thrombosis, that mere restriction of dietary cholesterol serves no purpose, immediate or late, in the prevention or treatment of coronary artery disease, and that the development of atheroma is not dependent on the cholesterol in the diet. This conclusion is in agreement with the findings of Keys *et al.* (1950), who showed that lowering of the blood cholesterol cannot be achieved by mere reduction of dietary cholesterol, but only by a diet entirely free from cholesterol, such as in a rice diet. Humans therefore resemble the majority of omnivora, in whom it has been shown that blood cholesterol concentration is not readily influenced by ingested cholesterol (Duff, 1935).

The present investigation finds no justification for the restriction of the cholesterol content in the diet of patients suffering from coronary thrombosis, as advocated by some authorities.

The results in Group 2 are of interest in confirming that the test dose of cholesterol was sufficient to raise the blood cholesterol significantly in patients suffering from some diseases, and therefore in the atheroma group the rise, which did not exceed the limits reported by Brun (1939), was not due to an inadequate dose of cholesterol. But of even greater interest was the effect of thyroid therapy on the cholesterol-tolerance tests of the myxoedematous patients. With one exception, which was in a myxoedematous patient not long on thyroid and later found to require a larger dose, the cholesterol-tolerance test showed, after the ingestion of cholesterol, a fall of the serum cholesterol below fasting levels. Turner (1933) showed that when thyroid was administered along with cholesterol feeds, atheroma failed to appear in rabbits. Herrmann (1946, 1947a, 1947b) also found thyroid effective in lowering the blood cholesterol in coronary thrombosis, but in view of the undesirable effect on the metabolic rate its use in coronary thrombosis cannot be advocated. He also showed that choline was even more effective, and Morrison and Gonzales (1949) reported worthwhile results in the treatment of coronary thrombosis with choline. This would appear to be a more hopeful measure in the correction of the hypercholesterolaemia of coronary thrombosis than dietetic restrictions.

Summary and Conclusions

The method of a cholesterol-tolerance test is described.

The results showed that there was no abnormal post-absorptive increase in blood cholesterol in coronary thrombosis. Reasons are given for considering that atheroma is not dependent on the cholesterol content of the diet, and that treatment of coronary thrombosis by a low cholesterol diet is unlikely to be of benefit.

The association of hypercholesterolaemia with atherosclerosis was once more confirmed.

The results of this cholesterol-tolerance test suggested that there might be intolerance of ingested cholesterol in a small group of patients—namely, those with nephritis (type 2), diabetes mellitus, and myxoedema.

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SOME OBSERVATIONS ON SUBTERTIAN MALARIA

BY

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As one becomes familiar with the features of subtertian malaria one is struck by the inconstant clinical picture which it presents. I therefore venture to record my impressions gained from several years' experience and several thousand cases of this disease.

Whereas in benign tertian and quartan malaria the clinical picture is more or less uniform, cases of subtertian malaria differ considerably. To confirm my previous impressions I have analysed 50 consecutive cases of acute subtertian malaria admitted to hospital. It is of course impossible to draw any rigid conclusions from such a small number of cases: this article merely attempts a general discussion of the clinical features of subtertian malaria, and the cases analysed do no more than lend support to my contentions. The series analysed consists of 12 adult males, 6 children, and 32 adult females. All these patients were Africans, except one child, who was a European.

Symptoms

Rigors.—One or more rigors are usually regarded as typical of malaria, taken in conjunction with other symptoms and signs. In subtertian malaria, however, they are by no means invariably present, and my impression is that they occur in only about two-thirds of cases. In malarial children convulsions do not as a rule replace rigors as they do in some other systemic infections. Rigors are unlikely to occur in the early or incubation period of subtertian malaria while the temperature is high and continuous (see below). In the present series 60% of patients had rigors, but this figure is probably low. The rigor itself, consisting of the cold stage, the hot stage, and the sweating stage, is in many cases typical, but a large proportion of patients complain only of feeling cold, and never show the hot and the sweating stages. A fair number complain of feeling cold, say, in the afternoon and, without feeling hot, sweat profusely during the night. It is worth while to keep in mind these different patterns of rigors.

