A number of patients with healed dissecting aneurysms have no history of an acute attack (Case 2); they have no history of pain, and they commonly die of cardiac failure (Flaxman, 1942). However, it is not clear if this is a characteristic feature of dissecting aneurysms that heal, since Baer and Goldburgh (1948) found that 50% of acute aneurysms presented without pain. It would be interesting to relate the speed of development of the dissection—of which pain may be an index—with the incidence of healing. Tyson (1931) has described dissecting aneurysms due to vasal haemorrhage that have no communication with the aorta; as these are of capillary origin they must develop more slowly than those associated with an early intimal tear. Tyson believed that intimal rupture was a secondary event in the development of a dissecting aneurysm, and there is no reason why both entrant and re-entrant apertures in healed aneurysms should not follow the production of a silent medial split.

The signs of healed dissecting aneurysms differ from those of the commoner acute type. Since the aortic valve is not often involved, regurgitant aortic murmurs will be unusual. However, Frothingham *et al.* (1939) believed that aortic regurgitation in dissecting aneurysms was caused by ectasia of the aortic ring rather than by deformity of the ring due to the dissection, and if this is accepted it is possible to have an aortic diastolic murmur in the presence of a distal aneurysm which does not involve the intrapericardial aorta. Shennan (1934) described one case with a rough, strong, diffuse bellows murmur over the arch and another with a rough systolic murmur over the manubrium, but these were not clearly related to circulatory abnormalities through the sac, and he concluded that there were no specific diagnostic signs of healed dissecting aneurysms. In most healed aneurysms the heart is found to be enlarged as in both the present cases, but this is not invariable (Weiss *et al.*, 1940).

Differences in pulse pressures are less characteristic of healed aneurysms than of acute cases. This is due to the fact that most healed aneurysms begin at the level of the attachment of the ductus arteriosus distal to the left subclavian artery, and the arteries of the head, neck, and upper limbs will not be involved. In addition, the canalized sac appears to transmit enough blood to equalize the pressures in the upper and lower limbs, and any such differences may be expected to diminish with the development of a patent sac. Radiological changes seem to be the most characteristic findings; Kienbock and Weiss (1931) and Weiss *et al.* (1940) reported that the light shadow of the dissection could be distinguished from the darker aortic shadow in cases of typical "double-barrelled" healed dissecting aneurysms. As in the case of aortic murmurs, these radiological changes will be complicated by the presence of ectasia of the proximal aorta if this coexists with the aneurysm.

In conclusion, it appears that if 5–10% of all dissecting aneurysms heal, then patients with long-sheath-like dissections distal to the arch have a good chance of recovery, and the location of the aneurysm is of prognostic importance. Careful clinical and radiological examination of patients who survive the initial episode should be expected to demonstrate the development of a circulation through a healed dissecting aneurysm.

Summary

The establishment of a circulation through the sac of a dissecting aneurysm of the aorta is the characteristic finding in healed dissecting aneurysm.

It is suggested that patients with a distal sheath-like dissection have a reasonably good prognosis compared with those with proximal dissecting aneurysms involving the intrapericardial aorta. Two cases of distal dissecting aneurysms in which the patients survived for several years are described.

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TWO SURVEYS TO INVESTIGATE THE RELATION OF SICKLE-CELL TRAIT AND MALARIA

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Raper (1949), Brain (1952), Mackey and Vivarelli (1954), and Allison (1954a and b) have suggested that the presence of the sickle-cell trait is a protection against infection with falciparum malaria. Allison further stated that the high sickle-cell-trait rates found in many African tribes can be accounted for on this assumption, and he attempted to relate sickle-cell-trait rates in tribal groups to the severity of malaria. In our view this work was of doubtful validity, since only the trait rates were determined by Allison. His estimations of the malaria distribution were those of other workers; in fact he compared his own sickling rates calculated in 1953 with malaria rates based on Wilson's map for Tanganyika of 1943 (Atlas of Tanganyika, 1948).

