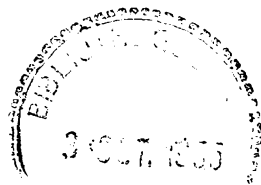


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The Chief of the Malaria Section
has the honour to communicate hereunder the
following note:

SICKLE-CELL TRAIT AND MALARIA
IN AFRICA

by

Dr G. M. EDINGTON
The Medical Research Institute, Accra, Gold Coast

and

Dr H. LEHMANN
St Bartholomew's Hospital, London

In the last ten years a great deal has been learnt about certain inherited haemolytic anaemias.

Thalassaemia

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. The other physiological haemoglobin, foetal haemoglobin (haemoglobin F) 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 under a 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 gene for the formation of A.

Abnormal Haemoglobins

There are however now known 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.

Normal - Abnormal Heterozygotes (Traits)

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.

Homozygotes

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 - 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.

Heterozygotes for two abnormal Genes

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.

Limitations of genetic Theory of Disorder

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 is indicated. We have recently discussed these exceptions⁽¹⁾ and it can be stated that the SS combination may not always cause anaemia, and that the AS combination is not always harmless. We do not yet know the extent to which these exceptions exist. Similarly Singer and his colleagues⁽²⁾ 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 responsible for the inheritance of abnormal haemoglobins in a population must result in an overall 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 should not be found in a high incidence unless there was a balancing factor.⁽³⁾

Abnormal Haemoglobins and Population Dynamics

Surveys of incidence of abnormal haemoglobins have disclosed a very high incidence 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 of them in

British West Africa. In the Southern Gold Coast where there is also a high incidence of haemoglobin C, 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.

Compensation by high mutation rate

One of the compensating factors 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,⁽⁴⁾ and the rate of mutation required would be many times greater than is known for any other human gene.

Compensation by balanced polymorphism

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. "Professor Haldane ha suggerito in comunicazione verbale che gli individui microcitemici, i quali fra l'altro hanno resistenza globulare aumentata, possono essere più resistenti all' infezione malarica." (Motalenti, 1949⁽⁵⁾). For the sickle-cell gene similar suggestions were made by Raper,⁽⁶⁾ Beet,⁽⁷⁾ Brain⁽⁸⁾ and Mackey & Vivarelli.⁽⁹⁾ Beet went as far as to examine blood slides of sicklers and of non-sicklers for malaria parasites, but the results were not of statistical significance. Sir Ernest Kennaway⁽¹⁰⁾ 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.

Allison's Investigations

It was thus a considerable step forward when Allison⁽¹¹⁾ 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%. Upon inoculation of highly immune East-African adults with an African or a Malayan strain of P. 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.

Further Investigations into the Relation between Sickling and Malaria

There has been much controversy over Allison's results. Raper⁽¹²⁾ stated that "this difference seemed so striking that it was reasonable to wonder why it had not been noticed already". Allison⁽¹³⁾ 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⁽¹⁴⁾ 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,⁽¹²⁾ nor Moore, Brass & Foy⁽¹⁵⁾ in two samples, nor Edington⁽¹⁶⁾ in two samples could confirm an association between parasite rate and sickling such as claimed by Allison. When Beutler, Dern & Flanagan⁽¹⁷⁾ 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 et al.

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". Subsequent positive results were all obtained by concentrating on malignant tertian malaria rather than on malaria as a whole. Raper⁽¹²⁾ examined over 2,000 individuals in Kampala. Concentrating 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, he obtained statistically significant evidence of much lower P. falciparum densities in sicklers than in non-sicklers. Sickling infants would therefore be expected to die to a lesser extent of malaria. Colbourne & Edington⁽¹⁸⁾ in Accra 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 holo-endemic area acquired immunity would be expected to protect sickler and non-sickler alike, and only the children who have not yet acquired their immunity die from malarial infection in holo-endemic surroundings.

Other Lines of Research

While 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.

Geographical distribution of thalassaemia and abnormal haemoglobins

The distribution of thalassaemia and of the abnormal haemoglobins may serve as indicating 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 Caucasoid 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 at considerable incidence 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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