

SCIENCE

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PARASITISM AS A FACTOR IN DISEASE¹

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THE study of etiology or causation is a study of the entire field of medicine from a certain point of view. Every phenomenon assumes an etiological aspect whenever we study it not as an effect to be simply contemplated and described, but as a cause or necessary condition of something that is going to happen. Provided with the information that for certain events to take place certain necessary conditions must precede, we can take steps by controlling the necessary conditions to allow the event to occur or not. Modern medicine has made the concept of causation its own. On it is founded all rational progress in prophylaxis and therapy. First to comprehend the cause, then to intercept and suppress it and thereby to prevent the next step is the kernel of medical science and practise. We project ourselves into the immediate future. The present is only the boundary between what has occurred and what is to happen. To control events we must know how to distinguish those conditions which are necessary from those which are merely associated and coincident.

The history of medical science, notably during the past half century, has clearly shown that observation of disease as it occurs in everyday life must be associated with the experiment. By observation I mean a survey or study of the phenomenon as a whole; by experiment, the observation of isolated parts of the entire phenomenon, the other parts being meanwhile eliminated or controlled by special devices. Observation and experiment, alternating, cooperating, and reacting on each other, are the only sure guides to a rational interpretation of disease. Nature is continu-

¹ Paper read at the annual meeting of the Association of American Physicians, May 10, 1921, as part of a symposium on etiology or causation of infectious diseases.

ally experimenting and observation is simply taking notes in this great life experiment. Without it the laboratory experiment would lack reality, for it is simply a page torn out of the book of nature with the unknown factors controlled or eliminated. To get at the facts of disease it has been found necessary to bring experiments as close as possible to the natural phenomena without losing control of the details.

The necessary association of observation and experiment in interpreting the conditions determining disease may be illustrated by the familiar one of the noise and the flash of gunfire. At a distance we see the flash and then hear the explosion. We might infer that the flash was a cause of the explosion, since it always precedes it. As we approach the scene of operations the noise follows the flash more and more quickly and close by the two reach our senses almost simultaneously. We then are in doubt whether the flash is a cause or merely an accompanying phenomenon. Our static observation at a distance fails to inform us correctly. The experiment of approaching the firing compels us to revise our original notion of causation and to make a further study of the entire phenomenon. The gist of the etiological problem is thus to determine what are necessary conditions and what merely secondary phenomena. The experimental method has been of immense service in laying bare the dynamic or causal relation, in other words, the true sequence of events. On the other hand, experiment too far removed from the actualities has frequently led astray when its results were too literally accepted and not controlled by observation of the entire phenomenon.

In the environment of man and within the human mechanism itself there are many conditions operative towards disease. This entire group or sequence of conditions, rather than any single factor in the group or sequence, may be regarded as the cause. If any one of these conditions is neutralized or controlled, the disease may not occur or if in progress it may take another course. Naturally these conditions have different values. They may

be judged from their accessibility to control, *i.e.*, from a practical standpoint, or from the point of view of the physicist weighing them according to their energy values. We have hardly reached the stage, however, when the conditions favoring disease can be accurately measured. We must still deal with them as entities. Their qualities must engross our attention and their quantitative relations remain for a future, more exact medical science to weigh and measure.

The forces and conditions controlling disease are a mixture of heredity, environment, and parasitism. How can these factors be taken from their natural relations and studied individually without upsetting the delicate balances of causation? Where can we begin to test experimentally the observations we make about natural occurrences? Obviously some very careful surgical operation is necessary in carving out our field of work. In so doing we must realize that we become piece workers tinkering with only a part of nature's mechanism. Our finished product must be skillfully fitted into the larger mechanism. In attempting to limit our discussion to parasitism as an etiological factor in disease, I realize the difficulties mentioned. We have not only the different categories of environment, heredity and parasitism acting on one another, but within each category we have the animal body reacting with the factors like a chemical process swinging back and forth towards a state of equilibrium. Finally, we have in parasitism two living variable organisms capable of adjusting themselves towards each other in a remarkable degree.

