

SUPPRESSION OF MALARIA WITH PYRIMETHAMINE IN NIGERIAN SCHOOLCHILDREN

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SYNOPSIS

The authors describe a two-year investigation carried out on a group of Nigerian schoolchildren with the object of assessing the effect of suppressing malaria infection with pyrimethamine on the physical development of the African child. The results showed that the average gain in weight of the treated children over the period of the investigation was significantly greater than that of the untreated children. Despite the relatively high weekly dose of the drug no side-effects were observed, and no alarming manifestation of malaria was noted when administration of the drug was discontinued.

One of the many problems concerning the epidemiology of malaria in tropical Africa is the assessment of the effect that the untreated chronic infection has on the physical and mental growth and development of the indigenous child born and raised in the holoendemic malarious area.

The effect of long-term suppression of malaria on the physical development of the African child has rarely been reported in studies carried out in Africa on mass chemoprophylaxis, although a preliminary report by McGregor⁸ and a recent paper by Colbourne⁶ are notable exceptions.

The present paper describes a two-year investigation carried out on a group of Nigerian schoolchildren, about half of whom were given pyrimethamine to suppress malaria. This drug was selected because earlier work done with it in Nigeria had shown that it would be suitable for the long-term suppression of malaria in Africans (Archibald;² Bruce-Chwatt & Archibald⁴).

Method of Investigation

The children selected for the investigation were pupils of St. Jude's School, which is situated in one of the suburbs of Lagos. Most of them were children of African middle-class parents. The investigation commenced in January 1953, when, permission having been obtained, 277 children between five and ten years of age were selected. On the basis of a preliminary

investigation the children were then divided into two groups as equivalent as possible with regard to mean age and other attributes. One group was to be given a suppressive drug while the other was to be used as a control. To each child in the first group one tablet of 25 mg of pyrimethamine was given once each week of term over a period of two school years. The tablets were swallowed under supervision and no trouble was experienced in getting the children to take them. The children in the second group received no medication and as they did not object to this, the distribution of a placebo was not considered necessary.

By the end of 1954, 219 children were still under observation, and it is with them that this paper deals in detail. Of these children, 119 were in the group getting pyrimethamine and 100 were in the control group.

The 58 defaulters, 20.9% of the number originally included, consisted of 32 from the control group and 26 from the drug group. They were followed-up by visits to their addresses to discover the cause of their lapsing from the investigation. Change of residence of the family was much the commonest cause disclosed and accounted for 44 children, while seven more had lapsed as a result of changes in school classes. The remaining seven defaulters were all from the control group; three of them died during the investigation from causes which we have not been able to ascertain and the other four have not been traced.

At the start of the investigation, the age of each child was assessed on the basis of its height. Such an assessment was necessary because accurate information on age is not obtainable from Nigerians as a rule. The method of assessment chosen was that described by Anderson¹ and adopted by him for Nigerian children of the Yoruba tribe, to which the majority of the children at St. Jude's School belonged.

According to this assessment the mean age of those in the drug group was 6.3 years and of those in the control group, 6.6 years. At monthly intervals throughout the two years covered by the investigation, records were kept for each child of weight, height, spleen size and liver size, and of parasite presence and density. In the latter months of 1954 these observations were supplemented by data on the occurrence of the sickle-cell trait in the children's blood, on red and white blood-cell counts, and on percentage haemoglobin. Finally an analysis of each child's record of school attendance was made from the school registers.

The measurement of weight was made with a spring weighing-machine. The children were weighed in their normal school clothing, which in this tropical environment usually weighs about two pounds (1 kg). Height was measured with a metre-stick fitted with a sliding headpiece. Spleen and liver palpation was carried out by a seated observer on standing children, the spleen sizes being classified in the manner described by Hackett,⁷ and liver enlargement being noted as "fingerbreadths below the costal margin". Parasite densities were determined by examination of thick films and were

assessed on the parasite-leucocyte ratio; specimens were declared negative if no parasites were observed on inspection of a hundred fields. The percentage haemoglobin was estimated by means of a Gower's haemoglobino-meter, and sickling was determined by mixing a drop of blood with an equal amount of 2% sodium metabisulfite solution, sealing with a vaselined coverslip and examining the slide between two and three hours after collection.

