

Some Observations on Malaria Occurring in
Association with Pregnancy.

WITH SPECIAL REFERENCE TO THE TRANSPLACENTAL PASSAGE OF
PARASITES FROM THE MATERNAL TO THE FOETAL CIRCULATION.

BY

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THE epidemic that swept with such astonishing rapidity over the country, affecting very nearly half a million of the population in four different provinces, provided sufficient clinical material at the De Soysa Lying-in Home to enable me to observe during pregnancy, labour, and puerperium a large number of women suffering from malaria of various types and varying degrees of severity. A study of the many varied and uncommon clinical features which have been observed or the factors responsible for the epidemic is outside the scope of this paper. I propose to discuss on this occasion only those aspects of the disease which are of importance to the obstetrician.

I. THE TRANSPLACENTAL PASSAGE OF PARASITES FROM THE
MATERNAL TO THE FOETAL CIRCULATION.

The placenta has the power to prevent noxious substances passing on to the foetal circulation. This is spoken of as the "barrier action" of the placenta and is one of its important functions. But the placental barrier, though it is unquestionably of value and affords some degree of protection to the foetus *in utero*, is not insuperable: besides many chemical poisons, bacteria are known to pass from mother to foetus, the outstanding example being syphilis. Intra-uterine smallpox, too, is not unknown, and it is said that Mauriceau, one of the world's greatest obstetricians, came into the world pock-marked.

So far as malaria is concerned, it is generally stated that the parasites do not pass the placental barrier. Johnstone,¹ for instance, says "normally there is no passage of maternal blood-cells to the foetal blood, nor do large parasites like that

of malaria pass through the placenta." Eden and Holland² are still more emphatic, and state "the malaria parasite is never transmitted to the foetus." Thomson and Robertson (*Protozoology*)⁴ refer to this subject thus: "As a rule no parasite can be detected in the foetal circulation, and even in intense maternal infections no infection of the child results, unless some breach, such as a haemorrhage into the placenta is made in the placental barrier." Greenhill,⁵ speaking in this connexion, states that "the question of whether or not malaria is transmitted to the foetus is still unsettled." De Lee⁶ states that "Williams could not find the plasmodium in 15 infants when it had been demonstrated in their mothers," yet Bodenhäuser reports a case of such transmission and states that "foetûs have been delivered with enlarged spleen and pigmentation." Castellani and Chalmers⁷ say that "congenital infection is a much debated subject," and mention Dunelard and Viallet as having recorded a case in which a woman suffering from malaria gave birth to a child in which blood from the umbilical cord during life and from the heart after death contained parasites identical with those in the maternal blood and placenta. A similar case has also been recorded by Leger.

Stitt⁸ has the following reference to congenital malaria: "There has been some question as to the possibility of congenital malaria. Heiser has recently recorded the case of an infant which showed crescents in its blood by the end of one week from birth. The mother showed the same infection, and the child must have been infected through the placental circulation. Clark, in numerous examinations of the blood of the newborn, failed to find infection even when the mother's blood teemed with parasites. In one case in which the child showed infection shortly after birth there had been an accident to the placenta, and he believes that instances of so-called congenital malaria are to be explained in this way."

Manson-Bahr⁹ states that "congenital malaria is very exceptional and probably only occurs when accidental tears of the placenta allow passage of parasites from maternal to foetal circulation. Bass,¹¹ on the other hand, makes the definite assertion that "malarial parasites cannot pass from the mother to the foetus and there is therefore no inherited malaria." According to this author, "a newborn child has no malarial parasites, but is of course susceptible to infection, and if it is born in a house where the mother and perhaps other members of the family suffer from malaria, the chances of early infection

are great." He is thus definitely of opinion that transplacental foetal infection with malaria does not even come within the realm of possibility.

