Medical Memoranda

Sickling and Malaria

It has been suggested (Allison, 1954) that the sickle-cell trait affords a considerable degree of protection against *P. falciparum*. Allison's results with inoculated malaria showed that sickling was an almost complete protection against infection. In the field, however, it has been found that this relationship does not always exist. For example, amongst the Jalu, whose sickle-cell trait is 28%, malaria is highly endemic. Amongst the Nilotes of the Southern Sudan, where malaria is similarly highly endemic, the sickle-cell trait is less than 2% (Foy *et al.*, 1954).

PRESENT INVESTIGATION

We therefore decided to study the association between malaria and sickle-cell trait in two tribes on the coast of Kenya that have widely different sickle-cell trait rates. The investigation was carried out on 400 Duruma and 400 Kambe. These subtribes form two divisions of the Nyika tribe. The method used to determine the sickle-cell trait was that used by Foy *et al.* (1951) in their survey of the sickling rates in Kenya and the Southern Sudan. Malaria was examined by the usual thick and thin smear method, and checked by different observers.

Preliminary results for 302 Duruma and 220 Kambe are presented here. The numbers include both adults and children. Table I shows the number and incidence of the condition for the Duruma and Kambe. It is immediately

TABLE I

	Duruma	Kambe
Total examined	302	220
Sicklers	31 (10%)	75 (34%)
Parasites	185 (61%)	135 (61%)
Enlarged spleen	104 (34%)	95 (43%)

obvious that for the two groups the parasite rates are identical, but the percentages of sicklers are very different. The proportions with enlarged spleens are nearly similar, although the difference is statistically significant at the 5% level. It should be noted, however, that the higher percentage is for the tribe with the greater sickling rate.

Before we investigate the relationship between sickling and malaria in individuals we should discuss the assumptions upon which tests of associations are based. This is necessary because too little attention has been paid to this subject in past surveys of this type, and we believe that this may have introduced major errors. The usual χ^2 test determines whether the characteristics are randomly related at any level of probability. If the random hypothesis is rejected, however, it does not follow that there is a genuine association for individuals. It is quite possible for associations to arise through fortuitous variations within the group studied. Thus, to take a simple case, if the sample consisted of two groups, each of which was homogeneous with respect to malaria and sickling, but the incidence of these two characteristics happened, by chance, to be higher in one group than the other, there would be an association which had no medical as opposed to statistical significance. If the sickling rate were constant throughout the population from which the groups were selected for study, such false associations could not occur, but it has been shown that variations in sickling exist, not only between tribes but even within tribes themselves (Foy *et al.*, 1954).

We believe that unless great care is taken in the design of a survey so as to eliminate these effects as far as possible, and unless the data are examined carefully from this point of view, there is a considerable chance that meaningless associations will be discovered.

The present survey was restricted to two small areas, and the homogeneity of the data was tested by studying the results in small sets in the order in which they were collected. This method detects any non-random variation in the rates

within the samples. These checks are not given in full here, but it was found that for the Kambe there were no appreciable non-random variations in rates, whereas with the Duruma there were such variations for sickling, malaria, and spleen rates. It should be noted that the Kambe are a small, geographically restricted tribe, while the Duruma are more numerous, more widely distributed, and more urbanized.

Sickling and Malaria Parasites.—Although there was a slight positive association introduced for the Duruma by the non-homogeneity of the data, it had no appreciable effect on the overall results (Table II). There is no indica-

TABLE II

	Duruma			Kambe		
	No. Examined	Sicklers		No. Examined	Sicklers	
		No.	%		No.	%
Parasites positive	185	22	12	135	45	33
" negative	117	9	8	85	30	35
Total	302	31	10	220	75	34

tion here of any association between the presence of parasites and sickling, the slight differences in the percentages being well within the limits of sampling fluctuations. Table III compares the number of cases showing both sickling and parasite infection with the number expected on the "hypothesis of no association" by type of parasite. Where a double infection was found it is shown against each parasite. The differences between the number observed

TABLE III

Parasite	Duruma			Kambe		
	No. of Cases	Sicklers		No. of Cases	Sicklers	
		No. Expected	No. Observed		No. Expected	No. Observed
<i>P. falciparum</i>	144	14.8	17	54	18.4	16
<i>P. vivax</i>	16	1.6	3	30	10.2	9
<i>P. malaria</i>	7	0.7	2	21	7.2	8
Not identified	22	2.3	1	36	12.3	13

and expected are of no significance for any of the species of parasites.

Sickling and Enlarged Spleens.—The overall results are shown in Table IV. There is clearly no association for

TABLE IV

	Duruma			Kambe		
	No. Examined	Sicklers		No. Examined	Sicklers	
		No.	%		No.	%
Spleen enlarged	104	4	4	95	31	33
" not enlarged	198	27	14	125	44	35
Total	302	31	10	220	75	34

the Kambe, but for the Duruma there appears to be a negative association between enlarged spleens and sickling. χ^2 (with Yates's correction for continuity) is 6.07, which gives a probability of about one in seventy of obtaining the difference by chance. When the data are examined in small sets, however, it is found that the low probability is introduced by the non-homogeneity of the sample. Thus, when the Duruma are broken down into sets of 30 Africans (with 32 in the tenth to include all examined) the distributions of the characteristics shown in Table V are found. It so happens that there is a very high sickling rate in the second set, and a very low proportion with enlarged spleens. When allowance is made for this (by considering sets 1 and 2 separately from the rest because of the low enlarged spleen rates, and then applying a combined test) it is found that the association is not statistically significant despite the result found above for the Duruma when the correction is not made.