The investigation was rounded off in the last week of the 1954 term by giving each child two tablets (400 mg) of amodiaquine—a dose which had previously been found adequate to clear the blood of Lagos schoolchildren of malaria parasites (Bruce-Chwatt & Archibald ⁴). During the first term of 1955, the children were examined at monthly intervals, the reappearance of parasitaemia being noted and changes in spleen sizes being observed. This was done to obtain some indication of whether the resistance to malaria, usually manifest in such schoolchildren, had been impaired by the two years' suppression to which the drug group had been subjected.

Results of Investigation

That pyrimethamine was successful in suppressing malaria in these schoolchildren is indisputable. The initial crude parasite-rate in the children getting the drug was 48.7%, 58 children being positive in this group. By the next examination, a month later, no trophozoite was detectable in the blood of any child in that group, and although three children showed gametocytes at this time, the latter, too, had disappeared by the next examination. With exceptions which are detailed later, this group remained parasite-free throughout the rest of the investigation. In marked contrast to this was the parasitaemia in the controls. Initially this group had a crude parasite-rate of 50%, 50 children being positive. Throughout the investigation the rate fluctuated quite widely, and in December 1954 it was 42%. The fact that nearly all the children in this group showed parasites in their blood on numerous occasions throughout the investigation indicates that regular domestic suppression was not practised by these children's families. The occasional use of antimalarials to control bouts of illness was, however, not uncommon.

The frequent appearance of patent parasitaemia in most of the controls contrasts strikingly with its rarity in the children getting pyrimethamine.

Twenty-seven of the latter group did, however, show parasites in their blood on some occasion during the two years of observation. In sixteen cases, the parasites were observed only immediately after a holiday, when the break (usually for four weeks) in school attendance had led to discontinuation of drug administration. The eleven remaining cases, however, showed parasites during term, although usually on one examination only and in small numbers.

Plasmodium falciparum was by far the commonest parasite found during this investigation. It was present in all except four of the children who were positive in January 1953, and in all save two of those positive in December 1954. These six exceptions were found to be infected with *P. malariae*, which was also seen, together with *P. falciparum*, in seven mixed infections in January 1953, and in four mixed infections in December 1954.

P. falciparum gametocytes were scanty. In January 1953, they were seen in twelve children only and in December 1954, in only four.

The effect of pyrimethamine administration on the enlarged spleen was very pronounced. At the start of the investigation the spleen-rate in the drug group was 62.2%, 74 children having palpable spleens. A month later, this rate had fallen to 43.6%. It was 34.2% after three months, 18.5% after six, 11.8% after twelve, and stood at 4.2% at the end of 1954. This last figure represents the persistence of five palpable spleens in the group of 119 children.

The spleen-rate in the control group was 64% at the start of the investigation. It fluctuated from month to month and was 52% in December 1954.

The average enlarged spleen, which is the weighted average size of palpable spleens, remained substantially unchanged in both groups throughout the investigation. In January 1953, this index was 2.2 in the drug group and 1.9 in the control group. In December 1954, the same results were obtained. In the drug group it was noticeable that during the transition from palpable to non-palpable, there was a period when the spleens were labile, fluctuating in size from examination to examination over a period of some months before shrinking out of reach of the palpating hand.

The changes observed in the two main malarimetric indices in both groups of children are shown in Table I.

