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THE IMPORTANCE OF ECOLOGY IN RELATION TO DISEASE[1]

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THE scientific study of the mutual relationship between organisms and their environment in regard to pathological processes is obviously a subject of great complexity, and one which may be discussed from many different standpoints. The importance of geographical ecology and of phyto-ecology is apparent in many investigations of this character, for the geographic, the climatic and meteorologic conditions influence the flora, and all these in turn affect the fauna; while both vertebrate and invertebrate animals may act as the intermediate hosts of the disease concerned. Indeed, so closely are animal and vegetable forms of life limited by physical barriers and environment that it has been proposed to classify climate according to prevalent species.

Again, ecological studies with reference to disease may often require a consideration of the reaction of the organism to environment—physiological or pathological ecology. In the development of parasitism, a transition in the life cycle of an organism may convert a physiological or harmless process into a pathological one.

In regard to the effect of climatic environment upon the human host, it may be recalled that even in the Middle Ages health and disease were firmly believed to be subject to cosmo-meteorologic influences. Soothsayers or authors of this period attributed epidemics of infectious diseases especially to atmospheric and to terrestrial phenomena, such as earthquakes, volcanic eruptions, severe storms or droughts, and even to the

[1] The Maiben Lecture before the American Association for the Advancement of Science, given at Minneapolis on June 25, 1935. (Illustrated with lantern-slides and moving pictures.)

appearance of meteors and comets. More recently sanitarians looked to the great variations in atmospheric moisture and temperature as favoring outbreaks of disease, to miasmatic influences, especially in malaria; and the rise and fall of water in subsoil, Von Pettenkofer's theory, in relation to cholera. So firmly did Pettenkofer believe in his theory that he later swallowed a culture of the cholera microorganism which Koch had meanwhile discovered, but he suffered from a mild attack of the disease.

So, etiological and ecological studies, which have revealed in many instances the cause and method of transmission of different infectious parasitic diseases, soon dispelled the majority of these fantastic or dogmatic ideas, or explained their influence in a more rational way or upon a scientific basis. Such discoveries have become not only of inestimable value in the introduction of intelligent public health campaigns against these diseases, but in a number of instances have revolutionized sanitary procedures which before had been erroneously regarded as valuable. Noteworthy examples of these facts have been seen in the prevention and eradication of yellow fever and malaria.

To-day, therefore, many of the biological processes which were formerly empirically attributed to climatic influences—the effect of the sun, the atmosphere and the surface of the earth upon the production of diseases in man—may be explained by the influence which environment exerts in furnishing unsanitary conditions, and especially, the parasites which cause and the insects which transmit infectious disease.

Thus true climatic diseases are exceedingly few. Examples which may be cited that are familiar to you are sunstroke, snow-blindness and frostbite. However, it is as a predisposing agent to disease that climate plays a most important rôle, and the resistance of the host is often profoundly altered by physical environment. Individuals are rendered more susceptible to a number of diseases by chilling and cold, and bronchial and other respiratory and lung affections, as pneumonia, are more common in winter than in summer.

On the other hand, a tropical, moist, monotonous climate may weaken resistance against infections, not because it disturbs metabolism, as has been emphasized by some, but on account of its failure to stimulate sufficiently the thyroid, adrenal apparatus and the sympathetic system.

Climate also plays a rôle in other physiological and pathological processes. The effect of sunlight, high temperature and humidity upon the central nervous system, the endocrine system and the metabolism have all been recognized. Also, there are many subtle effects of tropical sunlight and climate upon the white man which are not understood. Unquestionable is it that prolonged life in such a climate exerts a depressing influence which results in a more or less constant lassitude and tends to lower the vitality and energy.

Climate may influence the prevalence of another form of disease—avitaminosis, in quite another way, with reference to flora. For example, in the tropical countries of the world where rice is produced in such large quantities and hence consumed in its "polished" form in such abundance particularly because of its cheapness, in such countries, beriberi prevails.

In addition to these effects of the immediate environment upon the human host, ecological studies must often consider its effects upon the intermediate hosts in instances where they exist. Here, also, climate plays an important rôle, not only in the character of the vertebrate fauna which the region harbors, but especially of the invertebrate fauna. Also, at temperatures below a certain degree the parasites in the insects which transmit them may be unable to multiply or the insects satisfactorily to breed or even exist, as, for example, the parasites and insects concerned in the transmission of sleeping sickness and of malaria.

Ecological studies must also sometimes include the effect of environment upon the infecting organism, both that of the *milieu extérieur* and of the *milieu intérieur*. In regard to the former, the effect of meteorological conditions, especially the rainy season in the tropics, is often of great importance with reference to the spread of a number of tropical diseases, especially cholera and dysentery, and low temperatures and a low water deficit favor the spread of respiratory diseases, as pneumonic plague. In regard to the *milieu intérieur*, the invading microorganism in one individual may give rise to a fatal infectious disease, while in another individual, protected through his natural or acquired immunity, this identical microorganism produces no visible, or only slight, pathological effect. In the case where a natural immunity exists, the invading microorganism may remain in the individual as a harmless commensal.

Examples of this nature are seen in individuals with diphtheria bacilli (*Bacillus diphtheriae*) or with pneumococci (*Diplococcus pneumoniae*) in their throats who have never had either diphtheria or pneumonia. In some instances, when through cold, producing circulatory disturbances, inflammatory conditions of the respiratory tract occur, especially the *Diplococcus pneumoniae* may assume an increased activity. Under these changed environmental conditions the resistance or the protective mechanism of the patient may become lowered or the infective power of the microorganism enhanced—the microorganism acquiring what has been termed an increased virulence. Under such circumstances the microorganism may now invade more exten-

sively the tissues, and especially the lungs, giving rise to an attack of pneumonia which may result fatally.

