but the data do not permit a frequency estimation (Stijns and Charles, 1956). At the moment it would appear legitimate to infer that, in addition to the haematological characteristics mentioned earlier, at least some of the tribes of south-eastern Liberia are also distinguished by a relatively high frequency of the thalassaemia gene or a gene behaving much like thalassaemia. In a number of haematological respects, then, they manifest a closer affinity to certain of the peoples of North Africa than to the tribes who now surround them, tribes some of whose ancestors apparently have migrated westwards from the vicinity of Nigeria in relatively recent times (Livingstone, 1957).

Summary

This report deals with evidence for the occurrence of thalassaemia in Liberia, and for a gene independent of thalassaemia associated with the production of high concentrations of foetal haemoglobin. This evidence is based on the cases of two children seen at the Firestone Hospital, in south-eastern Liberia, presenting the clinical and haematological features characteristic of thalassaemia major together with significant findings in several members of the family of one of them (Dukwe); and on a preliminary survey of thalassaemia minor in this part of Liberia indicating a minimum frequency of 11%. A new haematological entity is proposed in the case of the father and sister, representing a heterozygous state both for the thalassaemia (or high A_2) gene and for the high F "haemoglobin" gene. The possibility that the disease of the propositus (Dukwe) is the result of a new subtype of thalassaemia major is also considered.

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In presenting the Sixth Annual Report of the National Fund for Poliomyelitis Research, Sir CHARLES DANIEL, the chairman, said, "The total sum raised this year is some £9,000 greater than last year's figure, but the relative cost of raising this amount has also increased slightly. This is due to two main factors. On May 1, 1958, the National Fund announced its special appeal for £500,000. This entailed considerable initial expenditure on advertising. The second cause is a slight but definite hardening that we have detected in the attitude of the public. There is no doubt that, with the more general availability in this country of poliomyelitis vaccine, the emotional appeal connected with poliomyelitis has to a certain extent lessened. This is not to say that there is any feeling that the Fund's usefulness has diminished. Nor is there any suggestion that considerable work does not still remain to be done in the field of poliomyelitis prevention, while, of course, there is no decrease in the problems of poliomyelitis treatment and rehabilitation."

DISTURBANCES OF PIGMENTATION WITH CHLOROQUINE

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The use of antimalarial preparations in the treatment of rheumatoid arthritis originated in an observation by Page (1951) that two patients with coexistent rheumatoid arthritis showed a marked amelioration of joint symptoms while under treatment with mepacrine for chronic discoid lupus erythematosus. This finding was substantiated by later workers (Bagnall, 1957; Fuld and Horwich, 1958). Mepacrine has now been abandoned in favour of chloroquine because the former drug was shown to cause discoloration of the skin and agranulocytosis (Custer, 1946; Bagnall, 1957).

The value of chloroquine in the treatment of rheumatoid arthritis has not yet been fully assessed, and it will take some time before its worth can be accurately determined. A recent report (Fuld and Horwich, 1958) suggests that it is a successful form of therapy with minimal side-effects when used in a dose of 400–600 mg. daily.

In view of this report of the comparative lack of side-effects it is felt that attention should be drawn to the following disturbances of pigmentation which have been observed in three patients treated with chloroquine. Two of the patients have rheumatoid arthritis, and the third suffers from disseminated lupus erythematosus.

Case 1

An unmarried medium brunette aged 22 was seen in November, 1957, and gave a history of pain and swelling in the wrists, hands, knees, and ankles of five months' duration. The appearance of the joints was typical of early acute rheumatoid arthritis. The sedimentation rate was 42 mm. in one hour (Westergren). Initial treatment with aspirin and phenylbutazone did not produce satisfactory improvement, and it was then decided to try chloroquine diphosphate ("avloclor"). This was given in a dose of 250 mg. b.d. for one week and then increased to 250 mg. t.i.d. for a further week. Within the two weeks objective and subjective improvement occurred; the joints were less painful with increased range of movement, and the sedimentation rate fell to normal. Treatment was maintained with 250 mg. b.d. thereafter.

