Original Articles

FOLLOW-UP OF A MASS TREATMENT WITH INJECTABLE ATEBRIN

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IN March 1936 (*Indian Medical Gazette*) I reported on a 'blanket' treatment for malaria covering a mill area in the Southern Deccan with a total population of 5,600 souls, all of whom received two injections of atebrin. The two injections were followed up by 0.01 g. plasmochin simplex on three consecutive days. No further treatment was given. The district was highly malarious and at the time of the mass treatment, which was completed in nine days, the malaria incidence was of epidemic magnitude.

The relapse rate for the following six months was given in the paper and appeared surprisingly low. Similar experiments carried out during the Ceylon epidemic of 1935 on a much smaller scale, and not so carefully controlled, showed equally satisfactory results, and it was therefore very fortunate that in the mill area results could be carefully watched over a period of 2½ years. The measures adopted after the 'blanket' treatment were as follows :—

(1) Intensive propaganda was carried on in the village to bring every fever case to the doctor. This propaganda was successful because the villagers all knew that two painless injections would bring instant relief of all symptoms of malaria. 'Every concealed fever case is a menace to all; every concealed case might make them all as ill as they were before the treatment, etc.'

(2) Every new case of malaria was treated at once with two injections of atebrin (no plasmochin).

(3) No quinine whatsoever was dispensed.

(4) Simple anti-larval measures, such as oiling of pools in the river-bed during the dry season, were done, the local carrier being *Anopheles culicifacies*.

The chart gives the monthly malaria incidence for 2½ years prior to and 2½ years after the 'blanket' treatment. In the second half of the chart the black part of the blocks represents the number of re-injections, and the white part the number of injected new-comers, including a few cases from outside villages which have availed themselves of the mill dispensary. The black and white parts together give the total number of cases treated every month.

In the chart every re-injection has been registered as a 'relapse' although obviously a large number of these so-called 'relapses' are reinfections, particularly as it was noticed that most of these 'relapses' occurred after leave to the native village. But even leaving this point aside and registering all re-injections as relapses, the results are much better than clinical experience would lead one to expect, and if it is borne in mind that these figures are from a population including women and children varying around 6,000 souls, malaria can no longer be considered highly endemic, as it was for 15 years preceding the mass treatment for which reliable records exist. In fact the relapse rate is so surprisingly low that some sort of explanation of this phenomenon must be attempted.

It may be argued that the benign tertian strain in this particular area was an unusually benign one and exceptionally sensitive to atebrin; that the rainfall in the years following the mass treatment was particularly unfavourable for the propagation of *A. culicifacies;* that the simple anti-larval measures were unusually effective; and, finally, that owing to the excellent social welfare amenities provided by the mill management, the general condition of the population was particularly good. But even taking these points into consideration the results at Gokak seem so surprisingly satisfactory that there is still room for a more sweeping explanation. Perhaps the following observations may prove helpful.

In private practice in Bombay I see many cases of *fresh* malaria picked up from all parts of India, and having seen the excellent results of parenteral atebrin in Ceylon and Gokak I applied the same abbreviated method in these cases. The immediate clinical results were just as favourable but the relapse rate was practically 100 per cent within one to six weeks. It was therefore soon decided to follow up the two injections with a full course of tablets, followed by a full course of plasmochin, so as to get the almost immediate clinical response attainable with injections and the satisfactory relapse rate of the oral method combined. The results of this method were better but by no means as satisfactory as I have been accustomed to see with tablets only. I therefore returned to treating fresh infections by the oral method only, and relapses again became the exception instead of the rule.

The above observations on first infections are unfortunately not based on a large series of experiments; they were made on cases as they occurred in the routine of private practice. The conclusions drawn from them may therefore be misleading, but the discrepancy between sporadic first infections and epidemic malaria has struck me so forcibly that I feel justified in attempting an explanation, which may lead to further investigations by workers more fortunately placed.

Thus, further experience with injectable atebrin has led to two seemingly contradictory results.

In the highly endemic or epidemic areas in which it has been tried, the abbreviated two-injection method yields excellent results, whereas in sporadic first or fresh infections it is a hopeless failure. Particularly the observation that the combined parenteral and oral method gives

less satisfactory results than the oral method alone in fresh cases, whereas the injections alone seem to be sufficient in epidemic malaria, points strongly to an immunological factor.

