MALARIA: THE GREAT UMBRELLA*

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A CENTURY ago the study of infectious diseases received a strong stimulus. The application of scientific methodology to the concept of vector-borne diseases began in this period. Sir Patrick Manson's work on filariasis in 1877 set the pace and was followed in 1893 by Theobald Smith's demonstration of the transmission of red water fever by ticks. This work of Smith's provided clear guidelines for further revelations. The malaria parasites were demonstrated by Alphonse Laveran in 1880, but an understanding of the epidemiology of malaria did not follow for almost two decades, until the demonstrations by Sir Ronald Ross in 1897 and by Battista Grassi and Amico Bignami in 1898. Surprisingly soon thereafter, at the turn of the century, came the demonstration of the vector transmission of yellow fever by Walter Reed and his associates. Carlos Finlay had erected the hypothesis and it can be surmised that his thinking had been conditioned by the earlier work of Manson and Smith. The actual virus of yellow fever was not isolated until several decades later.

Along with the rigid scientific demonstrations of etiologic agents and arthropod vectors and the emergence of epidemiological concepts which have proved of enormous value for the control of disease, there was a continuing struggle in the field of medical diagnosis and treatment. It is my thesis that progress in medical diagnosis has not been as scientifically satisfying as that in parasitology, medical entomology, and epidemiology.

Hints of diagnostic trouble are strewn all along the way. Yellow fever provides a difficult problem, early recognized by Josiah Nott, who said in 1848:[1] "If a physician were called in the forming stages of a number of cases of plague, smallpox, yellow fever, some forms of

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typhus and other diseases arising from morbid poisons . . . he would be much at a loss how to distinguish them in 2-3 days." Austin Kerr, in his admirable section in Tice's *Practice of Medicine*,[2] repeated the same injunction. Descriptions of the classical disease seem to provide many diagnostic hints, but only a small fraction of cases in a modern epidemic fulfill such descriptions. The majority of cases present as mild, quite undifferentiated fevers resembling early stages of malaria, typhoid, typhus, or dengue. So we have returned to Nott's statement of 126 years ago.

But I am here, not to unravel the yellow fever mystery alone but to untangle it—and several other important diseases—from a disease that is still more frequently misdiagnosed in certain parts of the world: malaria.

An 1898 editorial in the *Indian Medical Gazette*, titled "That Comfortable Word: Malaria,"[3] expresses the same concern for the accurate diagnosis of malaria that was voiced by Nott, Kerr, and others concerning yellow fever. The writer states: "Any disease may be grafted upon malaria, or rather supervene in a patient already malaria-stricken, and it is easily understood that the debility and anemia produced by repeated attacks of ague may even create a predisposition to other diseases, but this is a very different thing from classifying these diseases as 'malarial.' "

I shall outline this field of malarial diagnosis with truisms, which may be very well known as individual items, but which are not always so well comprehended in an interdependent situation. I shall restrict my comments to Africa, particularly to West Africa, a region which exceeds 8,000,000 square miles in area and holds a population in excess of 150,000,000 people. A considerable fraction of this population exists in regions characterized as hyperendemic to holoendemic for malaria, particularly for *Plasmodium falciparum*, known also as subtertian or malignant tertian malaria.

Hyperendemic malaria, shading up to holoendemic malaria, is an epidemiological concept which tells us that almost all or perhaps all, of the inhabitants of a given region are repeatedly infected with malaria parasites unless they take quite extraordinary precautions, and exist in a state of infection loosely referred to as "chronically malarious." A heavy toll may well have been exacted by the disease among the very young, but as the outsider sees the population, they may present only relatively

infrequently with recognizable signs or symptoms of the disease.

In such a region a conscientious practitioner of medicine may take a blood smear on every patient who presents with fever. He is likely to find that malaria parasites are present in many. When the patient then receives antimalarial therapy a favorable response can be anticipated in most. Only if the temperature fails to come down or the patient fails to improve is further diagnostic consideration given. Typhoid fever is apt to come to mind and a typhoid regime instituted. If the patient is still alive—he usually is, and may even recover—the case is considered straightforward. Should he die, since malaria parasites were demonstrated malaria is likely to be considered the cause of death.

