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SOME PROBLEMS IN INFECTION AND ITS CONTROL[1]

I EXPERIENCE a high sense of honor on this occasion with which is mingled no less trepidation in view of the master in whose memory this lectureship was founded, and the great names that in the past have been linked with the post I am to-day asked to fill. I must believe that Huxley would have felt a deep interest in the theme which I have chosen to discuss before you and would have found in its intrinsic importance a compensation for any shortcoming that may appear in the presentation. For Huxley evinced a penetrating appreciation of that branch of biological science that has come to be called bacteriology, and as president of the British Association in 1870 devoted the occasion of his address to an illuminating examination of the doctrine of abiogenesis, or spontaneous generation, versus the doctrine of biogenesis or descent from living ancestors. This subject, long holding a merely academic interest, had become in the two decades immediately preceding the ground over which the conflict raged and out of which was to emerge the modern science of microbiology. While Huxley clearly pointed out that Redi in the seventeenth century and Spallanzani in the eighteenth had delivered the first telling blows that later, through Pasteur, led to the overwhelming defeat of the spontaneous generationists and the establishment on an indisputable basis of the extrinsic origin of the contagious and infectious diseases, he did not fail

[1] The Huxley lecture, delivered at Charing Cross Hospital School of Medicine, London, October 31, 1912.

to preserve in the discoveries just being made in reference to fermentation, putrefaction, and certain fungus and other diseases of insects, the herald of the new science that was to throw its protecting mantle not about man alone, but about all the higher animals and even about the plants, in order that the useful and indispensable should be protected from that inevitable contest in nature between higher and lower forms of life which constitutes disease and leads to premature decay and ruthless destruction.

Bacteriology has, up to now, distributed its favors unequally, but we must not be daunted by this circumstance. It has yielded, in some instances, knowledge of diseases of small, and withheld, in others, knowledge of diseases of great importance. In respect to the common and highly contagious diseases, measles and scarlet fever, for example, progress has been slight. A ray of hope has been cast upon this quest by the announcement[2] that measles can be caused in the monkey by inoculation of infected blood, but this awaits certain confirmation. Similar announcements have been made recently regarding scarlet fever.[3] Since a flood of knowledge has always suddenly flowed from the successful transmission of an obscure disease to the lower animals these reports have been viewed with eager expectation. In the case of scarlet fever I fear the expectation is not yet to be realized. We[4] spent last winter in the study of this subject and failed completely to infect or produce scarlet fever in a wide variety of lower monkeys. Possibly, but not certainly, the higher anthropoid ape, which is still less removed from the human species, is subject to inoculation.[5] The path of success in relation to the refractory diseases is marked by heavy obstacles, but it must be travelled none the less. How often indeed has crowning success come to the brave, thoughtful and adventurous when all but an expiring glimmer of hope had gone! Witness in this connection the sudden conquest of syphilis, in which the initial victory was won when it was ascertained that anthropoid apes can be infected experimentally. There followed in rapid succession the discovery of the causative spirocheta, the Wassermann clinical test and the fabulous drug, salvarsan,* the usefulness of which outruns the wide bounds of syphilis itself.

But even after such a victory the drama had not come to an end. The spirochetal cause could now be discovered regularly where it had been as constantly missed before; doubts and disbeliefs in it were quickly yielding before the rapidly accumulating evidence; but the microorganism itself resisted all attempts at artificial cultivation. That the spirocheta is a parasite nicely adjusted to living tissues was clear from the difficulties surrounding the experimental inoculation of animals. Now this act also has been played.[6] The pallida has yielded to artificial culture by Noguchi and the method sufficing for it has suddenly exposed the whole class of disease-producing spirochetæ and some innocent species as well, to cultivation and ex-

[2] Anderson and Goldberger, *Bulletin of the U. S. Public Health and Marine Hospital Service*, 1911, No. 62.

[3] Cantacuzène, *Comptes rendus de la Société de biologie*, 1911, LXX., 403. Bernhardt, *Deutsche medizinische Wochenschrift*, 1911, XXXVII., 791, 1062; *Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten*, Abteilung 1, Referate, Supplement, 1911, I., 27.