TABLE I. SPLEEN-RATES AND PARASITE-RATES IN TREATED AND UNTREATED GROUPS OF CHILDREN AT BEGINNING AND AT END OF INVESTIGATION

	Drug group *				Control group **			
	January 1953		December 1954		January 1953		December 1954	
	positive		positive		positive		positive	
	no.	%	no.	%	no.	%	no.	%
Spleen-rate	74	62.2	5	4.2	64	64.0	52	52.0
Crude parasite-rate	58	48.7	0	0	50	50.0	42	42.0

* 119 children

** 100 children

TABLE II. WEIGHT GAINS IN TREATED AND UNTREATED GROUPS OF CHILDREN

I. Drug group

Age (years)	Number	Mean and S.D. of weights		Mean gain of weight (pounds)
		January 1953	December 1954	
5	51	36.9±3.3	44.0±3.9	7.1
6	23	42.1±3.4	49.8±4.7	7.7
7	15	46.3±3.8	55.3±3.9	9.0
8	18	47.2±3.8	57.1±4.8	9.9
9	12	55.3±5.4	67.3±5.9	12.0
Total	119	42.5±7.0	50.9±8.7	8.4

II. Control group

5	33	37.4±3.8	43.3±4.7	5.9
6	24	41.5±3.1	48.2±4.3	6.7
7	10	48.6±5.1	56.5±5.8	7.9
8	21	49.6±4.9	58.5±6.7	8.9
9	12	54.7±4.3	65.8±6.3	11.1
Total	100	44.1±7.4	51.7±9.5	7.6

III. Comparison between the two groups

Age (years)	Difference in mean gain of weight between drug group and control group	Mean percentage of gain in weight	
		drug group	control group
5	1.2 pounds	19.2	15.8
6	1.0 ..	18.3	16.1
7	1.1 ..	19.4	16.3
8	1.0 ..	21.0	17.9
9	0.9 ..	21.7	20.3
Total	0.8 ..	19.8	17.2

Enlargement of the liver was unusual in the schoolchildren observed in this investigation. Only six had enlarged livers, and of these only one showed enlargement in excess of one fingerbreadth.

Of the 145 children initially placed in the drug group, 119 continued in it for two years without any toxic effect being noticed.

Other Effects of Suppression

In the analysis of the mean weight increase in the two groups of children, those taking pyrimethamine showed higher gains. This occurred consistently throughout each of the age-groups analysed and is shown in Table II, which records both the average gain in pounds in each age-group and also the average individual gain, expressed as a percentage of the child's weight at the commencement of the investigation.

From Table II it can be seen that the mean gain in weight of the children given pyrimethamine over those in the control group was 0.8 pound during the two years of the investigation.

In order to find out whether the difference observed between the two groups was statistically significant, an analysis of variance was carried out. Table III summarizes the results obtained.

The value of the F ratio is 9.81 with 1 and 213 degrees of freedom. It exceeds the corresponding critical value at the 1% level of significance, so that the gain in weight is significantly greater for the children in the drug group than for those in the control group.

The results of the observations on the average gain in height in the two groups of children showed an average gain of 9.1 cm in the children of both groups, with hardly any individual differences between the drug group and the control group.

In both groups the blood picture (Table IV) shown by the percentage haemoglobin and by the red and white cell counts was very similar. Figures from both groups showed less than optimum results; in the main the children's blood in both groups had about 80% haemoglobin and gave red cell counts of about 4 million per mm^3 and white cell counts of about 6000 per mm^3 . There were, however, individuals whose blood pictures differed markedly from the average.

The sickle-cell trait was observed in 18.6% of the children under investigation. At the start of the investigation the parasite-rate in these sicklers was 46.3% and the spleen-rate, 53.7%. This contrasts little with a parasite-rate in the non-sicklers of 49.7% and a spleen-rate of 64.8%. The density of parasitaemia was between 200 and 500 parasites per mm^3 in both sicklers and non-sicklers.

The records of absences from school kept during 1954 showed that the number of absences per child was 2.1 in the drug group and 1.9 in the control group, with the number of days lost averaging 4.5 and 3.2 per child, respectively.