The first indication of toxic reaction presented after seven weeks' treatment, when she complained of "glare" when looking at lights, blurring of vision, and nausea. Ophthalmological examination showed no abnormality. At this time the dose of chloroquine was reduced to 250 mg. daily; her joints remained pain-free and the visual upset subsided. After 11 weeks of treatment it was noticed that her eyebrows and eyelashes had become fairer and the proximal ¼ in. (6 mm.) of the scalp hair had become much lighter in colour. When seen again after 20 weeks' therapy there was obvious bleaching of the scalp hair. The eyelashes, eyebrows, and axillary and pubic hair were also bleached. She complained that on exposure to sunlight her

skin had become unduly red and did not tan normally. The dose of chloroquine was then reduced to 125 mg. daily. Despite this her hair continued to grow in fairer than normal. After a further eight weeks' treatment, hydroxychloroquine sulphate ("plaquenil"), 400 mg. b.d., was substituted for chloroquine, and with this her symptomatic improvement has been maintained. When last seen in October, 1958 (14 weeks after starting hydroxychloroquine sulphate), her eyebrows and eyelashes remained bleached, but her axillary hair had darkened and there was a return of normal colouring to the roots of the scalp hair.

Case 2

An unmarried medium brunette aged 26 developed rheumatoid arthritis in May, 1956, with involvement of fingers, wrists, right shoulder, neck, knees, and elbows. A course of gold injections was given from November to December, 1956, without any obvious improvement.

In December, 1957, she was started on chloroquine diphosphate, 250 mg. q.i.d., which over a period of a month was reduced to 250 mg. t.i.d. There was a satisfactory response to this therapy as shown by a fall in the sedimentation rate and relief of joint symptoms. Treatment was continued with a dosage of 250 mg. b.d. for a further 12 weeks, until April, 1958, when because of the appearance of toxic effects (see below) the dose was reduced to 250 mg. daily, and this dose has been maintained since.

The first toxic manifestation appeared about the fifth week of treatment, when she complained of a "white glare" in front of the eyes and of diplopia. The latter cleared when methylpentynol ("oblivon"), which she had been taking, was discontinued. The "glare" gradually cleared spontaneously, and on ophthalmological examination four weeks later no abnormality was found.

In January, 1958, she had bleached her hair with "hiltone" (a proprietary hair bleach) to produce a reddish-blonde appearance, and two months later (March, 1958) she noticed that the proximal portions of the hairs were growing in lighter than the treated distal portions. Simultaneously, the entire body hair, including lanugo growth, became very fair. These changes contrasted with those of her sister, whose hair, treated with the same proprietary bleaching agent at the same time, soon reverted to normal brunette. Thereafter the dose of chloroquine was reduced to 250 mg. daily, and when she was seen in August the new growth of scalp and body hair was of usual colour.

Other features noted were that freckles, which normally appeared in the summer, did not develop that year, and strong sunlight had to be avoided as her skin had become unduly sensitive to exposure, with a marked erythematous reaction. The hair had a finer texture than normal and did not curl so readily.

Case 3

A married brunette aged 38 had suffered from disseminated lupus erythematosus since 1955. Cortisone therapy was used until February, 1958, and at this stage the features of cortisone overdosage became marked. Treatment with chloroquine diphosphate was substituted in an initial dosage of 250 mg. t.i.d. In March she complained of blurring of vision, particularly in the left eye. A subcapsular radial cataract which was thought to be congenital was observed in the left eye, otherwise no abnormality was noted. The dose of chloroquine was reduced to 250 mg. b.d., and the visual disturbance subsided. In May she felt better than at any time since 1955, but at this interview it was noted that her eyebrows and lashes were becoming fairer. In June her eyebrows and lashes were distinctly blonde, but no change was seen in the scalp, axillary, or pubic hair. Chloroquine was stopped and hydroxychloroquine sulphate substituted in a dose of 400 mg. b.d. In September the bleaching of the eyebrows and lashes was noticeably less.