When, about forty years ago, methods were devised by Robert Koch to make a beginning in the accurate study of bacteria as living agents of disease the contemporary scientific world realized that here were, to all appearances, agencies that could be separated from their environment, their life history and activities subjected to rigid investigation, and their relation to disease opened to demonstration. It is not surprising, therefore, that the bacteriologists of somewhat more than a generation ago, started on their way by these

methods, were inclined to regard the discovery of the pathogenic agent of some well-known disease as the beginning of the end of its prevalence. To have isolated, recognized, and cultivated a bacterium and produced some sort of pathological changes in an inoculated animal was considered equivalent to half or more of the battle won over the depredations of such organism. For many years these living agents, but more particularly the unicellular organisms among them, overshadowed all else and they became synonymous with the causes of disease. To-day we know that to have identified the microbic agent of any pathological process is but the beginning of the solution of the immediate problem and that it answers but one of a long series of questions. In spite of this somewhat discouraging fact, a very remarkable series of discoveries in the biology of disease have originated in this study of microorganisms. I need mention only the bringing to light of bacterial toxins, the discovery of their anti-toxins, hypersensitiveness or anaphylaxis, the phenomenon of acquired immunity and the collateral phenomena associated with it, such as the production of agglutinins, precipitins, complement-fixing bodies, and above all the specificity associated with the action of disease agents and the reaction of the host. Every one of these fundamental discoveries has had a far-reaching influence on the immediate development of the medical sciences. Every one in its way has dominated the thoughts and activities of large groups of investigators and there has resulted a very unequal, even chaotic, development of our knowledge of the conditions governing disease processes. Throughout this period dominated in turn by disinfectants, toxins, anti-toxins, agglutinins, opsonins, complement fixation, and hypersensitiveness, there is evident some system, some purpose, and that is to find the exact place of living agents in the phenomenon of disease. From the more or less exaggerated point of view held at the start of their dynamic energy in the process there has been a more accurate, more scientific conception of their place as necessary conditions of disease making headway.

It is now evident that the relation of living agents, from the ultramicroscopic forms up to the higher parasites, is different for every agent or at least for every group of biologically related agents. We know now that the depth and extent of their etiological significance varies from an almost exclusive causation to one of relatively insignificant proportions. For the latter group the environmental and hereditary conditions completely dominate the situation and the particular germ found in one place may be replaced by others in another place. In most disease processes, therefore, the living agents are more or less governed by other factors. This is indicated by the great variation in the intensity of specific infectious diseases, by their seasonal appearance, by the sudden appearance and disappearance of outbreaks, and the difficulty of maintaining an epizootic among animals experimentally. Again, it is indicated by the difficulty of inducing disease with pure cultures in species of animals in which the disease occurs spontaneously and in the decline of virulence in artificial cultures.

Now it may be answered that when we fail to induce disease we do not know how to introduce the agent and where to deposit it. But the how and where are in themselves limitations of the activities of the specific agent. It may also be answered that the microbe with which we try to induce the disease has been attenuated by culture. True, the microbe needs the host to maintain its virulence. This is a significant limitation. Any one who has been confronted with a disease of unknown etiology and has in due time found the living agent knows how little or how much this means when he tries to construct the mechanism of the disease with its aid. In many cases the mystery remains as deep as ever until other necessary conditions have been isolated from the complex of causation.

Perhaps one of the most promising movements to bring into correlation with parasitism the other necessary conditions of disease is the study of epidemiology not from a statistical but from a biological viewpoint. To observe that of a given number of exposed

animals only a certain per cent. contract the disease and only under certain conditions inevitably leads to an inquiry into the causes other than the mere presence of infectious agents.

At this point it might be well to call attention to the necessity for including all invasive living agents however diverse in a study of the factors leading to disease and recovery. In pathology it has been customary to distinguish between parasitic invasion and bacterial infection, the former producing relatively slight disturbances in the host, the latter the acute, often highly fatal epidemic and epizootic diseases. The distinction is useful but it can be made to apply only to extremes. Gradations of all shades occur. For the sake of a more exact terminology, the distinction between invasion and infection might be made to hinge upon the capacity of parasites to multiply in the host. Thus the number of nematodes and related worms in the host is not larger than the number of fertile eggs introduced or of those individuals which actively penetrate as larvæ.² The formidable power of the infectious agents is due to their capacity for indefinite multiplication in the host. Sexual reproductive stages are not known. Certain protozoa such as sporozoa not only pass through sexual stages, but they may also multiply asexually and more or less indefinitely in the host tissues. They may be considered both invasive and infective. It is thus best to class all living invasive organisms as parasites, subject more or less to the same host mechanisms of repression and destruction. At one end of the scale are the highly specialized forms, adapted to one host species or even one race. At the other end are types emerging from the predatory or saprophytic stage and acquiring parasitic habits.