TABLE III. ANALYSIS OF VARIANCE OF GAIN OF WEIGHT

Source of variation	df	Sum of squares	Mean square
Ages ignoring treatment	4	566.34	
Treatment eliminating ages	1	61.70	61.70
Error	213	1 339.96	6.29
Total	218	1 968.00	

TABLE IV. AVERAGE PERCENTAGE HAEMOGLOBIN AND BLOOD-CELL COUNTS IN TREATED AND UNTREATED GROUPS OF CHILDREN

Age in January 1953	Drug group				Control group			
	number examined	average percentage haemoglobin	average red blood count (millions per mm ³)	average white blood count (thousands per mm ³)	number examined	average percentage haemoglobin	average red blood count (millions per mm ³)	average white blood count (thousands per mm ³)
5	51	79.2	4.1	6.3	33	79.8	4.0	5.9
6	23	77.9	3.9	6.4	24	76.9	4.0	6.2
7	15	81.6	4.1	4.7	10	80.5	4.2	5.2
8	18	78.9	4.2	5.9	21	76.5	4.0	5.9
9	12	78.3	4.1	5.6	12	77.7	4.0	5.8
Total	119	79.1	4.1	6.0	100	78.2	4.0	5.9

Cessation of Suppression

At the end of 1954, i.e., two full years after commencement of the suppressive regimen, the distribution of pyrimethamine was discontinued. Amodiaquine, at the dose of 400 mg, was given to each child in both groups with the object of clearing the blood of all the children. At the beginning of the next term, one month later, and for the two subsequent months, all the children were examined to find out whether parasites had reappeared in their blood.

On the resumption of school in January 1955, there were thirteen defaulters from the 219 children who had been observed over the previous two years. Nine of these defaulters were from the drug group and four from the control group, and the absences were due mainly to change of domicile.

Table V shows the spleen- and parasite-rates of the remainder of these children at the end of each of the first three months of 1955.

**TABLE V. SPLEEN-RATES AND PARASITE-RATES
IN CHILDREN OBSERVED IN 1955**

Index	Date	Drug group	Control group
Spleen-rate	January	28.5 %	28.4 %
	February	17.4 %	25.5 %
	March	19.8 %	24.1 %
Parasite-rate	January	24.0 %	14.8 %
	February	16.8 %	17.3 %
	March	25.7 %	33.8 %

The spleen- and parasite-rates in the drug group were substantially lower in February than in January. This was not the case in the control group, and it suggests that there may have been some children in the former group who received medication at home during January. It has been remarked previously that such medication is practised for the relief of actual sickness, and this leads us to believe that the first re-exposure to malaria may have produced signs of obvious illness in some of the children who had belonged to the drug group.

The average density of parasitaemia in the positives of both groups during the follow-up period was 500 parasites per mm³, which is somewhat higher than is usually found in such a sample of Nigerian schoolchildren not undergoing any suppressive medication.

Nevertheless these results do not suggest that there has been any marked increase in susceptibility to reinfection in the drug group as compared with the control group.

Discussion

It is evident from this investigation that pyrimethamine at the dose of 25 mg once a week is a reliable suppressant of malaria in African children. The speed of the decrease in the malarionometric indices as a result of the described regimen is impressive. The parasite-rate declined from about 50% to nil within one month, while the initial spleen-rate of about 62% was halved in 3 months, halved again in 6 months, and halved once more in 12 months.

An investigation parallel to ours, dealing with 176 children but lasting only one year, was recently concluded in the Gold Coast and has been described by Colbourne.⁶ In this investigation, the parasite-rate decreased

slightly more slowly, taking two months to fall from about 60% to nil, but the spleen-rate decreased slightly faster, taking only seven months to fall to one eighth of its initial value of 38%.

The records of the weight gains made by our drug group as compared with the control group are suggestive of the handicap malaria may be to African children in Southern Nigeria. The average gain of the former group exceeds that of the latter at corresponding ages by about one pound over the two years of investigation. This difference, although small, may nevertheless be more indicative than is at first apparent. Our investigation was carried out on schoolchildren who had presumably already developed a fair degree of individual tolerance to the malaria parasite and who had passed through the early phase of precarious balance of the host-parasite relationship so obvious in West African children in the 2-4 years' age-group (Bruce-Chwatt³). Moreover, the social class from which our children were drawn differed considerably from that of the poorer urban or entirely rural stratum in which the effects of malaria infection are most pronounced. It is conceivable that the better economic background of our children protected them from some of the ill effects of malaria and other chronic infections, and that the effect of the removal of malarial parasitaemia was less spectacular than it would have been in a poorer or less well-nourished group. The low incidence of hepatomegaly in our sample is suggestive in this respect.