Discussion

Bagnall (1957) reported a series of 125 cases of rheumatoid arthritis treated with chloroquine diphosphate in a dosage of 250 mg. daily. In 56% of cases some toxic reaction was reported, but in only 12 cases was it necessary to stop treatment. The reactions mainly consisted of alimentary upset, although dermatitis also occurred. Fuld and Horwich (1958), in their series of 39 patients treated with chloroquine sulphate, recorded gastro-intestinal upset in 7.7% of cases. No other toxic effect is mentioned. Bleaching of the hair or visual upset was not reported in either of these series of cases.

Hobbs and Calnan (1958) reported a complaint of visual disturbance, including "blurring" of vision, coloured rings round lights, and difficulties in focusing, in 68% of patients receiving chloroquine therapy for dermatological disorders such as disseminated lupus erythematosus and actinic dermatitis. They described changes consisting of fine deposits in the corneal epithelium in three-quarters of these. In more than half of those with no complaint they found similar changes. It was their impression that these changes were due to chloroquine. After this interesting communication slit-lamp examination was undertaken in our three cases, but no abnormality was observed.

Sharvill (1955) observed toxic reactions, similar to those which we have described, in a patient with disseminated lupus erythematosus treated with chloroquine sulphate and drew attention to earlier reports of depigmentation of hair occurring during chloroquine administration (Alving *et al.*, 1948; Tye *et al.*, 1954).

The cases reported here were receiving chloroquine diphosphate with a satisfactory therapeutic response. The initial dosage used was larger than that used by other authors, but the maintenance doses have been comparable. In each of these three cases the first untoward reaction was visual upset, and this occurred within four to seven weeks of starting treatment. The time of onset of bleaching of the hair was also remarkably consistent, appearing after about 12 weeks of treatment in each instance. All three patients had taken at least 750 mg. of chloroquine diphosphate daily for a period of two to four weeks before they complained of visual disturbance. Before the appearance of bleaching of the hair the dosage had been reduced to 500 mg. or less in each case for a period of seven to eight weeks. Allowing for a rate of hair growth of 1–3 mm. a week (Glaister, 1950) the appearance of bleached hair would have been expected in the early weeks if the initial high dosage was the responsible factor, while in fact the earliest sign was observed between the 11th and 12th weeks. Therefore it would seem that this toxic manifestation was induced by a dose not exceeding 500 mg. daily.

Sharvill's (1955) patient was given a comparatively small dose (200 mg.) of chloroquine sulphate for five weeks and then the dose was increased to 400 mg. daily. From his excellent chronological account of the case it can be seen that the first record of bleaching of the hair was after 18 weeks' treatment, by which time the first 20 mm. of the scalp hair was white. It can therefore be estimated that the abnormal hair first appeared at approximately the 11th to 12th week of treatment. It will be seen that this time interval is almost identical to that in our three cases, although he used a different salt

of chloroquine and a much lower dosage. The number of cases is too small to draw any firm conclusions, but the remarkable similarity in the features suggests the possibility that it is the duration of treatment with chloroquine and not the dosage employed that is responsible for this toxic reaction. However, in Case 2 restoration of normal hair-colouring occurred when the dosage was reduced to a minimum, although this was not effective in Case 1. This would suggest that duration of treatment is not the only factor concerned. In both Cases 1 and 3 normal colouring has returned since changing from chloroquine diphosphate to hydroxychloroquine sulphate.

The first two patients also complained of severe erythema of the skin on exposure to sunlight. This did not arise in the third patient, who has disseminated lupus erythematosus and had been specifically warned to avoid bright sunlight. The patient treated by Sharvill made a similar complaint. This observation is of particular interest, as chloroquine is an accepted form of treatment for actinic dermatitis.