It appears that immunity in malaria may be considered a sort of balance between resistance and intensity of infection. In first infections therefore the 'infection scale' is loaded and the 'resistance scale' is empty. On the other hand in persons residing in endemic areas both scales are heavily loaded and, as no treatment can completely eliminate all parasites from the body, first infections treated energetically from the onset will always have a balance in favour of the infection. This will result in a high relapse rate because the body has had no time to build up any resistance. If on the other hand the vast majority of parasites are suddenly destroyed in a case residing in an endemic or epidemic area, the balance will turn in favour of the previously acquired immunity and a low relapse rate result, even after an abbreviated treatment which would be utterly inadequate in a fresh case.

Moreover, it has frequently been observed, and was again seen during the Ceylon epidemic, that 3 to 10 days after the parasites had been removed from the peripheral circulation with atebrin, they again appeared for several days without producing any clinical symptoms and disappeared spontaneously without any treatment. I have never seen this in first infections treated at the onset of fever, where reappearance of parasites always seems to indicate a pending relapse, indicating that the final clearing of the body can only take place in the presence of a high immunity, which easily outweighs the mild infection remaining after treatment with atebrin.

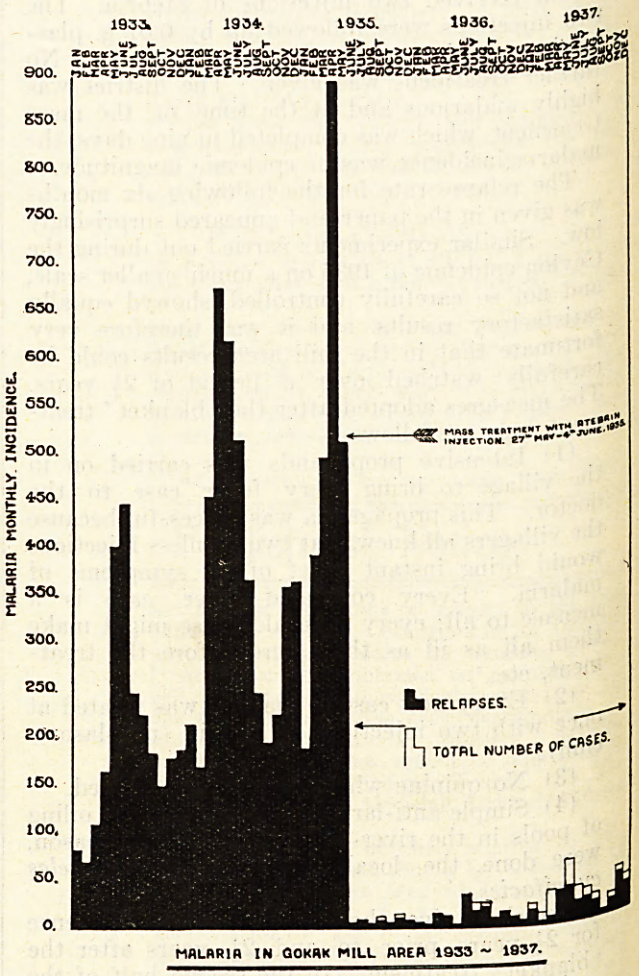
Some hold that a first infection should not be treated at once with a powerful parasiticide like atebrin, others are convinced that oral atebrin does not impair the development of a resistance. While I am inclined to agree with the latter I am most emphatically of opinion that atebrin musonate, through its quick and powerful action in fresh cases, reduces the parasite count so suddenly that the body is no longer called upon to produce an immunity, and hence an unchecked multiplication of parasites recommences and ultimately results in a clinical relapse.

Exactly why atebrin tablets do not appear to interfere with the development of resistance in fresh cases, while injections obviously do, is a problem outside the scope of this paper. It can only be said at present that it has nothing to do with the quantity of atebrin given, as injections *plus* tablets appear to obstruct immunity to a greater extent than tablets only. If a high degree of resistance to superinfection has been attained through years of exposure the body appears to become quite capable of coping with the few parasites remaining alive after treatment or introduced by a mild reinfection. This I venture to suggest may be an explanation why the 'relapse rate' or susceptibility to reinfection at Gokak as shown in the chart seems to be very slowly increasing, as resistance becomes less.

What I have hitherto experienced with atebrin musonate has led me to adopt the following principles :—

(1) In first infections that are seen from the onset of fever—tablets only, followed by plasmochin, have given me the lowest relapse rate (although clinical relief is not as prompt as with injections).

