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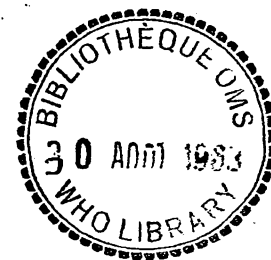
CONTROLLED TRIAL OF PYRIMETHAMINE AMONG A GROUP
OF PREGNANT WOMEN IN AN AFRICAN VILLAGE

by

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A longitudinal study of consecutively born African children, beginning in 1957, has been undertaken in a dispensary in the village of Imesi, 100 miles north-east of Ibadan, in Nigeria. The observations began during the pregnancy of the mother, continued till the child reached his fifth birthday and were particularly concerned with the effects of frequent infections and poor nutrition. Preliminary investigations had suggested that these factors were primarily responsible for the high mortality in infancy and early childhood. It was estimated that about half the children born alive died before their fifth birthday (Morley 1963).

This paper describes the effect on the mother during pregnancy, and on the new-born child of one or other of two forms of antimalarial treatment. One group of mothers was given regular dosage of pyrimethamine for the suppression of malaria, and treatment with chloroquine on contraction of any fever not obviously due to acute bacterial infections; the other, the control group, was given placebo tablets (lactose) at regular intervals and treated with chloroquine on the appearance of fever, as for the first group.

1. Background to the Study

Imesi lies 600 metres (2000 feet) above sea level in a small plateau among hills, north-east of the town of Ilesha. Surveys have shown this to be a holo-endemic area for malaria, as is most of southern Nigeria; the majority of infections

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are due to Plasmodium falciparum, and few, if any, mothers and children are protected by antimosquito or antimalarial measures. There is ample opportunity for mosquito breeding in the village in water storage pots and in the 12 streams and pools used as sources of water. The population of just under 5000 is Yoruba. The majority farm and produce yam, maize and cassava, with cocoa as the principal cash crop.

2. Design of the Trial

As the pregnant women were registered at the dispensary, they were given consecutive numbers and allotted to one or other of two groups. There were 504 mothers pregnant in the village during the 20 months at the beginning of the survey. Seventy-two of these failed to attend for antenatal care and three left the village. Of 429 who attended, 217 were in the pyrimethamine treated and 212 in the lactose control group. All women with even numbers were given two tablets (50 mg) of pyrimethamine once a month. If the mother attended the village dispensary with fever, a single dose of 600 mg of chloroquine sulfate was given, this being the dosage advised by Covell, Coatney, Field & Singh (1955). The control group (the odd numbers) were given two tablets of lactose once a month. Chloroquine sulfate was also given, as in the first group.

Blood films were examined in the hospital laboratory by locally-trained technicians, and spot checks of a proportion of the films were made by one of us (McLley). The technicians did not know to which group a mother belonged.

3. Results of the Study

Pregnancy. The records of 429 pregnancies and their outcome were studied to determine the effects of drug administration. One of the observations made was the small gain in weight of the women during pregnancy. The changes in weight of 164 pregnant women who attended regularly from early pregnancy in the two groups were analysed, the results being set out in Table 1. Further details of the gains in weight are being prepared for publication.

Table 1 shows that the women who received pyrimethamine as a malaria suppressant gained more in weight during pregnancy than those receiving anti-malarial therapy only when they attended the dispensary with fever. The mean

difference between the two groups was about 2 lb (850 g), which is statistically significant ($P < 0.05$). The mothers giving birth to boys gained more weight, in both groups, than those giving birth to girls. This difference just achieves statistical significance, but because no explanation can be offered for it, further investigation is required to determine whether or not it may have occurred by chance alone.

Birth weight. The suppression of malaria in pregnancy was considered likely to have some effect on the mean birth-weight of the children. In Table 2 the effects of treatment and the parity of mothers on the mean birth-weights of live born singletons from 460 mothers are shown; 17 still births and 10 twin deliveries have been excluded. Mothers who took pyrimethamine, even if irregularly, gave birth to babies that weighed on average 157 g (5-1/2 oz) more than those in the control group. A further analysis of the control group did not demonstrate a difference between those receiving occasional treatment with chloroquine from those who had lactose alone.

The placenta. When examining placentae infected with malarial parasites, a macroscopic change was evident. The infected placenta was frequently darker than a normal placenta. It was thought possible that such infected placentae might weigh less than a normal placenta, and that this might be responsible for part of the increase in weight of the pregnant mothers receiving pyrimethamine. The placentae from 137 mothers were weighed. The mean weight of the placentae from 68 women given pyrimethamine was 581 ± 13.3 g (20.5 ± 0.47 oz), the corresponding weight in the control group of 69 women being 584 ± 13.3 g (20.6 ± 0.47 oz). There was thus no evidence that prevention of malaria affected the weight of the placenta.

The placentae from 115 mothers receiving pyrimethamine were examined microscopically. Only one of these was found to contain a few malarial parasites. From the mothers on lactose tablets, 105 placentas were examined and 18 showed malarial parasites. Of the mothers with infected placentae, one gave birth to twins, and another to a still-born child whose sex was not recorded. In the remaining 17, the mean weight of the 13 singleton boys was 2551 g (5 lb 10 oz), and of the four singleton girls 2664 g (5 lb 14 oz).

