was only Hb A, while his wife (IV 6) who was not related to him showed 3.3% Hb A_2 in her blood and was therefore classified as a Cooley trait. There are two boys (V 5 and 7) from this marriage. Each of them showed traces of Hb A_2 in their bloods, but these are within normal limits.

The daughter is the propositus, and showed 54.4% of Hb S and 10.7% of Hb F and is clinically a case of Hb S thalassaemia disease or drepanocytic anaemia.

The youngest daughter (IV 10) of III 3 shows 1.7% of Hb A_2 and her husband is normal, but three of her children whose bloods were investigated showed excess of Hb A_2 (V 10, 11, and 12). We were not allowed to investigate the blood of the youngest male infant aged 4 months (V 13).

The findings suggest that their mother (IV 10) was a carrier of the Cooley gene even though the level of the Hb A_2 discovered in her blood was within normal limits (A_2=1.7%). The grandmother of the propositus (III 3) by her second marriage has produced two sicklers, a girl aged 12 years (IV 12) with 39.4% Hb S and a boy aged 13 (IV 11) with 43.1% Hb S. They were not anaemic on inspection (Hb 8.8 and 9.2 g./100 ml.), but both of them showed signs of vitamin-A deficiency in their eyes.

Summary

The interest in this family lies in the following facts.

It has shown the sickle-cell gene in three generations of a family in which 17 members were investigated. We were not able to investigate generations I and II. Only the propositus, who had Hb F as well as Hb S in excess, was clinically affected.

One of the members (III 1) showed a Hb E trait. His family was not available for further investigation.

Hb F was shown in excess only in the propositus and her paternal grandmother.

Hb A_2 or the Cooley gene was found in five members, including the mother and paternal grandmother as well as in all three children of the paternal aunt of the propositus (V 10, 11, and 12). The mother of these children, however, only showed 1.7% Hb A_2, which is well within normal limits. Two brothers of the patient showed only small traces of Hb A_2 in their blood.

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The Medical Officer of Health, Stockport, has issued the fifth edition of the handbook "A Guide to the Health Services of Stockport." It is in three sections. Section I outlines the services provided by and under the direct administration of the local health authority. The hospital and specialist services administered by the Stockport and Buxton Hospital Management Committee on behalf of the Manchester Regional Hospital Board are described in Section II. The following services are directly administered by the Board: tuberculosis, venereal diseases, laboratory services, and mass miniature radiography. A brief description of the general medical practitioner, dental, pharmaceutical, and ophthalmic services is contained in Section III.

COMBINATIONS OF HIGH LEVELS OF HAEMOGLOBIN F WITH HAEMOGLOBINS A, S, AND C IN GHANA

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From Ghana came the first report of the existence of a benign condition in which haemoglobin S together with a high level of foetal haemoglobin persists into adult life (Edington and Lehmann, 1955a). The two subjects concerned were originally thought to be adult sickle-cell homozygotes, but family studies showed that their high levels of foetal haemoglobin were transmitted to their children independently of haemoglobin S (Edington and Lehmann, 1955b). Although in both propositi haemoglobin S was the major component, they appeared fit and exhibited neither microcytosis nor anaemia. This was in direct contrast to other conditions in which a mixture of haemoglobins S and F may be found—namely, sickle-cell disease and sickle-cell thalassaemia. Similar reports of subjects showing persistence of haemoglobin F in combination with haemoglobin A or S came from Uganda (Jacob and Raper, 1958) and Jamaica (Went and MacIver, 1958), and the absence of any of the morphological stigmata of classical thalassaemia was noted by these workers. Lehmann (1959) termed the condition non-microcythaemic thalassaemia, but this description failed to get official recognition (*British Medical Journal*, 1960). There have been full reviews of the now considerable number of observations of this condition by Rucknagel and Neel (1961), Bradley, Brawner, and Conley (1961), and Huisman (1962).

Comparable combinations between haemoglobins C and F were reported from America by Kraus, Koch, and Burckett (1961) and Schneider, Levin, and Everett (1961), and from Jamaica by MacIver, Went, and Irvine (1961).

The present paper is concerned with two families in Accra whose members demonstrate combinations of haemoglobins S and F in one instance, of haemoglobins C and F in another, and of A and F in several.

Methods

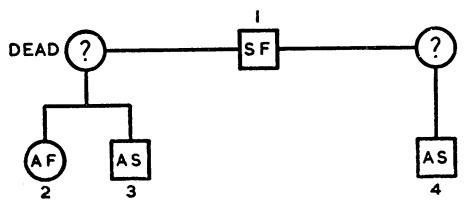
Venous blood was obtained from all the subjects concerned and submitted to paper electrophoresis and alkali denaturation. Electrophoresis was performed in hanging strip tanks on Whatman No. 1 paper using barbitone buffer at *p*H 8.8. Alkali denaturation was performed using the one-minute method of Singer, Chernoff, and Singer (1951). The presence of haemoglobin S was confirmed where indicated by sickling tests, using 2% sodium metabisulphite (Daland and Castle, 1948). Leishman-stained thin blood films were examined for evidence of microcytosis and target cells. Haemoglobin concentrations were determined with a photoelectric colorimeter. Haemoglobin A_2 levels were

determined by paper electrophoresis using TRIS buffer (*p*H 8.9), the resultant patterns being compared with those of other samples whose haemoglobin A_2 percentages had previously been determined by elution after starch block electrophoresis (Lehmann and Ager, 1960).