[4] Draper, George, unpublished studies.

[5] Landsteiner, Levaditi, and Prasek, *Annales de l'Institut Pasteur*, 1911, XXV., 754.

[6] Noguchi, *Journal of Experimental Medicine*, 1911, XIV., 99; 1912, XV., 90; 1911, XIV., 557; 1912, XVI., 199.

ploitation under laboratory conditions. It is obvious that the more nicely a parasitic organism is adjusted to its host the more difficult it will be to cultivate it outside the host and the more quickly it will lose in culture its pathogenic power. The pallidum, which for so long resisted the efforts to transmit it artificially to animals and then to cultivate it outside *in vitro,* loses after a few generations, as was to be expected, its disease-producing virulence, while the blood parasites of relapsing and tick fevers in man and spirillosis in fowls, which are strictly parasitic and pass a stage of their life in biting insects, retain this power for many generations. In turn, the culture of the pallida has yielded luetin which by causing a local allergic or hypersensitive skin reaction has provided clinical medicine with a new means of detecting latent luetic infection.

With this introduction to the more general theme of the hour I shall invite you to follow with me somewhat minutely the biological investigations of a disease that is still claiming the absorbed attention of both physicians and people, namely, poliomyelitis, or infantile paralysis. The disease has just been making the rounds of the world, coming as a very unwelcome intruder to many different countries. Until the present pandemic it was surrounded with mystery and fortified by superstition. It is the story of the working out of the natural history of poliomyelitis, now elucidated in many ways, that I propose to tell you. I have been led to choose this particular disease as my theme, both because it has claimed much of my attention during the past several years, and because it illustrates admirably certain general truths to which I desire to call your attention.

Poliomyelitis has been endemic in northern Europe for many years, but it is only five years since it started on that unique, and as yet unexplained, movement that has carried it around the globe. In America there is no previous history of a general prevalence or epidemic, although local outbreaks of infantile paralysis have from time to time arisen. Some significance attaches to the fact that the first two foci of the present epidemic—I say present, because since 1907 the disease has prevailed severely each summer and autumn at some places in the United States and Canada—arose in the Atlantic coast cities and in the state of Minnesota in the middle west. The former receive the mass of emigrant population from Europe, and the latter, secondarily, the large contingent of Scandinavian emigrants. The imposition of the infection upon America can thus be accounted for; but no explanation is afforded of the many years of immunity while Scandinavians were constantly arriving, and for the penetration of the disease to other European countries and to far distant parts of the world. However, within the pandemic period the disease has taken on new activity in Norway and Sweden, and as recently as 1911 the latter country has suffered a severe visitation.

On clinical grounds Scandinavian observers[7] had recognized the essentially infectious nature of poliomyelitis and had followed the evolution of the outbreaks and traced the connection between many of the cases. They became the defenders of the notion of human carriage, and by establishing certain unusual clinical forms of the disease—such as meningeal and abortive—placed this idea on firm ground. The notion was further extended to include healthy carriers of the infection who act as intermediaries between the actively ill and the new victims of infection. These

[7] Wickman, "Beiträge zur Kenntnis der Heine-Medinschen Krankheit," Berlin, 1907.

views have all alike been treated with more or less scepticism by the medical profession; in how far they have come to be supported by later acquisitions of knowledge will appear.

Apart then from these deductions, disputed and disputable, because not supported by certain tests, five years ago the mystery of the disease was wholly unfathomed. The outlook was suddenly brightened when Landsteiner and Popper in 1909[8] announced the successful transmission of poliomyelitis to monkeys, but the high hopes raised were as quickly dampened by the failure to propagate the experimental disease beyond the first generation. This obstacle was immediately removed when intracerebral was substituted for intraperitoneal inoculation, as was done by Lewis and myself[9] and by Landsteiner and Levaditi.[10] By this means the disease could be and has been transmitted through an indefinite number of monkeys. The inoculating matter is, first, the sterile spinal cord of a fatal human case, and, afterwards, the spinal cord of paralyzed monkeys.

