without any regulation. Coke at one time was regarded as a by-product and its quality varied accordingly ; to-day it is standardised as carefully as is gas and distributed graded as to size, ash content and burning capacity, so that it requires a minimum of supervision when burnt in closed stoves. A great amount of scientific work has been applied to realise these high standards of quality of gas and coke, and the achievement is no mean one. The penetration of the chemist into the gas industry largely coincides with the Jubilee period : he is being regarded more and more as one of the key men in the industry and there are not wanting those who regard its future as largely on the chemical side.

The gas engineer continues to develop improvements in detail and to organise gas matters on a larger scale, including carbonising, purification and distribution. Condensing practice has changed in favour of the horizontal tube form of welded steel construction, electric precipitation removes the last traces of tar. Centrifugal and static type washers are in use, and it has become customary to remove naphthalene and benzole by washing. Unfortunately, the ammonia recovery has received a setback owing to the fall in price due to the competition of the synthetic product. Purifying is almost exclusively done with oxide of iron, which enables the sulphur to be recovered in a marketable form ; in some cases the sulphur is almost completely removed by a catalytic process, though generally this problem is still left for the future. For storage purposes, the waterless holder now competes with the old-fashioned gasometer : in Great Britain it is still in the experimental stage in regard particularly to economy of maintenance and the extra supervision required, though both on the Continent and in America it has become widely adopted.

High pressure distribution of gas has brought new problems, largely solved by the use of welded steel tubes. The introduction of spun cast iron pipes has increased their length and given a more homogeneous material than ordinary cast iron.

For a long time the output of the industry increased each year. Latterly, there has come a great change in the domestic habits of the people, and gas also has to face intense competition from other sources of light and heat. In consequence, there is an awakening to salesmanship with the provision of show-rooms. In particular, a great stimulus has been given to the improvement of gas-cookers and fires which, since 1910, have been bettered in all respects almost beyond recognition. The same applies to water heating and to the use of gas for industrial heating, a field in which there is great development taking place. Lastly, gas holds its own for street lighting, as an evening in the streets round Whitehall or in South London will testify. Here the physicist has been called into co-operation so that the maximum light can be directed along the length of the road.

This brief sketch indicates the virility of what is now an old industry, largely due to the more scientific outlook which it is showing towards its problems. There is a tendency to concentrate the industry in larger units, either by regional absorption or amalgamation of the smaller companies by the larger, or by the purchase of isolated companies by holding groups. The former plan obviously makes for greater efficiency and benefit to the consumer ; the latter move is regarded with some unrest by many.

Chemotherapy of Malaria*

By Colonel S. P. James, F.R.S.

WITH the distressing effects of the malaria epidemic and famine in Ceylon still fresh in our minds, the subject of the chemotherapy of malaria may very appropriately be discussed at the present time. The area affected was not so large as Yorkshire, but the cost of relief measures was about £350,000, and during the six months from November until April, 14½ tons of quinine, costing £50,700, was used. About £20,000 was also spent on the new antimalarial remedy called atebrin. The epidemic reminded the world once again that no royal road or short cut to the prevention of malaria has yet been found. During recent years similar reminders have come from British India, Malaya, East and South Africa, Nigeria, the Sudan, Mauritius, Trinidad, Barbados and other British territories overseas. A few years ago an epidemic in British India prostrated the whole population of an area twice as big as England. The ordinary business of large cities was interrupted, no labour could be obtained, transport was disorganised, and even sellers of food ceased to carry on their trade. In one group of towns and villages the deaths during the month

* Opening of a discussion in Sections B (Chemistry) and E (Geography) of the British Association at Norwich on September 9, 1935.

of October, instead of being as in a normal year about 6,840, were 76,250.