In view of such conflicting statements and the undoubted rarity of transplacental foetal infections in general, and in malaria in particular—only a stray case here and there being recorded in the available literature—and the fact that an authentic case has up to date not been recorded in this country, I feel that my own investigations on the subject will not be without interest. In one of my earlier cases I was struck by the uncommon appearance of the placenta, which was unusually dark in colour and soft and friable in consistence. It was this uncommon appearance of the placenta that made me think of the possibility of transplacental foetal infection and which eventually led to the present investigation. Since then many maternal and foetal post-mortem examinations have been made, numerous maternal and foetal blood-films have been examined; smears from foetal brains and spleens have been subjected to the most careful scrutiny, and smears and sections from placentae have been studied. This study clearly indicates that not only are malarial parasites transmitted to the foetus but also that such transmission is not an uncommon cause of death of the foetus *in utero*. Thus in at least three out of my six proved cases of transplacental infection, the death of the foetus could be attributed to malaria contracted *in utero* (see cases 2, 3 and 5). Our studies at the De Soysa Lying-in Home suggest that congenital malaria should be regarded as a definite clinical entity, notwithstanding the opinions of so many eminent authorities to the contrary. A persistent, though slight, pyrexia is not uncommon in the newborn child when the mother had suffered from acute malignant malaria during pregnancy and particularly at the time of labour. The majority of such cases are instances of congenital malaria, but are not diagnosed as such owing to the failure in many instances to demonstrate parasites in the blood. When it is remembered that in quite a fair proportion of cases of undoubted clinical malaria occurring even in the adult, parasites cannot be demonstrated in the blood, the inability to demonstrate parasites in many cases of congenital malaria will be easily appreciated.

According to Clark¹² 250,000,000 parasites would produce in the blood a concentration of about 50 parasites per cubic millimetre of blood, a number which can be detected microscopically but which will not produce fever normally, though the

next generation will produce sufficient parasites to cause fever. It is, therefore, evident that a foetus may be born alive without showing any clinical evidence of malaria but with parasites in its circulation which may or may not be demonstrable, depending on their concentration and rate of multiplication in the blood. Such an infant may, shortly after birth, develop clinical malaria with parasites in the blood, and may even succumb to it if the rate of multiplication of the parasites be rapid; on the other hand, if the resistance of the newborn infant be sufficiently great, the few circulating parasites may be destroyed and the child may escape developing the clinical disease. It should also be remembered that quinine administered to the mother during pregnancy will not only render the detection of parasites in the blood of the newborn difficult or impossible but will also tend to prevent the development of congenital malaria by destroying the parasites which may have already gained entry to the foetus.

It is therefore conceivable that a congenital malarial infection can exist without showing any clinical evidence of its presence. For these reasons the inability to demonstrate parasites in the blood of the newborn does not negative the diagnosis of congenital malaria. In those instances in which the child is born with a pyrexia and with parasites in the blood the diagnosis of congenital malaria cannot, of course, be questioned. However, the possibility, undoubtedly very remote, of direct inoculation of the parasites from the mother into the child as a result of cutaneous abrasions during the act of birth, must also be remembered. This, of course, is not true congenital malaria.

Many children are born dead as a result of congenital infection, foetal death often taking place long before delivery. It must not be argued, however, that all stillbirths occurring in the course of malaria are brought about in this manner. The majority occur not from congenital infection but from infection of the placenta. Owing to the sluggish circulation in the intervillous spaces, the parasites tend to be aggregated in the placenta, as proved by stained smears from the placenta always showing a very much heavier concentration of parasites than in the peripheral blood; also it is not uncommon to find positive placental smears in cases in which the peripheral blood has been repeatedly negative; a few cases have also been encountered in which the placental infection had persisted for months after the disappearance of parasites from the peripheral blood and long after clinical cure has been effected. For instance, a patient had

clinical malaria with parasites in the peripheral blood in the seventh month of pregnancy. She made a complete recovery after a course of treatment with atrebrin, the peripheral blood being repeatedly negative. A placental smear taken after delivery at term was, however, positive, showing the same type of infection as before. It would thus appear that the placenta may act as a storehouse for parasites in a manner analogous to the spleen. These facts prove that the placenta is usually the seat of the heaviest infection and that such infections may lurk for long periods. The consequences of this placental infection must undoubtedly be disastrous to the foetus. As J. G. Thomson and Andrew Robertson⁴ have observed, "there is no doubt but that toxic substances are absorbed from the intensely infected placenta and, further, the accumulation of large numbers of infected cells must interfere seriously with the oxygenation and nutrition of the foetus." Blacklock and Gordon¹⁰ also found a positive correlation between the maternal infection of the placenta and death of the child *in utero* or shortly after birth. Our experiences at the De Soysa Lying-in Home are in accord with the views of these workers. Our studies further indicate that transplacental foetal infection with malaria is not such a negligible factor in the causation of foetal death as was formerly thought. If routine post-mortem examinations are made in all cases of stillbirths occurring in malaria, I feel confident that such congenital infection will be found to account for a larger number of foetal deaths than is at present believed.

Factors Influencing Transplacental Foetal Infection.