The choice of the intracerebral route as superior to the intraperitoneal was not haphazard. All the severe effects of poliomyelitis are inflicted on the nervous system, and upon reflection this fact at once suggested that the parasitic cause of the disease must find favorable conditions for multiplication within the nervous tissues. When the material carrying the germ is put first into the peritoneal cavity it must traverse the blood before it can reach the nervous system, and the blood, as we know, has the power to destroy many forms of germ life. It could, of course, also be reasoned that the specific parasite, in nature, can not enter the nervous tissues directly but must use some external route to reach them, and it must, therefore, be capable of surviving outside the brain and spinal cord; and it could be further reasoned that an inoculation into a more accessible part of the body than the brain and spinal cord should be effective, and if effective would bring stronger proof of the actual existence of a parasite in the inoculated matter. This reasoning is unconvincing for two causes: first, the monkey is not naturally subject to poliomyelitis and is, therefore, presumably more difficult to infect at all than is man so that what may suffice to cause infection in man may fail in the monkey; and, second, it might be possible for pathogenic microbes to reach the central nervous system even in man without entering the blood at all so that in nature the infectious cause of poliomyelitis might avoid the blood altogether. That this possibility really exists has been proved by experiment, as we shall see. Doubtless the first material inoculated into the abdominal cavity carried besides the living parasites toxic or other injurious substances that promoted infection in the monkey; but when the nervous tissues of the monkey were similarly injected, being less harmful, the inoculation failed. Bacteriology contains many instances of similar, and apparently of paradoxical nature.

The discrepancy has been further elucidated, as will soon appear, but in the meantime it is desirable to inquire whether

[8] Landsteiner and Popper, *Zeitschrift für Immunitätsforschung, Originale,* 1909, II., 377.

[9] Flexner and Lewis, *Journal of the American Medical Association,* 1909, LIII., 1639; *Journal of Experimental Medicine,* 1910, XII., 227. Flexner, *Journal of the American Medical Association,* 1910, LV., 1105. Flexner and Clark, *Journal of the American Medical Association,* 1911, LVII., 1685. Howard and Clark, *Journal of Experimental Medicine,* 1912, XVI., 850.

[10] For a general bibliography, see Römer, "Die epidemische Kinderlähmung" (Heine-Medinsche Krankheit), Berlin, 1911.

still other routes of infection exist for the monkey. Since nervous tissue is favorable to the parasite it was injected into large nerves—such as the sciatic—in order to ascertain whether these furnished a suitable medium of propagation. The parasite grows along the nerve until the spinal cord is reached and produces injury of the cord first at the point of entrance before it extends to and attacks other parts. The injection into the nerve causes no paralysis but paralysis of the innervated muscles appears after the lapse of a time sufficient for the necessary multiplication of the parasite and its passage into the spinal cord.

Meanwhile the inoculated monkey shows no other signs of illness, and no other organ is severely affected; the injury is centered upon the nervous tissues. And not only does the parasite grow or flow along the nerve but it ascends along the spinal cord from lower to higher levels and eventually reaches the medulla and brain. At last the centers governing respiration are involved and death by paralysis ensues.

We have now been able to arrive at several important conclusions. The monkey can be made regularly to develop an experimental disease agreeing in all essential respects with poliomyelitis in man. Inoculation is necessary since keeping healthy and paralyzed monkeys together does not lead to infection. The parasitic cause of the disease can traverse the blood, in the monkey, to reach the central nervous organs, but with difficulty, while it easily traverses the peripheral nerves. That the natural, spontaneous disease, so called, in man and the induced disease in monkeys are very much alike is further shown by microscopic study of the spinal cord and brain which exhibit changes that are identical.