Another concept which we as medical men should have clearly before us is that the phenomena which medical science is chiefly interested in, namely, those of disease, are merely

² We must except from this broad statement the nematodes of the genera *filaria* and *trichinella* since their progeny develops within the same host to the larval stage and stops there.

epiphenomena in an evolving parasitism, by-products which tend to lessen and disappear as the parasitism approaches a biological balance or equilibrium. How rapidly this evolution may progress we have no means of knowing. We do know that among animals epizootics tend towards a lower level of mortality and morbidity. If we are actually studying by-products, it is obvious that to understand them we must first understand the main processes that give rise to the by-products and that disease is studied most successfully by studying the necessary conditions that give rise to it. If the by-products are in themselves necessary antecedents of other pathological conditions, they would of necessity be included in any study of causation.

A sufficient number of living agents of disease and of parasites has now been studied to permit a tentative classification into highly specialized parasites adapted to and dependent on a given host and those that are more or less predatory, awaiting adaptation provided their organization should permit it. The highly adapted microorganism which depends upon one host for its existence, as, for example, the still unknown smallpox organism, has through natural selection established between itself and its host a certain balance or equilibrium. This can be defined as a condition of both host and parasite which permits the latter to enter the body, multiply enough and escape so that the arrival of its progeny in another host is assured. On the basis of this relationship we may define four critical phases in the life cycle of the microbe: first, its entry into the body and through protecting tissues; second, its transportation to and multiplication in certain tissues; third, its escape from those tissues and from the host as a whole; and fourth, its transfer to another host. Each one of these phases is capable of subdivision into a larger or smaller number of sequences according to the special living agent involved. In the insect-borne diseases the insect acts as transfer agent and as introducer into the blood. The fourth and the first stage merge. In general the fourth stage, or stage

of transfer from one host to another, has been greatly modified by civilization. It is therefore necessary in any attempt to formulate the problems of etiology to take into consideration the primitive conditions under which the infectious diseases originally flourished and from which they have come down to us. We do not know whether they originated with man or earlier among his progenitors. But it is safe to take the ground that infectious diseases flourished among the earliest races and that they flourish to-day among savage and semi-civilized peoples as they do among domesticated animals in our midst. That is to say the infectious agents developed in an environment in which transfer from host was direct, immediate, and easily brought about. Furthermore, the infusion of susceptible subjects, except during wars and migrations, was slight. These two conditions tended to counteract one another and to bring to an approximate perfection the parasitic habit of the invading organism.

It is this fourth stage of transfer that engaged the entire attention of the early bacteriologists. They created the era of isolation and disinfection by improving diagnostic methods and studying the modes of exit of infectious agents and their resistance in transit. It was tacitly hoped and expected in this great work that infectious diseases could be easily controlled and suppressed by destroying the agents in the environment of the sick. The science of one generation becomes the practise of the next. Disinfection, isolation and the widening of the danger space between the sick or infected and the well is the chief occupation of modern sanitation. The actual significance of this practise needs to be evaluated from time to time if only in the interests of economy of effort. While it is generally conceded that the movement of the agents of disease should be restrained as much as possible and while heroic efforts are being made to this effect by health officials, economic forces are driving people together and condensing populations and thereby largely neutralizing the efforts of sanitarians. If any value can be put on this work at present, it might be to the

effect that it tends to keep individuals from getting an overdose of infection.

When we come to the first phase in the cycle, the entrance of the virus into the body and its penetration through the skin and mucous membranes, our knowledge is on the whole neither accurate nor abundant. While the fourth stage has been pretty thoroughly exploited, the first is hardly at all known in its details. Each well established infectious agent will have its own story to tell of this phase. In extenuation of the deficiencies of our exact knowledge it should be stated that the problem is a very difficult one. Microorganisms leave the body in armies, having multiplied to supply a progeny ample to cover losses in transit. On entering only single individuals or small groups are involved and unless their morphology is characteristic, like that of the sporozoa and the metazoan parasites, the entry is well beyond the ken of the observer. It can only be got at indirectly. The difficulties of this stage are well illustrated by the prolonged discussions concerning the entry of tubercle bacilli. Much has been done and written in the attempt to clarify this problem. The doctrine of the inhalation of dried bacilli in dust, the droplet infection of fresh sputum, and the theory of the alimentary origin of infection have had their day in court. Similarly the portal of entry of the virus of the eruptive diseases has been the subject of much study and discussion.