1. *Type of infection.* In every one of my six cases of proved transplacental foetal infection the infecting parasite was the plasmodium falciparum (malignant tertian parasite). This has also been the offending parasite in the few cases recorded in the literature. In many benign tertian infections where the child was born dead, post-mortem examination failed to demonstrate parasites in its tissues. It would therefore appear that transplacental foetal infection occurs chiefly, if not entirely, in malignant tertian infections. This is not surprising when it is remembered that the malignant tertian parasite is the most destructive of the malarial parasites and therefore the one most likely to cause disease of the placenta.

2. *Infection and disease of the placenta.* Some sort of breach in the placenta has to be assumed in all cases of transplacental foetal infection. The few authentic cases of transplacental

passage of parasites recorded in the literature have been explained on the assumption that there had been in such cases an accident to the placenta during birth, such as a tear or an intraplacental haemorrhage. The fact that no such macroscopic damage was demonstrable in all six cases recorded in this paper indicates that the lesion in the placenta must be of a different nature. The massive infection of the placenta with parasites and the high temperature which such infection engenders, together with the effects of the toxic products of the parasites themselves, must undoubtedly induce pathological changes in the placental substance. It is extremely probable that the necessary breach in the placenta is established as a result of such pathological changes. One has merely to see a stained placental smear in a positive case to be convinced of such a possibility. The severity of the placental infection may be gauged from the fact that in a stained placental smear one at times finds it rather difficult to pick out a non-parasitized cell. The smear shows not merely a few parasites but one mass of parasites in each field—a picture never seen in films taken from the peripheral or visceral blood. In view of the rapid multiplication of parasites in the absence of effective treatment, their concentration in the intervillous blood must progressively increase. The degenerated chorionic epithelium of the second half of pregnancy which separates the two circulations may fail to withstand the effects of this ever-increasing infection in the intervillous blood. The barrier may thus be broken through and an overflow of parasites may occur from the maternal to the foetal circulation. If labour supervenes it is not unlikely that the uterine contractions may act as a *vis-a-tergo* and force more and more parasites to the foetal circulation, once a breach has been created in the placenta. But the supervention of labour does not appear to be necessary for transmission of parasites as cases 4 and 6 demonstrate. A study of microscopic sections of placentae in positive cases should help in the elucidation of the pathological processes at work in the placenta.

3. *The efficacy of treatment adopted.* This is a factor of very great importance. In all our positive cases the patients had not received effective treatment. Most of them had had repeated attacks of malaria during the pregnancy. All had high temperatures at the time of delivery. The heavier the placental infection and the longer it has persisted the greater is the probability of transmission of parasites to the foetus. Prompt and effective treatment by causing rapid disappearance of

parasites must undoubtedly minimize infection of the placenta and thus prevent transplacental infection or, at any rate, diminish its incidence.

The following are particulars of six cases:

CASE 1. The case was one of cerebral malaria, wrongly diagnosed as eclampsia and, therefore, the patient had not received appropriate treatment until admission to hospital. There was a massive infection of the placenta with malignant tertian parasites. The abnormally soft and friable consistence of the placenta suggests that the heavy infection with malarial parasites had affected its integrity and damaged the trophoblast, thus permitting a few of the parasites to cross the barrier. The finding of parasites in the blood from the umbilical cord is positive proof that the barrier had been successfully traversed and that parasites had invaded the foetus, though in very much less concentration than in the maternal blood, as it was after a very careful and patient search that a few malignant tertian ring forms and crescents were detected in the blood of the umbilical cord.

The baby must be considered to have had congenital malaria for the following reasons: (1) The finding of malignant tertian ring forms and crescents—the same infection as that found in the mother and placenta—in a drop of blood from the umbilical cord of the baby. (2) The fact that the baby was born with a high temperature of 103.4°F. which persisted for several hours. (3) The fact that the baby had a subsequent rise of temperature on the fifth day after birth for no obvious cause. Unfortunately, the baby not being under observation in hospital, its blood could not be tested at this stage.

The placental barrier having prevented a heavier invasion of the foetus, the baby escaped lightly. Had the delivery been delayed, however, it is likely that the additional number of parasites entering the foetus would have either caused its death *in utero* or produced a more severe attack of congenital malaria.

CASE 2. A case of uncomplicated malignant malaria occurring in an ill-nourished and debilitated woman, who had no proper treatment. The case demonstrated (1) intra-uterine death of foetus from malaria, parasites being found in foetal brain and spleen; (2) congested and pigmented spleen; (3) premature separation and intense infection of placenta with malarial parasites.