The pathological effects are of two kinds: injury to nerve cells not in the anterior gray matter alone but in the posterior gray matter of the spinal cord and in the intervertebral ganglia, medulla and brain; and cellular invasion of the pia-arachnoidal membrane of the spinal cord and medulla that follow the blood vessels into these parts and pass into the adjacent gray and white matter. The altered vessels permit an escape of albuminous fluid and blood cells into the meshes of the membrane where they mingle with the cerebrospinal liquid, and into the spaces in the tissue composing the solid white and gray matter. Sometimes the nerve cells, sometimes the meninges, vessels and supporting tissues suffer most. When the nerve cells are extensively injured the paralysis is marked; when the meninges are much affected, the symptoms are like those of meningitis. The virus of poliomyelitis displays a high affinity for nervous tissues, but it is the wide involvement of the nutritive vascular system in the pathological process that subjects the sensitive nerve cells to so high a degree of injury and destruction.

The microscopical conditions we observed in the course of our experiments were suggestive of two things: first, the nature of the parasite itself, and, second, the process of generation of the effects or lesions themselves. Up to this time no definite parasite could be detected in the nervous tissues either in human beings or monkeys, nor was anything of the kind found in the blood or other organs. The scarcity of polynuclear leucocytes in the altered cerebrospinal liquid and spinal cord itself spoke against a simple bacterial parasite. The large number of mononuclear cells spoke rather for a protozoal parasite. Neither could be found, although the most varied methods of staining and cultivation were employed. There remained the possibility of the parasite being invisible or ultramicroscopic and filterable. This it

proved to be, for when a portion of the spinal cord of a recently paralyzed monkey was made into an emulsion with sterile distilled water, or simple saline solution, and then centrifugalized to remove the coarse suspended matter and afterwards pressed through a Berkefeld earthenware filter, which excludes ordinary cells, bacteria and protozoa, the clear liquid resulting was still capable of transmitting the disease. The activity of the filtrate is very great, since a fraction of a cubic centimeter still suffices to cause paralysis and death. The only distinction to be noted between the action of corresponding amounts of the emulsion and filtered fluid is that the former acts more quickly, as would be expected from the fact that it contains a greater number of the invisible organisms. This difference is soon compensated by the multiplication of those in the filtrate so that the end result is the same. By employing somewhat greater quantities of the filtrate for inoculation the incubation period of the disease can be made the same as that following the use of the emulsion. The disparity is strictly a quantitative one, since the filters retain a part of the minute organisms in their pores and thus reduce the number escaping with the filtrate. The greater the quantity of protein matter present in the fluid the fewer the parasites that pass the filter, and merely because the large protein molecules themselves tend to be held in the pores and thus render them impervious for the minute organisms. For this reason, also, fluids containing small numbers of the filterable parasites, but still sufficient to cause infection in the crude state, may fail, when filtered, to produce disease merely because those retained by the filter so far reduce the numbers as to bring them below the surely infecting dose. This reduction sometimes leads to another effect; namely, the slight degree of infection that forms the starting point of active immunization. By building upon such a beginning a high and enduring state of immunity has been achieved.

The first filterable parasite was discovered by Loeffler fourteen years ago, in the fluid lymph obtained from the vesicles of cattle suffering from foot and mouth disease. At the present time eighteen diseases are known that are believed on good ground to be caused by this class of minute living organisms. One alone among them is on the verge of visibility—the parasite causing pleuropneumonia of cattle. It alone has certainly been obtained in artificial culture. The methods of artificial cultivation need still to be worked out; and once they are discovered it is a safe prediction that control over the diseases produced by ultra-microscopic parasites will be quickly increased. The degree of infectivity of certain of the parasites—or viruses, as they are also called—is almost fabulous. One thousandth of a cubic centimeter of a filtered 2.5 per cent. suspension of a spinal cord of a paralyzed monkey suffices to cause infection and paralysis in another monkey; 0.020 of a cubic centimeter of infected lymph suffices to produce foot and mouth disease in a healthy calf, and the blood of fowl suffering from chicken plague is still active after being diluted 1,000 million times with water.