Headache.—Severe headache is usual in malaria, and is seldom absent. Almost every febrile patient has some headache, but the malarial headache is characterized not so much by its severity as by its situation. It is in my experience both frontal and occipital, and extends down into the neck. In this series headache was present in 88% of patients.

Vomiting.—This is regarded as typical of the bilious remittent form of malaria, but, in fact, it occurs in most forms of this disease, and severe intractable vomiting should on occasion warn one of impending cerebral malaria.

Vomiting as a symptom is not common in subtertian malaria, and in the present series only 24% complained of this symptom.

Feverishness.—This is common in malaria patients, and subtertian malaria is no exception. Often feverishness and sweating occur together, with or without a rigor. In the present series 90% complained of feverishness.

Generalized Pains.—In this part of the world "pains all over the body" are very common, and may mean anything from a subclinical vitamin deficiency to influenza and malaria. Generalized body pains, together with one or more of the symptoms mentioned above, are, however, common in malaria patients, and are more often present than absent. In the present series 72% complained of this symptom, together with other symptoms. One patient (Case 1) had "pains all over the body" only.

Uncommon Symptoms.—Diarrhoea, with or without blood and/or mucus in the stools, is an occasional symptom, usually accompanied by other features of malaria, though in Case 3 diarrhoea was the only feature present at the beginning. Coma is uncommon, except in cerebral malaria, which is not discussed here. Jaundice, a feature sometimes seen in severe attacks of subtertian malaria, is not common in my experience, and in the present series did not occur.

Signs

Pyrexia.—This is usual, and is to be expected in all cases of malaria. Absence of pyrexia throws considerable doubt on the diagnosis of malaria. In the present series 98% were pyrexial, the only apyrexial case (Case 1) presenting features which merit separate discussion. The highest temperature recorded in this series was 105.4° F. (40.8° C.), the lowest 99° F. (37.2° C.). In all these cases the average pyrexia was 102.6° F. (39.2° C.), a not inconsiderable fever. The average duration of pyrexia in all treated cases was two and a half days, though there were great individual variations. Thus the shortest duration of pyrexia was one day, and the longest nine days (Case 2).

Malarial pyrexia, even that of the subtertian variety, is said to be intermittent. A large proportion of patients, however, show a remittent fever, and only where the typical rigors are present is it intermittent. In a number of cases one even sees a continuous pyrexia for several days. In the present series the fever was intermittent in 42%, remittent in 44%, continuous in 12%, and absent in 2%. The fall of temperature usually occurs by crisis, but in some it falls by lysis. In the present series 88% falls occurred by crisis and the remainder by lysis.

Subtertian malaria is particularly apt to show a continuous high temperature in the prodromal or "incubation" period. In the absence of treatment this will become intermittent after some days, when the rigors, if any, appear. Otherwise there is a fall by lysis or crisis, with or without treatment. If treatment is instituted early a fall by crisis can be expected, and rigors may then never occur. A recurrence of pyrexia is occasionally seen even after treatment has become effective, and may last two or three days. There was such a recurrence in 24% of cases in the present series.

Palpable Spleen.—In subtertian malaria a large percentage of patients never develop a palpable spleen: in this series splenomegaly was found in 56% of cases, which is in accord with my previous experience. The degree of splenomegaly varies considerably. In acute attacks occurring in subjects of chronic malaria the spleen tends to be large; in other cases only the tip may be palpable. On the average the usual degree of enlargement is two fingerbreadths below the costal margin. It is interesting to note that in one patient, not in the present series, who had chronic malaria, the spleen was palpable per vaginam.

Positive Blood Smear.—All patients in the present series had at least two thin smears taken. Thick smears were not done, as my experience of them is not sufficient for their competent interpretation. Of the cases described here, 60% had positive blood smears, but this figure is very low.

Under ideal conditions experienced observers, using thick as well as thin smears, should obtain nearly 100% positives. In this series only smears showing the typical ring forms of *Plasmodium falciparum* were labelled positive. Indeed, other forms were not seen at all. A point worth noting is that if smears taken at the height of the pyrexia fail to show the parasites the latter may at times be found in smears taken when the temperature is subnormal.

Herpes Febrilis.—This is mentioned because from some reports it seems to be common. In my experience herpes febrilis in subtertian malaria is uncommon: in the present series it was absent.

