Chemotherapy in Relation to Possibilities of Malaria Eradication in Tropical Africa

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The value of chemotherapy with regard to malaria eradication by residual insecticides can be envisaged from two main angles: (1) as an important safeguard after the cessation of residual spraying, for elimination of actual or potential foci of infection maintained by remaining carriers of malaria parasites, and (2) as an adjuvant method capable of speeding up the success of a residual insecticidal campaign, especially when a development of resistance by the local vector is likely to occur.

There is little doubt that over most of the continent of Africa we are still far from contemplating the first of the two possibilities. No large area in tropical Africa has seen the elimination of malaria by residual spraying alone and until this has been achieved it is difficult to plan in terms of an early continent-wide eradication of this disease.

Methods that will improve the present situation and speed up the beginning of malaria eradication from Africa are now being extensively investigated.

General aspects of mass chemotherapy in rural areas of Africa. Following in the steps of the Expert Committee on Malaria,[a] and of the Second Asian Malaria Conference held in Baguio (1954),[b] the Second African Malaria Conference held in Lagos (1955), justly alarmed by the recent finding of dieldrin resistance in *A. gambiae* in Nigeria, [c] emphasized the importance of carrying out malaria control schemes with the object of obtaining a complete local interruption of transmission as soon as possible. The Conference recommended that chemotherapeutic methods be used in conjunction with residual insecticides wherever this combined attack may lead to the rapid elimination of malaria.

This recommendation, however logical and right, was accepted by some of us with mixed feelings. It would be an exaggeration to say that it constituted a veiled admission of defeat of residual insecticides so brilliantly successful in many other parts of the world. It is true, however, that the advocated use of combined methods of control of the vector and of the parasite greatly increases the difficulty of our task in vast rural areas of Africa.

It appears that in addition to dealing with the relatively inaccessible but at least static rural dwellings one will have now to find, to persuade, to treat repeatedly and regularly the far more numerous, varied, widely dispersed, extremely mobile and often elusive human element with its particular socio-economic background of an under-developed area.

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[a] World Health Organization, Expert Committee on Malaria (1955) *Wld Hlth Org. techn. Rep. Ser.*, **80**

[b] World Health Organization, Malaria Conference on the Western Pacific (Second Asian Malaria Conference) (1956) *Wld Hlth Org. techn. Rep. Ser.*, **103**

[c] Elliott, R. & Ramakrishna, V. (1955) *Nature (Lond.)*, **177**, 532

One must not forget that in the holoendemic African tropics epidemics of malaria do not occur and that the steady wastage of young lives and human assets due to this disease has few elements of personal drama, unlike that of yaws, leprosy or sleeping sickness which are obvious in all groups of the population.

Holoendemic malaria is an insidious, ever-present enemy, killing infants and young children, sapping the energy and strength of the people, interfering with education, preventing or slowing down the economic development, but all this is obvious chiefly from the perspective of an investigation on large samples of the population.

A general impediment of large-scale chemotherapy of malaria rests partly on the fact that a proportion of the population in Africa has established a precarious, short-term balance in its specific host-parasite relationship and thus might not eagerly seek treatment in the absence of clinical symptoms. The other and probably more disappointing prospect of mass chemotherapy of malaria is linked with the particular pharmacological aspects of such an enterprise.

In the application of residual insecticides for malaria control, one of the most important characteristics of the toxicant itself or its formulation is the duration of its residual activity. Similarly, in any large-scale chemotherapeutic campaign the question of the " residual " action of the drug will always be in the foreground. And yet our present drugs are excreted rapidly and thus have a short " carry over " value. There is little doubt that this is the main drawback of all known antimalarials and the main practical difficulty in their mass administration. The frequency of the distribution of antimalarials for mass treatment in rural areas varies usually between once a week and once a month. The more frequent the regimen, the greater the chances of its irregularity, and the greater the difficulties of correct administration in large areas with a low population density, poor communications, primitive educational level and inadequate rural health service organization. What we need for mass chemotherapy is an antimalarial similar to pentamidine for trypanosomiasis, which when administered at a dose of 200-250 mg will protect an individual for 3-6 months.