In other instances in which active immunity has been acquired by the host, the invading microorganism, even when fully virulent, is not permitted to multiply even as a commensal in its host, but is destroyed at the time of its entrance or very shortly afterwards. This phenomenon may be illustrated in the laboratory by a convincing experiment. A guinea pig is inoculated intraperitoneally with a small amount (some 4 milligrams) of a killed culture of the organism of Asiatic cholera (*Spirillum cholerae*). A week later the animal may be inoculated with ten times the fatal dose, for it, of living cholera organisms, yet the animal remains apparently healthy, no unfavorable symptoms in it being noted. As a result of the primary inoculation with the killed bacteria, the blood serum of the guinea pig has acquired properties which permit it to destroy by bacteriolysis the cholera spirillum as soon as this bacterium is brought into contact with it. This experiment can be repeated many times invariably with the same result. Here a changed environment has been produced by active immunization of the host (through protective inoculation), which is inimical to the life of the invading organism.

Especially in relation to many of the most important diseases in tropical countries have ecological studies given us invaluable information regarding their origin and prevention, and in a number of instances a newly recognized environmental feature has cleared up problems which hitherto were entirely obscure.

On account of the intricate and comprehensive nature of the subject, I shall only attempt in the time at my disposal this evening to emphasize a few of the very apparent and striking ecological relationships regarding several of these diseases which I have particularly studied from this standpoint, but I shall not be able to consider all the environmental influences even in relation to these few diseases. Also, as this audience is composed of specialists in different branches of science, as well as of the laity, I shall discuss particularly such examples as I can illustrate pictorially.

You will probably recall that in the early and Middle Ages, in fact frequently during the first twelve centuries A. D., Europe was afflicted with severe epidemics of plague, in which the lymphatic glands were especially involved and inflamed, forming buboes, hence the name bubonic plague. But in the fourteenth century (1347) a form of the disease appeared of much more virulent type, known as the Black Death, and especially characterized by hemorrhages from the lungs—pneumonic plague. This disease destroyed, according to the estimate of contemporary writers, at least one fourth of the population of Europe.

The virulence, rapid spread and mortality of the epidemic of the Black Death was in great probability due to the pneumonic and septicemic form which the disease assumed.[2] The historical data of the period, the subsequent history of plague and the experience of the writer in the study of plague, in epidemics in different parts of the world since 1900, are in favor of this view.

The bubonic form of plague evidently was also present during this pandemic, but, as Guy de Chauliac emphasizes, it was the form attended by coughing of blood that was invariably fatal in three days, and this form was so severe and so contagious that it was contracted merely by being in the presence of the infected. However, history does not ascribe any reason acceptable to-day for the origin of this remarkable epidemic.

Coming to modern times, we know that bubonic plague still prevails in many parts of the world, especially in tropical countries, at times in epidemic form, as in India, and still gives rise to a very high morbidity and mortality. We know now that this disease is primarily an infection of rodents and that the microorganism causing it (*Bacillus pestis*) is transmitted from rat to man through the agency of the rat flea, *Xenopsylla cheopis;* the infection usually occurring by the entry through the skin of the plague bacilli, either regurgitated from the esophagus or discharged from the intestine of the flea into the wound made by the insect in biting to secure nourishment, or by scratching.

After the great outbreak of pneumonic plague in the fourteenth century, the disease disappeared in epidemic form and no extensive epidemic of it again occurred until six centuries later, in 1910 and 1911. Then, as history at times seems strangely to repeat itself, it broke out suddenly and apparently with most of its old fury or virulence in Manchuria and North China, and these countries were ravaged for three months in midwinter by an epidemic which in modern times has known no parallel either in magnitude or in the character and severity of the infection. Some of the episodes in this epidemic recall the horrors of the Black Death in the Middle Ages, for large numbers of the people of the Manchurian towns fled for their lives from the infected regions and their homes, leaving the sick to die unattended. Shops and factories were abandoned, trade and commerce came to a full stop. Dead bodies lay unburied in the houses, streets and fields, in some cases being partially devoured by dogs or by wolves and vultures. When help arrived the ground was frozen so hard to some depth that burial of the dead bodies in the ground was often impracticable, since temperatures of from 20 to 30

[2] These facts were emphasized by the writer in the Lowell Lectures upon "The Plagues of Man," delivered in Boston, 1916.

degrees below zero frequently prevailed. Finally, when the number of corpses became very large, wholesale cremation was resorted to, in spite of the protestations of the Chinese who hold the dead body sacred. Every person afflicted with the disease died of it. Nevertheless, in spite of many difficulties, this outbreak was carefully studied in this new environment, its nature and origin ascertained, and what is more important, the methods to prevent it were developed.[3]

Thus it was shown that while the germ of primary pneumonic plague is essentially the same as the organism of bubonic plague (with the exception of exhibiting a uniformly great virulence throughout the epidemic), the portal of entry of the microorganism is different from that in bubonic plague; and that in an epidemic of primary pneumonic plague, rats and fleas play no part in the transmission of the disease, the infection occurring directly from man to man by the droplet method of infection in a somewhat similar manner as in influenza. Overcrowding of the inhabitants in midwinter in small huts (sometimes thirty to forty people in one room) with very little ventilation was an important factor in the spread of the disease in Manchuria.

In the prevention of bubonic plague, for the reasons I have already given, the public health campaign must center upon the location of cases of the disease and the destruction of rats and fleas in infected areas; but in the prevention of epidemic pneumonic plague the public health campaign must center upon the early detection and isolation of cases and of contacts, evacuation of infected areas and masking. Individual masking in this disease is perhaps more effective than in protection against influenza, on account of the great difference in size of the etiological factors involved. In influenza, the virus, being ultra-microscopic, would probably not be interrupted to the same extent by the mask as the plague bacillus.