It has been shown that sickle-cell-trait rates vary widely, not only within small areas, but also within small subdivisions of the same tribe inhabiting the same area (Foy *et al.*, 1954; Moore *et al.*, 1954; Hiernaux, 1952). Even greater variations occur in malaria incidence at different times and in different places, so that much of Allison's work on this aspect of the subject must be discounted. Our surveys in the field have shown that (*a*) two adjacent tribal groups with almost identical malaria parasite rates (60%) had very different sickle-cell rates (33% Kambe and 9% Duruma), examinations for the trait and malaria parasites being made on the same individuals (Moore *et al.*, 1954); (*b*) the sickle-cell-trait rates in the Dinka, Nuer, and Shilluk of the Equatorial Province of the Sudan are 2 to 4%, but malaria is stated to be hyperendemic. It is therefore apparent that, even if the sickle-cell phenomenon and malaria were very closely associated, the attempt to relate the two from data giving the rates for tribal groups as a whole would have little chance of success.

The sickle-cell-trait rate can vary only through genetic drift in small isolated intermarrying groups, through having a positive or negative survival value, or as a result of recurrent mutations. A negative survival value must result from the deaths from sickle-cell anaemia; the hypothesis has been put forward that this is offset by a protection against death from malaria inherent in the possession of the sickle-cell trait. The effect of the selective disadvantage at its most extreme can easily be calculated. If all the persons homozygous for the gene develop anaemia and all of them die before reaching reproductive age, and if there is (*a*) no differential fertility, (*b*) no differential mortality other than that of the homozygotes, and (*c*) the effect of recurrent mutation is negligible, then the frequency of the gene would decrease at the rate $q_n = \frac{p}{1+nq}$, where q is the gene frequency at the initial stage and q_n the frequency after n generations. The frequency would then be halved in $n = 1/q$ generations. Hence it would take ten generations to reduce the frequency from 10% to 5% (and thus the trait rate from 20% to 10%) and twenty generations to reduce the trait rate from 10% to 5%.

There are strong reasons for supposing that the rate of change would be considerably slower than this because (*a*) the effect of deaths in young children—or *in utero*—on the gene frequency might be smaller than would be expected, since the African woman would then be able to bear another child earlier than if the child had survived, this being linked with the custom, almost universal in East and Central Africa, of long periods of lactation during which coitus is prohibited; (*b*) some homozygotes do reproduce; (*c*) it is doubtful whether as many suffer from the anaemia as is implied by the homozygous–heterozygous hypothesis; and (*d*) if recurrent mutations do occur, they will slow the rate of decrease in gene frequency from homozygous deaths.

There are a number of records of children with the anaemia whose mothers have not got the trait. In some of these children the presence of haemoglobin C was excluded. The indications are, however, that mutation alone cannot maintain gene frequency at the levels encountered (Vandepitte, 1954; Hiernaux, 1952). The possibility exists that all the above factors acting together might maintain gene frequency without any selective advantage. Even if this is not so, the conclusion is that the effect of the selective advantages or disadvantages would take hundreds of years to become appreciable. Changes in rates due to genetic drift could, in small intermarrying groups, be more rapid. In contrast to the relative constancy of gene frequencies, the incidence of malaria in a population can change rapidly as a result of alterations in environment due to control measures or from population movements into areas where they will encounter parasites to which they have no immunity.

Present Surveys

In our view, then, the relationship between sickle-cell trait and malaria can be studied only by examining these two characteristics in individuals and not in groups. With the object of determining whether there is any association between parasite rates and parasite density and sickling, two surveys were undertaken in which sickling and malaria were compared for each individual: (1) Among the Kambe and Duruma, two subdivisions of the same Nyika tribe living in close contiguity on the coast of Kenya and having sickle-cell-trait rates of 33% and 9% respectively, the parasite rate in the two subdivisions being almost identical (about 60%). In this survey the sample consisted of 991 adults, children, and babies; preliminary results have been previously reported (Moore *et al.*, 1954). (2) Among the Jaluo, a tribe on the eastern and northern littoral of the Kavirondo Gulf of Lake Victoria, a hyperendemic area (Garnham, 1949) where children under 6 years of age were examined. Children were chosen in order to eliminate, so far as possible, the complicating factor of immunity, 1,305 in all being examined.