Diagnosis

Of the cases analysed here 72% were diagnosed as malaria when first seen, and from my experience I would say that about three-quarters of patients show sufficiently characteristic initial symptoms and signs to make the diagnosis almost certain. The remainder, barring the afebrile case, were sent to hospital as cases of pyrexia of unknown origin, and one patient was sent in as a case of splenitis (Case 6). Of the P.U.O.s none showed evidence of any other disease. In all these cases the occurrence of rigors and/or splenomegaly, or the demonstration of parasites in the blood smear, clinched the diagnosis, though occasionally a patient may need exhaustive investigation before suspicion is either confirmed or negated.

Treatment

In the acute attack quinine, mepacrine, or proguanil is used. It is interesting to compare the effect of quinine and proguanil in the acute case. Quinine was given as the dihydrochloride, in doses of 30 gr. (2 g.) a day for three days, and 15 gr. (1 g.) a day for four days. Children and infants were given proportionately less. Proguanil was used according to two schedules: (1) four tablets (0.4 g.) the first day, then two tablets (0.2 g.) daily for five days; and (2) one tablet three times a day for six days. There was no noticeable difference in the results obtained by these schedules.

In my experience there is no doubt about the superiority of quinine over proguanil in the acute attack. With quinine the temperature is usually normal or subnormal by the end of the second day, and the patient feels much better. The action of proguanil is more uncertain, and it is not surprising to see the temperature still up on the third or fourth day. One patient in the present series developed symptoms and signs of cerebral malaria on the third day in hospital while receiving proguanil. Intramuscular quinine produced rapid improvement within twelve hours, and the patient made an uneventful recovery.

The results with mepacrine are as a rule prompt and good, though not as rapid as with quinine. Mepacrine must be given in adequate doses from the start, and it is my practice to give one tablet (0.1 g.) six-hourly for the first two days, sometimes for the first three days, and to follow this by one tablet three times a day for four or five days. My impression is that results with mepacrine are better than with proguanil in the acute attack, and they are slower than with quinine but equally good.

Pamaquin (plasmoquine) in falciparum malaria has a specific action on the sexual forms of the parasites, and is used when these are present. As a routine there is no need for pamaquin in the acute attack.

Two more recent antimalarial compounds are chloroquine and camoquin. Both are very effective, and may in time become the treatment of choice in subtertian malaria.

Chloroquine.—The diphosphate is used for oral medication and the dihydrochloride for parenteral administration. Chloroquine diphosphate is given as an initial dose of 1 g., followed by 0.5 g. after six hours. This is usually enough to terminate the acute attack, and then 0.5 g. is given daily for another two days.

Camoquin.—This is also highly effective. Three tablets of 0.2 g. each are given together at the start, and this single dose is curative in most cases. It is good practice to give

a further two tablets three or four days after the initial dose to prevent a relapse, though this additional dose is not commonly needed.

The above doses of chloroquine and camoquin are adult doses, and children and infants are given proportionately less.

Some Interesting Cases

Most of these have been referred to above, but two cases of malarial pneumonia are here included.

Case 1.—An elderly man who had been ill for one week complained of slight headache, had pains all over his body, and felt tired. There was no shivering, no vomiting, and no feverishness. Physical examination, apart from revealing severe anaemia, was entirely negative. He was afebrile, and the spleen was not palpable. He was admitted for investigation, and to my surprise malaria parasites were found in his blood. He was given antimalarial therapy, and remained in hospital ten days. During this time his temperature remained subnormal, and the spleen did not become palpable; also there were no rigors. Quinine followed by pamaquin, and iron preparations for the anaemia, brought about a cure within three months.

Case 2.—A young woman complained on admission of headache, generalized body pains, and feverishness. There were no rigors and no other symptoms. Physical examination, apart from a pyrexia of 100.8° F. (38.2° C.), was entirely negative. Malaria parasites were present in the blood smear, and proguanil therapy was begun. On the fourth day her temperature was 101° F. (38.3° C.), and there was no subjective improvement. No further physical signs developed, and the blood smear was again positive. Examination of the urine and stools showed nothing abnormal. As the patient was not very ill, it was decided to continue the proguanil and await further developments. On the seventh day she was still pyrexial, and parasites, though scanty, were still present in the blood smear. Quinine was then given, since the proguanil had been discontinued after six days. Within 48 hours the temperature was down, and fell by crisis over two days, being normal on the ninth day. The further course was uneventful.

