Reviews

YELLOW FEVER

BY

Sir RICKARD CHRISTOPHERS, F.R.S.

Yellow fever appears first to have been recognized as a disease entity in the seventeenth century. It has always been popularly considered an American disease, but it may have been originally introduced from Africa. As "yellow jack" it was in the early days of shipping a terror to sailors and a threat to ports and shipping throughout the tropical world. It has now been virtually abolished in its urban epidemic form even from areas where it was once prevalent, and with due precautions it is no longer any threat to shipping or to other countries. This virtual conquest of a deadly disease has been possible through the discovery in 1901 by the U.S. Yellow Fever Commission in Cuba that the disease was transmitted by the mosquito now known as *Aedes aegypti*, and to a considerable extent to the demonstration by General Gorgas at Panama that yellow fever could be controlled by measures directed against this mosquito and protection of man from its bites.

The story of these events half a century ago is still one of the epics in the history of medicine, and many will enjoy reading in the recently published biography of General William C. Gorgas,¹ by John M. Gibson, the interesting intimate account there given of the life and work of Gorgas and of the circumstances under which the United States Yellow Fever Commission worked in Havana and reached so successful an end to their labours. It would appear from this account that Gorgas was not at first convinced that the mosquito theory was true. But, once he was convinced by the work of the Commission, he lost no time in making use of the discovery and in instituting at Panama an entirely new type of disease control—in other words, anti-mosquito measures. This type of control was later to be extended and developed by others to include even such gigantic undertakings as the permanent nation-wide measures against *Aedes aegypti* initiated in Brazil in 1932, dealing with an area of almost half a continent (Soper *et al.*, 1943).

There can be no doubt but that Gorgas, by his striking demonstration of the possibility of control of yellow fever by anti-mosquito measures, greatly hastened the adoption and development of such measures not only in America but as a necessary precautionary action in other parts of the world. It was, however, the discovery of the mechanism of infection by the Commission which enabled sanitation and administration to achieve these results.

The Yellow Fever Commission

The members of the Commission were Dr. Walter Reed, a surgeon in the United States Army and president; Dr. James Carroll; Dr. Jesse W. Lazear, the first of a number of martyrs to science who were to lose their

lives in the investigation of yellow fever; and Dr. Agramonte, a name later very familiar in the literature of yellow fever. The centenary of Reed's birth is celebrated this year.

The Commission had originally been formed and proceeded to Cuba to investigate the claims that an organism isolated by Sanarelli was the cause of yellow fever. They remained to test out the mosquito theory. They were not the originators of the theory of mosquito transmission of yellow fever. This had been suggested before and had been strongly advocated at the time of the Commission's visit by Dr. Carlos J. Finlay, of Havana. Nor had Finlay been satisfied by mere hypothesis, for he had made a close study of the mosquito known to him then as *Culex mosquito* Desv., now *Aedes aegypti*, pointing out that this was the domestic mosquito of Havana and bringing forward much evidence pointing to its probable role in the spread of yellow fever. He failed, however, to give the convincing proof of this, for in such experiments as he had made to transmit the disease he failed, not knowing of the necessity for an interval required for infection to develop in the vector.

So it fell to the skilfully conceived and perfectly carried out series of critical experiments by the Commission to bring fact in place of theory. Nor was this so simple as it may seem, for the more the work of the Commission is studied the more able, efficient, and skilled would their work appear to have been. They soon clearly and concisely showed that the *Leptospira* of Sanarelli was not the cause of yellow fever, their first task as a Commission, and that the mosquito did transmit the disease from man to man, that it did so only after a considerable interval, and that the disease was not contracted, as had always been thought, by contagion, fomites, or general filth. Moreover, Reed and Carroll showed early in the investigations that the cause of yellow fever was a filterable virus, the first time any human disease had been shown to be due to such an agent.

It is one of those curious happenings which sometimes occur in scientific research that, just when it seemed there was no further problem connected with yellow fever, a number of puzzling observations began to come into the picture that did not fit in with accepted ideas about the disease. Thus, while the general belief had been that yellow fever was entirely a New World disease, Boyce had early shown there was reason to believe that yellow fever had long been, and still was, present in West Africa.

Later observations not only confirmed Boyce's findings, but through the use of the "mouse test" showed that throughout a large part of tropical Africa, and extending far to the east of that continent, there existed in the indigenous population a considerable percentage of immunes, this discovery showing that yellow fever must quite recently have been present, if it was not still so, over large areas where its presence had never before been suspected. Work in America, too, had shown that all epidemics of yellow fever could not be ascribed to transmission by *Aedes aegypti*, or even to infection derived from man, and that there existed a form of the disease characteristically contracted in the forest, which differed in its aetiology from that usual in urban epidemics, and which was not transmitted by *Aedes aegypti* or due to man-derived infection, a form now known as jungle or forest yellow fever.

¹Physician to the World. The Life of General William C. Gorgas. By John M. Gibson. (Pp. 316. £1 14s.) London: Cambridge University Press. 1950.

