the upper respiratory tract sometimes aggravated the existing allergy or induced a fresh allergy. The paediatrician was of course more likely to see the failures after operation than was the surgeon. Great caution was needed before surgery was undertaken in allergic subjects. A history of recurrent and prolonged colds suggested the possibility of allergy plus infection. In addition to the more commonly recognized symptoms of allergy, a persistent, unproductive cough, worse at night than in the day and not responding to the ordinary remedies, was often complained of. Skin tests were, on the whole, disappointing, as also was specific desensitization based on such tests, though occasionally a dramatic cure might be obtained. Swabs of the posterior nares, allowed to remain *in situ* for at least a minute, often showed the presence of eosinophilia. Radiological examination could be most helpful.

Treatment should, so far as possible, be conservative. Besides avoidance of contact with the offending allergen, non-specific desensitization might be useful. Antihistamines were disappointing, except for promethazine hydrochloride, in seasonal rhinorrhoea. Theophylline with small doses of phenobarbitone sometimes helped. In combined sinusitis and allergy postural instillations of decongestants were sometimes useful, especially when combined with antibiotics in the early stages and with physiotherapy. Surgery should be undertaken only when recurrent severe upper respiratory tract infections had proved a serious handicap to the child's physical and educational development. The parents should always have possible sequelae explained to them, and rehabilitation exercises should always follow the operation.

Dr. J. PEPYS (London) described three ways in which allergy and infection might be associated—infection leading to the development of bacterial allergy (a view not generally accepted); infection predisposing to the onset of allergy by lowering the clinical threshold; and allergy complicated by infection, a common condition in which disturbed nasal physiology due to allergic mucosal swelling was the determining factor. Hence control of the allergy was essential if lasting results were to be achieved by treatment of the infection. In the diagnosis of nasal allergy a history of frequently recurring colds, lacking the usual sequelae, was important, in addition to sneezing and rhinorrhoea. Nasal itching was characteristic. Continuity of care over long periods was necessary, as the allergic state was apt to persist throughout life, though the nature of the allergen might change. From early infancy up to 4 to 5 years of age food allergens—for example, milk, eggs, chocolate, and nuts—were important, but in later years these were largely supplanted by inhaled irritants. In older children desensitization to inhaled irritants could help, but must be done for long periods. Ephedrine or antihistamines by mouth could be most useful, though prolonged administration might lead to anorexia and depression. Local nasal vasoconstrictors should be used with care, lest "rhinitis medicamentosa" developed. The potentially allergic infant should be recognized early, as this might well lead to a reduction in the incidence of allergic disorders.

The main speakers then answered a number of questions. In reply to Mr. R. G. MACBETH (Oxford), who asked, "Was the pneumococcus the commonest organism found in infection associated with allergy?" Mr. ANGELL JAMES stated that he had found the staphylococcus, streptococcus, and pneumococcus in that order of frequency. Mr. I. SIMSON HALL (Edinburgh) asked what decongestant was advisable, ephedrine or the longer-acting ones: to which Mr. ANGELL JAMES replied that ephedrine was used most, "pristine" and "neophryn" occasionally. Mr. F. C. W. CAPPS (London) asked if it was often advisable to remove the allergic child from its parents for a time. Dr. BRAND replied that the child did very well, but on return home almost invariably relapsed. A long period of absence was necessary—say, two or three weeks in hospital, followed by a long convalescence, preferably not at the seaside. Dr. C. EISINGER (London) and Mr. A. MACKENZIE ROSS also contributed to the discussion.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Treatment of Acute Malaria

SIR,—In his letter (*Journal*, July 4, p. 41) Sir Gordon Covell, possibly unconsciously, has thrown a spanner into the therapeutics of malaria. As a sincere student of malariology may I be pardoned for asking, "*Quo vadis?*" And if a specialist in this subject finds himself in a quandary regarding the effective drug treatment of malaria, what must be the state of mind of the practitioner in the Tropics, and, more so, that of the unfortunate student who has to be examined on this subject?

Is the object of his letter a proposal of "back to Methuselah," which in this case indicates a return to quinine as adumbrated by his expression of a "more rapidly acting schizonticide"? If this should be the case then it is permissible to inquire why our old friend quinine has been so persistently relegated to obscurity in recent years. It has even been stated in an annotation (*Journal*, March 15, 1952, p. 590) that the use of quinine in the treatment of chronic *Plasmodium falciparum* infections should be discontinued altogether. If any other evidence were required of the present medley regarding the most effective treatments of malaria, it is to be found in the *Journal* of January 20, 1951 (p. 149), where a puzzling complex combination of drugs is suggested for the various forms of this fever.

