RECENT ADVANCES IN THE KNOWLEDGE OF YELLOW FEVER*

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In order to open a discussion upon our increased knowledge of yellow fever I feel that I should very briefly summarize the facts concerning the pathology and epidemiology of the disease which have recently been brought to light, and that I should devote my time mainly to a discussion upon the application of this knowledge to the problems affecting the control of the disease and the prevention of its spread to infectible countries which have as yet escaped infection. I have no personal knowledge of the recent work upon yellow fever except such as has been gained by a close association with the workers of the West African Yellow Fever Commission of the Rockefeller Foundation and by a visit to the Rockefeller Institute in New York, but the facts which that Commission has exposed recently with regard to the exceedingly wide distribution of the disease in West Africa have profoundly altered the views of my colleagues and myself, and in discussing the control of the disease I must bring into prominence the local difficulties which face the sanitary authorities in a country such as Nigeria.

RECENT RESEARCH UPON YELLOW FEVER

An excellent summary of recent work upon yellow fever has been made by Sawyer¹ in the Lamar Lecture given at the school of hygiene at the Johns Hopkins University. I shall follow his example and date recent knowledge from the discovery in 1927 by Stokes, Bauer, and Hudson² of the susceptibility of the *Macacus rhesus* and *M. sinicus* to yellow fever. This discovery led to the isolation of the "asibi" strain, upon which so much work has been done in West Africa. It was confirmed by Mathis, Sellards, and Laigret,³ working at Dakar, who isolated the French strain and, later, by Aragao⁴ and by Davis and Burke,⁵ who isolated the Brazilian strains.

The discovery of a susceptible laboratory animal led to the confirmation of the work of the Reed group upon the *Aedes* vector of the disease and to the proof that yellow fever is due to a filterable virus and not to the *Leptospira icteroides*. The development of the "protection test" in monkeys followed, when the workers in West Africa showed that the injection of a small quantity of serum from a patient who had recovered from the disease protected a monkey from a simultaneous injection of yellow fever virus, and this test incidentally settled the much-discussed point as to the identity of the disease in West Africa and in the Western Hemisphere. Sawyer, Kitchen, Frobisher, and Lloyd⁶ proved conclusively by cross-immunization experiments that the disease was identical. The protection test proved that the immunity conveyed by an attack of the disease is usually lifelong—the serum from one patient who had suffered from the disease seventy-eight years previously protected monkeys. A recent advance in the application of the protection test has been due to the discovery of Theiler⁷ that the yellow fever virus injected intracerebrally into white mice produces an encephalitis with intranuclear inclusions in the ganglion cells. By frequent passage a fixed neurotropic virus with heightened virulence was produced. This protection test has been elaborated by Sawyer and Lloyd,⁸ and is the test now usually conducted. Briefly the

principle consists of an intraperitoneal injection of the serum to be tested and the virus, while at the same time a mild irritant (starch solution) is injected into the brain to fix virus which enters the circulation.

The development of the protection test has profoundly modified our views upon the epidemiology of the disease, and it is upon the results of these tests, carried out by the Rockefeller Commission in West Africa, that I wish to base my discussion. Before proceeding to this, however, I must briefly refer to other recent discoveries which affect our knowledge of the disease.

MOSQUITO VECTORS

The use of laboratory animals has enabled experiments to be carried out with a large range of mosquitos. Many species of *Aedes* have been proved to be potential vectors. Practically, the important facts have emerged that *Aedes aegypti* is the common vector, but that in West Africa *Aedes univittatus* (Sugens) and *Taeniorrhynchus africanus*—both common domestic mosquitos—are also potential carriers.

PATHOLOGY OF THE DISEASE

The work of Klotz⁹ has clarified our knowledge of the pathological findings in yellow fever, and has freed the pathology of the disease from the confusion caused by mistaken diagnosis of epidemic jaundice. The typical mid-zonal necrosis of yellow fever has been used in Brazil for an epidemiological study of the distribution of the disease, modified post-mortem examinations being carried out by means of an ingenious apparatus known as a viscerotome, by which a small portion of liver tissue is removed through a stab wound in the chest wall.

The work of Torres,¹⁰ and, later, of Cowdry and Kitchen,¹¹ further identified yellow fever among the diseases caused by filterable viruses by describing cell inclusions in the liver cells comparable to the inclusions found in other virus diseases.