In the spread of respiratory diseases, the recent investigations of Wells and Stone (1934)[4] upon airborne infections are of interest, in which they point out the importance of dried infected droplet nuclei derived from droplets less than one tenth of a millimeter in diameter.

The influence of the environmental temperature is also of importance in the spread of respiratory diseases. Teague,[5] in connection with our Manchurian studies, especially emphasized that atmospheric temperature is an important factor in determining the spread, or failure to spread, of pneumonic plague. With Barber it was also pointed out that fine droplets containing plague bacilli remained longer in an atmosphere with a very small water deficit, such an atmosphere under ordinary circumstances being of common occurrence in very cold climates, as Manchuria in winter, whereas it is extremely rare in warm ones.

The writer found in Manchuria that the plague bacillus will remain not only viable but fully virulent after weeks in frozen sputum or in frozen corpses. When such sputum becomes frozen and pulverized it may be blown about and remain infective for considerably longer periods of time than when in the form of moist droplets. Isolated or small groups of cases of pneumonic plague (more commonly of pneumonic plague secondary to bubonic) have since the Manchurian epidemic occurred in various parts of the world, generally in tropical but sometimes in temperate climates. However, under the environmental conditions where these outbreaks occurred, the disease has not assumed epidemic proportions. One of the most important of these occurred in California in the winter of 1924. The first case in the outbreak was of bubonic character. Subsequently, thirty-two cases of pneumonic plague developed rapidly from contact, all terminating fatally. The immediate sanitary measures undertaken by the efficient health authorities prevented the further spread of the disease. The conditions in winter in Manchuria which can not be described in detail here still greatly favor outbreaks of primary pneumonic plague. Since the great epidemic there in 1910–11 the Chinese have had an efficient plague prevention service there under the direction of Dr. Wu Tien Teh. Last week Dr. Wu wrote me this work had been taken over by the Japanese.

We have spoken previously of the importance of environment upon the infecting microorganisms within the host. Such effect upon *B. pestis* is well shown in these two forms of plague—bubonic and pneumonic. In bubonic plague the organism entering through the skin at first becomes localized especially in the lymphatic glands, and these frequently may be said to act as filters against the general invasion of the host by the plague bacillus; often until an immunity is gradually produced in the host. However, in primary pneumonic plague there is no such mechanism for the defense of the host. The bacilli which have entered through the respiratory tract invade the circulation in every instance in a comparatively short time, and apparently before the host has had time to produce any appreciable quantity of immune substances. The plague organism also finds in the pulmonary tissues a much more favorable medium for its multiplication and its diffusion than it does in the lymphatic glands. Confirmatory evidence of these facts is seen in the

[3] Strong and Teague, Report of the International Plague Conference, held at Mukden in April, 1911. Manila, 1912.

[4] W. F. Wells and W. R. Stone, *Amer. Jour. Hygiene*, xx: 611 and 619, 1934.

[5] O. Teague, *Philippine Jour. Sci.*, Sect. B, viii: 241, 1913.

fact that the mortality in different bubonic plague epidemics varies from 30 per cent. to about 75 per cent., but the mortality in the Mukden epidemic of primary pneumonic plague was 100 per cent. From a consideration of these facts the importance of ecological influences in the production of these two types of disease, pneumonic and bubonic plague, must be apparent.

A second striking example of the importance of environment with reference to infectious disease occurred during the world war. In the Middle Ages epidemics of an affection known as sweating sickness, Piccardy sweat or as miliary fever were also common in northern Europe, especially in Flanders. Two forms of the disease were described—one very virulent, in which death usually occurred; the other much milder in type. In the first form were probably included many cases of typhus fever, influenza and probably meningitis. The severe form of sweating sickness had apparently disappeared entirely from Europe by the latter part of the nineteenth century, but the reasons for its disappearance are not evident.

During the world war a perhaps somewhat analogous disease to miliary fever was again encountered, particularly on the western front to which the term trench fever or Volhynia fever was applied, and in which severe sweating was often a striking symptom, as was pointed out by Swift and others. Trench fever caused a greater morbidity in the British army during the war than any other disease.

The question naturally arose as to why this sudden and extensive outbreak of trench fever occurred. It should be recalled that many of the troops in the trenches, dugouts and billets were crowded at times and they lived under conditions which simulated in some respects those in the Middle Ages. They were often exposed to rats, their clothing was not frequently changed and washed, they did not bathe frequently and they became very lousy. We were able to prove by 103 experiments made in a tent hospital in Flanders upon human beings—volunteers from our army—that the organism causing this disease is present in the blood serum of infected individuals and that the disease is transmitted from man to man by the body louse *Pediculus humanus.*[6] A British commission (Sir David Bruce, Byam and Bacot), working upon cases of trench fever imported into England, also conclusively demonstrated this fact. Hence it seems evident that it was especially because of the unhygienic environment of the troops, overcrowding and filth, that this disease recurred and prevailed to such an extent on the western front, for since the war, it has almost disappeared. Only an occasional case has subsequently been reported among the poor in parts of Russia.[7] Perhaps this virus is still kept alive in rats and pediculi.

In the great European epidemics of typhus fever, and especially in the epidemic of typhus in Serbia in 1915, the most virulent in modern times with the possible exception of the recent Russian one that exceeded it in magnitude, we have had important epidemiological evidence of the fact that the disease is transmitted from man to man by the body louse, *Pediculus humanus,* as was first demonstrated by Nicolle in 1910, and the favorable effect of delousing in the prevention and eradication of the disease in Serbia was especially demonstrated.