Virus Research

It was here that work in the laboratory on the virus came to the assistance of epidemiological work in the field. Ever since the discovery by Stokes, Bauer, and Hudson in 1928 that monkeys were susceptible to infection, and later that some other small mammals were so and could be used as laboratory animals in the study of the virus, there has been much work in this direction. It has given more information on the nature and behaviour of the virus and opened up many new lines of research in other directions. The "mouse test"—the intracerebral inoculation of white mice—has been a particularly valuable help to research. Not only has it been used, as already noted, in mapping the disease over large areas in the New and Old Worlds, but it has enabled us to test the power of different species of mosquitoes to retain or transmit the virus. In America this has shown that forest yellow fever is mainly contracted through mosquitoes of the genus *Haemogogus*, which receive infection from forest monkeys. Mosquitoes of this genus are strictly forest species breeding in tree holes. *Haemogogus* is a genus which does not occur in the Old World, and other species play this role in Africa, notably *Aedes simpsoni* and *Aedes africanus*, both of which species have been shown capable of transmitting the virus and have been found naturally infected.

A curious feature in the aetiology of forest yellow fever is that the vertical distribution of species of mosquito has been found to be important. Thus in the American forests it is especially when trees are felled, bringing down their high level mosquito fauna, that the chief danger of infection arises. In Africa it seems that *A. africanus* is the chief vector in maintaining the virus, receiving and transmitting infection in the high-level monkey community, but not ordinarily infecting man, who mainly receives infection from *A. simpsoni*, which frequents human neighbourhoods on the borders of the forest and acquires infection from monkeys infected by *A. africanus*.

These are not the only lines of investigation opened up by virus research. One important line of inquiry is directed to the production of a safe and effective vaccine which can be used on a large scale in human protection. At one time human immune serum was used to provide such protection, but naturally only on a very limited scale. Another method, now disused, was the simultaneous injection of mouse virus and immune human serum. There have been still other methods employed. Viruses, according to the strain or host used, may be mainly viscerotoxic, affecting chiefly the liver, etc., as in man and monkey, or neurotoxic, as in the mouse, the white mouse being susceptible only to intracerebral inoculation. The strains used for vaccine have been principally the Asibi strain of human source, which is mainly viscerotoxic, and the so-called French neurotropic strain. A vaccine, 17 D, giving modified action of both types has been prepared at the Yellow Fever Laboratory of the International Health Board from virus cultivated on the chick embryo (Theiler and Smith, 1937), of which 28 million doses have been issued for use in human protection.

Those who wish to learn more of these lines of research and much else about yellow-fever work should read *Yellow Fever*,¹ issued under the editorship-in-chief

¹*Yellow Fever*. Editor-in-chief, George K. Strode, M.D. (Pp. 710; 77 figures. £4 1s.) London: McGraw-Hill Publishing Company. 1951.

of George K. Strode. It gives the results of the work carried out on yellow fever over a period of more than 30 years by the Rockefeller Foundation and by other agencies with the support and co-operation of this body. This is in effect a monographic study of the whole subject of yellow fever, comprising a number of sections relating to different aspects of the disease by authorities who have themselves been recently engaged in and largely responsible for results in the work they write about. The book is attractively printed, very readable, and interesting throughout, and it will clearly be the chief reference book on yellow fever for a long time to come.

REFERENCES

- Boyce, R. (1910). *J. trop. Med. Hyg.*, **13**, 357.
Soper, F. L., Wilson, D. B., Lima, S., and Antunes, W. Sa. (1943). *The Organization of Permanent Nation-wide Anti-Aedes aegypti Measures in Brazil*. Rockefeller Foundation, New York.
Theiler, M., and Smith, H. H. (1937). *J. exp. Med.*, **65**, 787.

HORMONES AND CARCINOGENESIS

Steroid Hormones and Tumors. Tumorigenic and Anti-tumorigenic Actions of Steroid Hormones and the Steroid Homeostasis. Experimental Aspects. By Alexander Lipschutz, M.D. (Pp. 310; 111 figures. £2 6s. 6d.) London: Baillière, Tindall and Cox. 1950.

The role played by steroid hormones in carcinogenesis is one of the most intriguing problems of experimental medicine, not only because cancer of the breast, uterus, and prostate gland are common sites of cancer in the body, and are organs normally under endocrine control, but because the growth and behaviour of tumours derived from these particular organs can under certain conditions be influenced by means of endocrine therapy. Although cancer of any of these organs cannot at present be permanently cured by this form of treatment, most encouraging results have been demonstrated clinically with the control of prostatic cancer in man by the application of anti-androgenic measures. The results obtained by hormonal treatment of the breast, and particularly of the uterus, have been less satisfactory, and for this reason Dr. Lipschutz's book is of exceptional interest. Many of the issues he raises are controversial, but he does attempt by his experiments with guinea-pigs to fill in certain gaps in our knowledge of the relationship of sex hormones to the genesis of uterine tumours. These tumours, and particularly carcinoma of the endometrium, are thought by many investigators to be related to hormonal disturbance, but whether uterine fibromyomas result from ovarian dysfunction is more debatable.

This volume consists of a series of original papers and observations by the author and his numerous colleagues, dating from 1936, some of which have never previously been published. Both clinicians and research workers will find it something more than just another of the detailed works of reference which so many modern textbooks tend to be.

The book is in three parts. The first is mainly on the induction by oestrogens of uterine fibromyomas and abdominal and thoracic fibroids in guinea-pigs. Controversy exists on whether these induced uterine lesions in the guinea pig are comparable histologically to those which occur spontaneously in human beings, but the fact that they can be induced by hormonal treatment is significant. It is also true that attempts to induce similar