Three affections of human beings are contained among the eighteen diseases caused by filterable viruses: They are yellow fever, dengue and poliomyelitis. With one exception, the mosaic disease of tobacco, the remaining fourteen are maladies of domestic animals and include among them foot and mouth disease, horse-sickness, cattle-plague, sheep-pox, rabies,

vaccinia, hog-cholera and chicken-plague. We can at present form no reliable conception of the biology of this class of parasite, although the virus of pleuropneumonia shows affinities with the bacteria, while that of yellow fever that passes a stage of its existence in mosquitoes probably belongs to the protozoa. It should be remembered that we possess no criterion of their presence other than the power to produce infection. Probably the list of these pathogenic parasites would be increased if methods were known for testing their symbiotic relations or cooperative effects with the usual bacteria and protozoa. Rous's[11] discovery of a filterable agent that causes sarcomatous tumors in the fowl has opened up new fields to exploration. We can make a rough guess as to their sizes since some pass through thick filters, the pores of which are smallest, while others pass the more porous filters with larger interstices only. Were the viruses as large as one fifth the size of the influenza bacillus, they would be beyond visibility with the most powerful optical system of the modern microscope. The dark-field microscope and the instrument devised for employing, for photographic purposes, the ultraviolet rays of the spectrum, that has doubled the potential power of the microscope, have failed to bring them into view. On the whole they resist drying well and show considerable resistance to disinfecting agents.

The ultramicroscopic viruses employ no single means of effecting entrance into the body. Some utilize insects to inject them into the blood. Mosquitoes inoculate the parasites of yellow fever and of dengue in man, and the virus of horse-sickness among animals; while flies inject the virus of parrot-fever; and worms and other insects, through close contact with infected and then with uninfected tobacco plants, disseminate the parasite of mosaic disease. The viruses of rabies, vaccinia and fowl-pox gain entrance through skin wounds, those of hog-cholera, foot and mouth disease and chicken-plague, by swallowing, while the parasites of variola and of pleuropneumonia are inhaled with air. These are the main avenues but not the sole routes of infection, since viruses that ordinarily enter the body by the respiratory mucous membrane may occasionally enter through a skin abrasion, etc.

It is significant that upon recovery from this class of infections a high and enduring degree of immunity is left behind. We have no knowledge of toxic substances, in the common sense, being produced by the filterable viruses, and therefore know nothing of the formation of antitoxins or bodies that neutralize poisons. The principles upon which the immunity depends appear to be chiefly microbicidal or substances that act directly upon the living parasites and destroy them. In some instances it has been possible to produce an actively immune state without at the same time causing severe disease, by employing for inoculation modified and weakened viruses and viruses combined with immune sera carrying the corresponding microbicidal substances. Once a certain active immunity is obtained it can be heightened by repeated injections of more active materials until a high degree is achieved. In the same manner immune animals that have recovered from disease are capable of having this immunity reinforced by subsequent injections of the active virus. Blood taken from the immune animals has been employed in practise in two ways: to protect for a brief period exposed animals from acquiring infection, and to bring

[11] Rous, *Journal of Experimental Medicine*, 1911, XIII., 397; *Journal of the American Medical Association*, 1911, LVI., 198.

about an actively immune state through inoculation with adjusted mixtures of virus and corresponding immune serum. The injection of viruses into animals not themselves subject to infection has, in a few instances, yielded immune sera. In this way a serum for foot and mouth disease has been prepared in the horse. Speaking generally, homologous sera are more active than heterologous, or, in other words, an immune cattle serum will act better in cattle than will immune horse serum; but curative sera in a real sense have not yet been produced for this class of diseases.

It is of great interest to determine the correspondence between the general data I have just reviewed and the special facts of poliomyelitis which have been shown to arise in consequence of an invasion of the nervous tissue by an ultramicroscopic or filterable virus. We may proceed to check off rapidly the main facts. The virus stands midway in point of size between the finest and coarsest examples. It passes readily through the more coarse and slightly through the finest filters. It is highly resistant to drying, and to light and chemical action. In dust, especially within protein matter, it survives weeks and months; in diffuse daylight indefinitely, and resists the action of pure glycerine and carbolic acid in 0.5 per cent. solution for many months. When animal tissues containing the virus suffer softening and disintegration or disorganization by mould, the virus survives. Recovery from poliomyelitis in man and the monkey is attended and produced by an immunization of the body. During this process microbicidal substances appear in the blood that are capable of neutralizing the active virus. This acquired immunity has, in the monkey, been reinforced by subsequent injection of large quantities of the living virus. Active immunity can be achieved by first injecting minute and later large amounts of the virus, and an adjusted mixture of immune serum and active virus will confer a beginning low active immunity capable of being heightened. Certain alien large animals, among which the horse and sheep are especially worth mentioning, are subject to immunization through injections of emulsions of the spinal cord and brain of paralyzed monkeys, and can thus be made to yield sera possessing microbicidal power and capable of conferring, as do human and monkey immune sera, a degree of passive immunity. Thus far no immunizing effect has been accomplished with the dead virus. Unless some growth and multiplication take place no immunity arises.