This consideration comes into better perspective when it is realized that the measurements of British children made at different times throughout the last century show an accelerated rate of growth which parallels the social improvements during that period. British children 6-8 years of age were about 8 pounds heavier in 1947 than in 1910, the retardation at the earlier date being related to social deprivation (Clements⁵). In comparison with that gain, the effect of relieving the children in our investigation of their malaria burden is substantial.

It is of interest that Colbourne's results differ in this respect from ours, although his general conclusions are similar.⁶ The Gold Coast children kept on pyrimethamine for one year showed only 0.17 pound difference in weight gain over those not protected by drug administration. On the other hand, they showed a notable reduction of absenteeism from school on account of sickness. No other definable benefit from pyrimethamine administration could be demonstrated and it is difficult at the present time to explain this disagreement between two parallel investigations otherwise than by assuming that the two samples differed more markedly than was at first apparent.

Our results, however, agree fairly closely with those obtained by McGregor⁸ in a peri-urban area in the Gambia where a similar investigation was carried out on a total of 66 infants, 37 of whom were protected by a weekly dose of chloroquine or pyrimethamine. In this case the mean

weight gain over one year was about 8 ounces (225 grams) higher in the protected group than in the control group.

The complete lack of any side-effects in our 119 children, who took a relatively high dose of pyrimethamine nearly every week for two years, merits special consideration.

The eventual cessation of suppression occasioned no alarming manifestation of malaria in the children who had been protected from it for two years. It seems that if any loss of immunity was suffered by this group, it was only transient.

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RÉSUMÉ

L'effet du traitement antipaludique sur le développement physique et psychique de l'enfant indigène, né et élevé en zone d'holoendémie, est l'un des problèmes épidémiologiques que pose la lutte contre le paludisme en Afrique tropicale. On ne s'est préoccupé que récemment de cet aspect des campagnes clinoprophylactiques, et les travaux publiés à ce sujet sont encore peu nombreux.

Les auteurs ont suivi durant deux ans 277 écoliers nigériens de 5-10 ans, dont la moitié recevaient de la pyriméthamine à raison de 25 mg par semaine scolaire, les autres servant de témoins. Chaque mois, on pesait et mesurait les enfants; on évaluait le volume de la rate et du foie, ainsi que la parasitémie.

La pyriméthamine, aux doses indiquées, a eu d'heureux effets. Alors que le taux parasitaire brut était de 50% environ au début du traitement, on ne décelait, un mois après, aucun trophozoïte dans le sang des enfants traités. Chez les témoins, le taux initial de 50% environ était de 42% à la fin de la seconde année. L'indice splénique initial, de 62% environ dans le groupe traité, s'abaisse à 4,2% à la fin de la deuxième année de traitement. Ces chiffres étaient de 64% et de 52% respectivement dans le groupe témoin.

L'augmentation moyenne de poids des enfants traités dépassait d'une livre environ celle des enfants témoins, différence statistiquement significative.

Le traitement à la pyriméthamine n'a provoqué aucun effet secondaire chez les enfants et ne paraît pas les avoir rendus plus sensibles à une éventuelle réinfection.

REFERENCES

1. Anderson, D. (1953) *Biometrika*, **25**, 61
2. Archibald, H. M. (1951) *Brit. med. J.*, **2**, 821
3. Bruce-Chwatt, L. J. (1952) *Ann. trop. Med. Parasit.*, **46**, 173
4. Bruce-Chwatt, L. J. & Archibald, H. M. (1953) *Brit. med. J.*, **1**, 539
5. Clements, E. M. B. (1953) *Brit. med. J.*, **2**, 897
6. Colbourne, M. J. (1955) *Trans. roy. Soc. trop. Med. Hyg.*, **49**, 356
7. Hackett, L. W. (1944) *J. nat. Malar. Soc.*, **3**, 122
8. McGregor, I. A. (1953) *Observations on the effect of malaria on Gambian infants and young children* (Mimeographed report, CCTA/NUT/Min.4)