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QUININE AND WORLD WAR

The war has taught us at least one lesson: it has emphasized the importance of saving. We have had to save money, clothes, metals, paper, and now rubber. It looks as if we might also have to save quinine, for the greater part of the world's quinine supply comes from the Dutch East Indies.[1] We were authoritatively informed at the beginning of the war that the amounts of quinine available were enough to meet all contingencies. It is doubtful, however, if Whitehall had at that time even considered the possibility that the Dutch East Indies might pass into enemy hands, or, worse still, that the cinchona plantations might be "scorched." If the plantations were to be taken by the Japanese and the war to last for some years more there might well be a quinine famine, at least for a short time; if, in addition, the cinchona plantations were destroyed the famine would last for many years.

Cinchona plantations do not grow in a year, and the area of the world's surface that provides the right climatic conditions for the cultivation of cinchona trees is very limited. Although efforts have been made to increase the area under cinchona cultivation in the Himalayas these plantations do not yet supply a tenth of the quinine needed even by India, nor are those in Guatemala of any great importance at the moment. Faced with these possibilities what course is it best to pursue? Conceivably the world consumption of quinine might be drastically reduced. Most malariologists, however, are agreed that the present world consumption of quinine is already far too small, for malaria still remains the most serious disease of the Tropics, numbering its annual victims in India and Africa not by hundreds but by millions. In time of war, however, it is essential that the fighting Forces should have adequate antimalarial drugs, for not one but many military operations have been brought to nought by malaria. In the Walcheren expedition of 1809 the troops died from fever—347 per thousand as contrasted with 16.7 per thousand killed by enemy action—malaria and typhoid were the main causes of death. In the Rangoon expedition of 1824-5 there were only 35 deaths from wounds, but 450 out of every 1,000 engaged died of malaria. In the Burma expedition of 1826 the enterprise in Aracan had to be abandoned owing to fever, for "everyone who was not dead was in hospital." In the war of 1914-18 malaria came into its own. In Macedonia the high total of 160,000 admissions among the British troops was reached. The French were as hard hit, and as a result active operations came to a standstill. In East Africa there were 107,700 admissions, giving the highest rate per thousand.

It is obvious that quinine cannot be dispensed with unless there are other antimalarial drugs as efficient and as cheap. The possible substitutes for quinine are totaquina, atebrin (now called mepacrine), plasmoquine (now known as pamaquin), and some of the sulphonamide derivatives. Totaquina consists of 70% of crystallizable alkaloids and not less than 15% of quinine; it must not contain more than 20% of amorphous alkaloids and not more than 5% of water. Two types of totaquina are available. Type I is prepared from the total alkaloids of *Cinchona succirubra*. It is doubtful whether there are enough trees of this species to provide large supplies, although the bark of *Cinchona robusta* may replace that of *C. succirubra*. Type II contains more cinchonine than Type I and is prepared from *C. ledgeriana* residues, with the addition of sufficient quinine to bring it up to specification. The compulsory use of totaquina would undoubtedly conserve the present stocks of quinine, but totaquina would not provide an inexhaustible supply of cinchona alkaloids. Although the newer synthetic antimalarial drugs have been used in place of quinine in the treatment of malaria, it is now generally agreed that mepacrine and pamaquin together are more toxic than a combination of quinine and pamaquin, the simultaneous administration of mepacrine and pamaquin apparently increasing the toxicity of both. In benign tertian and quartan malaria the association of pamaquin and quinine represents an efficient method of treatment. Efforts might be again made to test the efficacy of mepacrine alone, followed after an interval by pamaquin and quinine. Perhaps more quinine is used up in prophylaxis than in the actual treatment of malaria. Although it is recognized that quinine is not a true causal prophylactic, in that it will not prevent infection, it undoubtedly reduces the number of clinical attacks in a given period, and in addition, when given to large bodies of troops, it has the advantage of extremely low toxicity. Mepacrine and pamaquin, on the other hand, are much more likely to produce toxic reactions if used for any length of time.

A new field of chemotherapy has recently been opened up in the discovery that certain sulphonamide derivatives possess antimalarial activity. Thus Coggeshall, Maier, and Best[2] found that sodium *p.p'*-diamino-diphenylsulphone-N, N'-didextrose sulphonate (promin[3]) had a curative effect on seventeen patients infected with either benign or malignant tertian malaria. The benign infections were more resistant than the malignant tertian, while infections in negroes were more responsive to the drug than those in relatively non-immune whites. Sulphadiazine produced a demonstrable effect in ten out of thirteen patients. It is obvious that further experiments are required on the effect of sulphonamide derivatives in malaria either alone or in association with other antimalarial drugs. Such experiments might well indicate a way in which a considerable saving of quinine could be made.

Two other investigations might also be actively pursued in view of the possibility of a shortage of natural

[1] See *British Medical Journal*, 1942, 1, 78.

[2] Coggeshall, L. T., Maier, J., and Best, C. A., *J. Amer. med. Ass.*, 1941, 117, 1077.