YELLOW FEVER AS REPORTED FROM WEST AFRICA IN RECENT YEARS

In dealing with the distribution of cases of yellow fever which have been notified in recent years I shall touch only upon the West African cases, and shall not mention the occurrence and distribution of the disease in South and Central America. During 1931 cases have been reported from Senegal (Ivory Coast), Haute Volta (French Sudan), and Dahomey among the French Colonies, and from the Gold Coast and Nigeria in the British Colonies, and the striking fact about the incidence of these cases is the exceedingly wide distribution and the occurrence of cases far in the interior. The disease has in fact not been a coastal disease. In recording the incidence of yellow fever in West Africa it must be emphasized that the European is merely the indicator—hundreds of cases must occur among Africans which are not recognized, and the number of cases which occur in Europeans depends more upon the degree of segregation of Europeans in residential areas than upon the actual incidence of the disease among the African population. The disease in Africans may be a serious illness, but it may be, and usually is, a trivial illness occurring in infancy. The typical highly virulent strain, now known as the "asibi" strain, was recovered from an African patient who had only transitory fever, headache, and pain in the back, only a trace of albumin on the second day of illness, and none subsequently. In native infants the disease is particularly difficult to recognize, and I saw a case recently of a child of 6 months who had suffered from a long attack of jaundice and whose blood gave absolute protection against yellow fever. So difficult is it to recognize among the African population that I was recently informed by a highly efficient African

* Read in opening a discussion in the Section of Tropical Medicine at the Centenary Meeting of the British Medical Association, London, 1932.

doctor of wide experience that Africans do not contract yellow fever.

The occurrence of yellow fever among Europeans in places widely separated has always been difficult to explain unless we imagine a widespread native epidemic, and the protection test has lent support to the idea that these may occur with so low a mortality that they do not come to notice. Thus in 1931 two isolated cases of yellow fever occurred in the northern provinces of Nigeria, at and near Kaduna; protection tests carried out among African children in the township showed only 2 per cent. positive, but in the surrounding pagan villages 83 per cent. of the population gave a positive protection test, and in the more sophisticated Hausa villages 29 per cent. of the population showed a positive protection test. It should be noticed that in the interior of West Africa the European is a less reliable indicator of the incidence of yellow fever than in the southern and coastal region, because, owing to Mohammedan custom, there is less intimate contact, both in business and in living, among the Africans and Europeans.

PROTECTION TEST STUDIES UPON ENDEMICITY AND EPIDEMICITY

The publication by Beeuwkes, Bauer, and Mahaffey¹² of a study of the endemicity of yellow fever in West Africa upon epidemiological factors with special reference to the protection test opened a new field for sanitarians in West Africa. In this work the authors suggested that the main endemic centres of West Africa might be found in the large towns of the south-west of Nigeria. Subsequent work by members of the Yellow Fever Commission has shown an enormously wide distribution of the disease, which may be due to an extensive area, or areas, of endemicity, or to a recent widespread epidemic. Many difficulties exist in the interpretation of protection test figures; the test indicates whether or not the disease *has* occurred in a locality, and by testing a series of age groups whether it is being maintained from year to year. Whereas a high positive rate in adults with negative results in children suggests that an epidemic has occurred in the past but that the disease is not endemic, a high positive rate in both children and adults suggests either endemicity or a recent epidemic among a susceptible population. It is not possible to determine the actual current status, since blood can rarely be obtained from very young children; moreover, in dealing with an African population, it is difficult to be certain that the donors of blood specimens have resided all their lives in one area.

The Yellow Fever Commission has concentrated upon Nigeria in performing protection tests, but has carried out series of tests from the Gold Coast and from Freetown. Although some 2,000 serums have been tested the work is at present so incomplete that I do not feel justified in accepting the most courteous offer of Dr. Beeuwkes, the director of the Commission, to publish the figures which he has placed at my disposal. Beeuwkes, Bauer, and Mahaffey¹² pointed out that upon epidemiological factors the south-west section of Nigeria must be regarded as an important endemic area owing to the closely associated large towns, which contain exceedingly high populations for African towns, as will be seen from the following population figures: Ibadan, 234,000; Lagos, 144,000; Ogbomoso, 85,000; Iwo, 54,000; Abeokuta, 53,000; Oshogbo, 51,000; Oyo, 40,000.

Protection test figures obtained by these workers supported the conception that this area is an endemic centre of the disease, but recent figures obtained from other parts of Nigeria make it unsafe to assume that this section is the only, or even the main, endemic focus of the disease. It should be noted that the occurrence of the few reported cases of yellow fever in Europeans in Nigeria

during 1931 has been supported by finding mild cases among Africans, as at Mamfe in the Cameroons, where a high proportion of these cases gave positive protection tests, or by finding a high protection test figure in the surrounding population among which no cases of the disease had been recognized, as at Garkida in Adamawa Province, and at Kaduna.