These facts show a close correspondence between the properties of the virus of poliomyelitis and those of the ultramicroscopic organisms in general. There remain to be considered the data bearing upon the manner of entrance of the poliomyelitic virus into the body or, in other words, upon the mode of infection. Analogy with other diseases produced by filterable viruses excludes no one of the possible modes, since their manner of entrance is widely varied, as we have seen. This question is of the utmost importance, since with all diseases prevention is far better than the most perfect cure, and for poliomyelitis there exists at present no specific or true curative treatment. Moreover, for the most part when the disease is first recognized it has already caused irreparable damage, and though the more general examination of the spinal fluid obtained by means of lumbar puncture for purposes of diagnosis may possibly lead to a much earlier recognition of the disease, yet its

prevention will always remain the result to be aimed at. It is quite certain that an understanding of the mode of infection would lead inevitably to the framing of measures of prevention that with reasonable certainty could be expected to exercise control over the epidemic spread.

Two answers may be returned to the question: one based upon observation of human cases of poliomyelitis, and the other based upon experimental tests arranged to elicit specific replies. The first answer can not achieve anything higher than strong probability; the second, to be valid, must explain the phenomena attending the human infection as well as those of the experimental disease. We are asked to account for certain data, of which the following is a brief statement. Epidemic poliomyelitis is preeminently a disease of early childhood and finds the highest percentage of its victims in the first five years of life, but does not wholly spare older children or even adults. It is admittedly infectious; and while it is true that many more instances of single than of multiple cases occur, yet multiple ones are not by any means rare. The prevailing views on this topic are being modified rapidly by the recognition of the abortive and ambulant examples of the disease. The period of greatest prevalence is during the months of August, September and October in the northern hemisphere, and the corresponding months in the southern hemisphere, but the epidemic begins in the early spring and summer months and the disease does not wholly disappear during the winter months. It does not, therefore, necessarily die out at any period of the year. In endeavoring to trace the avenue of entrance of the virus into the body certain facts regarding its distribution in the body should be recapitulated and considered.

The infectious agent of poliomyelitis attacks chiefly the central nervous system. Indeed, it has been detected regularly in the spinal cord and brain and in the mesenteric lymph nodes among all the internal organs. It has also been detected in the mucous membrane of the nose and throat, and in the mucus secretions of this membrane, and in the mucus secretions of the stomach, and the small and large intestine. The virus has not been detected in such important organs as the spleen, kidneys, liver or bone marrow. The fact is significant, but in attempting to interpret it, account should be taken of the circumstance that at present we possess one means only of detecting the virus, and that is its transmission to monkeys, in which it produces characteristic paralyses and anatomical changes. On this account small quantities of the virus may conceivably escape discovery. However, the conclusion is none the less inevitable that detectable amounts of the poliomyelitic virus exist only in the few situations and organs mentioned. The distribution of the virus is identical in human beings, the subjects of the so-called spontaneous poliomyelitis, and in monkeys, in which the experimental affection is produced. Nor does it matter how the experimental inoculation is accomplished and whether the virus is introduced by injection into the brain or large nerves or subcutaneous tissue or peritoneum, or whether it is merely applied to the nasal mucous membrane, which, it should be emphasized, next to direct intracerebral injection, affords the surest means of causing the experimental disease. In whatever way the infection is produced purposely, the distribution of the virus in infected monkeys is the same as in infected human beings.