All this is certainly not new. It has been well recognized that collective drug prophylaxis sensu stricto in rural communities " can seldom be efficiently applied and is beset with administrative and other difficulties ".[d] But it is more than probable that the intermittent or short-term " mass treatment " will present a problem of nearly equal magnitude in rural areas of tropical Africa.

A large-scale programme of regular drug distribution has never been tried out in malaria control in tropical Africa. Nevertheless, the experience of modern leprosy control in French and British African territories is already available and a great deal can be learned from it. Leprosy control is based today on chemotherapy by sulfone drugs with an average 3 years' duration of treatment. For the greater part of this period, the administration of the drug is usually on a weekly basis. This high frequency of drug-taking

[d] Covell, G. et al. (1955) *Chemotherapy of malaria*, Geneva (World Health Organization : Monograph Series, No. 27)

necessitated either a relatively small number of extremely mobile large units (as is the case in French territories) or a relatively large number of more static small units (leprosy clinics) as is the case in British West Africa. According to the French system, the mobile units go into the field to seek out patients and to treat them regularly, using if necessary a certain amount of administrative pressure. The British system attempts to make the lepers come to the clinics as voluntary out-patients. The large French mobile unit can deal with 4000 lepers, while the small British static unit is designed for the treatment of 100 lepers.

In both methods the organization is complicated and the respective values of each system are undergoing the trial of time. On one side, there are the problems of communications handicapped by the absence of roads, short life of vehicles, cost of running and maintaining the transport ; on the other side, there is the decentralization with its difficulty of supervising, maintaining, supplying and manning the numerous small units.

Two new trends are already obvious with regard to the organization of mass leprosy control and they illustrate the difficulties of the task in tropical Africa. One instituted in French Gabon, is the attempt to devise a monthly treatment to replace the weekly or fortnightly cycle. The other is to devolve the leprosy treatment on the " polyvalent " (as the French call it) medical field units which deal with all endemic diseases. The advantages and disadvantages of this transfer of responsibility for dealing with a specific disease from a specialized to a general health unit are obvious and need not be discussed here in detail.

When trying to apply the logistics of mass leprosy control to malaria control by chemotherapy, one should remember that the prevalence of leprosy averages 4% in Nigeria. The intensive effort needed for regular treatment of 4% of the rural population will place in a proper perspective the difficulties of chemotherapy of malaria applied to such an area as our pilot project in western Sokoto with its population of 125 000 composed of about 45% of children with a crude parasite-rate of 75% and adults with a parasite-rate of about 20%.

There is another element contributing to the uneasiness felt at the thought of combining large-scale chemotherapy with large-scale vector control. Of all the criteria of successful malaria control by residual insecticides, the use of malariometry applied to the protected population is the most appropriate, the most logical and emotionally the most satisfying to the medical man. There is no greater thrill than to watch from month to month the steady decrease of spleen-rates, parasite-rates and other indices showing how the community is slowly relieved of the burden of malaria infection through the control of its vector.

Association of chemotherapy with vector control has the obvious disadvantage of depriving us of this sensitive gauge. Though we shall certainly see an impressive drop of all malariometrical indices we shall not be able to distinguish clearly between the specific cause and the actual effect. In order to assess the results of residual spraying we shall have to depend entirely on entomological data with their indirect significance and with numerous not easily standardized variables in their composition.

Criteria of demographic trends so impressively brought to light in Madagascar by Joncour (see page 711) could be obtained only where a system of vital registration is already available or where it can be set up ad hoc by the malaria control organization. In every other case in rural areas of tropical Africa this method of assessment of the state of public health will be either exceedingly difficult to obtain, or exceedingly unreliable, or both.

Undoubtedly, the use of chemotherapy either alone or in association with residual spraying was successful in several rural areas though in rather special circumstances.

In Viet Nam, Farinaud & Choumara [e] reported excellent results obtained by a weekly distribution of antimalarials for a few months together with spraying of residual insecticides. It should be remembered, however, that this careful work was carried out during a period of 2 years on a total population of about 10 000. In the Belgian Congo, Vincke [f] used the method of weekly administration on a total population of 5500 during a period of 3 years.