The penetration of living agents through the skin and mucous membranes is full of unanswered questions. The resistance of the normal mucous coverings has probably been greatly underestimated. The effect of injuries in removing this barrier has been similarly underestimated. From a practical standpoint this problem may seem academic since the mucous coverings for example may rarely be free from minor lesions and such lesions may remain, at best, undetected. But the object of genuine medical science is to get away from the benumbing influence of such consideration. Do typhoid bacilli, for instance, penetrate the normal mucosa, or are they dependent on slight lesions? Do protozoa assist them

at certain seasons? Do phagocytes ever migrate out under normal conditions and carry bacilli back into the tissues? Might this take place when inflammatory processes are active? Is the entry of certain viruses prepared by other viruses acting only on the epithelium and destroying it or in some other way making the tissues involved more vulnerable? Epithelium-destroying parasites are well known among the sporozoa. It is not improbable that other types of microorganisms, especially those not within the range of the microscope, are specifically adapted as genuine parasites to invade these cells and so prepare the way for the saprophytic, predatory types which are readily recognized because easily cultured and therefore regarded as summing up the entire etiology.

After the living agencies have entered the tissues they must run the gauntlet of the blood, lymph, and the phagocytic cellular elements to reach those tissues where they multiply. Multiplication is essential, for a large progeny is necessary to cover the losses in transit. This stage of multiplication involves the problem of specific resistance or immunity and susceptibility, and also the practical problem of treatment by therapeutic agents, serums, vaccines, and the like. The biological requisite to be fulfilled by the parasite in this second stage, or stage of multiplication and sexual development within the host, if such a stage exists, is that multiplication must take place in such a way that escape in large numbers from the host after the parasites have assumed a more or less resistant form becomes possible. This is best accomplished when they settle down and multiply near some portal of exit, first the skin or subcutis, second the respiratory tract, third the digestive, and fourth the genital tract. A brief consideration of the localization of the different groups of parasitic agents will show that these various superficially located tissues are the chief seats of multiplication. Localization in other tissues or organs is rare and so far as the parasite is concerned abnormal. If it should happen that a race of *Treponema pallidum* arose which promptly and exclusively localized in the cen-

tral nervous system, it would die out for want of an exit to another host. The tendency to locate and multiply in tissues of lower vital dignity, *i.e.*, near the surface of the body or the mucous membranes, safeguards the host as well as the parasite.

Among the parasitic invaders of man and the higher animals the metazoan and protozoan parasites have developed relatively perfect, in some cases complicated cycles. The same is probably true of those highly specialized microorganisms which produce the eruptive diseases and of some of the so-called filterable viruses. In fact, all diseases or parasitic states which maintain themselves indefinitely in a host species and are manifestly transmitted from case to case have complete, even though not necessarily elaborate cycles.

The tubercle bacillus is frequently referred to as a highly adapted parasite, but its parasitism is crude compared with that of the smallpox organism. It has no well-defined cycle except in phthisis, in which it is inhalation and expectoration. If for the sake of illustration we conceive the primary lesion as leading in every case to a secondary military tuberculosis in which there is extensive invasion of the skin with subsequent ulceration, the tubercle bacillus would then be inhaled and after multiplication shed from the skin, in so far as approaching the smallpox organism in its cycle. But there is no indication that such a complete cycle ever will be established. On the other hand, the leprosy bacillus appears to have in a bungling way reached this stage, for the shedding of leprosy bacilli takes place from skin and mucous membranes, notably, of the nasal passages.