Laboratory Method

The method used for determining sicklers was that previously described. Wet sealed preparations were incubated for from 12 to 24 hours. Malaria was diagnosed by examining the thick and thin films. All the malaria slides and their parasite densities were examined by the same worker in order to avoid bias. Density was measured only in the Jaluo survey, thick films being made and densities measured as the number of parasites per oil-immersion field. The following grouping was used: (1) light = one parasite in five or more fields; (2) medium = more than one parasite in five fields, but less than two parasites per field; and (3) heavy = two or more parasites per field. Only a very few slides had more than five parasites per field.

Methods of Analysis

One of the difficulties in investigating the relation between sickling and malaria is to guard against heterogeneity in the sample, which may lead to false associations. A useful method of reducing this risk is to make a series of comparisons between pairs instead of an over-all comparison between groups; for each sickler in the samples a non-sickling control was chosen. We did this by taking the non-sickler with the examination serial number closest to that of the sickler; fixed rules were adopted for cases of equal closeness. The control numbers were chosen independently of the results of the examinations for malaria parasites. This method ensured that comparisons were made between individuals who lived in the same small area, and sometimes in the same family. Data from areas with different sickling and malaria rates could then be put together without the risk of false association. With this type of comparison χ^2 tests are not legitimate. Instead the difference between the results of the malaria examinations for each pair was measured. These differences, taken with due regard to sign (+ or −), were treated as values from a distribution, and the test was of the hypothesis that the algebraic mean of these values was zero. Since the results for parasite infections were found from the slides only as a positive or a negative in the Nyika survey and in broad parasite density groups in the Jaluo survey, it was necessary to introduce quantitative measurements. Malaria positives were given the value of one, and negatives that of zero, and the density groups were ranked in increasing density from one to three. This is essentially the same as a transformation of the variable for the measurement of parasite density. The significance tests used were, in general, more sensitive than the corresponding χ^2 tests.

Results

Table I shows the parasite rates for sicklers and non-sicklers obtained in the two surveys; the results for the Kambe and Duruma from the first survey are given separately.

There is little indication of any association between sickling and parasite rates for the Kambe and Duruma, but some association would appear to exist among the Jaluo. In fact, for this tribe the difference in rates between sicklers and non-sicklers is just significant at the 5% level.

A closer study of the Jaluo data reveals that they are by no means homogeneous but divide naturally into two parts—Group A, the first two areas surveyed; and Group B, the remainder. The results are shown in Table II.

For Group A the percentage of positives was actually lower for non-sicklers than for sicklers, although not significantly so; but for Group B there was a substantially higher

rate among non-sicklers. The probability that the difference for the latter group was due to chance is considerably less than 1 in 100. In Group A the parasite rate for sicklers was 5% higher than for non-sicklers; in Group B it was 17% lower. The difference between these variations is also significant at the 5% level—that is, there is a lower probability than this that the contrast in the comparisons was due to chance.

Malaria parasite densities were determined in the Jaluo survey and ranked as explained above. The results are given in Table III, Groups A and B being separated.

These comparisons extend and are consistent with those in Table II. There is some indication of a greater percentage

TABLE I.—*Parasite Rates*

	Kambe			Duruma			Jaluo		
	No. Examined	Positive		No. Examined	Positive		No. Examined	Positive	
		No.	%		No.	%		No.	%
Sicklers..	163	94	58	42	27	64	241	131	54
Non-sicklers	163	99	61	42	26	62	241	154	64
Total..	326	193	59	84	53	63	482	285	59

TABLE II.—*Results Among the Jaluo*

	Group A			Group B		
	No. Examined	Positive		No. Examined	Positive	
		No.	%		No.	%
Sicklers	79	43	54	162	88	54
Non-sicklers ..	79	39	49	162	115	71
Total ..	158	82	52	324	203	63

TABLE III.—*Parasite Densities Among the Jaluo*

Parasite Density	Group A		Group B		Total	
	Sicklers	Non-sicklers	Sicklers	Non-sicklers	Sicklers	Non-sicklers
Negative ..	36	40	74	47	110	87
Light	14	9	34	23	48	32
Medium	24	18	38	66	62	84
Heavy	5	12	16	26	21	38
Total ..	79	79	162	162	241	241

of heavy infections among non-sicklers than among sicklers in Group A, but there is little general tendency for densities to be greater. In Group B, on the other hand, the association is striking; 92 (57%) of the non-sicklers were infected with densities medium or heavy, and only 54 (33%) of the sicklers. The difference for Group B is highly significant, the probability that it was due to chance being far less than 1 in 1,000. As in the analysis of parasite rates, the difference between the comparisons for Group A and B is significant.

