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although not in such extensive form. The purpose of this declaration—
apart from any considerations of a fiscal nature—is to maintain disinsecti-
uation campaigns under constant control so that, in the event of there being
no apparent disease, they are not instituted only where vectors are present.
Malaria has always been characterized in Spain by the existence of clearly
defined foci. Its appearance is closely associated with agricultural irrigation,
the courses of certain rivers, the existence of marshy ground and, above all,
the growing of certain crops and the carrying out of work which calls
for the movement of a large labour force. All these facts have obliged
us to consider under what circumstances disinsectization should be made
compulsory.

Uniformity of agrarian factors (such as irrigated fields, non-irrigated
terrain, or wooded country) and of climatic conditions, similarity of
customs, identity of the vectors etc., combined with the existence of a
source of infection, define what we call a “geo-epidemiological unit”. The
more distinct are these characteristics, the more complete are the
results obtained, since it is from these zones, to which it was originally
confined, that malaria spread as a result of periodic movements of the
population.

In conclusion, we may note that, in implementing its malaria control
programme, the Spanish administration has had to rely on the country’s
own financial resources. Highly satisfactory results have been achieved,
at a relatively low cost, by adhering to a policy governed by the following
principles. Chlorinated insecticides are used only in the hyperendemic
zones, and the source of residual infection is eliminated by distributing
the most effective synthetic antimalarial drugs through a wide and well-
organized network of dispensaries.

Sickle-cell Trait and Malaria in Africa

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In thalassaemia major (microcythaemia, Mediterranean anaemia) the
production of normal adult haemoglobin (haemoglobin A) is inadequate.
The paradoxical picture results of a hypochromic microcytic anaemia, such
as is usually caused by an iron deficiency, with considerable iron deposits
in the bone marrow. Foetal haemoglobin (haemoglobin F), the other
physiological haemoglobin, is nearly always produced in this condition,
possibly to compensate for the shortage of A. F usually disappears from the
blood within the first six months of life, but in thalassaemia varying amounts
may be present at an age at which it is no longer found in normal persons.
The production of F does not appear to be subject to simple genetical
control and it is certainly not determined by an allele of the gene responsible
for the specificity of A. The presence of F in thalassaemia, or for that matter
in other congenital anaemias, does not indicate that there has been a
 genetic replacement of A by F. The thalassaemia gene, although influencing
the production of A, is also not an allele of the gene responsible for the formation of A.

There are, however, numerous conditions where A itself is replaced by abnormal haemoglobins—sickle-cell haemoglobin (S), C, D, E or G. Two genes, one from each parent, are responsible for the production of the adult haemoglobin and its variants, and each gene independently produces its quota of the corresponding haemoglobin, so that various mixtures of haemoglobins may result.

When a heterozygous combination of A and of an abnormal haemoglobin is present, the condition is usually called a trait and is generally considered harmless. AS denotes the sickle-cell trait, AC the haemoglobin C trait, AD, AE, AG denote the traits for C, D, E and G respectively.

As the thalassaemia gene is not an allele of the A gene the inherited haemoglobin composition in thalassaemia is AA. If one gene for thalassaemia is present, i.e., the individual is heterozygous for thalassaemia, the condition is called thalassaemia minor, and the person concerned is a carrier of the thalassaemia trait.

The homozygous inheritance of the abnormal haemoglobin genes usually leads to disease. SS is the composition found in sickle-cell disease, CC in haemoglobin C disease, and EE results in a mildly haemolytic condition, i.e., haemoglobin E disease. The one case of GG seen did not suffer from anaemia, and DD has not yet been observed.

In thalassaemia major the genes for haemoglobin A production are both present, but the thalassaemia gene is inherited in the double dose—with the result of a severe suppression of A formation.

Not only the homozygous inheritance of an abnormal haemoglobin, but also the heterozygous combination of two different abnormal haemoglobins, may cause disease. Furthermore in individuals doubly heterozygous for one abnormal haemoglobin gene and for one thalassaemia gene the combination of the two will not express itself in a co-existence of a harmless haemoglobin trait and the equally harmless thalassaemia minor. Four such heterozygous conditions are known so far, three of them resulting in a less severe form of sickle-cell anaemia:

- **AS** + one thalassaemia gene . micro-drepanocytic disease
- **SC** . . . . . . . . . . sickle-cell haemoglobin C disease
- **SD** . . . . . . . . . . sickle-cell haemoglobin D disease
- **AE** + one thalassaemia gene . a disorder showing the modified features of haemoglobin E disease and of thalassaemia

Though it can usually be assumed that the homozygous inheritance of the sickle-cell gene results in a severe haemolytic anaemia and that the heterozygote exhibits the harmless trait some modification of this theory may well be indicated. Certainly the AS combination is not always harmless; and we have recently suggested that the SS combination may not always cause anaemia, though on family study we found that our SS cases were in fact heterozygotes for sickling and thalassaemia—or a thalassaemia-like condi-
tion. Singer and his colleagues have recently described varying degrees of severity of micro-drepanocytic disease: "The severity of an anaemia does not depend only on the rate of disintegration of the red cells but also on the ability of the bone marrow to compensate for this mechanism." Nevertheless the fact remains that the presence of these genes, which are responsible for the inheritance of abnormal haemoglobins in a population, must result in an over-all picture of congenital haemolytic anaemia or disease in the homozygotes and in the doubly abnormal heterozygotes and that, according to the laws of natural selection, these genes would not be found in a high proportion of the population unless there were a balancing factor.