A long procession of antimalarial drugs has been witnessed in recent years. Hardly has there been time to assess the merits of one before another, allegedly more powerful, synthetic makes its appearance. It is useful to reiterate at this juncture what Sir Samuel Gee is reported to have said: "Gentlemen, go on using your drugs just as long as they cure."

The difficulties of understanding the present situation commenced with the introduction of pamaquin ("plasmoquin") in 1926 by W. Roehl.¹ Up to this time nobody had had the temerity to suggest that any other drug could supersede quinine in the treatment of malaria. Unfortunately, it proved too toxic in routine use for man. Then came mepacrine in 1931, introduced by W. Kikuth,² and this had properties which appeared to outstrip those of quinine. Although at first most doctors in Africa and in this country were disposed to despise it, yet mepacrine maintained its position until the outbreak of the second world war. Nobody ever suggested that its schizonticidal action was as rapid as that of quinine, though the combination of the two proved most efficacious in the treatment of acute subtertian malaria. The official Army view in 1939 was that mepacrine was too poisonous for mass administration to troops in spite of the fact that its prophylactic value had already been proved in Yugoslavia, U.S.A., and E. Africa.³⁻⁶ Here these properties were not rated high at that time, so that it was not until 1942 and the fall of Java that the shortage of quinine forced the attention of malariologists to the potentialities of mepacrine as a prophylactic as well as a curative drug, with the result that malaria was banished as a dominating factor in the war in the Far East. All this is now a matter of history, but we have reached the stage when the virtues of quinine as a powerful schizonticide have already been forgotten by many of the present generation of doctors. The end of the war (1945) saw the introduction of proguanil,⁷ which was the result of intensive research and represented an achievement of great scientific value. The first reports from Liverpool (1945-6) on the treatment of both subtertian and benign tertian malaria were so favourable that they made a very wide impression. To commence with, the doses were so small as to suggest an almost ultra-optimistic attitude. Similar claims were made for its prophylactic properties, the dose for which was stated to be 100 mg. once a week. As the years rolled on the fallacies of this appraisal have become apparent and *pari passu* the doses of proguanil have been stepped up, so that its advocates now suggest as a curative dose for subtertian malaria 12 times that advocated in 1945. But at the present moment, as Sir Gordon states, its value as a powerful schizonticide in this disease is more than doubtful as its action is far too slow, even

in these large doses. Furthermore, another difficulty in the mass treatment of malaria has arisen in the facility with which resistance to this drug is acquired, and this has led to a further increase in the prophylactic dose of proguanil. In order to counteract this tendency some modern workers have been led to advise the combination of quinine with proguanil to increase its effective action. This suggestion begs the question of why one should employ proguanil at all under these circumstances, since it is considered to play such a minor part in extirpating the malaria parasites. Now we have pyrimethamine, which is the latest comer on the stage. In this case, as related in recent issues of the *Journal*, the story appears to be following the proguanil model. At first minute doses were advocated, 25 mg. a day; then, after a few months' delay, papers are published portraying optimistic results, especially in subtertian malaria, and then others follow which appear to give the opposite impression,⁸⁻¹⁰ but Sir Gordon writes that, as in the case of proguanil, in subtertian malaria pyrimethamine should not be used unless in combination with a more powerful schizonticide. One principle seems to emerge from this conflicting mass of evidence—namely, that when the 8-aminoquinolines, such as pamaquin, were introduced, the therapeutic dose was too large, and the longer the drug remained in use the more consistently was it reduced. In this case it was from 0.12–0.03 g. daily. In mepacrine, which at first was thought to have no side-effects, the reverse has happened and it has risen from 0.3–0.6 g. daily, or even higher, with the result that patients are made actually ill; but in the less toxic compounds, such as proguanil and pyrimethamine, the therapeutic doses become increasingly bigger and bigger as time goes on, and even then, as Sir Gordon states, they do not appear to be powerful enough to halt a subtertian attack.

This letter is not to be taken as a disparagement of these antimalarials which have been forged as a weapon in the fight against malaria, nor is it asserted that the disappearance of malaria from great tracts has not been, in some measure, due to their mass application, but I would like to stress the danger of discarding old friends for new without due consideration. It takes a long time to digest all this new information, and it also takes many years for an antimalarial drug to establish a permanent and lasting reputation, so I am glad to see that this question is so fairly and adequately handled in the newly published book *Clinical Tropical Diseases*, by A. R. D. Adams and B. G. Maegraith. —I am, etc.,

London, W.1.

PHILIP MANSON-BAHR.