Under a different environment in this country and in Mexico, and more recently elsewhere in Europe, in South America and in the Far East, much milder forms of typhus are encountered. The form which occurs in this country is known especially as Brill's disease or as mild sporadic typhus. The investigations of Zinsser, Castaneda, Mooser (1931), of Rumreich and of Dyer (1931) and of Maxcy (1928) give evidence to the effect that the rat may serve as the reservoir for this type of virus and that man may acquire infection not only directly from man to man through the louse, but from the rat flea, especially *Xenopsylla cheopis.* Here again the influence of environment upon these two forms of typhus virus is emphasized.

Obviously we refer here not only to the influence of geographical environment alone, but also to that environment furnished by different intermediate hosts in different regions, by the immunity of the human host, modified by racial qualities, by habits and customs of the people which bring the individual into contact with the source of the infection. Thus in different parts of the world we find evidence of changes in the insect-animal cycle of transmission of these typhus viruses, for example in the Far East in Tsutsugamushi disease by mites to field mice or rats, or in Montana in Rocky Mountain spotted fever by ticks (Wolbach, 1919).[8] Zinsser (1935)[9] has recently discussed the subject from many different standpoints, which include the subjects of latent infection and immunity, but he has pointed out that there is still an element of speculation in the explanation and that opinions are not entirely unanimous.

Onchocerciasis is another disease the occurrence and character of which are especially influenced by environment. It is characterized by the presence of subcutaneous fibroid nodules or tumors, varying in size from 2 to 3 millimeters up to 5 or 6 centimeters

[6] "Report on Trench Fever." American Commission, 1918.

[7] P. I. Braslawsky, *Munch. Med. Wochenschr.*, lxxxi, 172, 1934.

[8] S. B. Wolbach, *Jour. Med. Research,* 1919, 1, xli.

[9] H. Zinsser, "Rats, Lice, and History," Boston, 1935.

in diameter. The location of these nodules or tumors and their number vary greatly in different individuals and in different parts of the world. Thus in Guatemala and southern Mexico they are found in the great majority of cases in the region of the head, especially about the scalp, comparatively few upon the trunk. In number they usually vary from 1 or 2 up to 5 or 6, though rarely even more nodules may be present. But in parts of Africa, as in Sierra Leone, Liberia and some districts in the Belgian Congo, the tumors are usually found upon the trunk, especially in the intercostal spaces or in the region of joints, rarely on the head. Usually only 1 or 2, but sometimes more, have been observed.

On the other hand, in the Province of Lusambo, Central Africa, one may find nodules very commonly present on the scalp, over the shoulders and trunk. In a great many individuals in this region there are numerous small nodules scattered over the head, shoulders and trunk, varying in number from several up to 150 or sometimes even more.

These nodules are of parasitic origin. The adult parasites, both males and females, of the species *Onchocerca volvulus* or *caecutiens,* are found in the central portion of the nodules in which there are often cavities or softened areas. Immediately about the adult parasites there are usually more or less evidences of an inflammatory process. The outer portions of the nodules are composed largely of fibrous connective tissue in which the fibroblasts are few in number, and the fibroglia fibrils not abundant. In many instances the greater part of the tumor is composed of collagen fibers forming wavy bundles. The adult male and female parasite mate in the tumor and the female gives birth probably daily to an enormous number of microfilariae, which may measure from 150 μ (at the time of their birth) up to 350 μ in length. These circulate, not in the blood, but in the lymph spaces, and apparently show a tendency to seek the light. They are found usually in the upper portion of the corium of the skin and the tissues of the eye, particularly in the conjunctiva, iris and cornea. The adult parasites are evidently the inciting factor of the nodules which are formed about them. The enormous number of microfilariae circulating in the skin and tissues of the eye give rise to inflammatory changes in many individuals that possess an especial susceptibility to the products of metabolism and to the presence and movements of the parasites. Thus in the skin, isolated or confluent, pruriginous areas may occur, and the inflammatory process be further increased by scratching. In such areas sections of the skin usually show numerous microfilariae in the corium, with perivascular proliferation and infiltration of the corium, with lymphocytes, polymorphonuclear leukocytes or plasma cells. The eosinophils of the blood are usually increased, counts of from 25 to 50 per cent. being usual.

In cases of long standing in which there is severe infection with microfilariae, a xerodermatous condition of the skin may be produced. Sections of such skin, in addition to the large numbers of the parasites, show more or less extensive cellular infiltration in the corium. In some areas the sebaceous and sweat glands are few or absent, and changes in the thickness of the horny layer in the skin may occur.

In the eyes the lesions particularly consist of a pericorneal conjunctivitis, iritis and keratitis, which not infrequently lead to loss of sight.

Histologically one finds in such eyes extensive infiltration of the tissues with microfilariae, accompanied by perivascular proliferation, and infiltration with endothelial cells. Small groups of lymphocytes, polymorphonuclear leukocytes and plasma cells are frequently seen. In more advanced cases vascularization of the cornea may occur, and a proliferation of fibroblasts. Infiltration and destruction of Bowman's membrane and even of Descemet's membrane sometimes occurs. Apparently it is the continual presence and passage of large numbers of microfilariae through the tissues of the eye and especially through the compact cornea that give rise to the inflammatory processes. It also appears probable that the microfilariae, through their metabolism or death and destruction in the tissues of the eye, may exert a pathological effect. The circulatory disturbances in these tissues may also predispose to secondary bacterial infections.

The disease is transmitted by the bites of several species of small black flies of the genus *Simulium,* and this fly is found breeding in the rather swiftly flowing streams or brooks that abound in the infected districts, the larvae and pupae of the flies being attached particularly to the leaves and stems of plants, especially floating grasses growing or immersed in the running water, as well as to the surfaces of stones.