In certain cases the cycle is limited to a mucous membrane parasitism and the disease is the result of a diversion of the organism into the tissues of the body. The cycle of the typhoid bacillus may be some locus of the digestive tract with incursions into the blood. Whether the invaders perpetuate themselves, *i.e.*, escape again, depends upon ulceration of the lymphoid tissue of the intestines. The meningococcus resides in the upper respiratory tract. We do not know whether the cocci

which enter the central nervous system escape or not. This is an important question for it is probable that the degree of virulence of the microbe depends upon some contact with the host tissues more intimate than that of a mere saprophytic existence in recesses of the mucous membranes. If such an organism could associate itself with some living or dead factor which assisted its entrance and exit, a definite disease might thereby become established, and we might expect the disease to rise and fall in epidemic style according as the helping factor is active or not. Contact with and multiplication in living tissues, either cellular or humoral, appears furthermore to stabilize the microorganism. If we look over the immunological and serological data which have accumulated about the various groups of parasitic agents we find the relationships established by these reactions much more uniform among strictly invasive than among the secondary organisms which depend upon formidable factors to open the way into the system for them. Or to put it another way, there is a much larger number of serological types among the hangers-on than among those capable of direct invasion.

If the picture I have drawn of the parasitic cycle is fairly accurate, it follows that the localization of disease agents or parasites in all tissues and organs except those from which ready escape to the exterior is possible is abnormal and unnecessary for the continued existence of the parasite. Hence, typical, characteristic, recurring infectious or parasitic diseases affecting the central nervous system, the ductless glands, the liver and kidneys, the muscular system and the joints do not occur excepting as secondary localizations of diseases involving the more external tissues. If such localization should occur regularly without some superficial localization as well, we must look for some source of infection belonging to another species in which the cycle is normal and from which a constant supply of parasites is available even though they fail to escape from the new host. The invasion of the human body by the bovine tubercle bacillus is a familiar case in point. In some

infectious diseases several invasions of the same host may be necessary to bring the parasitic cycle to completion or, viewed from a medical standpoint, to bring the disease to the clinical level. In bovine tuberculosis, which can be studied anatomically and topographically by killing animals in early stages, the first tubercle bacilli to enter the system usually land directly in regional lymph nodes. To complete the cycle the virus must enter the blood and establish secondary foci in lungs or other tissues from which the bacilli may escape to another host. The cycle is, however, more easily explained by reinfection. The inhaled bacilli lodge now in the lung tissue due to a changed reaction of the host tissues at the point of entry and the cycle—inhalation and expectoration, assisted by discharge in the feces through swallowing the sputum—is established.

There are two factors that may modify the normal cycles more or less. One is a relative immunity, which may be either natural or acquired. Through immunity cycles may be cut short chiefly in the stage of multiplication and the parasite fail to escape at all or in sufficient numbers to maintain further existence. If for any reason the normal resistance of the host is reduced, the parasite may multiply unduly or invade more territory and cause death of the host before the cycle is completed. This condition may be explained by regarding parasitism not as a condition of peace but of armed truce. As soon as one of the two organisms falls below a certain level, the other takes the advantage. In case the microorganism gets the advantage, it may be fatal for both host and parasite. This latter condition of reduced natural resistance is supplied by civilization either by bringing into the original disease other parasites and greatly complicating what might have been a simple situation, or else by conditions arising from inherited defects, over-exertion, abnormal diet, exposures to heat, cold, which are supposed to favor the parasite in its entry and multiplication. These conditions furnish the many modifications of disease types which may be as varied as the number of individuals at-

tacked. It is this increasing complexity of affairs which supports from the scientific side the dictum that the physician is to treat the patient rather than the disease for there is no longer a type disease to be recognized regularly.

This brings us back to the original subject of etiology. A careful biological study of the many parasitisms of man and the higher animals brings out the fact that the highly specialized parasites have no obstacles to their activity, except one and that is immunity, either acquired or natural. As a result all host individuals pass through the disease early in life provided opportunity for invasion is given. The highly specialized diseases tend to become, in endemic localities, children's diseases.

In the case of many other diseases certain non-parasitic factors are necessary to start the disease or to check it, as the case may be. They are part of the mechanism of causation and represent necessary conditions. These necessary conditions may far outweigh the living agents in etiological significance. The relative importance of the living factors may be so low that their place may be taken by other living agents or even non-parasitic factors in the sequence leading to or continuing existing disease processes. This is probably true of certain diseases of intestinal origin. Such diseases are frequently described as due to different microbic agents in different localities because the endemic flora happens to be different.