Sharvill noticed that his patient's hair gave a bluish-white fluorescence similar to that of a suspension of chloroquine sulphate when viewed with Wood's lamp. This we have been able to confirm in the affected parts of the hair in our cases, using a suspension of chloroquine diphosphate for comparison. The part of the hair grown since changing to hydroxychloroquine sulphate did not fluoresce. Although not confirmed by chemical analysis, this finding suggests that the "bleached" appearance is due to the deposition of chloroquine in the hair instead of the natural pigment. The fact that freckles did not appear and the skin did not tan normally with sunlight suggests that, in the skin also, chloroquine may replace the natural pigment, or at least interfere with the deposition of pigment. It would appear that in the hair these changes are reversible. Further observation during the summer months is required to see whether or not the skin will tan normally.

Three preparations of chloroquine have been mentioned: chloroquine sulphate, chloroquine diphosphate, and hydroxychloroquine sulphate. All three are in current use for the treatment of rheumatoid arthritis. Pigmentary disturbance has been recorded by Sharvill using the sulphate preparation ("nivaquine"), and in this paper when using the diphosphate salt. From our limited experience, these manifestations do not occur or persist when hydroxychloroquine sulphate is used.

Summary

Three cases under treatment with chloroquine diphosphate are described—two of rheumatoid arthritis and one of disseminated lupus erythematosus.

All three presented similar toxic reactions—namely, visual upset and bleaching of the hair—occurring at similar stages in treatment.

Two of the cases also had undue erythema of the skin on exposure to sunlight.

The possibility that chloroquine interferes with the deposition of pigment or replaces normal pigment is suggested. These changes appear to be reversible.

Cases 1 and 2 were shown to the North British Dermatological Society by one of us (J. L. C. D.).

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HYPERTHYROIDISM ASSOCIATED WITH PERIODIC PARALYSIS AND HYPOPOTASSAEMIA

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Disturbance of muscular function is a common occurrence in thyrotoxicosis. This is shown by the almost constant finding of creatinuria, the common complaint of muscular weakness, especially of the iliopsoas and quadriceps, and the histological finding of lymphocytic infiltration in skeletal muscle. Very occasionally the muscular symptoms are the most prominent, and in a review of the subject Millikan and Haines (1953) recognize the following varieties of muscular disorders in thyrotoxicosis: (1) chronic thyrotoxic myopathy, (2) exophthalmic ophthalmoplegia, (3) thyrotoxicosis and myasthenia gravis, and (4) thyrotoxicosis and periodic paralysis. They believe the first disorder is fairly common, while the last is very rare.

We have recently had the opportunity of seeing a patient with thyrotoxicosis associated with periodic paralysis, and with hypopotassaemia during the paralytic attacks.

Case Report

A 36-year-old officer from the merchant marine was admitted to the neurological department on June 10, 1958. Fifteen years previously he had had diphtheria, but had otherwise been in good health. He had never had attacks of paralysis, and there were no relatives with periodic paralysis. From the beginning of April he had been suffering from palpitations and increased sweating, and though he did not have diarrhoea he defaecated four or five times a day. He had lost 10 kg. in weight during four months. Since the middle of April he had been having several attacks of paresis in the proximal parts of the lower limbs and a feeling of weakness in the arms. The attacks always occurred in the evening or during the night, and often he woke up with paresis. The attacks disappeared spontaneously after some hours in bed. One week before admission he had the first attack of complete paralysis, involving both legs. The attack lasted four to five hours and then gradually disappeared. On the evening before admission he developed increasing paralysis of the proximal muscles of the lower limbs. The paralysis gradually extended distally, involving all the muscles of the legs. Later also the muscles of the body and arms were included, the shoulders being first affected. By midnight he was completely paralysed.

On admission on June 10 at 1 p.m. his temperature was normal. The skin was moist and hot, and the thyroid gland