In East Africa, Jones [g] and Clyde & Shute [h] reported on interesting results of chemotherapy in rural areas based on samples of population not exceeding 2000 individuals. On the West Coast, Miller (unpublished data) in Liberia investigated samples of population of about 200.

It is only in Madagascar that one finds a unique example of a successful, large-scale chemoprophylaxis combined with residual spraying and protecting directly nearly 700 000 children and indirectly a population of over 3.6 million. It must be pointed out, however, that Madagascar with its tradition of chemoprophylaxis enforced by law since 1949, with its wide coverage of rural dispensaries, school centres, " gouttes de lait ", etc., is hardly comparable with any rural area of tropical Africa that I know. It can be used, however, as an excellent example of the possibilities of endemic disease control on the basis of a pre-existing advanced public health service organization.[i]

One more point should perhaps be mentioned. Mass treatment in Madagascar and Viet Nam was limited to children and pregnant women, thus reducing the proportion of the treated population by about one-half. It remains to be seen whether this method would work in tropical Africa, where the parasite-rate of the adult population averages 20% with seasonal peaks of 30% and where the gametocyte-rate in the adults, admittedly very low, might nevertheless constitute a small reservoir for the infection of the vector.

Thus it is true that the mass administration of antimalarial drugs gave impressive results in several relatively small areas and in special circumstances. It is, however, equally true that logistic difficulties of supervised, frequent drug administration in tropical Africa will increase in direct

[e] Farinaud, M. E. & Choumara R. (1954) *Bull. Wld. Hlth Org.*, **11**, 793

[f] Vincke, I. H. (1954) *Bull. Hlth Org.*, **11**, 785

[g] Jones, S. A. (1954) *E. Afr. med. J.*, **31**, 47

[h] Clyde, D. F. & Shute, G. T. (1954) *Trans. roy. Soc. Trop. Med.*, **48**, 495

Bernard, P. M. (1954) *Bull. Madagascar*, **96**, 387

proportion to the frequency of drug administration and in inverse proportion to the population density of any area. It was suggested that, occasionally, ways could be found of utilizing the spraying personnel for distributing drugs to all or to selected groups of population (Pampana [j]). Had we a chemotherapeutic drug with a long " residual " action it is very likely that this idea could be fully utilized by treating the population at the time of spraying. However, even with spraying cycles repeated as often as every 3 months the duration of the chemotherapeutic action of the drugs at our disposal would not have a sufficient " carry over " effect.

Mention should be made of the possibilities of Pinotti's method of addition of an antimalarial to common salt. According to recent reports [k] chloroquinized common salt distributed in three small mesoendemic districts of Brazil, at a calculated daily dose of 30-45 mg of the drug, gave excellent results within two to four months of its introduction. From the Nigerian experience of difficulties (still unsolved) of the introduction of iodized salt in areas where endemic goitre is prevalent, one hesitates to be too optimistic with regard to chloroquinized salt. Standardization of the dose would not be easy in Nigeria where in the south the consumption of salt is well over 15 g per diem, while in the north it often does not exceed 5 g. Moreover, a considerable proportion of the population, particularly in northern territories, prefers to use the cheaper " native " salt obtained from the Sahara instead of the imported, refined salt.

The considerations outlined above must not be interpreted as a reluctance to combine large-scale chemotherapy with residual spraying in rural areas of west Africa. We should realize, however, that the application of this method faces us with an entirely new situation, which must be soberly assessed in the light of experience to allow for sound planning.

Pointing out the difficulties of large-scale chemotherapy in tropical Africa should not prevent us from using it under some special conditions, more numerous than would appear at a cursory glance.