4. Discussion

Although attention has often been drawn to the possible effects of malarial infection of the mother during pregnancy, few statistical records are available. The association of malarial parasites in the placenta and low birth-weight has been the subject of four previous studies in Nigeria. Bruce-Chwatt (1952) first reported this association in Lagos. His findings were confirmed by Archibald (1956) at Ilaro, by Cannon (1958) at Ilesha in the Western Region and by Spitz (1959) at Nsukka in the Eastern Region. These investigators found that the mean birth-weight of infants born to a mother with a placenta affected with malarial parasites may be from 89 g (2.9 oz) to 311 g (10 oz) less than that of infants born to mothers with placentas free from parasites. In the last three of these reports information is given on the parity of the mother. The relationship to parity is important and the relevant data are summarized in Table 3, which shows that more than one-third of the primiparous mothers in rural Nigeria are likely to have infected placentae. These mothers are more likely to produce lighter "premature" or still-born infants. Infants born to primiparous mothers in all communities so far studied are lighter on the average than subsequent children. In Nigeria and other malarial areas there is probably an additional factor, namely, that the primiparous mother is more likely to have a placenta containing malarial parasites and with it an infant of low birth-weight. In Nigeria the difference in mean birth-weight between first and second infants was found to be 272 g (9.6 oz) (Morley & Knox, 1960), whereas in England the difference was 119 g (4.2 oz) in male infants and 91 g (3.2 oz) in female infants (Martin, 1931). Table 3 suggests that there is a decreasing liability for the placenta to be infected with increasing parity of the mother.

In this study the mothers given pyrimethamine gained more weight during pregnancy than those in the control group. The babies born to such mothers in the treated group were heavier. This provides further evidence of the value of a cheap suppressive antimalarial drug suitable for pregnant women in regions where malaria is endemic. In this trial adequate suppression was apparently obtained with only two tablets (50 mg) of pyrimethamine monthly, and a single dose of four tablets (600 mg) of chloroquine if the mother came to the dispensary with fever. More frequent doses of pyrimethamine may be advocated, however, if this means that the number of mothers who receive suppressive treatment has to be reduced, the total

TABLE 1. MEAN WEIGHT GAINS OF MOTHERS RECEIVING
PYRIMETHAMINE OR LACTOSE DURING PREGNANCY

Treatment	Sex of child	Number of mothers	Weight at 16-20 weeks kg	Weight at term kg	Weight gain kg
Pyrimethamine	M	41	52.32	56.44	4.12 (9 lb 1 oz)
	F	45	53.94	57.91	3.97 (8 lb 12 oz)
	M & F	86	53.17	57.20	4.03 (8 lb 14 oz)
Lactose	M	30	54.31	57.91	3.60 (7 lb 15 oz)
	F	48	53.31	56.21	2.90 (6 lb 6 oz)
	M & F	78	53.68	56.86	3.18 (7 lb 0 oz)
Over-all mean and numbers		164	53.42 (117 lb 10-1/2 oz)	57.04 (125 lb 10 oz)	3.62 (8 lb 0 oz)

Mean gain in weight of mothers receiving pyrimethamine was 852 g (1 lb 14 oz) more than that of control mothers receiving lactose ($P < 0.05$).

Mean gain in weight of mothers delivering boys was 450 g (1 lb) more than that of those delivering girls ($P < 0.05$).

TABLE 2. MEAN BIRTH-WEIGHT OF CHILDREN BORN TO MOTHERS RECEIVING PYRIMETHAMINE OR TO MOTHERS RECEIVING LACTOSE PLACEBOS (CONTROL GROUP)

Sex of infant	Parity of mothers	Pyrimethamine group grams	Control group grams	Difference grams
Boys	0	2 854 (14)	2 772 (10)	82
	1 to 3	2 958 (47)	2 886 (36)	72
	4+	3 076 (40)	2 827 (39)	249
Mean weight and total births		2 989 (101)	2 846 (85)	143
Girls	0	2 681 (13)*	2 473 (18)	208
	1 to 3	2 865 (46)*	2 816 (54)*	49
	4+	3 059 (36)*	2 814 (39)	245
Mean weight and total births		2 915 (95)	2 759 (111)	156
Over-all mean weights and total births		2 954 (196) (6 lb 8 oz)	2 797 (196) (6 lb 2-1/2 oz)	157

Figures in parentheses denote numbers of single births and not number of weights recorded.

* Indicates that the birth-weight of one infant was not recorded.

The difference in mean birth-weight between pyrimethamine and lactose groups of 157 g (5-1/2 oz) was significant ($P < 0.05$).

TABLE 3. INCIDENCE OF PLACENTAE CONTAINING
MALARIAL PARASITES IN MOTHERS OF DIFFERENT PARITY

Observer	Parity									
	1		2		3 - 5		6+			
	Non-malarious	Malarious	Non-malarious	Malarious	Non-malarious	Malarious	Non-malarious	Malarious	Non-malarious	Malarious
Archibald (1956)	138	35	91	15	139	15	17	1		
Cannon (1958)	45	75	41	22	133	24	43	9		
Spitz (1959)	82	47	88	30	194	46	76	12		
TOTAL	265	157	220	67	466	85	136	22		
Proportion malarious		(37%)		(23%)		(15%)		(14%)		

benefit to the community may be decreased. Although this method has been used during the last five years, pyrimethamine-resistant strains of malarial parasites have not so far become apparent.

Summary

1. In an African village where malaria is holo-endemic, 429 pregnant women were divided into two groups. Those in the first group received 50 mg of pyrimethamine monthly, and those in the second group similar tablets containing only lactose. All women were given a single dose of 600 mg of chloroquine if they reported to the dispensary with fever.
2. The women in the treated group gained 852 g (1 lb 14 oz) more than the women in the control group during pregnancy.
3. Infants born to women in the treated groups had a birth weight 157 g (5-1/2 oz) greater than that of those in the control group.
4. Suppression of malaria had no apparent effect on the weight of the placenta.

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