Raper has shown that the Baganda show no effect of sickling on malaria, but obtained an association among a

TABLE V.—*Distribution of Characteristics in Duruma*

Set	Sicklers	With Enlarged Spleen
1	2	2
2	9	2
3	4	8
4	5	15
5	3	6
6	1	11
7	—	12
8	3	14
9	2	14
10	2	20

mixed group of other tribes. In view of what has been said above, it would not seem that it has yet to be established that this has much meaning.

In conclusion, it would appear from the results given above that there is no confirmation of the theory that there is an association of any magnitude, such as suggested by Allison, between sickling and malaria.

A paper is in course of preparation in which fuller details will be given.

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Superior Sulcus Tumour

A superior sulcus tumour producing the typical syndrome reported by Pancoast (1932) may be caused by a variety of space-filling lesions of which the least uncommon is carcinoma of the bronchus. The following case is an example of such a tumour, and is reported because of its unusual longevity.

CASE REPORT

A man aged 55 was admitted to hospital on April 3, 1945, complaining of dyspnoea and pain in the right chest. An area of consolidation was present in the upper third of the right lung. A course of sulphathiazole resulted in some improvement, but abnormal signs persisted and on July 9 he was transferred to a thoracic surgical unit. He had had rheumatic fever at the age of 15 and had always had a slight productive morning cough, which had become more persistent since Christmas, 1944. In February, 1945, he had been in bed for ten days with a febrile respiratory illness.

Physical examination showed a gaunt man with gross finger-clubbing; vital capacity 3,500 c.cm. There were signs of consolidation with cavitation at the right apex posteriorly. He produced 1–2 oz. (28–57 ml.) of mucopurulent sputum daily, but numerous examinations by film and culture revealed no tubercle bacilli. No malignant cells, actinomycetes, or elastic fibres were seen. Bronchoscopy on July 12 revealed no abnormality apart from pus in the right bronchial tree. A chest radiograph on admission showed displacement of the trachea to the right, with an opacity in the upper zone of the right lung. On August 1 the radiologist reported an extension of the lesion and suggested neoplasm as the cause. Two attempts at bronchography did not reveal any bronchiectasis in the upper lobe segments, but the apical bronchus was incompletely filled. A diagnosis of possible carcinoma was made, and he was discharged home on October 13 with a recommendation to remain under observation, which he ignored.

He did not come for examination again until October 19, 1953, when he was referred to the orthopaedic out-patient department of the Bedford General Hospital with a six-months history of pain in the right shoulder and down the inner aspect of the right arm. Haemoptyses lasting a week had occurred nine months previously, and hoarseness had been noted for six months. His appetite was poor, lassitude marked, and he had lost a stone (6.4 kg.) in weight over the previous year.

On examination he was emaciated, had a right Horner's syndrome, restriction of right shoulder movement, and loss of power with wasting of the right arm accompanied by venous engorgement and trophic changes in the limb. A mass was palpable in the right supraclavicular fossa. Radiographs showed an opacity in the upper zone of the right lung and erosion of the neck of the third right rib and bodies of D3 and 4 on the right side.

He was admitted to hospital for investigation and soon developed a spastic paraplegia with sensory loss below D2. Laminectomy was performed on December 9, when the tumour mass was found to have involved D2 and 3 and caused considerable cord compression. Pressure was relieved and radiotherapy was started. He recovered for a while, but succumbed to a respiratory infection and died on January 9, 1954.

At necropsy both lungs showed bullous emphysema and terminal bronchopneumonia. A soft white tumour occupied the upper part of the right lung, and this had invaded the cervical muscles and vertebral column, penetrating to the cord, and had obliterated the right cervical sympathetic chain. There was no demonstrable connexion with a main bronchus. Histologically the tumour was a highly keratinized squamous-cell carcinoma. No evidence of tuberculosis or other pathological condition was found in the upper part of the right lung except tumour tissue and emphysema.

COMMENT

Superior sulcus tumour is a relatively uncommon growth, 151 cases having been reported up to 1946 (Herbut and Watson, 1946) and several since then, not all of which had been confirmed histologically. The survival time of these cases is usually short, the average time being about ten months from the onset of symptoms; this is four months less than the average for untreated bronchial carcinoma in other sites. Certain treated cases have, however, been reported with longer survival times: Haas *et al.* (1954), at least three and a half years; Chardack and MacCallum (1953), at least two and a half years; while Malcolmson (1947) recorded a case in which the diagnosis of lymphoblastoma in the apex of the lung was made at the Mayo Clinic and the patient lived for 18 years after x-ray therapy.

Untreated cases of bronchial carcinoma in any site which survive longer than eight years are themselves uncommon. Several authors report individual cases, the majority taking as their onset the development of definite signs or symptoms. Such durations are obviously open to question, as unequivocal diagnosis may not be obtained until very much later, but a few cases have been reported in which the patients have survived several years after definite diagnosis.

The case reported here was not confirmed histologically as a bronchial carcinoma in 1945, but there has been very little x-ray change in the right apical opacity during eight and a half years. The absence of tubercle bacilli on repeated examinations and the absence of any histological evidence of tuberculosis or chronic inflammatory condition, save terminal bronchopneumonia, in the right lung suggest that this was a case of peripheral carcinoma which had a long "silent period" in its development. It would be surprising, moreover, in this case for a neoplasm to arise, in the months prior to death, in an area of pulmonary fibrosis and to invade that area so exactly as to show almost no change on x-ray examination.

In view of the lasting radiographic evidence and post-mortem findings it is reasonable to suggest that this man had a tumour for at least eight and a half years before death.

I wish to thank Dr. N. Wynn-Williams for permission to publish this report.

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