It is especially through ecological studies that our knowledge of this disease and its control has been advanced. Thus it has been shown that the prevalence and spread of the infection are especially dependent upon the geographical, climatic and botanical conditions which are favorable for the breeding and life of the fly which transmits the infection.

The agricultural pursuits of the inhabitants evidently are also of importance in connection with the dissemination of the infection. In Guatemala and southern Mexico, the disease is only found upon the Pacific or southern slopes of the volcanic ranges, at altitudes between about 2,000 to 4,500 feet. It does not occur at lower altitudes in Guatemala, and it is especially connected with the coffee production, the best coffee being produced in these regions and at these

altitudes. It is in connection with the production of coffee that the inhabitants are especially brought into contact with the fly that transmits the disease. In Guatemala, in the different coffee plantations in which we worked, we found from 40 to 66 per cent. of the inhabitants infected.

Onchocerciasis does not exist endemically in Guatemala and Mexico at altitudes below 2,000 feet, because the species of *Simulium* fly which transmit the disease there, *S. avidum* (syn. *metallicum*), *S. ochraceum* and *S. mooseri,* do not breed below that altitude. Nevertheless, in certain coffee-producing districts in which the altitude and climatic conditions correspond to those of districts in which the disease is endemic, and in which these three species of *Simulium* abound, and the inhabitants are similar, onchocerciasis is not found. This emphasizes the fact that human beings infected with the disease constitute the most important focus of infection.

In the Province of Lusambo, in Africa, where onchocerciasis is prevalent to an even greater extent than in Guatemala, there is no coffee production. Here the production of cotton is one factor which predisposes to infection, and it is the agricultural pursuit which especially brings the inhabitants into contact with *Simulium* flies. Prior to 1910 there was no cotton exported from the Belgian Congo, but since 1915 the amount has steadily increased, and in 1930 over 10,000 tons were exported.

In Africa, *Simulium damnosum* is the species of black fly which is particularly concerned in transmission of the disease. This fly is frequently found breeding at altitudes below 1,000 feet. Corresponding to this distribution of the fly, we find that onchocerciasis prevails very extensively at altitudes below 1,500 feet, as in Liberia, Sierra Leone and parts of the Belgian Congo, especially Lusambo and Katanga.

While the infected *Simulium* is the only means of the transmission of onchocerciasis from man to man in the endemic regions, owing to the habits of these flies they probably do not play an important rôle in spreading the infection to distant localities. The infected individual constitutes a more important means of transmission of the disease to distant localities than does the *Simulium.* From ecological studies carried out in different countries, we are able to explain in part the great variation in the number of nodules or tumors in different districts, as, for example, in Guatemala and Lusambo, or even in the same locality, on the basis of the different number of times that the individual has been bitten with infected flies. In Guatemala, where the number of nodules per infected person is not usually over 1 to 3 or 4, we never found in any district in which we worked more than 5 per cent. of the *Simulium* flies caught in the villages infected with the parasite, but in Lusambo, Bequaert, Sandground and the writer found as high as 33 1/3 per cent. of such flies infected. Cases in Lusambo with 20 to 50 *Onchocerca* nodules were not uncommon. Such individuals had been bitten probably by at least that number of infected flies, probably by more. However, in some instances it seems extremely likely that a single fly may at one biting introduce several infective forms of the parasite. In some villages in Lusambo practically every inhabitant was found to be infected.

On the other hand, we are not yet able to give a satisfactory explanation of the location of the tumor upon different parts of the body. It has been suggested that the point at which the fly bites may be an important factor in determining the location of the tumor. We have been unable to find any convincing evidence of this fact. In Guatemala where the nodules occur so commonly upon the head, the flies were found very frequently biting upon the legs. This fact would not satisfactorily explain the absence of tumors on the lower extremities or trunk except in 2 per cent. of the cases, and the location of the tumor upon the head in 98 per cent. of the cases if the point of the fly bite determined the location of the tumor. We have no evidence demonstrating that the tumor forms in the vicinity of the point where the fly bites. Most of the tumors in Guatemala are upon the scalp, which is generally covered with coarse bushy hair, and most of the natives also wear hats during the daytime. Nothing is known of how far or how long a period of time the infective form of the parasite travels before it becomes surrounded by the cellular inflammatory exudate and embedded in the fibrous connective tissue, which is the first step in the production of the nodule. From the fact that the tumors often form on parts of the body where pressure for various reasons is likely to occur, it seems possible that the frequency of the nodules on the head in Guatemala may be influenced by the lymph vessels of the subcutaneous tissues of the head becoming constricted in some way by hats or head bands worn in the daytime, or by the head resting upon a hard pillow or some wooden object at night. It seems clear that in those individuals in which the tumors are located upon the head or shoulders, there are more likely to be disturbances in the eyes, and that in cases in which the tumor is located at considerable distances from the head, ocular lesions are usually not present. In this connection it has been conclusively demonstrated that the microfilariae are found in greatest number in the skin in the vicinity of the tumors, and that at considerable distances from the tumors very few or no microfilariae may be encountered. In Guatemala we found the microfilariae in the skin most abundant in that of the face; usually very

few or none in that over the ankles or feet. Whether or not the microfilariae are positively phototropic, it seems obvious that the tissues of the eye are localities in which they are especially encountered, and the microfilariae are much more numerous generally in the ocular conjunctivae in cases with nodules about the shoulders and head than in cases with nodules elsewhere on the body.