CASE 3. This case demonstrated the following facts: (1) The invasion of the foetus by parasites, fresh cerebral smear and splenic smear both showing parasites. (2) Intra-uterine death of foetus undoubtedly due to malaria contracted *in utero*. There were no signs of intracranial haemorrhage to account for the foetal death. (3) Pigmented liver and spleen—further indirect evidence of malaria of the foetus. (4) Retroplacental clots showing some degree of premature separation of placenta. (5) Placenta showed infection with parasites when the maternal blood was negative.

MALARIA ASSOCIATED WITH PREGNANCY

CASE 4. The patient, a subject of advanced hook-worm disease and associated nephritis, had an intercurrent attack of malignant malaria. She died undelivered in spite of intensive treatment with atebirin. Post-mortem examination of the foetus revealed a congested and pigmented spleen. The finding of malarial pigment in the foetal spleen similar to that found in the maternal spleen confirms the view that parasites had invaded the foetus. The foetal invasion being a light one, actual parasites could not be demonstrated. The specific antimalarial treatment administered to the mother may also have probably caused their disappearance from the foetus.

CASE 5. The case was one of cerebral malaria that ended fatally in spite of intensive treatment with intravenous and intramuscular quinine. The patient collapsed and died shortly after delivery of a premature stillborn baby. Foetal death had taken place several hours before delivery. The case demonstrated the following interesting features: (a) a heavy invasion of the foetus with malignant tertian parasites, smears from the foetal spleen, liver, heart-blood and cord, all showing malignant tertian ring forms (two or three in every field); (b) congested foetal liver; (c) enlarged and pigmented foetal spleen; (d) haemorrhagic effusion in the foetal pericardium and peritoneum (but no search was made for parasites in these effusions); (e) placental smear showed massive infection with malignant tertian parasites. The placenta appeared to be the seat of the heaviest infection. Practically every red cell in the film was infected and it was a problem to see a non-parasitized cell, such was the intensity of the placental infection. The placenta appeared unhealthy and numerous white infarcts were clearly seen, but there were not any intraplacental haemorrhages. There were, however, some retroplacental clots which were intimately adherent to the placental surface. The foetal surface of the placenta and the membranes were meconium-stained. The placental end of the cord was dark and oedematous. Apart from these findings, the naked-eye appearance of the placenta did not suggest anything pathognomonic. The finding of malignant tertian parasites, identical with those circulating in the maternal blood, in the various tissues of the foetus, the massive infiltration of the placenta with the same type of parasite, together with the early disappearance of the foetal heart-sounds, are positive proofs that foetal death had resulted from heavy infection of malaria contracted *in utero*. This case also demonstrates that malarial parasites do at times invade the foetus in such heavy concentration as to be quite easily demonstrable in the foetal tissues.

CASE 6. Also a case of cerebral malaria. The patient died undelivered in spite of vigorous treatment with intravenous and intramuscular quinine. Labour had not started up to the time of death. Post-mortem examination on the foetus failed to demonstrate parasites in the foetal spleen or liver; but a smear taken from the blood of the cord showed a few crescents and malarial pigment, thus showing that parasites had traversed the placental barrier and invaded the foetus. The failure to demonstrate parasites in smears from the foetal spleen and liver shows that the parasitic invasion had been a light one, intensive treatment with quinine probably having prevented a heavier invasion of the foetus. This case also demonstrates that the supervention of labour is not an essential factor for transmission of parasites.

Conclusions.

(1) Transplacental foetal infection with malaria occurs more often than is supposed.

(2) It occurs chiefly in severe and untreated malignant tertian infections. Owing to the sluggish circulation in the intervillous spaces and the barrier action, the parasites tend to be aggregated and arrested in the placenta. The intense infection of the placenta with parasites and the accompanying high temperature may cause either premature separation or injury of the placenta, permitting at least some of the parasites to cross the barrier. Adequate treatment causes rapid disappearance of the parasites from the maternal circulation and thereby minimizes the infection and injury of the placenta. This probably explains why the foetus escapes so often in properly treated cases of even the most severe infections. It may be mentioned here that quinine is one of those drugs which can pass on to the foetus through the placenta. Quinine administered to the mother may thus cause the disappearance of any parasites which may have succeeded in crossing the barrier, and in this way can prevent, not only the occurrence of congenital malaria, but also intra-uterine death of the foetus from malaria.