Discussion

From this analysis it can be concluded to a high degree of probability that in some circumstances parasite infection rates and parasite densities are substantially lower for sicklers than for non-sicklers, while in other circumstances this is not the case. The reason for this difference is at present unknown. The sickle-cell-trait rates were 33% for the Kambe, 9% for the Duruma, and 20% for the Jaluo of Group A and 18% for those of Group B. Parasite rates were almost the same in the various samples (about 60%). Among the Jaluo of both groups, all but 1% of the parasites were *Plasmodium falciparum*. For the Duruma and Kambe the bulk of the parasites were *P. falciparum*, although a larger percentage were of other species (*P. vivax* and *malariae*). Tests for *P. falciparum* were made separately, but gave the same results as for total parasites. In none of these characteristics, therefore, is Group B of the Jaluo sharply differentiated from the other samples.

The Duruma and Kambe samples contained Africans of all ages. In the first area included in Group A of the Jaluo only children under 6 months were taken; in the second area of Group A and all the areas in Group B the majority of the children were aged 2 to 6 years. Although, therefore, the association of sickling with parasite rates and densities may be a function of age, it is clear that this function is not a simple one, since parasite density and age are themselves related in a complex fashion. If it be accepted that the acquisition of immunity in hyperendemic areas is associated with age, parasite rates, and densities (Wilson *et al.*, 1950), then it follows that if sickling reduces rates and parasite densities it would interfere with the process of malarial immunization. Ultimately a stage may be reached where the greater immunity of the non-sickler may be balanced against the assumed protective effect of sickling. There may also be variations in the degree of congenital immunity associated with the sickling characteristics of the mothers which could influence the relation between sickling and densities in their babies.

Although it has been shown that in some circumstances individuals with sickle-cell trait have lower parasite rates and densities than those without it, this does not prove that the sickle-cell trait is a protection against *mortality* from malaria (Foy *et al.*, 1955).

Garnham (1949) and Wilson *et al.* (1950) consider that under hyperendemic conditions primary attacks in infants cause little morbidity and negligible mortality. It follows that if there is no mortality from malaria, then sickling can have no influence on it; the sickling rate, having no selective advantage, might fall as a result of homozygous deaths. In endemic and epidemic areas, on the other hand, where premunition is lower and variable and infantile mortality from malaria does occur, a protective effect of the sickling gene might operate to increase gene frequencies over a long period under stable conditions.

Shortt (1951) and Macdonald (1951), on the other hand, maintain that malarial immunity is acquired only at the cost of a considerable mortality. In the absence of reliable vital statistics we know of no satisfactory data from which this question can be settled.

Conclusion

We have demonstrated a negative association between the sickle-cell trait and parasite density in certain areas, but the relationship is not constant. The connexion between this finding and any possible differential mortality is obscure. If a relationship between parasite density and mortality is assumed, then it must be realized that the factors influencing it are complex. Previous workers have stated that high gene frequencies for the sickle-cell trait are maintained solely by the protective influence of the trait against malaria. We consider this so far unwarranted, since they did not demonstrate any relation between parasite densities and malarial mortality.

Summary

Two surveys were made to compare sickling and malaria in individuals. In the first, 991 adults and children from among the Kambe and Duruma, with sickling rates of 33% and 9% respectively and a parasite rate of 60%, were examined; for neither tribe was there any indication of an association between sickling and parasite rates.

In the second survey 1,305 Jaluo children under the age of 6 years were examined; the sickle-cell-trait rate was 18% and the parasite rate about 60%. Parasite densities as well as rates were determined in this survey. The results fell into two area groups, in one of which there was no association between sickling and parasite rates or densities, whereas in the other there was a very strong association. There appear to be no obvious reasons for these differences. It is clear that the relation between sickling and malaria is complex.

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CHLORPROMAZINE, RESERPINE, AND ISONIAZID TREATMENT IN MENTAL DISORDER

A PRELIMINARY COMMUNICATION

BY

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Chlorpromazine, reserpine, and isoniazid have all been used recently in psychiatry with apparent benefit, but their place in the therapeutic field has not yet been fully established. There is considerable need for carefully controlled investigations to assess their individual and combined effects.