The unexpectedly high protection test rate in both children and adults which has been found in widely separated areas in Nigeria points, however, to the possibility of a recent extensive epidemic. In this connexion it is of interest to find that Gumel, a town upon the extreme northern border of Nigeria, gave a positive rate of 60 per cent. among twenty-five adults tested and of 44 per cent. in twenty-five children tested, whereas Sokoto, in the north-west, gave negative results in twenty-five children tested.

Admittedly the study carried out by the Yellow Fever Commission by means of the protection test is as yet too incomplete to enable reliable conclusions to be drawn, and a far wider study in Nigeria and in other colonies must be carried out before we can obtain a clear picture of the situation. The important fact which has been brought to light is that the disease has been exceedingly widespread in the African population, even in the dry northern belt, and in view of the distribution of reported cases of the disease throughout the hinterland of West Africa we may suppose that this situation has been almost universal.

INFECTIBILITY OF THE DRY NORTHERN PART OF THE HINTERLAND

Apart from isolated cases of yellow fever which have occurred from time to time in the northern provinces of Nigeria we now have the evidence of the protection test to show that the disease may exist in epidemic form, or even possibly in endemic form, among the African population of the dry northern country. Generally speaking, towns are far apart, and are of no great size, so that conditions would not appear to be favourable for endemicity, but towns are connected by scattered hamlets, and weekly markets attract large attendances, so that "regional" or "circulating" foci of endemicity may exist. If such areas were free from the mosquito vector during part of the year a true endemicity could not exist, but I shall show that the vector is actually present, though in reduced numbers, throughout the dry, cold season. To a traveller in the extreme northern section of Nigeria in the cold harmattan season the country appears desiccated and entirely unfavourable for an *Aedes* population, but even in this season the temperature is high during part of the day, and the shortage of water leads to storing in innumerable earthenware water-containers in towns and villages. The following table shows the meteorological conditions of this northern belt during 1931:

	Jan.	Feb.	March	April	May	June	July	August	Sept.	Oct.	Nov.	Dec.
Kano: absolute max.	100	110	108	109	105	100	97	92	93	100	93	99
" min.	51	54	64	72	71	68	67	68	67	58	56	54
Mean ...	76	79	85	91	89	83	79	79	79	80	73	74
Relative humidity	25	21	24	48	58	73	81	82	80	53	30	24
Rainfall in inches	—	—	—	0.78	1.72	5.40	14.53	15.14	8.87	0.09	—	—
Katsina: abscl. max...	95	104	107	108	105	108	93	92	92	99	93	96
" min...	52	53	61	70	66	67	65	64	62	61	59	54
Mean ...	76	78	83	92	89	84	81	80	80	80	79	75
Relative humidity	22	18	28	39	55	71	80	93	83	37	28	45
Rainfall in inches	—	—	—	0.17	3.80	3.15	6.17	5.40	6.41	—	—	—

The *Aedes* population of Kano and Zaria has been studied by the members of the Yellow Fever Commission, who made careful surveys of those towns at four seasons throughout the year—that is, during the hot, dry season before onset of rains, during mid-rains, during the hot period after rains finished, and during the cold, dry harmattan season. At the same time a study was made by A. W. Taylor, entomologist attached to the Tsetse Investigation at the Tsetse Camp at Gadau, also in the dry belt, working in co-operation with the Yellow Fever Commission, who made similar surveys of a typical village (afterwards proved by the protection test to have suffered from yellow fever), and carried out longevity experiments with local and coastal species of *Aedes* kept at room temperature and in a moist chamber. The results of these surveys and experiments will be published in due course. Briefly the high larval *Aedes aegypti* house index of 69 and 34 for Zaria and Kano respectively in the wet season fell to 45 and 24 in the hot, dry season, and was still as high as 22 and 16 during the severe cold harmattan season. Similarly, the percentage of adult *Aedes* caught per room varied in Zaria and Kano respectively from 0.8 per room and 0.4 per room in the wet season to 0.4 and 0.2 per room in the dry, hot season and 0.2 and 0.04 during the harmattan season. At the small village near Gadau the room index for adult *Aedes* was still as high as 0.7 during the severe harmattan season. The longevity of *Aedes* was shown by Taylor to depend more upon temperature than upon humidity. No experiments have been made upon the infectibility of *Aedes* with yellow fever virus during the cold harmattan season, although this factor may be of some importance epidemiologically. It has been shown by the Nigerian Tsetse Investigation that temperature plays an important part in the infectibility of *Glossina* with *Trypanosomum gambiense*.