(3) *Post-mortem* examination of stillborn foetus born of mothers suffering from acute malignant malaria often shows pigmentation of spleen and liver, which is further indirect evidence of malaria of the foetus.

(4) In positive cases it is most easy to demonstrate parasites in the fresh foetal brain squash under the microscope without any staining. Living and dead parasites are easily seen in the cerebral capillaries in these positive cases.

II. THE INFLUENCE OF MALARIA ON PREGNANCY, LABOUR AND THE PUERPERIUM.

Influence on Pregnancy.

Malaria can modify the natural course of pregnancy in the following ways:

(1) *Spontaneous interruption before term.* This is a very common occurrence in women suffering from malaria. While a mild attack of malaria may not adversely affect the course of the pregnancy, a severe attack, or more particularly repeated attacks, are very liable to bring on abortion, miscarriage or premature labour, to which fact the epidemic has focused atten-

tion still more strongly. Very often the treatment adopted to cure the malaria is unjustly blamed for this occurrence, and quinine has earned a notoriety—altogether undeserved in my opinion—in this connexion. Many years of experience in malarial districts and the lessons learnt from the present epidemic have convinced me more than ever that malaria *per se* is a far more powerful oxytotic than any of the known drugs. In the ill-nourished, poverty-stricken and hook-worm infested individual, even a mild attack of malaria is the last straw, as it were. In such an individual, an interruption of pregnancy is inevitable, and is even likely to be followed by disastrous consequences.

(2) *Intra-uterine death of foetus.* This is fairly frequent, if one were to judge by the frequency of births of macerated foetûs in cases of malaria. The high temperature of malaria, particularly malignant malaria, can not only bring on miscarriage or premature labour but can also cause the death of the foetus *in utero*. A far more important factor in causing intra-uterine death of the foetus is the massive infection of the placenta with malarial parasites which is seen in almost every case of malaria of any degree of severity. Blacklock and Gordon (1924)¹⁰ found a positive correlation between the maternal infection of the placenta and death of the child *in utero* or shortly after birth. J. G. Thomson and Andrew Robertson (*Protozoology*) state “there is no doubt but that toxic substances are absorbed from the intensely infected placenta, and, further, the accumulation of large numbers of infected cells must interfere seriously with the oxygenation and nutrition of the foetus.” Another possible though rare cause of intra-uterine foetal death is direct invasion of the foetus by malarial parasites, as my six cases prove. This possibility, however, is denied by most authorities. But I am convinced that direct invasion of the foetus does occur in exceptional cases of malignant malaria, particularly in very severe and untreated infections.

(3) *Toxaemia of pregnancy.* As a result of the impairment in hepatic and renal activity which is so obvious in many of the severe cases, malaria must be considered to be a predisposing factor in the production of toxaemic pregnancy. A majority of the untreated patients, and also those who have several relapses, showed more or less marked albuminuria with casts of various types, including blood-casts and general anasarca and intense anaemia. Few also showed a moderate degree of hypertension,

but the majority had a normal blood-pressure with a failing circulation. The frequent association of such toxæmic manifestations cannot be regarded as purely accidental, and women suffering from malaria must be considered more prone to develop toxæmia, especially in the second half of pregnancy, when the strain on the liver and the kidneys is most felt. In a number of cases the urea concentration test revealed a markedly defective renal function, while post-mortem examination in some of the fatal cases showed fatty degeneration and necrosis of the liver. It is well known that malaria can cause nephritis in the non-gravid (malarial nephritis). It is not unreasonable to suppose that the disease may produce nephritis in the gravid patient far more easily and on less provocation than in the non-gravid patient. Nephritis may thus be set up at any time during the course of the pregnancy, depending on the nature and virulence of the malarial infection and the time of its occurrence, more particularly in the later months when the kidneys are subject to the greatest strain. A convulsive fit occurring at this stage will be difficult to diagnose, for it may be true eclampsia or uraemia resulting from a malarial nephritis, or a fit originating from an attack of cerebral malaria. A careful consideration of the history, examination of the blood for parasites, blood-urea estimation, the blood-pressure and the urinary findings will aid in the differentiation. Hyperpyrexia, though it can occur with eclampsia, is more in favour of cerebral malaria, and an absolute diagnosis of cerebral malaria can be made by the discovery of malarial parasites in the blood. Hypertension similarly is in favour of eclampsia. Haematuria or an excess of red cells in the urine or blood-casts suggests nephritis. Examination of a sample of urine for the percentage of urea will help in the diagnosis of uraemia. If the percentage of urea is 2.5 or more,¹³ uraemia can be excluded. If, however, the percentage of urea is low, say one per cent or so, the kidneys are very inefficient and uraemia is present. In true uraemia the blood urea is raised, unlike in eclampsia in which it is within normal limits, unless the kidneys are secondarily damaged from prolonged toxæmia, when the blood urea may be raised. It is of the highest importance to arrive at a correct diagnosis, and that as early as possible. To treat a case of cerebral malaria as one of eclampsia is a mistake of the first magnitude and one which is certain to be attended with disaster. Similarly uraemia is a much graver condition than eclampsia and may have to be treated on quite different lines.