The relation between the factors of parasitism on the one hand and those of heredity, environment and the like on the other may be briefly summarized as follows:

In the saprophytic or predatory type representing the so-called septic infections the other parasitic and non-parasitic factors are of great, even predominating importance in the production of disease.

In the highly parasitic type they are of little, if any, importance unless it be hereditary characters brought out by the selective action of the parasites themselves upon the host species through many generations. Many

gradations exist between these extremes and the relation of parasitic to extra-parasitic factors is different for the different grades.

Moving parallel with the degree of adaptation and specialization and the development of more nearly perfect cycles by the parasites the mortality drops and the morbidity at first spreads and finally tends to decline in certain types of parasitism, provided always that other types of parasitism do not accidentally enter to modify and complicate the normal course.

In tracing the various living agents through the body of the host we find that we do not know the details of any parasitism to our satisfaction. These details, of course, include also the non-parasitic factors or conditions essentially favoring or hindering the parasite in its sojourn in and its journey through the host tissues. It is perhaps needless to refer at length to the conditions which control the acquisition of such knowledge. The hope of finding some preventive or cure dictates the course of many workers. When something approaching this has been found the etiological significance of all the other factors bearing on the disease falls below the horizon for the time being. The importance of continuing the study of the disease persists however even for practical reasons, for the remedy or preventive may not prove to have the success anticipated. To induce men to fill the gaps of our knowledge seems quite as important as the pioneering for entirely new vistas or outlooks. Great discoveries are, as a rule, half-truths that must be brought into line by patient after-research. The filling of gaps may be necessary to stage the next great discovery.

There is beyond the mere knowledge that gaps exist the difficulties of the problems involved to be considered. Are we prepared to solve them directly or must we rely on indirect approaches and on the solution of analogous problems to satisfy our etiological sense? Added to these difficulties inherent in some phases of the parasitic cycle, notably that phase which takes place within the host, is the fact that the various disease agents attacking the same species, man for instance, are so different from one another that we may safely

consider them surviving types. It would seem that where two or more parasites follow the same route and multiply in the same tissues a certain competition tends to eliminate one or the other. If two closely related types exist they rarely multiply in the same host at the same time. Such competitive elimination would leave a divergent assortment of parasitic organisms and resulting diseases, none of which would be an exact copy of the other. In this case the working out of one cycle does not necessarily enable us to predict what another would be. They must each and all be studied individually.

In this dilemma we may gain assistance from a study of parasitisms in those remote and isolated regions which have not yet been seeded by the white man's diseases, where the prevailing maladies may still be "pure lines," rather than mixtures and combinations. Another source of material are the many characteristic parasitisms of animal life, notably of the mammals and birds. Comparative pathology may furnish us with that information which experimental pathology finds it impossible to produce. Taking all the diseased and abnormal states due to living agents in man and the higher animals together, a series may be established which fills in many gaps and which may furnish the suggestions and clues needed to bring about a better insight into the dynamic relations between host and parasite. Only through the cooperation of comparative and experimental methods may we hope to gain enough general underlying concepts to explore with some show of rationality new diseases successfully. Since science is valued in proportion to its capacity to predict successfully certain events, medical science will be judged by the way it takes hold of a new phenomenon to determine its etiological antecedence. If, in the course of its development, it has failed to take cognizance of factors necessary to build the science into a consistent whole, it should retrace its steps and make up the deficiency.

Parallel with the continued analysis of phenomena there should be another process going on to simplify the complexity resulting

from the former and to bring the results of scientific inquiry more or less within the reach of everyday life. What is needed is a synthesis of the many data resulting from analytic study of phenomena. Perhaps I can make myself clearer by using as an illustration some recent investigations. If we examine the various diseases in which the virus is conveyed by insects and arachnids, we shall find that many of the data pertaining to the dissemination of the virus had been accurately worked out before the mode of transmission was discovered. There was lacking, however, a something to harmonize and coordinate them. When the insect carrier was defined these various discrete, apparently unrelated data fell into line. Here was a synthesis which not only substantiated older observations but it enabled the scientist to use the deductive method to develop new inquiries and thereby lift the subject up to a higher level for further analysis. For some years we had known that a certain disease of young turkeys, due to the invasion of the tissues through the intestinal tract by a protozoan parasite, could be prevented by raising these birds away from older turkeys and common poultry and on soil uncontaminated by them. The explanation came through the discovery that a common worm of these species was needed to injure the mucous membrane and thereby open the way for the protozoan parasite. The nematode also accounted for certain disturbances in the application of the above rules in the rearing of these birds. It synthesized, in other words, the accumulated data.