Case 3.—A boy aged 4½ years complained of severe diarrhoea. The stools were loose, though they contained no blood or mucus. The mother said there had been about 20 motions during the preceding 24 hours. The child had vomited once at the onset of the disease; there were no other symptoms. On examination his temperature was 105° F. (40.6° C.), but, apart from some abdominal tenderness, no abnormal physical signs were found. He had been receiving proguanil prophylactically twice a week. Examination of the urine and stools was repeatedly negative, and as a last resort a blood smear was taken. This showed a very heavy falciparum infection. The child responded well to quinine and symptomatic treatment. His spleen became palpable on the third day in hospital. At no time did he have a rigor.

Case 4.—A young woman was admitted as a case of lobar pneumonia, with typical signs of consolidation at the left base. There was no splenomegaly, and she had had only one rigor at the onset of the disease. She had a cough with blood-stained expectoration. She did not respond to sulphadiazine and penicillin, and a blood smear taken on the fourth day showed a falciparum infection. After quinine the pneumonia rapidly resolved.

Case 5.—This woman was a maternity patient, and on the fourth day of the puerperium developed a temperature of 104° F. (40° C.) and a severe dry cough. Consolidation was found in the right mid-zone, and this did not respond to antibiotics. On the sixth day of the puerperium the spleen became palpable, and a blood smear showed falciparum infection. She responded satisfactorily to anti-malarial therapy.

Case 6.—A young female was admitted complaining of severe upper abdominal pain, incessant vomiting of blood-stained matter, and headache; there had been one rigor. She had become ill two days before admission. Examination

showed a pyrexia of 101° F. (38.3° C.), which rose that evening to 104° F. (40° C.). There was rigidity of the left upper quadrant, with tenderness in the left hypochondrium. No other abnormality was found. The provisional diagnosis was splenitis of unknown aetiology. Examination of the urine and stools was negative, but a blood smear was positive for malaria. It was decided to treat expectantly, and quinine with symptomatic therapy produced a fall of temperature by lysis, beginning on the third day in hospital; she made a complete recovery in eight days.

Conclusions

These can best be summarized in tabular form. The figures in parentheses refer to the incidence of symptoms and signs in the 50 analysed cases.

Symptoms		Signs	
Rigors	Over half (60%)	Pyrexia	Usual (98%)
Headache	Usual (88%)	Splenomegaly	Over half (56%)
Vomiting	Not common (24%)	+ Blood smear	Almost all (60%)
Feverishness	Usual (90%)	Herpes febrilis	Unusual (0%)
Generalized pains	Common (72%)		

The cases reviewed include patients of both sexes and all ages, and, though females preponderate, these patients form a fair cross-section of our hospital population.

Summary

The clinical picture of subtertian malaria is discussed. Cerebral malaria is not considered.

The variations in the clinical picture are discussed, and a series of 50 consecutive malaria patients admitted to hospital has been analysed.

Some illustrative cases are described.

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CONGENITAL DIAPHRAGMATIC HERNIA IN SIBLINGS

BY

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True congenital diaphragmatic hernia is a relatively uncommon anomaly, and its occurrence in siblings has been reported only once previously (Mäkelä, 1916). We record here the case of a woman who gave birth to two children, each of whom died from the condition shortly after birth.

Case History

A German woman, then aged 19, was admitted to hospital in 1948 for pre-eclamptic toxæmia and hydramnios necessitating induction of labour at 36 weeks. Forceps delivery was carried out because of maternal distress and the occipito-posterior position of the vertex. The infant, a boy weighing 6 lb. 14 oz. (3.1 kg.), gasped for about twenty minutes after birth, and then died. At necropsy there was a massive left-sided diaphragmatic hernia. The stomach and intestines, from the ileum to the transverse colon, were present in the thorax, together with the spleen and the left lobe of the liver. The left lung was collapsed and there was considerable displacement of the mediastinum to the right. Two-thirds of the liver, the duodenum, the pancreas, and kidneys remained in the abdominal cavity. There were no other congenital defects.

The patient became pregnant for the second time in 1951. She attended the antenatal clinic at 12 weeks, when her