(2) In first infections that are seen after several rigors, injections are only used if cerebral or circulatory symptoms call for very



MALARIA IN GOKAK MILL AREA 1933 ~ 1937.

prompt action. In these cases I have found it best to give no further treatment after two injections, to wait for the next relapse, and treat this with tablets and plasmochin. All other cases are treated with tablets only, followed by plasmochin.

(3) In chronic relapsing cases living in non-endemic areas either injections or tablets may be given, followed up by plasmochin.

(4) In malaria cases residing in endemic areas or during epidemics, and therefore having a high immunity, two injections only are the

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ENUMERATIVE STUDIES IN BENIGN TERTIAN MALARIA

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THE observations recorded in this paper were made at the Government Hospital at Watawala from December 1935 onwards. The great 1934-35 epidemic had affected the population served by this hospital. The intensity of the epidemic had waned by the end of the year 1935. Being a non-malarious district, the people had their first malaria attack during the epidemic. Thus, the cases investigated were those having subsequent attacks consequent to infection in the epidemic, and those who having escaped the epidemic itself were suffering from their first malarial attack later. Thus the cases are easily grouped into 'subsequent' and 'primary', respectively, from the histories. The hospital is situated at an altitude of 3,200 feet above sea level and the sick were drawn from places 800 to 2,000 feet above sea level.

The method

Patients were admitted and inquiry made into the previous malaria history; they were grouped into 'primary' and 'subsequent' cases. A primary case is one of less than two weeks' duration; while cases that had recurrent periods of illness alternating with periods of freedom from fever and had lasted for more than two weeks for the whole illness were considered subsequent; these were relapses and reinfections. No anti-malarial treatment was given. The blood was examined in both thin and thick smears for diagnosis, and the patient was watched until there was one or more paroxysms of fever. The time of onset of fever or rigor was noted and two-hourly temperature charts were kept. Then a few hours before the next anticipated paroxysm blood was secured for enumeration and for a thin smear examination. The fowl-corpuscle suspension method, as advocated by Sinton (1924), was used for the enumeration. The thin smear was examined and the different stages of the parasites were recorded. The temperature at the time of taking the blood sample was also noted, and the highest temperature attained in the subsequent paroxysm was recorded. The fowl-corpuscle suspension used contained 10,400 cells per c.mm.; one thousand fowl cells were counted in the majority of the cases.

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method of choice. The results, both immediate clinical relief and relapse rate, appear to be very satisfactory, while, where large numbers of patients have to be dealt with in a minimum of time by a short-handed staff, it is technically the only possible method of rational treatment.

There is ample opportunity for experiments with the injection method of 'blanket' treatment in India, which if carefully conducted would possibly further our knowledge of how to cope with and suppress epidemics without attaching too much importance to expensive, seldom adequate and never-ceasing anti-larval vigilance.

Summary

(1) Two and a half years' observation of malaria incidence in a highly endemic mill area, in which a 'blanket' treatment had been carried out with two injections of atebrin per inhabitant, showed a satisfactory result.

(2) This treatment in fresh infections gave an unsatisfactory result.

(3) Fresh cases treated with two injections at onset followed by a full course of atebrin tablets and plasmochin have a higher relapse rate than first infections treated with tablets only.

(4) An immunological explanation for this phenomenon is attempted.

(5) An immunological grouping of cases is suggested and the treatment for each group outlined.

A. *Counts in primary and subsequent attacks*

The primary cases generally gave much higher counts, with a few exceptions. The distribution according to numerical values is shown in table I.

TABLE I

Number of parasites per c.mm. finger blood	PRIMARY CASES		SUBSEQUENT CASES	
	Number	Percentage	Number	Percentage
Under 5,000 ..	7	32	13	47
5,000 to 10,000	2	9	7	25
10,000 to 20,000	9	41	5	18
Over 20,000 ..	4	18	3	10
TOTAL ..	22	..	28	..

It is seen that over 70 per cent of the subsequent cases showed parasite values under 10,000 whereas about 60 per cent of the primary cases showed values above this.

Sinton *et al.* (1931) investigated 54 cases of chronic infections with *P. vivax* among adult British soldiers. They divided their cases into three groups—the 'prepyrexial', the 'interpyrexial' and 'pyrexial'. Their inter-pyrexial group consisted of 11 patients and the counts in eight of these lay between 3,000 and 5,000 per c.mm. One low count (1,960) followed a pyrexia of only 99°F., while the other two were 8,000 and 9,240, respectively. This group is comparable with the cases under review, since in the majority of these the enumerations were done in the inter-pyrexial period.

Ross and Thomson (1910) made a series of counts on eight *P. vivax* cases infected in