A specific example may better illustrate this. In Trinidad in 1954 there was an outbreak of typhoid fever. Public health nurses rounded up suspects by house-to-house search in the hilly region north of Arima and put them in the Arima District Hospital. Trinidadian doctors and an epidemiological team from the United States Army tried several different therapeutic regimes on patients diagnosed by culture. One man was admitted as a typhoid suspect and treated: the culture was negative and he showed no clinical response. A blood smear was taken and malaria parasites were found. He was given antimalarial therapy and his temperature slowly dropped. Early in his illness a blood specimen taken in a routine survey for viral diseases yielded yellow fever virus on intracerebral inoculation of mice.[4] Fortunately, by this time the man had recovered from what?—from malaria, since parasites were seen—from yellow fever, since the virus was isolated. Had curious virologists not been on the scene yellow fever never would have been detected. But the diagnosis was of vital importance in getting activities for the control of yellow fever under way promptly in what proved to be a good-sized outbreak.[5]

To return to Africa, a common and defensible practice is to treat all patients with fever at dispensaries, clinics, and even hospitals with antimalarial drugs, without taking a blood smear and looking for parasites. Most will respond. If there is no response a blood smear may be taken, routine antityphoid therapy started, and other diagnostic possibilities explored. If the patient still survives but does not improve, even such esoteric possibilities as yellow fever may be considered. If the patient dies, the easiest conclusion is death caused by complications of malaria. It is uncommon in West Africa, even in teaching centers,

to have the diagnosis refined much beyond this point. There is a thin scattering of specialized laboratories—in virology, parasitology, and bacteriology—which are staffed and equipped to explore further.

In West Africa, moreover, only a small fraction of the more than 150,000,000 inhabitants has the remotest chance of getting to a teaching hospital. A larger fraction is served by governmental hospitals, mission hospitals, fixed clinics, and mobile clinics. But for the majority—a huge number of people—medical attention is lacking entirely or is quite inadequate. Knowledge of malaria and antimalarial drugs has penetrated deeply, however, and such drugs are often used in the villages with little or no medical supervision. Deaths, when they occur, are often tallied up to malaria, and medical workers may not be aware of large outbreaks of disease with high mortality until such outbreaks have been going on for weeks or months. This has happened repeatedly with yellow fever, even in recent years. In the central plateau region of Nigeria in 1969 an epidemic of yellow fever proceeded for two months and caused an estimated 100,000 cases before recognition.[6]

In some of our earlier efforts to diagnose febrile illnesses occurring in clinic and dispensary populations malaria was considered an intrusion and patients diagnosed as having malaria were excluded from further diagnostic study. It soon became apparent that the barn was being locked with the horse outside. When we tried to apply these criteria in Trinidad in 1953, we received only a trickle of patients. The doctors considered all febrile illnesses to be malaria as a starting diagnosis. So we reversed the criteria and announced that we particularly wanted malaria cases and, in addition, any other interesting cases that might come along. This proved to be the open sesame. We now had plenty of clinical material, and in due course isolated Oropouche virus from a patient who also had malaria parasites in his blood.[7] The virus was new and the disease was new. Subsequently there were repeated outbreaks of Oropouche virus infection in Belem, Brazil, with thousands of cases.[8]

Another example, this time from Senegal, will illustrate how malaria can mask other diseases. The virologists at the Institut Pasteur at Dakar, headed by Dr. Paul Brès and later by Dr. Yves Robin, were challenged by the large number of arthropod-borne viruses being uncovered, not only by their work in Senegal but also by workers of the Rockefeller Foundation at the University of Ibadan (headed by Ottis Causey and later by Donald Carey) and by workers at the Institut Pasteur in

Yaoundé, Cameroons, and in Bangui in the Central African Republic. So they established a clinic in a small town called Bandia, some 50 miles outside Dakar, and treated fever cases one day a week, also routinely taking a blood smear to be examined for malaria and a blood specimen for the isolation of viruses. Their findings were fascinating.[9] Work started in late 1968. In August 1969 they encountered a flurry of fever cases. In nearly every case they found malaria parasites. But they also isolated Tataguine virus from the patients and from anopheline mosquitoes. This was the second correlation of Tataguine virus with human disease, the first instance being in a feverish child in Nigeria.

Things then quieted down a bit, but beginning in August and peaking in October there was another flare-up. This time Ilesha virus was isolated from seven patients and from anopheline mosquitoes. Ilesha had been isolated several years earlier, once only, from a clinic patient in Ilesha, Nigeria.

Again there was a lull. Then came two isolations of Zika virus from clinic patients, one in November and one in December, and isolations from *Aedes* mosquitoes. The dry season was under way by this time and anophelines had disappeared. Finally, in February 1970, an isolation of Ilesha was made from a clinic patient during the full dry season, and in October 1970 a dengue-2 virus was isolated.

To recapitulate the Bandia story, malaria parasites had been demonstrated in all except one of 17 clinic patients from whom viral isolations were made. Had a virus laboratory not been in operation, it would have been defensible to consider—even to consider it proved—that the flurries of cases of fever were caused by malaria.