The case of Freetown, in Sierra Leone, may perhaps be quoted as an example of a possible solution to substitute eradication for control. In the capital of Sierra Leone malaria control by the use of larvicides and (recently) residual insecticides has been carried out with a recommendable energy and thoroughness during the past 10 years and has reduced the anopheline density to the very low level of 0.02 per room per day during the whole rainy season (Thomas, personal communication). It seems, however, that this very low anopheline density is still responsible for some amount of transmission, resulting in a parasite-rate in children of the order of 10%. With an anopheline daily survival-rate of 0.97, the low density of the vector is very close to the theoretical minimum density at which transmission is possible. It appears that in this particular circumstance the use of short-term mass chemotherapy would be fully justified and not too difficult to carry out in an urban population, particularly if limited to children. Another possibility of successful organization of large-scale chemotherapy with residual

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[j] Pampana, E. J. (1955) *Indian J. Malar.*, 9, 361

[k] Pinotti et al. (1955) *Rev. brasil. Mal. Doenç. Trop.*, 7, 5

spraying is in the densely populated and fairly accessible areas of south-eastern Nigeria, where the present mass campaign against yaws is producing excellent results and where the local population is suitably prepared for extension of modern control methods of endemic diseases.

Selection of drugs. Leaving aside general considerations, we might perhaps take stock of the existing drugs that could be used for short-term mass chemotherapy of malaria in tropical Africa. No discussion of chemotherapy of malaria can improve on the admirable summary of our contemporary knowledge of this subject produced by Covell et al. in their superb monograph.[l]

Any points raised here must be considered as mere reflections on a specific theme of chemotherapy from the point of view of mass administration in rural tropical Africa.

The ideal antimalarial combining the virtues of causal prophylaxis, suppression, rapid and complete curative action, sporontocidal effect and impossibility to create parasite resistance, together with low toxicity, very slow excretion, palatability and (last but not least) low cost, is still waiting to be discovered.

Of the modern synthetic drugs, 5 groups might be mentioned here. Their relative values with regard to the specific action on the malaria parasite are tabulated below (Table I).

Amino-acridines (mepacrine) have been superseded by newer drugs and it is unlikely that they will ever be manufactured on the same scale as before. Drugs of the 8-aminoquinoline series (type primaquine) are of little importance in the equatorial belt of tropical Africa where *P. vivax* is very rare, though north of latitude 15°N and south of latitude 30°S this parasite is far more common.

P. malariae is, however, frequently found in tropical Africa and in the 3-7 age-group of west African children this parasite may attain a proportional frequency of 20% or more of all infections The part that might be played by relapsing quartan malaria in an African population freed from active transmission by vector control is quite unknown although it is doubtful if it would be of great importance (Pampana[m]). Nevertheless, it would be wise to keep this point in mind and to assess it in any future investigation. Apart from the fact that they are poor schizontocides, drugs of the 8-aminoquinoline series have a narrow margin of toxicity and would not be suited for mass distribution without close medical supervision.

Dismissing for the time being this group of drugs we are left with 4 antimalarials, i.e., two representatives of the group of 4-aminoquinolines (chloroquine and amodiaquine), proguanil and pyrimethamine.

There is no doubt that chloroquine and amodiaquine are by far the best modern drugs for treatment of acute malaria and are powerful suppressants. They have a relatively low toxicity and there is no evidence that

[l] Covell et al. (1955) *Chemotherapy of malaria*, Geneva (World Health Organization: Monograph Series, No. 27)

[m] Pampana, E. J. (1955) *Courrier*, 5, 479

TABLE I. ACTION OF SYNTHETIC ANTIMALARIAL DRUGS

Drug group	Sporozoites	Early tissue phase (during the incubation period)	Erythrocytic phase		Late tissue phase during latency followed by relapses	Development of gametocytes in the mosquito (sporontocidal action)
			asexual parasites	sexual forms (gametocytes)		
amino-acridines	no action	no action	fact action	no direct action	no action	no action
4-aminoquinolines	no action	no action	fast action	no direct action	no action	no action
8-aminoquinolines	no action	active, but only in toxic doses	low activity	direct and fast action in all species	active	some evidence
biguanides	no action	active mainly against *P. falciparum*	active but relatively slow	no direct action	no direct action	active
diamino-pyrimidines	no action	active mainly against *P. falciparum*	active but relatively slow	no evidence of direct action	some evidence of direct action in *P. vivax*	active

they induce drug resistance. According to Coatney[n] amodiaquine is slightly less active than chloroquine and somewhat more toxic though the difference is immaterial.