The financial losses due to such an epidemic, or to the recent epidemic in Ceylon, are quite incalculable, but some idea of the cost of malaria is indicated by the amount of money spent in ineffectual attempts to combat it. For example, the island of Mauritius has spent more than 3½ million rupees on antimalarial measures since 1909, but the prevalence of the disease has not appreciably decreased, and local experts have recently suggested that the whole question should be studied anew with the object of discovering some less costly method of checking the scourge. Lagos, the capital of Nigeria, has spent even more money with less success, for the present position is that every native inhabitant of the town above one year of age has the disease.

Perhaps the most striking examples of failure to prevent malaria by applying the teachings of existing knowledge occurred during the War. One example must suffice. In June, 1916 a British division moved forward from Salonika to occupy the valley of the Struma river in Greek Macedonia. About a fortnight after entering the valley the troops of the division began to go down with malaria at the rate of more than 100 a day. During July and August there were 5,000 cases; in the whole year there were 30,000 and the next year 70,000. A French army corps under General Sarrail held the line next to our troops. That army entered the valley 115,000 strong, but within the next few months 60,000 were down with malaria, and by the end of the year only 20,000 were left in the line. General Sarrail reported to the French Government that his army was immobilised in hospital. The German army on the same front suffered equally, but it is not difficult to picture what would have happened if either of the opposing forces in that war region had been able to keep its soldiers free from the disease.

In view of these and other examples it has to be admitted that, despite some remarkable discoveries, existing knowledge on the prevention of malaria is not sufficient. Direct war on the malaria-carrying mosquito is too difficult and too costly for general use, and quinine has failed to maintain its old reputation as the sovereign remedy which meets all needs. More knowledge is needed in many different directions, one of them being chemotherapy, in which subject British chemistry has as yet played only a very small part. This seems surprising when we reflect that, of the 3½ million deaths from malaria recorded in the world every year, the great majority occur in the British Empire, and that the British Empire alone spends every year about £450,000 on quinine.

Quinine has been in general use for nearly a hundred years, but no one knows, and scarcely anyone is trying to discover, how this remarkable natural remedy acts. Even yet its merits and defects as an antimalarial agent are very imperfectly understood, and it has been said that there are almost as many methods of treating malaria with it as there are physicians who use it. To a considerable extent it satisfies the practising physician because it promptly stops most clinical malarial attacks, but it has grave defects from the point of view of preventive medicine for it does not prevent infection of either the human host or the mosquito, and it does not prevent relapses. These defects became strikingly evident during the War, and in consequence it was realised how advantageous it would be to have antimalarial remedies which would be effective for particular purposes for which quinine is known to fail.

To discover and prepare such drugs is the chief aim and object of antimalarial chemotherapy. What is aimed at is not to supplant quinine, but to supplement it with additional weapons for use in particular circumstances and for particular purposes. In Germany, two synthetic antimalarials, plasmoquine and atebrin, which to a considerable extent fulfil that requirement, have already been discovered, and now it is hoped that Great Britain will make adequate arrangements to pursue the subject in the same intensive way and with the same objects in view. Up to the present the chemical industries of this country have not concerned themselves with the matter, and the grants which have been allotted by Government during the last few years to assist antimalarial chemotherapeutic research have amounted to less than a two hundredth part of the Empire's annual bill for quinine.

If and when adequate arrangements for antimalarial chemotherapeutic research are made in Great Britain it will, of course, be one of the tasks of the biologist to tell the chemist all that he knows of the life-history and biological properties of the various species of malaria parasite, and for what particular purposes he is desirous of being supplied with drugs that are superior to quinine. As Sir David Prain said a few years ago: "When medicine is in a position to tell chemistry exactly what medicine requires, the chemist will in due course deliver the goods". Prof. Robinson has said much the same thing in other words, so I shall now give some indications on that subject by pointing out the chief defects of quinine as an antimalarial agent, and some of the merits of atebrin and plasmoquine as additional antimalarial weapons.

