficient. In this study, the screening test employed did not detect female (partially \(G-6-PD\) deficient) heterozygotes. The deficiency appeared to be localized to the oasis of the Eastern province, and in village studies a very high incidence was found in male children from the Qatif and Al-Hasa oases. The geographic limits of \(G-6-PD\) deficiency correspond precisely to the areas known to be hyperendemic for malaria in previous years. However, the population group affected represents a distinct minority in terms of religious and cultural tradition, and anthropometric type. In Saudi Arabia, \(P. falciparum\) malaria does not appear to be the only significant factor determining marked regional differences in the incidence of \(G-6-PD\) deficiency: this genetic marker is essentially confined to the Shiite muslim population. The Sunni population, regardless of its proximity to areas of endemic \(P. falciparum\) malaria, has a low incidence of \(G-6-PD\) deficiency.

**SUMMARIO IN INTERLINGUA**

Esseva effectuate un studio representative de carentia de dehydrogenase de glucosa-6-phosphato \((DG-6-P)\) del erythrocytos in 1296 sauditas. Esseva trovate que 13 pro cento del aleatorimente seligite subjectos mascule e 2,4 pro cento del femininas testate esseva carente in \(DG-6-P\). In iste studio, le test de detection general que esseva empletate non identificava heterozygoticos feminin (con carentia partial de \(DG-6-P\)). Il pare que le carentia esseva localisate in le oases del provincia oriental, e in le studios de villages un altissime incidentia esseva trovate in juveniles mascule in le oases de Qatif e Al-Hasa. Le limites geographic del carentia de \(DG-6-P\) corrisponde precisemente con illos del areas que priviemente esseva cognoscite como hyperendemic pro malaria. Tamen, le population affcite per le condition representa un distincte minoritate per su traditiones religiose e cultural e per su typo anthropometric. In Arabia Saudita malaria de \(Plasmodium falciparum\) non pare esser le sol factor significative in le determination de marcate differentias regional in le incidentia de carentia de \(DG-6-P\). Iste marca genetic es essentialmente restringite al chiitas. Le sunnitas, sin reguardo a si o non illes habita areas vicin a endemic malaria de \(P. falciparum\), ha un basse incidentia de carentia de \(DG-6-P\).

**ACKNOWLEDGMENT**

The technical assistance of Miss Margaret Butler (Dhahran, Saudi Arabia) is greatly appreciated.
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