Influence on Labour.

Malaria does not usually affect the course of the labour. Labour is not unduly prolonged and there is not any special tendency to post-partum haemorrhage. In the comatose type of malignant malaria, however, I have the impression that labour is prolonged. I have seen three such patients dying undelivered, though they had been long in labour and though labour had started before coma set in. It would appear that the onset of coma has an inhibitory effect on the uterine contractions.

Influence on Puerperium.

In consequence of the lowered vitality resulting from malaria, resistance to infection is diminished, and liability to septic complications is increased, and not infrequently the patient succumbs to a complicating puerperal sepsis. Pyelitis and enteritis are not uncommon complications of the puerperium. Those complications are liable to escape detection in the puerperium if not carefully looked for. Thus it is not uncommon for the patient to be wrongly treated during the greater part of the puerperium for malaria when she is really struggling with puerperal sepsis or pyelitis, the original malarial infection having been already controlled.

Conclusions.

- (1) Malaria *per se* is a powerful oxytocic.
- (2) Malaria causes intra-uterine death of the foetus by one or more of three ways: (a) Massive infection of the placenta with parasites. (b) A persistently high temperature. (c) Direct invasion of the foetus by parasites. This is rare and occurs chiefly in severe and untreated malignant tertian infections.
- (3) Malarial patients are more prone to develop toxæmic manifestations such as albuminuria, anasarca and hypertension.
- (4) An attack of malaria occurring in the second half of pregnancy in a predisposed toxæmic subject may precipitate a true eclampsia, and an attack of cerebral malaria may in turn closely simulate eclampsia or uraemia.
- (5) The onset of coma in cerebral malaria has an inhibitory effect on the uterine contractions and may thus prolong labour.
- (6) Malarial patients are more prone to develop sepsis and pyelitis as complications of the puerperium.

III. THE INFLUENCE OF PREGNANCY AND LABOUR ON THE NATURAL COURSE OF MALARIA.

Influence of Pregnancy on Malaria.

Pregnancy aggravates malaria to a marked extent. Some of the worst cases of malaria seen during the epidemic were encountered among expectant mothers. That the disease shows a marked exacerbation when it occurs in association with pregnancy is also proved by the heavy mortality noticed in the present epidemic among expectant mothers. I have seen numbers of otherwise healthy pregnant women rendered gravely ill by a week or two of malaria. The deterioration in health is rapid and marked, and death follows quickly if prompt and effective treatment is not instituted. Oedema is quick in onset and general anasarca is common. Anaemia soon becomes intense, cases with 10 per cent of haemoglobin being often encountered. A marked degree of albuminuria with casts is often present. In two cases haematuria was noted which disappeared after delivery. A specially noteworthy feature is the liability of those patients to develop cerebral symptoms without any warning, in spite of treatment and even when they appear to be doing well and progressing satisfactorily. I can still recall to mind the instance of a patient who sought treatment at the De Soysa Lying-in Home about a year ago. She was nearly at term and had slight pains on admission. She had a temperature of about 100°F., and an enlarged and palpable spleen. A blood examination revealed malignant tertian parasites. She was put on quinine, the temperature soon disappeared and she was seen walking about in the ward the following morning. Her blood-pressure was normal, and the urine contained a trace of albumin and a few granular casts. In the evening the patient was gravely ill and comatose. Even the nurse on duty was unaware that she was ill. The patient had not even complained that anything was wrong with her. She had become comatose suddenly. As I was examining her she developed a fit. Coma deepened, labour pains ceased, and she died in six hours undelivered in spite of vigorous treatment. A lumbar puncture showed clear cerebrospinal fluid under normal pressure. Quinine, 15 gr. intramuscularly, had no effect. Throughout the illness she was non-febrile. But for the finding of malignant tertian parasites in her blood immediately on admission and the enlarged spleen the case might have been diagnosed as eclampsia.