[3] See *British Medical Journal*, 1941, 2, 856.

cinchona alkaloids. The synthesis of quinine might well be accomplished in the laboratory if the need were really acute, although there are at least two snags which have so far impeded research. Some effort also might be made to recover cinchona alkaloids from the urine of those to whom they are given by mouth. Quinine, for instance, is partially destroyed in the liver, but about half of it is excreted in the urine. No satisfactory method of extraction on a large scale has ever been worked out. Necessity, which is the mother of investigation, might teach us much in the conservation of essential drugs.

INCOMPATIBLE BLOOD TRANSFUSION AND Rh FACTOR

As most transfusion reactions due to incompatibility between the blood of the donor and that of the recipient are caused by errors in blood grouping, every effort should be made to ensure accuracy, and by far the best thing that can be done is to examine a person's serum for agglutinins as well as his cells for agglutinogens; the check so given will prevent mistakes. The direct test between the recipient's serum and the cells which are to be transfused will in most cases disclose mistakes, but an unsuspected antigen in the donor cells may be missed if the corresponding antibody is present in only small amount, as is quite often the case with anti-B in the serum of A and O persons. If the direct test also includes a mixture of the donor's serum and the recipient's cells its efficiency as a check will be increased. A direct test should never be omitted when it is at all possible to make it. Besides incompatibilities within the A B O groups, reactions may be due to other antigens and antibodies. The possibility of trouble from the meeting of some rare and uncharted antigen and its antibody has long been recognized, and the A B O subgroups and M N factors have been regarded with suspicion. Only three cases of spontaneous anti-M and none of anti-N have been reported, and as they are not antigenic for man M and N are most unlikely to give trouble. The direct test is not always sensitive enough to detect incompatibility, but, as the failure is usually due to the antibody's being present in small amount, any consequent transfusion reaction fortunately tends to be slight.

Recent work[1,2] has shown that immune antibodies to a variety of agglutinogens in transfused blood may be formed in a proportion of recipients who lack the particular antigen, so that a later transfusion of blood containing this antigen may lead to a severe or even fatal reaction. By the study of cases in which incompatible blood has been given in error it has been shown that A and B are probably regularly antigenic for human beings lacking these antigens. For example, A blood given to a B or an O person will cause a reaction ranging in intensity from the very mildest to one severe enough to kill; in any case, if the recipient survives, the anti-A in his serum will, within about a week, almost certainly be enormously increased, so that another transfusion of the same or of another A blood will be fraught with the gravest danger. Similarly, a recipient may be immunized against a subgroup antigen and trouble may arise at a later transfusion, although at first transfusion reactions due to the subgroups are not of much importance, because the antibodies concerned are very seldom present in large amounts.

A cause of incompatibility reactions which may not be so rare as those due to the subgroups is the Rh property recently discovered in human blood by Landsteiner and Wiener.[3] Cells containing Rh react with immune sera prepared by injecting rabbits or guinea-pigs with the blood of rhesus monkeys. The property is inherited as a simple Mendelian dominant and is present in about 85% of American whites. The examination of a small series of negro bloods suggests there may be racial differences in distribution, and there are indications of the existence of more than one sort of Rh analogous with the different forms of A. Antibodies for Rh do not normally occur in human plasma, but when Rh blood is given to some of the persons lacking the property the body seems to recognize the injected blood as foreign and eliminates it. At the first transfusion the haemolysis may be so gradual as to be unsuspected, but Rh antibodies may then be produced, and Rh blood, given at a later transfusion, may cause the most serious reactions. The detection of the Rh antibodies in man is always difficult and may be impossible. The techniques usually employed for grouping are quite inadequate, and the use of small tubes at low temperatures is the one most likely to be successful; but because there have been instances where the reactions at low temperatures were not so definite as those in the warm the tests ought to be performed at refrigerator, room, and body temperatures. (In connexion with the use of small tubes at low temperatures it is suggested that mixtures of serum and washed red cell suspension, 2% of centrifuged deposit, be centrifuged at low speed in cups containing ice water after they have first stood for several minutes in the ice water. The mixtures should then be shaken gently and read both macroscopically and microscopically.) In a group of cases in which it has not been possible to detect the antibodies it seems permissible to ascribe reactions to the Rh factor, because the recipients have all turned out to be Rh-negative, and some of them have been given other transfusions of known Rh-negative blood which have been completely successful. Besides causing trouble at subsequent transfusions, immune antibodies appear to be responsible for reactions in women, transfused for the first time, who have recently given birth to a child or had a miscarriage or stillbirth, the antibodies having been formed in response to an antigen present in the foetus and inherited from the father, but absent in the mother. Rh is perhaps involved more often than other antigens, and this seems to be so, too, in cases of erythroblastosis foetalis,[4] a familial haemolytic disease of the newborn which, it is suggested, results from the passage of the mother's immune agglutinins through the placenta to act on the susceptible blood of the foetus.

[1] Wiener, A. S., *J. Immunol.*, 1941, **41**, 181.
[2] *Arch. Path.*, 1941, **32**, 227.
[3] *J. exp. Med.*, 1941, **74**, 309.
[4] *Science*, 1941, **94**, 371.