Family Studies

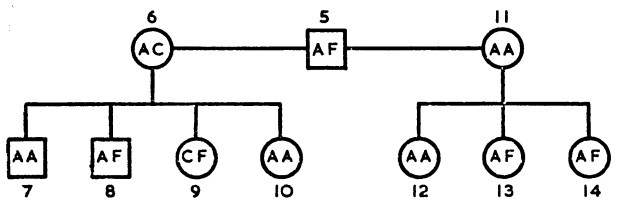
Investigations were initiated after abnormal electrophoretic patterns had twice been noted during a survey. In both instances a band of Hb-F was visible just proximal to where Hb-A would have travelled, the resultant patterns being similar to those observed with the haemoglobin S and haemoglobin C traits, but with reversal of the usual preponderance of A over S and C respectively, and with F substituted for A.

The Dagomba Family.—All members were normal on clinical examination and gave no past history of unusual symptoms. Examination of blood films showed no microcytosis.



DAGOMBA FAMILY TREE

The Dagarti Family.—Most members of this family could recall episodes of fever and abdominal pain, as can most Africans, but these episodes seemed to have been particularly severe and frequent in Cases 9 and 14. Clinical examination revealed no abnormalities; in particular there was no splenomegaly. Haematologically no microcytosis was observed in any of the films, but that of Case 9 contained numerous target cells.



DAGARTI FAMILY TREE

Personal and haematological data of the members of both families are summarized in the Table. No increase in haemoglobin A_2 was found among any of the carriers of the high F gene.

Table of Laboratory Data

Family	Case No.	Sex	Age in Years	Hb Type	Hb-F (%)	Hb (g./100 ml.)
Dagomba	1	M	42	SF	34·7	16·5
	2	F	10	AF	34·4	14·6
	3	M	9	AS	<2	12·7
	4	M	2½	AS	<2	11·7
Dagarti	5	M	48	AF	17·2	13·7
	6	F	40	AC	<2	14·9
	7	M	12	AA	<2	13·1
	8	M	9	AF	31·5	16·9
	9	F	7	CF	26·9	13·4
	10	F	4	AA	<2	13·1
	11	F	>20	AA	<2	10·9
	12	F	8	AA	<2	12·4
	13	F	5	AF	27·8	12·4
	14	F	2½	AF	31·2	14·9

Discussion

The study of the Dagomba family is incomplete, but reference to the Dagarti family tree indicates that haemoglobin F has been inherited in a manner suggestive of genetic control by a Mendelian dominant, which is in agreement with previously mentioned reports. MacIver, Went, and Irvine (1961) considered the high F gene to be an allelomorph of the A, S, and C genes, and that it resulted from a mutation of the gene responsible for formation of β-chains during the post-natal period of haemoglobin synthesis. Went and MacIver (1958) proposed that if high levels of foetal haemoglobin were present in all erythrocytes of haemoglobin-S/high-haemoglobin-F carriers, this would result in a lowering of the critical level of anoxaemia at which sickling would have occurred in the absence of such amounts of foetal haemoglobin. Bradley, Brawner, and Conley (1961) and Mitchener, Thompson, and Huisman (1961) did in fact demonstrate that foetal haemoglobin was evenly distributed throughout all erythrocytes of carriers of the high F gene, which may explain the benign nature of this condition.

At the 1961 International Congress of Human Genetics in Rome R. Ceppellini, A. Motulsky, and J. V. Neel all independently proposed a more detailed explanation, based on virus genetics, for the benign persistence of foetal haemoglobin into adult life. Haemoglobin A contains four peptide chains—two of them designated as α-chains and two as β-chains. The difference between haemoglobins A and F lies in the nature of the two non-α-chains—which in the case of haemoglobin F have been designated γ-chains. If both β- and γ-chains are available the β-chains claim the lion's share of the α-chains. Thus in α-chain deficiency, when there is a surplus of both β- and γ-chains, nearly all the available β-chains will be combined with α-chains to form haemoglobin A, and most of the γ-chains will remain uncombined to form the γ-chain tetramer γ_4-haemoglobin Bart's (Ramot, Sheba, Fisher, Ager, and Lehmann, 1959). Thus by merely increasing β-chain production in the infant the formation of haemoglobin A should take precedence over that of haemoglobin F. It is this switch-over from the production of the γ-chains to that of the β-chains of haemoglobin A which is impeded genetically in the "high F" condition.