Influence of Labour on Malaria.

The strain of labour may provoke an acute attack of malaria in one who has been free from it even for a considerable time, the slumbering malarial parasites being awakened to activity as a result of the physiological strain.

Labour at times intensifies the effects of malaria and many patients develop a fatal collapse shortly after delivery. The more marked the anaemia and higher the temperature at the time of labour the greater is the danger. When the haemoglobin percentage has fallen so low as 30 the danger is really great, and if this degree of anaemia is associated with any marked rise of temperature death is imminent. Many fatalities occur in the early days of the puerperium from cardiac failure, the already weakened heart being overpowered by the strain of labour. Several weeks and perhaps months of rest and treatment are needed to restore the patient to normal health.

Conclusions.

(1) Pregnancy aggravates malaria to a marked extent, and pregnant women, it would appear, are more liable to develop cerebral malaria than the non-pregnant.

(2) The strain of labour can not only activate a latent malaria but may also intensify the effects of an existing attack.

(3) A fatal collapse often follows delivery. The more marked the anaemia, and the higher the temperature at the time of delivery, the greater is the danger.

IV. THE PRINCIPLES OF TREATMENT OF MALARIA DURING PREGNANCY.

The importance of prompt and effective treatment of malaria during pregnancy will be obvious from the foregoing considerations. The epidemic has revealed not only the great frequency of miscarriages, premature births and stillbirths in malaria, but also the heavy maternal and foetal mortality associated with the disease. The prophylaxis and cure of malaria are, therefore, of paramount importance if the pregnancy is to be conserved and the health of the mother and child safeguarded. Considering that the interruptions of pregnancy and foetal death result chiefly from the malarial infection and disease of the placenta and the accompanying high temperatures, not to mention those rare instances of direct invasion of the foetus by malarial parasites,

vigorous measures must be adopted as early as possible to combat those adverse factors. The indications of treatment, therefore, are :

(1) To destroy and to eliminate from the maternal circulation as early as possible all the malarial parasites.

(2) To control the high temperature.

The first of these indications is by far the more important, as the high temperature is dependent to a great extent on the severity and the type of infection. Both these indications are best fulfilled by the early administration of quinine in effective therapeutic doses. As the infection has to be quickly controlled, even 10-grain doses of quinine two or three times a day are quite permissible in severe infections. The dosage of quinine should be determined by the severity of the illness and the urgency of the symptoms, and the fact of pregnancy should not debar its use. In view of its supposed oxytocic properties, which in my opinion are grossly exaggerated, it should always be combined with 15 gr. of bromide, or a separate mixture containing chloral, bromide and even opium may be administered as desired while the patient is on quinine treatment. Sodium bicarbonate, 30 grains, two or three times a day and glucose should also be administered. The oxytocic properties of quinine are in abeyance in malaria treated on the above lines. Our experience at the De Soya Lying-In Home indicates that the best results are undoubtedly obtained by the timely administration of quinine in therapeutically effective doses (5 to 10 grains three times in 24 hours) combined with bromides. Quinine administered in this way not only did not give rise to miscarriage or premature labour, but in the majority of cases it actually delayed or prevented the onset of labour when labour appeared imminent under the influence of malaria. In those cases in which premature labour occurs, I am convinced that it is due in the majority of cases to the general ill-health resulting from malarial and not to the quinine administered. That miscarriages occur so often in untreated malaria is not surprising when one considers the great frequency of infection of the placenta with parasites. In most of our cases the placenta was the seat of heaviest infection. Blacklock and Gordon¹⁰ discovered that in Sierra Leone 36 per cent of pregnant women infected with plasmodium falciparum sustain intense infection in the placenta leading to death of the foetus.

When the disease is brought under control the dose of quinine

is reduced. Quino-plasmoquine (quinine $4\frac{1}{2}$ grains, plasmoquine $\frac{1}{6}$ grain), one tablet two or three times a day, can then be given with advantage. The quinine causes the nonsexual forms of the parasites to disappear from the blood in a few days and plasmoquine has the special virtue of acting on the sexual forms (gametocytes) more powerfully than on the non-sexual forms. Green-Armitage says that quinine should be given unhesitatingly in doses of 10 grains three times daily to pregnant women suffering from malaria. His experience in the tropics and his eminence as an obstetrician qualify him to express an authoritative opinion on the subject.