The first and by far the most important defect of quinine is that it does not prevent infection:

it is not a true causal prophylactic. What we want is a drug which, taken in non-toxic doses, will entirely destroy the organisms injected by infected mosquitoes before these organisms begin to continue their developmental life-cycle in the human host. Until a few years ago quinine was thought to be effective for this purpose. It was thought that if persons in malarious places would take a dose of quinine at sunset and another at sunrise, all the germs injected by a mosquito which had bitten them during the night would be killed and they would not suffer from malaria. Clinical observations give no support to that belief. For example, the temperature chart of a person who took ten grains of quinine shortly before being bitten by mosquitoes, the same dose shortly after being bitten, and the same dose daily thereafter for ten days showed that these prophylactic doses had no effect in preventing or delaying the malarial attack. Another trial with larger doses of quinine showed the same failure. The attack occurs, even when prophylactic doses of 45 grains (3 grams) of quinine are used.

It is interesting and important that the same trials with either of the new synthetic preparations plasmoquine or atebrin give a quite different result. In a comparative trial with quinine and atebrin and plasmoquine against infections of malignant tertian malaria, all the controls who took no prophylactic drug and all those who took quinine as a prophylactic had their attack of malignant tertian malaria within the usual incubation period, but none of those who took atebrin or plasmoquine had any malarial attack.

Atebrin and plasmoquine do not work so well as true causal prophylactics against benign tertian malaria as they do against malignant tertian, but lack of time prevents my giving details on that subject. The point I wish to make is that these drugs are not simply substitutes for quinine: they are new weapons with a specific action on a phase of the parasite against which quinine has no effect.

A second defect of quinine is that it is not equally effective against all species and strains of the human malaria parasite. This defect is common to all known antimalarial remedies, and is the chief reason why it is desirable to have several drugs at disposal for treatment in order that, when one fails, another may be tried. For example, some strains of malignant tertian malaria are not at all susceptible to quinine, but are very susceptible to atebrin. On the other hand, some strains of benign tertian malaria react quicker to quinine than to atebrin, and for this reason many clinicians prefer to 'break the fever' (as they say) with quinine, and to continue later with atebrin.

A third defect of quinine is that it is not very effective in preventing the relapses which are such a troublesome feature of some cases of malaria. Here again a chief difficulty arises from the fact that different species and strains of the malaria parasite react differently to the various anti-malarial remedies at present known. In malignant tertian malaria, relapses may often be entirely prevented by treatment with atebrin instead of with quinine. On the other hand, the relapses of benign tertian malaria are much more difficult to prevent. The most important type is that which occurs about eight months after recovery from the primary attack. It is the type which causes what is called 'the spring rise of malaria' in northern Europe and other countries. It was the type responsible for the second wave of the recent malaria epidemic in Ceylon. No drug treatment yet known will prevent this type of relapse.

Lastly there is the problem of preventing the spread of malaria by what is called gametocyte therapy. Gametocytes are the forms of the malaria parasite which infect mosquitoes, and it has long been known that in malignant tertian malaria quinine is quite ineffective in preventing the infection of mosquitoes which feed upon persons suffering from this disease. Plasmoquine, on the other hand, is so effective against the gametocytes of malignant tertian malaria that doses even as small as two centigrams are sufficient to prevent mosquito infection. For this purpose, therefore, plasmoquine is a new antimalarial weapon of proved efficacy. But a further requirement in this category is a drug that will prevent the production of gametocytes in the human host and their appearance in the peripheral blood from which they are sucked into the stomach of the mosquito when it feeds on infected persons. Plasmoquine kills gametocytes *after they have been produced and have appeared in the peripheral blood*, but it does not arrest their birth and development.

From these few examples it will be evident that the epoch-making discoveries made by Prof. Schulemann and his colleagues at Elberfeld have placed in our hands new antimalarial weapons of great power and precision, but that there is still ample scope for further research in Great Britain and other countries. It is not expected, of course, that in England funds available for chemotherapy research will ever be provided on the same scale as in Germany, but the British Empire with its vast malarious territories in Africa, India and the Far East is more concerned with the provision of effective antimalarial agents than is any other group of nations in the world and, having regard to the humanitarian, economic and imperial interests at stake, it is greatly to be hoped that something will be done about it.