A series of genes have been found to be responsible for the formation of a peptide chain in viruses—one which actually causes the amino-acids to form the protein molecule, another which determines this gene to exert its effect, and yet another which controls the latter gene. The high F condition, which is essentially a failure to form enough normal β-chains, would then be based on the absence of one of the two controlling genes rather than on an abnormality of the β-chain formation itself, as is presumed to exist in thalassaemia or in the case of abnormal β-chain haemoglobins—such as haemoglobins S or C ($\alpha_2\beta^s_2$ and $\alpha_2\beta^c_2$). There is thus no immediate error, either quantitative or qualitative, in the actual β-chain synthesis, and this would explain why there is no haemoglobinopathy.

As regards the epidemiological role of the high F gene, it is tempting to speculate that it exemplifies yet another protective mechanism evolved by mankind in its struggle against *Plasmodium falciparum* malaria in Africa. Such a protective action has already been demonstrated for haemoglobin S (Allison, 1954; Raper, 1955) and for haemoglobin C (Thompson, 1962). On a

number of occasions attention has been drawn to the time relationship between the disappearance of foetal haemoglobin in infants and the onset of their susceptibility to malignant malaria (Lehmann, 1953; Allison, 1954; Davidson, 1955; Gilles, 1957). One of the possible explanations is a protective role of foetal haemoglobin. Haemoglobin-S/high-haemoglobin-F individuals and haemoglobin-C/high-haemoglobin-F individuals might then be especially favoured.

Summary

Two Ghanaian families are reported whose members illustrate interaction between the high F gene and the genes responsible for haemoglobins A, S, and C. Persistence of a high level of foetal haemoglobin was not associated with anaemia or morphological abnormality, except for numerous target cells in the haemoglobin C–F combination. The possible significance of the high F gene is discussed.

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"Representatives of the Library Association met the Libraries Committee of the Association of Municipal Corporations to discuss the provision of better library services in hospitals. Agreement was reached upon a number of principles which should govern the administration of these services and a memorandum embodying the views of the two Associations was subsequently circulated to the other associations of local authorities and to the voluntary bodies concerned. It was decided that if agreement could be reached between all the organizations interested, a deputation should be sent to the Minister of Health asking him to initiate action along the lines agreed." (*Annual Report, 1961*, Library Association.)

RICKETTSIAL AND VIRAL ANTIBODIES IN MULTIPLE SCLEROSIS

BY

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The presence of micro-agglutinating antibodies in sera from cases of multiple sclerosis has been reported by Le Gac (1960) and by Le Gac, Giroud, and Dumas (1960), the most common being antibodies to *Rickettsia burneti* (Q fever). Although no control cases were examined Le Gac concluded that rickettsiae might be causal agents in many cases of multiple sclerosis, and on the basis of his findings he advocated treatment with broad-spectrum antibiotics.

During the past year we have been carrying out a virological investigation of specimens from cases of multiple sclerosis. Part of this investigation has comprised serological examination by complement fixation (C.F.) for antibodies to several viral agents which have been associated with disturbance of neurological function. In view of the findings of Le Gac and his colleagues we have also examined the sera for C.F. antibodies to various rickettsial agents. It was realized that if a viral or rickettsial agent were responsible for initiating the disease it might have done so many years previously and that the antibody might no longer be detectable by C.F. technique. On the other hand, if the agent were latent in the central nervous system it might provide a constant antigenic stimulus manifesting itself in high C.F. antibody.

No control cases were included in this preliminary investigation as its purpose was to assess the distribution of several viral and rickettsial antibodies in sera from cases of multiple sclerosis so that subsequently, in an adequately controlled series of cases, there need be no examination for antibodies which were absent in the preliminary investigation.

Materials and Methods

Single specimens of sera were obtained from 36 patients aged 28 to 64 with chronic multiple sclerosis. From four other patients aged 19 to 47 paired sera were obtained during an acute relapse (in two of these cases the disease was of less than one year's duration), the first serum beng taken early in the relapse and the second serum 10 to 14 days later. In all 40 cases the diagnosis of multiple sclerosis had been made by a neurologist.

All 40 sera were examined by C.F. technique as previously described (Ross, 1961a). Rickettsial C.F. antigens comprised *R. burneti* (Q fever), *R. mooseri* (the causative agent of murine typhus but sharing a common C.F. antigen with epidemic typhus), and *R. akari* (the causative agent of rickettsialpox but sharing a common C.F. antigen with other members of the spotted-fever group). Viral C.F. antigens comprised psittacosis-lymphogranuloma group (P-LGV), louping-ill, lymphocytic choriomeningitis, herpes, and mumps. Both mumps soluble (S) and viral (V) antigens were used, as mumps S antibodies disappear within a few weeks of infection whereas V antibodies remain high for many years. Antigens and uninfected control antigens were prepared as follows: mumps S, mumps V, and P-LGV