This theme of malaria as an umbrella in diagnosis should not be dropped without consideration of Lassa Fever.[10] Several nurses—Wine, Shaw, and Pinneo—were suspected of having malarial infections, and treated for them. Indeed, at Presbyterian Hospital in New York there was a report of malaria parasites in Pinneo's blood. Had Lassa virus not been isolated, I do not know what diagnosis would have been appended to the three cases. Later outbreaks in Africa have had the thread of malaria curiously interwoven in the story of diagnosis. Within our limited comprehension of what the full epidemiological story of Lassa infection may be, we can speculate that malaria has obscured Lassa in the past as it has obscured yellow fever, and that it will continue to obscure the diagnosis of these and other infectious diseases in Africa.

Malaria has been considered in its evident role of a very prevalent disease, obstructing or confusing the diagnosis of other concomitant or unassociated illnesses. Malaria is also receiving consideration in a more subtle role: influencing the immunological status of the individuals afflicted. In the epidemiology of Burkett's lymphoma in tropical Africa malaria is being named, in its role of an immunosuppressant, as a contributing factor.[11] It is possible that the course of other diseases, noninfectious as well as infectious, may be altered by the malarial infection.

There is a long-term solution to the problems of improving the understanding of malaria in Africa: namely, increased and improved diagnostic facilities in Africa, back-up facilities in developed countries and medical personnel sensitized to the diagnostic problems of their regions and to the epidemiological implications of missed or tardy diagnoses of medically important diseases. This African solution applies equally to Southeast Asian, South Pacific, and South American foci of malaria.

Whose responsibility is it to engage in such a program? Certainly the local governments have prime responsibility, backed up by the World Health Organization for necessary inter-regional studies. Interested foreign governments, mission groups, and foundations, it is to be hoped, will provide backing, as they have done in the past. But I cannot permit myself to be optimistic. At this time what is being done by all parties combined to improve the situation with respect to the diagnosis of infectious diseases in Africa is utterly inadequate.

REFERENCES

1. Nott, J. C.: Yellow fever contrasted with bilious fever: Reasons for believing it is a disease sui generis—Its mode of propagation—Remote cause—Probable insect or animalicular origin. &c. *New Orleans Med. J. 4*:563-601, 1848. See also Downs, W. G.: Yellow fever and Josiah Clark Nott. *Bull. N.Y. Acad. Med. 50*:499-508, 1974.
2. Kerr, J. A.: Infectious Diseases: Yellow Fever. In: *Practice of Medicine,* Tice, F., editor. New York, Harper & Row, 1932 . . ., vol. 4, pp. 1-31.
3. Editorial. That comfortable word: malaria. *Indian Med. Gaz.:* 101-02, 1898.
4. Anderson, C. R., Spence, L., and Downs, W. G.: Report of a case of yellow fever in Trinidad, B.W.I. *Caribbean Med. J. 16*:68-70, 1954.
5. Downs, W. G., Aitken, T. H. G., and Anderson, C. R.: Activities of the Trinidad Regional Virus Laboratory in 1953 and 1954 with special reference to the yellow fever outbreak in Trinidad, B.W.I. *Amer. J. Trop. Med. Hyg. 4*:837-43, 1955.
6. Carey, D. E., Kemp, G. E., Troup, J. M., White, H. A., Smith, E. A., Addy, R. F., Fom, A. L. M. D., Pifer, J., Jones, E. M., Bres, P., and Shope, R. E.: Epidemiological aspects of the 1969 yellow fever epidemic in Nigeria. *Bull. W.H.O. 46:*

645-51, 1972.

7. Anderson, C. R., Spence, L., Downs, W. G., and Aitken, T. H. G.: Oropouche virus: A new human disease agent from Trinidad, West Indies. *Amer. J. Trop. Med. Hyg. 10*:574-78, 1961.
8. Pinheiro, F., Pinheiro, M., Bensabath, G., Causey, O. R., and Shope, R. E.: Epidemia de virus Oropouche em Belem. *Rev. Serv. Esp. Saude Publica. 12*:15-23, 1962.
9. Robin, Y., Cornet, M., Coulanges, P., Le-Gonidec, G., Dhiver, F., Marty, M., Hery, G., Vlassak, C., and Gueye, A.: Les arbovirus au Senegal. Etude dans la population humaine du village de Bandia. *Afr. Med. 10*:739-46, 1971.
10. Frame, J. D., Baldwin, J. M., Jr., Gocke, D. J., and Troup, J. M.: Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings. *Amer. J. Trop. Med. Hyg. 19*:670-76, 1970.
11. Edington, G. M., Maclean, C. M. U., and Okubadejo, O. A.: One-hundred and One Necropsies on Tumours of the Reticulo-endothelial System in Ibadan, Nigeria with Special Reference to Childhood Lymphosarcoma. In: *Symp. Lymphatic Tumors in Africa, Paris, 1963*. Basel and New York, Karger, 1964, pp. 236-52.