Surveys carried out in order to ascertain the incidence of abnormal haemoglobins have disclosed a very high prevalence of these genes in many populations. In particular in the tropical belt of Africa the number of individuals born with sickle-cell anaemia must be enormous, and it has been calculated that there must be a quarter of a million cases in British West Africa. In the southern Gold Coast, where the prevalence of haemoglobin C is also high, three out of every hundred children born should suffer from some form of abnormal haemoglobin disease. To allow for the persistence of these haemoglobins a balancing factor must be assumed.

One of the compensating factors which has been considered was a possible increase in the mutation rate for S sufficient to replace in each generation the loss caused by the death of homozygotes before the age of reproduction was reached. There has however been no convincing evidence of such an increased mutation rate in the populations concerned, and the rate of mutation required would be many times greater than that known for any other human gene.

A further possible compensating factor is "balanced polymorphism." While selection acts against the survival of homozygotes for the abnormal gene, the heterozygote for both the normal and the abnormal genes possesses a survival-advantage over the normal homozygote. Thus, as far as the genetic composition of the whole population is concerned the loss of abnormal genes by death of homozygotes is balanced by the loss of normal genes due to the greater mortality of normal homozygotes. From the beginning this advantage of heterozygotes over normal homozygotes has been thought to be an increased resistance against malaria. Haldane proposed this explanation when he discussed the population dynamics of thalassaemia (Montalenti). For the sickle-cell gene similar suggestions were made by Raper, Beet, Brain, and Mackey & Vivarelli. Beet went as far as to examine blood-slides of sicklers and of non-sicklers for malaria parasites,

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b Singer, K., Singer, L. & Goldberg, S. R. (1955) Blood, 10, 405
c Noel, J. V. (1953) Amer. J. hum. Genet. 5, 154
e Montalenti, G. (1949) Ricerca sci. 19, Suppl., p. 75
i Brain, P. (1952) Brit. med. J. 2, 880
j Mackey, J. P. & Vivarelli, F. (1952) Annual report of the Tanganyika Medical Laboratory, Dar Es Salaam
but the results were not of statistical significance. Kennaway has recently pointed out that it may be fallacious to concentrate too seriously on statistical significance when selective mechanisms in man are examined. Clearly unless they proceed at a lightning speed sufficient to change the human race in a few generations it will be impossible to gather by a mere contemporary survey results which equal in significance those obtained from a study of many generations of *Drosophila*.

It was thus a considerable step forward when Allison reported that he had in fact obtained statistically valid evidence on a negative correlation between the sickling trait and malarial infection. He compared the parasite-rates in children under 5 years of age in the Kampala region and found that 43 sickling children showed a parasite-rate of 27.9%, and 247 non-sicklers a rate of 45.7%. As a result of inoculating highly immune East African adults with an African or a Malayan strain of *Plasmodium falciparum* he found that only 2 out of 15 sickle-cell trait carriers (i.e., heterozygotes) developed malaria, while 14 out of 15 non-sicklers (i.e., normal homozygotes) developed malaria.

There has been much controversy over Allison’s results. Raper stated that “this difference seemed so striking that it was reasonable to wonder why it had not been noticed already”. Allison had gone as far as to suggest that there might possibly be no anthropological significance in the distribution of the sickle-cell gene, and that its possession might depend on whether a particular population lived in a highly malarious area or not. The anthropological significance of the trait will have to be reviewed in the light of the evidence for balanced polymorphism, but Roberts & Lehmann have pointed out that the Northern and Southern Nilotes though both living in a highly malarious area differ by the complete absence of sickling among the former and a high incidence in the latter. Neither Raper, nor Moore, Brass & Foy in two samples, nor Edington in two samples could confirm an association between the parasite-rate and sickling such as claimed by Allison. When Beutler, Dern & Flanagan inoculated sickling and non-sickling adults with malaria, all became infected and “though the parasitaemia tended to be somewhat less marked in the men with sickle trait . . . the difference observed was unimpressive and of questionable significance”. Nevertheless only Brass and his colleagues rejected Allison’s claims outright, the other workers believed with Raper that “Allison had accentuated a difference that was real but actually of lesser magnitude”.