We must conclude, therefore, upon the evidence now available that the dry northern country is both infectible and is possibly able to maintain infection throughout the year, and evidence has been given to support the view that a widespread epidemic has occurred recently. That such an epidemic can occur, and can be unrecognized among the African population, except in rare cases, is of supreme importance in the framing of quarantine regulations.

QUARANTINE REGULATIONS, WITH SPECIAL REFERENCE TO THE NEW FACTOR OF AIR SERVICES

Many years' work will be required throughout the whole of West Africa on the protection test before we can form a definite opinion, upon the evidence of this test, as to the main endemic areas in West Africa, and repeated tests upon age groups will be necessary to avoid the confusion between the condition of endemicity and that caused by a recent epidemic in a susceptible population. In the meantime, we must regard the whole of West Africa as potentially infected at any time, and must remember that this infection may escape notice. Any quarantine regulations based upon reported cases of the disease, or upon known areas of endemicity, can only lead to a false sense of security.

Quarantine regulations for aircraft have been tentatively drafted upon a basis of known endemic areas. In my opinion this is impracticable at present, and ignores the possibility of widespread and unrecognized foci of disease elsewhere between the coast and the Sahara, all of which country is infectible. It has been suggested that all aerodromes in endemic areas should be "anti-amaryl," which entails complete mosquito protection of all houses, isolation from native towns, residence of passengers for six days in the aerodrome before leaving for infectible countries, and the provision of complete medical and

pathological equipment. As it must be agreed that unrecognized infection is more dangerous than known infection, it is obvious that no other aerodromes than anti-amaryl aerodromes could be used throughout West Africa. Upon the grounds of expense and of delay caused to intending passengers this would be impracticable, and if air services from West Africa to infectible countries are to eventuate a compromise must be made. I would suggest for consideration the following general plan for West Africa:

1. Continuation and extension of the system, already partly practised in British Colonies, of the segregation of Europeans within European residential areas

2. Aerodromes to be confined to the neighbourhood of such European residential areas as are associated with native towns under close sanitary control. Such areas could be designated "sanitary areas."

3. Intensification of sanitary measures in both the residential areas and native towns mentioned in (2).

4. Aerodromes to have efficient disinfecting plant for baggage and suitable accommodation for medical inspection of passengers.

5. The success of sanitary measures to be checked by making detailed *Aedes* surveys of the "sanitary area" and by making protection tests upon young children from time to time. The results to be communicated to a central committee, such as that of the Bureau d'Hygiène.

6. Sanitary authorities in infectible countries to bear the responsibility of examining passengers and crew arriving from West Africa and of keeping them under (ambulatory) surveillance for six days from the date of their departure from West Africa unless they carry a certificate of residence in a "sanitary area" for the required time before departure.

Such action and regulation would, I think, cover the immediate risk while air services are limited and are used almost exclusively by European passengers. I have stressed the importance of the principle of European residential segregation, as experience has proved how rarely an infection has occurred in a European resident in such an area. I suggest that, as a possible development before air services become numerous, a system of protective vaccination of crew and intending passengers may have been worked out upon a practicable basis. The use of a formalized vaccine as described by Hindle¹³ has not been uniform in results, and has been abandoned for the mouse-brain virus, which has lost its power to kill monkeys, but which, as a measure of precaution, is given with a large dose of convalescent serum. The technique and results of this method have been described by Sawyer, Kitchen, and Lloyd,¹⁴ and the vaccine is satisfactory in conveying protection, but the large quantity of convalescent serum which is required, and the risk that active virus may be present in the circulation while protective bodies are being formed, makes the method as now developed only practicable of application to laboratory workers who are particularly exposed to infection.

CONTROL OF THE DISEASE IN INFECTED COUNTRIES

Whatever methods are used for protection of non-infected but infectible countries as an emergency measure owing to the development of rapid air service, it is obvious that the disease must also be vigorously attacked at its source with a view to final eradication. In West Africa improvement of sanitation must be of gradual development among the African population, and can never be truly effective until the population has developed a health sense. Direct sanitary control under the supervision of a European staff is impossible, except in localized centres, in a country of the size of Nigeria, for instance, with its population of over 19,000,000 people. Moreover,

the accepted principle of indirect rule involves the education of the chiefs and people to develop their own service—political, educational, and health—under the advice and guidance only of the European staff, and direct action taken by an energetic European sanitary staff in a native city may entirely destroy the delicate growth of a system of responsibility thrown upon chiefs, sub-chiefs, ward heads, and family heads, quite apart from the inherent difficulties of house inspection among a Mohammedan population. It must also be realized that a campaign against yellow fever alone will receive small support from a native population which is not impressed with the seriousness of the disease, and that the medical authorities in West Africa must face such serious diseases as small-pox, yaws, sleeping sickness, relapsing fever, leprosy, guinea-worm, and schistosomiasis, for the control of which organized campaigns undertaken by survey parties followed by treatment parties are necessary. Some 56,000 cases of yaws alone are being treated each year in Nigeria, and between 5,000 and 10,000 cases of sleeping sickness. An enormous expansion of health work among the population is taking place in West Africa, and in Nigeria this is becoming more and more effective through the native administrations, which are now entirely supporting eight large hospitals and 140 dispensaries, and are producing well-educated candidates for training as sanitary inspectors, dispensers, and medical assistants. Native administrations are also becoming more and more anxious to install pipe-borne water supplies into their cities.