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Experiences with Pyrimethamine in Kenya

SIR,—The results obtained by Sir Gordon Covell with pyrimethamine ("daraprim") in preventing non-immune subjects from developing malaria (*Journal*, May 16, p. 1081) are of special interest to practitioners working in malarious areas, such as the Kenya Highlands, where the disease is encountered very often among non-immune Europeans.

Our malaria is almost entirely sub-tertian, and this season it has been exceptionally severe. Numbers of settlers have been using pyrimethamine for prophylaxis, in the manner recommended by the manufacturers. The results which I have personally encountered have not borne out the claims made for this drug, though maybe many have been satisfactorily protected and therefore have not been seen by a doctor. But the fact that there have been fairly frequent failures is of sufficient importance to put on record, as most of the cases occurring after the use of pyrimethamine have been severe, and one, my own child, was nearly fatal.

I have recently treated three cases of malaria in children under 3 years old who had taken their half-tablet of pyrimethamine in the week before the attack. All these commenced with convulsions and the one noted above was an exceptionally severe case. All required intramuscular quinine and sedatives: one of these

cases had a positive blood slide. Two other cases in children under 2, both with positive blood slides, had diarrhoea or vomiting. Two adult men whose slides were negative had severe attacks. Thus there were seven cases, all severe, all of whom so far as could be ascertained had used pyrimethamine as a prophylactic. One other case serves to illustrate a characteristic of this drug which also can be dangerous or fatal. A boy aged 20 months swallowed about 15 tablets while in apparent perfect health. He developed convulsions in about three quarters of an hour which resisted all treatment, and he died two hours later. Necropsy showed cerebral congestion. Histological section did not confirm this, but did show congestion of both kidneys. Chemical examination of the stomach contents showed in various tests a substance which gave identical results to pyrimethamine. This was done to exclude the presence of any other poisonous substance. Two other cases of children consuming up to about 15 pyrimethamine tablets have occurred recently in this area, but the results were not severe. These cases underline the fact that the drug has a relatively attractive taste, and therefore needs to be carefully locked up.

Returning to the prevention of clinical cases of malaria, I would like to suggest that when research is carried out on a new antimalarial drug it should be tested not only on volunteers in Europe, or on the indigenous inhabitants of malarious areas, who probably have a high degree of immunity, and on whom pyrimethamine, at least, works exceedingly well, but also on Europeans living under normal conditions of life in the Tropics. These might well be subdivided into (a) infants, (b) children, (c) adults recently arrived in the Tropics, (d) adults with a long residence and history of many attacks of malaria, and (e) adults with long residence and few or no such attacks. Infants and children could be subdivided into those born in malarious regions and those entering at an early age from abroad. The clinical cases of malaria which are used in the experiments or trials also need careful definition into the various well-known types and grades of severity. It is not enough to say that malaria is prevented or attacks are controlled by a given dosage of a particular drug. The practitioner wants to know whether he can rely on a drug both to treat and prevent pernicious attacks of subtertian malaria, and the milder relapsing types in all cases and under all circumstances. Furthermore, malaria has strange variations in virulence in the same district which require consideration.

It may be that if the records of private practitioners in tropical countries could be made accessible to research workers, they would find much information of the nature indicated, and which would act as a useful check on their own highly controlled experiments.—I am, etc.,

Eldoret, Kenya.

R. Y. TAYLOR.

Post-inoculation Poliomyelitis

SIR,—Dr. James Grant, in his article on post-inoculation poliomyelitis (*Journal*, July 11, p. 66) describes eight cases which occurred in South Tyneside during 1952. Of these, four are shown as having followed the use of combined diphtheria and pertussis prophylactic, but I cannot gather from the text whether the diphtheria portion of this was alum-precipitated or not. He merely describes the material as combined diphtheria toxoid and pertussis vaccine.

I should be glad to know whether the diphtheria component of this material did contain aluminium hydroxide or not, as I think it is a matter of some importance. Admittedly pertussis vaccine alone is apt to be irritant, but there is no doubt that the combined prophylactic containing alum is even more so. To this end I devised a combined prophylactic of pertussis vaccine containing purified fluid diphtheria toxoid without mineral carrier, which I have been using subcutaneously for the best part of three years. This produces no more local reaction at the seat of inoculation than does the same pertussis vaccine when given alone. The Schick-conversion of this material, given as three injections at monthly intervals, is just a fraction under 100%, on observation of over a thousand cases three months after the final injection. The same applies to purified fluid toxoid (Holt) given as three-monthly subcutaneous injections of 0.5 ml. (30 Lf), and for primary immunizations in young children it will be found to cause virtually no reaction at all. It should not be used for boosting doses in older children. The Schick-conversion rate here is also near-optimal three months after the last injection.