Allison himself had already suggested “that the protection afforded by the sickle-cell trait is more effective against *P. falciparum* than against other species of plasmodia”. The subsequent positive results were all obtained

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References:

by concentrating on malignant tertian malaria rather than on malaria as a whole. Raper, in an examination of over 2000 individuals in Kampala, concentrated on the degree of parasitaemia rather than on the infection-rate, and on the age-group at which immunity is not yet acquired. i.e., on infants below the age of two. From this study he obtained statistically significant evidence of much lower P. falciparum densities in sicklers than in non-sicklers. It is therefore to be expected that sickling infants will have a lower mortality from malaria. In Accra, Colbourne & Edington, who originally did not obtain statistically significant results, have shown with a larger sample that not only densities but also parasite-rates of P. falciparum were considerably lower in sicklers under five years of age than in their non-sickling brothers. No difference was noted in adults. However in a holoendemic area acquired immunity would be expected to protect sickler and non-sickler alike, and only the children who are too young to have acquired immunity die from malarial infection in holoendemic surroundings.

Although work on the correlation of malaria and sickle-cell trait is only beginning, there are already problems which arise from it. Whether the sickle-cell haemoglobin protects against other diseases than malaria will have to be investigated. Similarly it is possible that abnormal haemoglobins other than the S variant may afford protection against malignant tertian malaria. Even the physiological foetal haemoglobin may have such a function. It is present in thalassaemia heterozygotes. Its normal presence in infants up to the age of six months may be one of the factors responsible for the lower infection-rate up to that age.

The geographical distribution of thalassaemia and of the abnormal haemoglobins could serve to indicate in which direction we may have to search for a possible part they play in protecting against disease.

Thalassaemia is present in nearly all Mediterranean countries, in the Middle East, India, Siam and possibly in Southern China.

Haemoglobin D has been found in three instances only, twice in Caucasian families in the USA and Great Britain respectively, and once in a Sikh in India.

Haemoglobin C is found in high frequency in certain parts of West Africa, but not in Central or in East Africa. Some examples have been reported from North and South Africa where the gene for C has presumably been imported with West African slaves. Mourant has suggested that the gene for haemoglobin C may arise from a mutation of that for S, and that it may carry similar advantages without the disadvantages of S. Haemoglobin C may, like S, be less palatable to P. falciparum than normal haemoglobin, and haemoglobin C disease is less severe than sickle-cell anaemia. As C does not cause the sickling phenomenon, crises and other catastrophes associated with intravascular sickling do not arise.

Haemoglobin E has been found in notable frequency in Siam and in Indonesia; it seems to be frequent in Burma, and has been reported in isolated cases from India and Ceylon.

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Since this note was submitted in September 1955, there have been rapid developments in the field of haemoglobinopathies: the condition DD has been discovered, and another doubly heterozygous condition (AH+one thalassaemia gene) has been described. More knowledge on the world distribution of the abnormal haemoglobins has been accumulated. Haemoglobin D has been found at a low but regular incidence in north-west Indians and in Gujeratis from what used to be the Bombay Presidency. Haemoglobin E has been traced in more populations in South-East Asia, and, more recently, haemoglobins such as H and J have been found in some populations at a definite though low frequency. More work on the connexion between sickling and malaria has been carried out in Greece, and in French African possessions. Of particular interest for Africa are perhaps the following investigations. Colbourne & Edington have extended their survey from the southern Gold Coast to the northern Gold Coast, an area where haemoglobin C is more frequent than haemoglobin S. In contrast to their observations in the south, no negative correlation between malaria and sickling could be demonstrated in the north. One possible explanation is that, as we have suggested above, haemoglobin C has to be taken into account in such surveys. In East Africa, Raper has brought some initial positive proof supporting the hypothesis that children who are heterozygous for the sickling gene have a greater chance of surviving than normal children when both are exposed to malarial infection. In Kampala, nearly ten times as many non-sicklers than sicklers were admitted to the children's ward for treatment of malaria. Of the 13 sicklers all suffered from uncomplicated malaria; of the 123 non-sicklers, only 70; of the others, 47 had cerebral malaria, and 6 blackwater fever.

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The Influence of Malarial Infection of the Placenta on the Incidence of Prematurity *

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In his investigation of the effect of malaria on African infants and children in Southern Nigeria, Bruce-Chwatt noted the influence of malarial infection of the placenta on the weight at birth of 310 African infants. He found that of 73 infants delivered from infected placentae, 15 (20.3%) were premature, as compared with 26 under-weight births from 237 non-

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b According to the WHO definition of prematurity, the weight of a premature infant at birth is 51/2 lb. (2500 g) or less (see Wld Hlth Org. techn. Rep. Ser., 1950, 27, 4).