With the aid of these illustrations it is possible to understand, at least in part, what must have been the effect of the rapid discovery of various living agents in the eighties of the last century on the medical mind of the period. Many apparently unrelated data suddenly moved into line and assumed definite relations to one another. The discoveries pertaining to acquired resistance to disease involving the action of antitoxins, agglutinins, precipitins and the like have not had as yet the desired effect of synthesizing the conception of immunity, because they may be ac-

cessories rather than essential factors, all grouped around some more fundamental, unifying, still undefined phenomenon.

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THE FIRST APPEARANCE OF THE TRUE MASTODON IN AMERICA

I HAVE recently published a paper¹ under this title, naming one species *Mastodon matthewi* from the Lower Pliocene of Snake Creek, Nebraska, and another species *Mastodon merriami* from what I supposed to be the Middle Pliocene of Nevada, in honor of Dr. William D. Matthew and Dr. John C. Merriam, respectively.

I have just learned from Dr. Merriam that *Mastodon merriami* is not, as I supposed, of Pliocene but of Middle Miocene age, which makes this species all the more important and interesting as the first to reach America. Dr. Merriam writes, June 24, 1921:

The locality described by Mr. Hills, namely, that at which G. D. Matheson secured his material, is, however, in the Virgin Valley formation, which is of approximately middle Miocene age, not far from the zone of the Mascall of the John Day region. The opal mines are in the Virgin Valley formation and lie between the two main forks which unite to form Thousand Creek. These streams are Virgin Creek and Beek Creek. They unite on the west side of the great Rhyolite mass which separates the lower part of the Virgin Valley beds from the areas of the Thousand Creek formation lying to the east. The change in the age of *Mastodon merriami* suggested by the data given above will, I am sure, interest you greatly as this evidently brings the appearance of these Mastodons back to near middle Miocene.

I am greatly surprised and interested by the Middle Miocene appearance of the true mastodons in America, if the above report by Dr. Merriam is correct, as I have no doubt it is. Middle Miocene age is, in fact, quite consistent with the structure of the superior canine tusks, which bear a broad enamel band on a

concave outer side, a fact that puzzled me greatly because Dr. Schlesinger describes the Lower Pliocene mastodons of Hungary as bearing an enamel band on a convex outer surface. We should expect the earlier mastodons to show just the difference in the curvature of their tusks which these two observations would indicate.

It now seems that the true mastodons may be traced back to the species *Palæomastodon beadnelli* Andrews, living along an ancient river corresponding to the Nile, in company with a primitive long-jawed proboscidean to which Andrews and Beadnell gave the name *Phiomia serripes* in 1902. This was in Upper Eocene or Lower Oligocene times. In Lower Miocene times the true mastodons appear in North Africa and reappear in the Middle Miocene of France, although far less abundant than the contemporary species of long-jawed animals named *Mastodon angustidens* by Cuvier, which are descended from *Phiomia*. The rarity of the true mastodons is attributable to their strictly forest-living habits. They occur rarely in the Miocene and Lower Pliocene of France and Switzerland, also in Austria as recently described by Schlesinger of Vienna.

If the *Mastodon merriami* of Nevada proves to be of Middle Miocene age, it will demonstrate that these true mastodons came to this country much earlier than we have been led to suppose. The earliest arrivals hitherto recorded in this country are the *Mastodon brevidens* and *M. proavus* of Cope, which hailed respectively from the Middle Miocene of Oregon and of Colorado. It is not yet positively known whether these two species are true mastodons or representatives of one of the other phyla.

HENRY FAIRFIELD OSBORN

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June 29, 1921

SCIENTIFIC EVENTS

THE SCIENCE CLUB OF THE UNIVERSITY OF
MISSISSIPPI

DURING the academic year 1920-21, the Science Club of the University of Mississippi,

¹ *Amer. Mus. Novitates*, No. 10, June 15, 1921.