In connection with the study of the origin of the disease, in Africa, during our recent expedition, investigations were made by the writer (assisted by Sandground and Bennett) to see if another mammalian host besides man could be found for the parasite *Onchocerca volvulus*. With this object in view, an examination was made of every animal shot. Though game was not plentiful in the region where the studies were made, investigations upon small mammals and of various species of antelope (reedbuck, roan, harnessed antelope, sable and eland), of wart hog, buffalo and hippopotamus were carried out. A species of *Onchocerca* was found in *Bubalis cafer*, and a single specimen in one sable antelope, but this parasite does not give rise to nodules in the buffalo or in this antelope, being found especially in the ligamentum nuchae, and resembling both in this respect and in many of its morphological characteristics *Onchocerca reticulata* or *O. gutturosa*, which have been found especially in the horse and in cattle. However, in eland, in studies carried out by LaRue and the writer, subcutaneous nodules were found in which a species of *Onchocerca* was present, apparently identical morphologically with *O. volvulus*. Sections of these tumors reveal cross-sections of the adult parasites and a similar histological structure to that observed in other nodules caused by *Onchocerca volvulus*.

In northern Rhodesia the cattle show a high rate of onchocercal infection. Here two forms are observed, and these have been studied especially by LaRue and subsequently by the writer. In one, the cervical and shoulder ligaments are specially involved by the parasite; in the other form, subcutaneous nodules are present or nodules in the musculature.

Onchocerca nodules have also been found in the intercostal regions of cattle on the Gold Coast, and Cameron has found that the parasite in these nodules does not differ morphologically from *O. volvulus*.

It seems evident, then, that in onchocerciasis, as is the case in sleeping sickness, a species of antelope may sometimes act as a reservoir for the parasite, and that, especially in regions where eland has been domesticated, cattle might acquire infection from these infected antelope. It seems possible also that human infection may even originally have occurred from wild animals, and subsequently from cattle. In a pygmy village where *Simulium* was highly infected, the inhabitants were badly infected with onchocerciasis. Pygmies, as is well known, spend a large part of their lives in hunting wild game; they do not till the soil or have any agricultural pursuits. From evidence obtained by LaRue and the writer in northern Rhodesia, the infection in cattle seems to be in favor of transmission by *Culicoides* rather than by *Simulium*, as Steward has shown to be the case in *Onchocerca cervicalis* of the horse in England.

It may be that in onchocerciasis we have an example of an invasion of man by a parasite which before had been well established within the animal kingdom and that infection of man may have originally occurred through new contacts with infected animals and insects to which man was not previously or extensively exposed. Whether the origin of the disease in man in Guatemala may also be explained in this manner is not yet clear. Obviously the strains of *Onchocerca* which have now, both in Africa and in Guatemala, become thoroughly established in man are transmitted by *Simulium* entirely independent of other mammals.

Sleeping sickness of the form caused by *Trypanosoma gambiense* or *rhodesiense* probably represents another disease of this nature and one that is limited endemically to the territory in which the important insect host, the tsetse fly, exists (especially *Glossina palpalis* and *G. morsitans*). However, while onchocerciasis and *Simulium* may be present at altitudes over 3,000 feet, *Glossina* is seldom seen above 3,000 feet, and sleeping sickness does not originate in higher altitudes. Also, brush-clearing, especially along streams and rivers, is sometimes the only certain method of freeing an area from some species of the tsetse fly and of thus limiting the spread of the trypanosomiasis. However, while brush-clearing is very effective with reference to *G. palpalis* and *G. tachnoides*, it is not often effective against *G. morsitans*, as this species will often cross carefully prepared clearings over a mile in width. In such areas it is far more effective to remove the population when possible. Many ecological problems have been solved with reference to sleeping sickness.

The effects of climate upon *Glossina* have recently furnished epidemiological facts of importance. It has been shown that there is a fairly narrow zone of temperature within which the fly can live satisfactorily. Temperatures between 25° to 30° C. are very satisfactory for *G. morsitans*, but above 35° C. it very frequently dies. Buxton and Lewis (1934) found that at temperatures above 40° C. the *G. morsitans* and *G. tachnoides* flies, which may survive for short periods, are more apt to do so in dry air than in moist. However, the effects of humidity, while very important to *Glossina*, are also very complex. With a temperature

of 30° C., a relative humidity of about 44 per cent. appears to be near the optimum at which the flies live longer and breed more rapidly than in drier or in moister air. A relative humidity of 65 per cent. was unfavorable, and in moister air the flies nearly always refused to feed and were found to die off very rapidly. The reason why high humidities were unfavorable is still obscure. Flies were found to metabolize fat most rapidly in dry air, and presumably to produce metabolic water to compensate for excessive evaporation. In general it has been found that when the humidity is high, the *Glossina* are scarce and that the flies do not breed so well in such an atmosphere. Johnson and Lloyd found that in the rainy season (May to October) only 20 to 40 per cent. of female *Glossina tachnoides* were pregnant, but in the dry season (November to April) 60 to 80 per cent. were pregnant.

Jackson (1934) found that during the dry season in Tanganyika, *Glossina morsitans* increases in numbers in the drainage valleys as distinct from the bordering woodland. Observations by him and by Burtt support the contention that the increase of the fly in the drainage valleys in the hot dry months is due not to a search for better shade conditions, but to the fact that these areas constitute a feeding ground and that the fly must visit them more frequently at this season when the onset of hunger is hastened by hot dry conditions.

In certain areas where large numbers of cases of sleeping sickness are congregated, even where *Glossina* does not abound, infections may sometimes occur if other blood-sucking Diptera, as for example *Stomoxys,* are present. It is now well known that the trypanosomiasis of horses in the Philippines and elsewhere in the Far East caused by *Trypanosoma evansi* is usually transmitted by *Stomoxys* mechanically. Duke, during the past year, has moreover shown that *Trypanosoma rhodesiense* was readily transferred from an infected to a healthy monkey by the process of interrupted feeding of from 7 to 10 wild *Stomoxys,* and that infection from antelope to antelope might also occur by *Stomoxys.* However, transmission of trypanosomiasis by *Stomoxys* in man is probably relatively rare, as sleeping sickness has shown no tendency to spread extensively in areas where *Glossina* does not abound.