Davey[o] pointed out how few really critical experiments have been made for comparative assessment of chloroquine and amodiaquine. He believes that amodiaquine cannot be used in any particular dosage regimen significantly different from the way chloroquine might be used and wonders whether one is really superior to the other. The results of our own field trials (Bruce-Chwatt & Archibald[p]) suggest that although the clearance time of *P. falciparum* infections is slightly shorter with amodiaquine than with chloroquine the difference of 3-5 hours between the two drugs is of little importance. Neither of the two drugs has any direct gametocidal action. A similar opinion was expressed by a research group in Malaya (Edeson et al.[q]). A more recent investigation designed specifically for comparison in groups of African schoolchildren of the two drugs at identical dosage gave the following clearance times for *P. falciparum* (Charles & Bruce-Chwatt, unpublished data).

Single dose	*Drug*	*Clearance time*
300 mg	amodiaquine	2.02 days
	chloroquine	2.40 days
200 mg	amodiaquine	2.33 days
	chloroquine	2.54 days

These preliminary data suggest that, for treatment of sub-clinical malaria in semi-immune persons, the possible superiority of amodiaquine over chloroquine is of slight degree and of no practical importance.

Proguanil and pyrimethamine are good though rather slow schizontocides with a pronounced sporontocidal action, preventing the future development of gametocytes in the body of the mosquito. They are also active against exo-erythrocytic forms of *P. falciparum*. Both are causal prophylactics and have a low toxicity at the usual dosage. Their recommended regimen for semi-immune communities though different in dosage is the same as far as the frequency of administration is concerned (once a week). Yet while it is unlikely that monthly doses would be of value with proguanil they might be practicable with pyrimethamine.

Unfortunately, both drugs are under a cloud for inducing resistance in malaria parasites. The problem of drug resistance was fully dealt with by Covell et al. and need not be repeated here. The main factors if its causation are the administration of small or widely spaced doses, or both, and high parasitaemia operating together, conditions which undoubtedly would be met with in any mass administration in Africa.

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[n] Coatney, G. R. (1955) *Therapy and chemoprophylaxis.* In: *Proceedings of the Second Conference of the Industrial Council of Tropical Health, Harvard School of Public Health, Boston*

[o] Davey, D. G. (1955) In: *Proceedings of the Second Conference of the Industrial Council of Tropical Health, Harvard School of Public Health, Boston*

[p] Bruce-Chwatt, L. J. & Archibald, H. M. (1953) *Brit. med. J.*, 1, 539

[q] Edeson, J. F. B. et al. (1955) *Med. J. Malaya*, 9, 252

Theoretically, this danger should be less marked with proguanil than with pyrimethamine, since the first drug is quickly eliminated, while with the second the parasite might be exposed for a long time to a very low concentration of the drug or some active principle of it. Considering how easy it is to produce experimental resistance in malaria parasites to proguanil and pyrimethamine, it is surprising that cases of natural resistance to both drugs have not been reported more often from the field.

Although the development of resistance to proguanil has undoubtedly occurred in Malaya, there is as yet no clear proof that it has occurred in Africa, though indirect evidence is suggestive.

On the other hand, resistance to pyrimethamine was definitely recorded in East Africa by Jones [r] and by Clyde & Shute.[s] The resistance has been shown to develop rapidly after 3 rather high doses of pyrimethamine once a month. A preliminary report on a new investigation by Clyde & Shute (unpublished data) seems to show that, despite an unbroken weekly administration of a standard dose of pyrimethamine, a number of East Africans retain a low level of parasitaemia due to *P. falciparum*. The tentative conclusion is that in this particular area strains of *P. falciparum* are inherently more tolerant of pyrimethamine, though the action of the drug on the sporogonic cycle remains to be assessed.

And yet neither Vincke [t] in the Belgian Congo nor Miller (unpublished data) in Liberia showed that pyrimethamine, given at half the dose given in East Africa at weekly or at monthly intervals, produced any resistant strains. A similar experience can be quoted on the basis of our own investigation (see page 775) carried out for two years in Southern Nigeria. A small proportion of African schoolchildren maintained an occasional low-level parasitaemia, while on a weekly pyrimethamine regimen. Nevertheless the next dose of pyrimethamine cleared the infection with ease.