There are many practitioners, however, in this country who hold views contrary to those expressed here and who are, therefore, very much averse to giving quinine to pregnant women. The opponents of quinine base their arguments on the well-known pharmacological action of quinine in originating and increasing the contractions of the uterus. All pharmacologists are agreed on this point, but it must be realized that these observations have been made on experimental animals. Experiments¹⁴ show that quinine in a concentration of 1 in 300,000 has no effect on the uterus. A concentration of 1 in 44,000 produces a tonic spasm which, if sustained, would cause asphyxia of the foetus from constrictions of the placental sinuses; but this concentration is never attained by quinine administered in therapeutic doses, and would occur only if the patient was nearly poisoned with quinine. Apart from those theoretical considerations, what does clinical experience teach us on this point? All obstetricians are aware that drugs in general, when administered in therapeutic doses, are altogether powerless in bringing on abortion or premature labour. Obstetrical interference is, as a rule, needed. Even Watson's³ castor oil-quinine-pituitrin method of induction is more likely to succeed in provoking the onset of labour only when undertaken at or after term than before term. Failures are numerous when undertaken before term.

Quinine is often given in the second stage of labour with the idea of strengthening the uterine contractions. I have never been impressed by its use when given for this purpose, and I feel certain those patients who delivered themselves after its use would have done so without it. I prescribe it rarely for this purpose and then only as a *placebo*. Clinical experience, therefore, does not suggest that quinine given in therapeutic doses possesses such oxytocic powers as to preclude its use in pregnancy.

ATEBRIN IN THE TREATMENT OF MALARIA.

Many practitioners employ atebtrin in the treatment of malaria as an alternative to quinine, and this appears to be the favoured drug with many in the treatment of the disease during pregnancy. I have had a few cases treated with atebtrin side by side with others treated with the usual quinine and bromide mixture, and the latter produced the better results. Atebrin undoubtedly controls the fever and seems to effect a cure in a good many uncomplicated cases. Relapses, however, are known to occur after its use, as with quinine. In a fatal case which had been treated with atebtrin a post-mortem examination was possible, and the following inferences can be drawn from this case :

(1) The patient was a subject of long standing hook-worm disease and pre-existing chronic nephritis who suffered from an intercurrent attack of malaria.

(2) Atebrin did not completely cure her of her malaria, as parasites were discovered in her blood after the full course of atebtrin during life and also in the tissues of her brain, spleen and placenta after death.

(3) That a relapse can occur after a full course of treatment with atebtrin.

(4) The congested and pigmented foetal spleen suggests invasion of the foetus with parasites. The finding of pigment in the foetal spleen similar to that found in the maternal spleen confirms this view. The increase in the oedema while she was on atebtrin may be due to the continuance of the pregnancy in a subject of pre-existing nephritis and hook-worm disease. The cause of the nephritis is obscure. The question also arises whether it is due to the long-standing hook-worm disease. The death of this patient created a suspicion, indeed a fear, in my mind, that the atebtrin may have contributed towards the fatal termination. I am still rather averse to prescribing atebtrin for pregnant women who are toxæmic, or who are subjects of pre-existing nephritis or advanced hook-worm disease. The toxicity of the drug has still to be determined. Further study and research are needed in my opinion before one can determine with any degree of certainty the exact place of atebtrin in the treatment of malaria in gravid, as well as non-gravid women.

Conclusions.

(1) Quinine is still indispensable in the treatment of malaria

in gravid as well as non-gravid women. Quinoplasmoquine quine and plasmoquine are necessary adjuncts in the treatment. Quinine causes the rapid disappearance of the nonsexual forms of the parasites while plasmoquine acts more powerfully on the sexual forms.

(2) Pregnancy is not a contra-indication to the use of quinine. Clinical experience does not suggest that quinine administered in therapeutic doses possesses oxytocic powers.

(3) Far from being an oxytocic quinine, administered in effective therapeutic doses, by rapidly controlling the malarial infection and the high temperature, prevents premature interruptions of pregnancy and intra-uterine foetal death.

(4) Atebrin is regarded by many as an alternative to quinine in the treatment of malaria during pregnancy. While it should be regarded as a useful addition to our therapeutic armamentarium, as it does not control the malarial infection and the high temperature so rapidly, it must be said to occupy but a subordinate place to quinine in the treatment of the disease during pregnancy. Relapses do occur after its use as with quinine, and whether it is as efficacious and as safe for general use as quinine is yet to be seen.

(5) Atebrin would appear to be contra-indicated in subjects of toxæmic pregnancy, pre-existing nephritis and advanced hook-worm disease.

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