Many other ecological problems are involved with reference to sleeping sickness. Both the insect and mammalian environment exert influences upon the trypanosome which emphasize that pathological manifestations are only incidents in a developing parasitism. Thus in the blood stream of the mammalian host, the trypanosome may at least for a long period give rise to only slight or no pathological manifestations, but when it invades the central nervous system, serious disturbances are usually produced. It is now generally recognized that, although *T. rhodesiense* when first isolated from cases of sleeping sickness in man exhibits considerable resistance to the action of normal human serum, this resistance is sometimes largely lost after a series of mechanical transmissions through experimental animals. However, little work has yet been done on the influence of cyclical transmission of this quality. Adams found that cyclical transmission of *G. palpalis* caused diminished resistance to the action of the serum, whereas Lester observed that experimentally produced serum-fastness in *T. brucei* was transmitted by *G. tachnoides.*

The relationship of *T. gambiense* (or *T. rhodesiense*) to *T. brucei* is regarded by some investigators as still somewhat obscure. As is well known, the latter trypanosome is considered to be capable of not only causing the disease nagana in cattle, but also as sometimes living as a commensal in some domesticated animals or wild game. Experimental inoculations of man with the blood of horses and mules containing *T. brucei* have frequently resulted negatively, as Taute and Huber in 131 human experiments have shown.

Duke has recently examined the power of *Trypanosoma rhodesiense, T. gambiense* and *T. brucei* respectively to develop in *Glossina,* and has found that *T. rhodesiense* is as a general rule more readily transmitted by *Glossina palpalis* than is *Trypanosoma gambiense,* and this notwithstanding the fact that *Glossina palpalis* is not considered to be the normal vector of *T. rhodesiense.* Whether these characteristics will survive repeated cyclical passage through *Glossina palpalis* is, however, a matter which will require further investigation. Duke suggests that *T. rhodesiense* may in reality be *T. brucei,* which has overcome man's resistance. However, there is an alternative explanation, namely, that *T. rhodesiense* is *T. gambiense,* which has enjoyed a longer or shorter association with *Glossina morsitans* instead of *G. palpalis.*

Extraordinarily slight changes such as these in the mutual adjustment between parasite and host may profoundly alter clinical and epidemiological manifestations.

Other changes of this nature may be seen in the study of the power of transmissibility by *Glossina.* It has been found that *Glossina* may be incapable of transmitting some of these strains of trypanosomes, and the strains may even have become incapable of infecting the fly. Some strains of *T. brucei* have shown somewhat greater stability in the power to infect than *T. gambiense.* Such behavior may suggest an expression of a more perfect adjustment of environment than is possessed by *T. gambiense,* the latter trypanosome, which is essentially dependent on man, having not yet attained biological equilibrium in

this its principal mammalian host. Duke (1935) however, believes that it is established beyond all reasonable dispute that *T. rhodesiense* may lose power of infecting man as a result of living for a long time in the blood of antelopes. In the course of maintenance for a year or more away from man by cyclical passage from monkey to monkey, some strains of *T. rhodesiense* retain the power of infection of man, but others lose it.

On the other hand, Corson (1935) has found that a strain of *T. rhodesiense* can be maintained in sheep and goats for nearly two years without loss of its transmissibility by *Glossina morsitans* or its power to infect man. However, in other experiments he was unable to transmit *Trypanosome rhodesiense* from man to laboratory animals by the bites of *Glossina,* and had to resort to direct inoculation of the blood to succeed in infecting them. He has also shown that this strain of trypanosome could be passed from man by inoculation of the blood to a guinea pig, and then from this animal by four successive flies, through three antelope, and finally by another fly back to man. Thus with this strain of the trypanosome no change in the infective power for man of the trypanosome had occurred during the cyclical passages through guinea pig, antelope and fly. Such discrepancies suggested by these different experiments of Duke, Corson and others are not impossible to explain rationally. The writer has pointed out elsewhere (1930) that extensive investigation has shown that *T. rhodesiense* is indistinguishable morphologically from *T. brucei,* but that *T. rhodesiense* usually exhibits greater pathogenicity for man. However, different strains of *T. rhodesiense* may in some instances lose this power to infect man by passage through animals more or less susceptible, but in other instances retain it. Human beings differ in their resistance to strains of trypanosomes, as do other animals. Man is probably, by the natural mode of infection, immune to the trypanosomes of animals. It is perhaps only in those instances in which an individual especially susceptible becomes infected through a large number of virulent trypanosomes that the trypanosome becomes adapted to life in human blood, and then may more frequently infect other human beings. While it is probable that some virulent human strains of trypanosomes are capable of infecting the majority of human beings, animal strains, feebly pathogenic for man, will probably only infect at first abnormally susceptible individuals, though later, when such strains have become thoroughly established as parasites in man, epidemics of sleeping sickness may be caused by them. The differences in power of infecting of *Glossina* and of man and other animals of *T. gambiense, T. rhodesiense* and *T. brucei* may all be explained as changes which one species of trypanosome may undergo under different environment.

Quite another problem is suggested by the fact that sleeping sickness in certain parts of Africa has undergone rapid retrogression, sometimes spontaneously, without the cause of this being apparent. In some areas, where tsetse flies abound and game are fairly plentiful, there are no evidences of human infection. In other areas the infection has persisted and spread in spite of the introduction of treatment and of other preventive measures. It is difficult to understand why in some areas trypanosomiasis readily yields to treatment, while in others it is resistant to the same treatment. Differences of race, of habitat, of absence of *Glossina* and of virulence of the trypanosome probably exert some influence in these respects, but these factors do not entirely explain such results. Whether the failure to successfully treat many chronic cases of sleeping sickness is due to the development of arsenic-fast strains of trypanosomes which are now being propagated by *Glossina* in such areas, as suggested by Yorke, has not yet been demonstrated.