It will be generally agreed that the right way to attack yellow fever is to improve general sanitation and to educate the local population. The programme which we are attempting in West Africa is upon the following lines:

1. Institution of pipe-borne water supplies.
2. Education in hygiene by means of hygiene lectures in schools, health weeks, and newspaper articles.
3. Education and training of African sanitary and medical personnel.
4. Dissemination of trained African staff throughout the country by establishment of scattered dispensaries, which will finally develop into rural and urban health centres.

In conclusion I must pay tribute to the work of the Yellow Fever Commission of the Rockefeller Foundation in West Africa. The value of the work which the members of that Commission have carried out is fully recognized from the papers they have published, but the appreciation of the West African Medical Service is also due for the charming contact which they have made with us, for their most ungrudging help and advice, and for the open manner in which they have placed at our disposal the results of their work. I am myself particularly indebted to the director of the Commission, Dr. Henry Beeuwkes, and to Drs. Mahaffey and Bauer, and I recall with immense pleasure a journey which I took with Dr. F. F. Russell, the director of the Health Division of the Rockefeller Foundation, through Nigeria early in 1931, and the hospitality of the Foundation to me upon a visit to America as their guest in 1930.

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COLLES'S FRACTURE*

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A simple and useful classification of fractures of the lower end of the radius is to be found in the admirable monograph on injuries of the wrist by Etienne Destot of Lyons, published in 1923.¹ Destot, who was one of the pioneers in radiology in France, divided these fractures into two main groups: (1) *anterior fractures*, which include three distinct types of injury—(a) fracture of the radial styloid process, (b) anterior marginal fractures, and (c) the so-called reversed Colles or Smith's fracture; (2) *posterior fractures*, consisting of (a) the classical Colles, or, using the French terminology, the Pouteau-Colles fracture, and (b) the posterior marginal fractures. In this group the term Colles's fracture embraces also the equivalent injury in early life—namely, separation of the lower epiphysis of the radius.

Among these several types of injury, Colles's fracture occupies a position of outstanding importance, not merely because of its frequency, but because of the special mechanical difficulties which may be encountered in its treatment, and the disastrous results which may follow the neglect of fundamental principles. As an indication of the comparative incidence of Colles's fracture in fractures of the lower end of the radius as a whole, figures may be quoted from the fracture clinic of my surgical unit at the Ancoats Hospital. During a five-year period a consecutive series of 835 recent fractures of the lower end of the radius was made up of the following: Colles's fracture (including the reversed Colles), 571; separation of the radial epiphysis, 174; styloid and marginal fractures, 90.

HISTORY OF COLLES'S FRACTURE

On the occasion of a centenary meeting, and with a subject for discussion of great antiquity, I believe it is appropriate to interpolate some reference to the history of the evolution of our knowledge concerning Colles's fracture. Until the middle of the eighteenth century this injury was universally regarded as one of the forms of dislocation of the wrist-joint. Thus, in 1726, we find J. L. Petit² writing on luxations of the wrist, and emphasizing two characteristic sequels: (a) limitation of pronation and supination (due in his view to injury to the triangular fibro-cartilage), and (b) undue prominence of the lower end of the ulna. It remained for another French master surgeon, Claude Pouteau³ of Lyons (1735-75), some thirty years later, to describe for the first time the common fracture of the lower end of the radius. Pouteau's description appeared in 1783 in his *Oeuvres Posthumes*, and no further reference to this injury can be discovered in French surgical literature until a generation later with the advent of Dupuytren (1777-1835). It is interesting to note that Dupuytren's career in Paris coincided almost exactly with that of Abraham Colles in Dublin. But in Dupuytren's famous clinical lectures,⁴ published just one hundred years ago, in a masterly exposition of fractures of the lower end of the radius there is no mention of the article written by Colles⁵ in 1814, in which the Dublin surgeon believed that he had described a lesion hitherto unrecorded.

If we may judge from contemporary surgical literature Colles's paper attracted comparatively little notice for

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