A controlled trial of this type is being undertaken at this hospital, using a factorial design as the method of statistical analysis. This method has not previously been applied in medicine, so far as we are aware, although its use in other scientific fields is well known. It enables an assessment to be made of different substances in various combinations, in addition to the effects of each substance individually. In our particular trial this requires the use of eight separate tablets to cover all possible combinations of the drugs, their single use, and the use of an inert substance alone. These tablets are, of course, of identical appearance.

The toxic effects of each drug, when used alone, are well known, but it was thought essential to investigate the effect of the three drugs in combination, which is the subject of this report.

The side-effects of chlorpromazine have been summarized by Charatan (1954), the main ones being toxic jaundice, pyrexia, tachycardia and dyspnoea, nausea, anorexia and epigastric distress, and variable alterations in the leucocyte count. Tasker (1955) has reported a case of fatal agranulocytosis. Postural hypotension and pallor have also been reported. A further complication, less widely known and occurring with large doses, is an effect on the extrapyramidal system. Kinross-Wright (1954), de Boucaud and Fournial (1954), and J. F. Donovan (1955, personal communication) have reported cases of temporary Parkinsonism with large doses.

The main side-effects of reserpine noted by Moyer (1954), apart from its hypotensive action, are bradycardia, nasal congestion, fatigue and weakness, dizziness, and increased bowel movements. Winsor (1954) also reported leg pains and dyspnoea. Weber (1954), using large doses, reported temporary Parkinsonism in psychiatric patients.

Isoniazid in normal therapeutic dosage rarely causes toxic symptoms. McConnell and Cheetham (1952) noted one case of pellagra, and Zabad (1953) mentions a case of mental disorder. Both cases probably occurred when the patient's original nicotinamide level was low and were cured when isoniazid was withdrawn and nicotinamide administered.

First Trial

Method.—Sixteen patients (eight males and eight females) with chronic psychoses and of widely varying somatic and physiological types were selected. The treatment lasted three weeks and consisted of the oral administration of a compound tablet containing chlorpromazine, 25 mg., reserpine, 1 mg., and isoniazid, 50 mg. Beginning with one tablet, the dose was increased every day until four tablets daily were being given. Daily clinical records were made in order to note any signs of toxicity at the earliest possible stage. Temperature, pulse, and blood-pressure readings were charted daily and weekly weights recorded. The following haematological and biochemical investigations were carried out before and during treatment : haemoglobin, W.B.C. and polymorph count, blood urea, total protein, albumin, globulin and fibrinogen, serum bilirubin, gold flocculation, thymol turbidity, and serum alkaline phosphatase.

The following side-effects were observed :

Cardiovascular System.—A definite fall in blood pressure (more than 20 mm. systolic or 10 mm. diastolic) occurred in eight patients. The average resting pulse rate fell from 86 to 73.

Autonomic System.—Nasal congestion in 3 patients, dryness of mouth in 2, pallor in 6, flushing in 4.

Central Nervous System.—Parkinsonism (rigidity, mask-like face, salivation, and tremor) in 6, tremor (without other Parkinsonian signs) in 4, drowsiness in 11, insomnia in 1, giddiness in 2, headache in 1.

Metabolism.—Increase in weight (1–11 lb.—450 g.–5 kg.) in 12, loss of weight (1–4 lb.—450 g.–1.8 kg.) in 2.

Other Symptoms.—Pains in trunk and limbs in 4, malaise and weakness in 8, shivering in 9, jaundice in 0.

All these side-effects cleared within a few days of stopping treatment. Six patients did not complete the course of treatment owing to the apparent severity of certain side-effects. No abnormal haematological or unequivocal biochemical changes were observed.

Second Trial

In view of the unexpectedly high incidence of extrapyramidal signs it was decided to carry out a further trial using a smaller dosage. Another series of 16 patients (eight males and eight females) were selected, and were given half the original dosage—namely, chlorpromazine, 50 mg., reserpine, 2 mg., and isoniazid, 100 mg., daily for four weeks.

From experience gained in the first trial laboratory investigations were reduced to blood urea, total proteins, serum