The relationship of wild game, especially of antelope, to human trypanosomiasis is still a controversial problem. Duke's recent experiments suggest that although some antelopes may be favorable hosts for *T. rhodesiense,* yet, as a reservoir from which tsetse flies can become infected with trypanosomes pathogenic for man, these animals do not constitute so great a menace as was hitherto supposed. Thus of six human beings (volunteers) exposed to twelve flies infected from antelopes (reedbuck) with *T. rhodesiense* that had been maintained in these animals for many months, only one volunteer became infected. A strain of *T. rhodesiense* after a survival of cyclical passage through a reedbuck and six monkeys was found to be non-pathogenic for man, although it was tested in nine different volunteers. Duke suggests that this strain owes its original association with man to meeting an abnormally susceptible individual. There was nothing to distinguish it from *T. brucei* except its isolation from man.

Corson has recently inoculated eight adult antelope, dik-dik and one duiker experimentally with *Trypanosoma rhodesiense.* In all these animals just before death, or just after death, trypanosomes were found in the cerebrospinal fluid. He remarks that it is hard to understand how these antelope can survive in sleeping sickness areas, where of course they are often present, unless exposure to tsetse fly bites and habituation to mild strains of *T. brucei* infection give them an acquired and selective resistance.

Epidemics of sleeping sickness in man have occurred in which game animals played no part in the spread of the disease, the trypanosome being carried

directly from man to man by the bite of the fly, frequently mechanically.

In connection with the wholesale destruction of game in parts of Africa, it should always be considered that if the game is so reduced that the tsetse flies of the *Glossina morsitans* group are driven to attack man for food, a much wider dissemination of these flies is likely to occur, and hence further spread of human trypanosomiasis may result. Several human outbreaks attributed to this influence have recently been recorded. In parts of Tanganyika a much wider dissemination of *Glossina* has recently occurred, and since the institution of the Masai Reserve in Kenya Colony the fly belts within its confines have extended their boundaries and increased in number. In the case of *Glossina swynnertoni* (a vector of human as well as of animal trypanosomiasis) Lewis (1934) has obtained evidence which shows that there has been an actual invasion of it from Tanganyika Territory. Swynnerton has shown that *G. swynnertoni,* in the presence of cattle but where game is scarce, attacks man readily. More recently Lewis has found that in the presence of an abundance of game and in the presence of cattle, this fly very readily approached man and was also attracted to moving vehicles. In view of all the facts the special merits of vegetational control of the disease become emphasized in which not only elimination of the favorable breeding places of the fly is attempted, but the character of the vegetation so altered that the fly no longer inhabits such regions.

The epidemic of malaria with its high mortality which has recently been raging in Ceylon, India, is a striking example of the effect that climatic conditions and environment may exert upon a disease. This epidemic has occurred in what has been hitherto regarded as the most healthy and prosperous portion of the island, the southwestern part, in which there has usually been a high annual rainfall and where there has been evidence that the percentage of the population infected with malarial parasites has been but small, and hence the population relatively non-immune to the disease. This year the prevailing rains which are brought so regularly by the southwest monsoon failed to supply the usual amount of water, resulting in a prolonged drought. Then came a few heavy rains, and then drought again. Thus conditions arose greatly favoring the breeding of the mosquito *Anopheles culicifacies,* which transmits the disease in this region, as many shallow pools were formed along the river beds and streams. Through these innumerable temporary breeding places, more perfect conditions for the production of mosquitoes could probably not have been devised.

The outbreak of malaria was followed by failure of the crops, also due particularly to the lack of rain. Thus the people became further impoverished and the general state of their health reduced, and within five months there were 113,811 deaths, of which 66,704 were estimated to be due to malaria.

Malaria only prevails in an unsanitary environment. During the year 1934 Dr. McKinley in a statistical survey found that over 54,000 cases of this disease had been recognized and reported in a few of our southern states, or 15,000 more cases of malaria in these regions than of tuberculosis. Other statistics show that the malaria mortality is over 20 in 13.5 of the counties, and over 50 in 3.03 of the counties in the southern United States. Malaria has been banished in this country from many localities where it formerly prevailed. It is a disease that we know can be eradicated by sanitary measures. In view of the enormous sums of money that have recently been appropriated by our Federal Government for conservation and reclamation, would it not be most appropriate and indeed a wise investment if at least a small fraction of this sum were devoted to the eradication of this dreadful disease from which so many of our citizens have already died and others still suffer and are thereby incapacitated for work?

Although in support of our subject many additional examples, particularly with reference to other infectious and parasitic diseases, might be discussed, the few which have been referred to in this lecture would appear to be ample for the purpose of emphasizing the importance of ecology in the study of disease—the importance of environment upon the vertebrate and invertebrate host and the infecting organism.

OBITUARY

CHARLES ELWOOD MENDENHALL

AMERICAN science lost one of its ablest devotees and American scientists one of their most beloved leaders as Professor Charles Elwood Mendenhall passed away on August 18, after an illness of less than a year. News of his death came as a shock to his friends who, outside the intimate circle at the University of Wisconsin, had not realized the serious character of his illness. At the age of sixty-three, he was at the peak of his effectiveness as an inspiring teacher, able investigator and wise counselor.

Charles Mendenhall was the second generation of distinguished physicists. His father, T. C. Mendenhall, a Quaker, was the first professor appointed at