It is possible that West African strains are less tolerant of pyrimethamine than East African strains, though there might be other variables such as the degree of immunity of the population. In the light of present experience the decision as to the choice between 4-aminoquinolines (represented by chloroquine) and one or other of the other drugs (proguanil or pyrimethamine) is difficult when it comes to mass administration. While chloroquine has a faster schizontocidal effect, its gametocidal action due to attrition is slow and probably irregular in *P. malariae* infections. Proguanil and pyrimethamine (particularly the latter) are almost as rapid schizontocides in malaria of semi-immunes and bring into action their sporontocidal effect. Unfortunately the two latter drugs might induce resistance in the parasite.

Attempts to combine two drugs were encouraging, and the results obtained by chloroquine and pyrimethamine were better than when each of the two drugs was used singly.[u] Summarizing the available data, one

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[r] Jones, S. A. (1954) *E. Afr. med. J.*, 31, 47

[s] Clyde, D. F. & Shute, G. T. (1954) *Trans. roy. Soc. Trop. Med.*, 48, 495

[t] Vincke, I. H. (1954) *Bull. Wld Hlth Org.*, 11, 785

[u] Schneider et al. (1954) *Bull. Soc. Path. exot.*, 47, 791

has to admit that there is still no clear-cut case in favour of chloroquine or pyrimethamine for mass treatment in tropical Africa. It seems that in some parts of East Africa chloroquine would be preferable to prevent the easy development of resistant strains. In central and tropical Africa, however (and providing that there is no evidence of a rapid development of parasite resistance), pyrimethamine might be equally valuable or even preferred because of its lack of bitter taste and its cheapness.

Problems of dosage and of frequency of administering antimalarials are of considerable importance. For mass administration to African populations, a simplified regimen is justified since the infection is often held in check by forces of immunity (premunition). Dosages quoted by Covell et al. are adequate also for African conditions.

Our own data indicate that a single dose of 300 mg of chloroquine or amodiaquine will prevent re-infection in an African schoolchild for about 4 weeks. A somewhat shorter period of protection was found by us for pyrimethamine given at 25 mg, though Miller reported with the same dose a satisfactory protection for at least one month.

In smaller pilot projects the bi-weekly frequency of drug-taking might be successful but will require a very thorough organization. However, it seems (on the basis of past experience with a large-scale pilot control project by residual spraying) that adequate administration of drugs in an area with a rural population between 50 000 and 100 000 would be exceedingly difficult if based on any greater frequency of supervised distribution than once a month. It should be emphasized that mass chemotherapy with the drugs available today cannot be expected to eradicate malaria from large rural areas unless it is associated with effective vector control. Should transmission be maintained at a moderate level, any interruption of regular drug administration would be followed within a few weeks by an increase of malariometrical indices. There is little doubt, however, that if the vector density is such that the transmission is kept at a bare " subsistence level " then mass chemotherapy will achieve a permanent effect either by slow attrition (as in the case of chloroquine) or by a more rapid sporontocidal action (pyrimethamine) on the reservoir of gametocytes.

The cost of the mass administration of antimalarials cannot be estimated in terms of total expenditure since there are too few data based on actual field trials. It appears, however, that the present cost of antimalarials for a mass campaign is considerably in excess of the corresponding costs of insecticides. If the per capita expenditure on any of the three modern insecticides used at a standard dosage is represented by the figure 1, then the cost of antimalarials is approximately as follows: pyrimethamine 1.3, proguanil 2.1, chloroquine 2.6 and amodiaquine 4.5. These proportionate figures exclude the costs of distribution of either insecticides or drugs.

It is possible that association of chemotherapy with residual spraying will be the only way of eliminating malaria from those tropical areas where the degree of transmission is extremely high. Any predictions of success or failure of this combined method are impossible on the basis of existing knowledge and practical experience. We shall not gain this knowledge until a vigorous effort has been made at field trials in rural areas and until our will

and ingenuity have been wholeheartedly applied to the solution of the problem.

If we succeed, there is hope that eradication of malaria from the African continent will be practicable without waiting for more powerful weapons to be placed at our disposal.

CORRIGENDA

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ESTIMATION OF BACTERIAL DENSITY OF WATER SAMPLES

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