The virus is one that is not known to increase aside from the infected body, and

hence in order that it shall be capable of propagating poliomyelitis, it must secure a means of escape from the infected animal. The escape is now known to occur along with the secretions of the nose and throat, and the discharges from the intestine. We are obliged, therefore, to ask ourselves what the means are by which the virus confined within the interior reaches these external surfaces of the body.

Let us begin by disregarding for the moment the essential point of the way in which the virus probably enters the body in infected human beings, and give our attention to the way in which it escapes in the infected monkey into the nose, throat and intestines. We may first consider the instance in which the virus is deposited in the brain, in which it becomes sealed, as it were, and cut off apparently from the exterior of the body. Having been injected into the brain, the infectious microorganism constituting the virus multiplies both within and about the brain tissue at the site of inoculation. As multiplication progresses, the virus leaves the original site of injection and wanders through adjacent and distant parts of the central nervous tissues, becoming implanted in the medulla, the spinal cord and the intervertebral ganglia, as well as reaching the pia-arachnoidal membranes, or meninges, in which it also spreads. Ultimately, when the virus becomes sufficient in amount, it brings about anatomical changes in the nervous system, one of the results of which is paralysis. The period intervening between the inoculation and the appearance of paralytic symptoms may be as brief as two or three days, or as long as three, four or five weeks. The great disparity in this period depends upon the amount and quality of the virus, as well as the degree of resistance of the inoculated monkey.

The virus, which has found its way to the meninges, does not long remain in the cerebrospinal fluid, with which it escapes in part into the blood, where it does not appear to undergo any further increase in amount, and indeed seems even incapable of surviving for long. A part also of the virus contained within the cerebral fluid escapes regularly by way of the lymphatic channels surrounding the short nerves of smell that pass from the olfactory lobes of the brain to the mucous membrane of the nose. It has long been known that there is an intimate connection between the lymphatic vessels of the nasal mucous membrane and the lymphatic spaces of the pia-arachnoidal membrane. The virus once having gained the mucous membrane of the nose may even escape into the mucus secretion, with which it is carried into the mouth, and in part swallowed, or it may become established in the substance of the nasal membrane, where it undergoes subsequent multiplication and increase. As a matter of fact both these things occur. The virus escapes with the secretions partly externally to the infected body, and a part of it is swallowed with the secretions themselves, while a persistent infection of the secretions is maintained by means of the increase that takes place in the membrane itself. In this way is assured the escape of the virus directly into external nature, as well as the contamination of the gastro-intestinal cavity, with the discharges of which it becomes commingled. Once implanted upon the intestine multiplication not improbably continues for a time, and another source of invasion of the body is thus afforded the parasite. From the intestine it reaches in some amount the mesenteric lymph nodes, and thus enables us to account for the occurrence of the virus in those lymphatic

nodes which thus form a notable exception to the general internal organs of the body.

We have now followed the route by which the poliomyelitic virus, implanted within the apparently closed cavity of the skull, reaches the exterior of the body. It is obvious that in the spontaneous form of the infection in man no such mode of introduction of the virus can occur. The virus must indeed enter the human body by some external channel, after which it seeks and becomes implanted upon the central nervous system. It is known that in monkeys the virus is incapable of passing the barrier of the unbroken or slightly abraded skin, of being taken up from the stomach or intestine unless the functions of these organs are previously disturbed and arrested by opium, and it is further known that it traverses with difficulty or even not at all the substance of the lungs. On the other hand, it is established that the virus passes with readiness and constancy from the intact or practically intact mucous membrane of the nose to the central nervous system.

To illustrate this point I wish to describe briefly an experiment. The spinal cord of a paralyzed monkey always contains the virus we are considering. If a camel's hair pencil or pledget of cotton is covered with some of the broken up tissue of such a cord and painted upon the mucous membrane of rhesus monkeys, these animals will develop in due time the paralysis and other symptoms of poliomyelitis. Hence the virus enters the body from this surface even though no gross injury has been inflicted upon the membrane. We should now ask ourselves if the virus actually ascends to the brain by the direct path of the olfactory nerves or indirectly after first entering the blood. This is the same question that has been buffeted about in regard to epidemic meningitis. The meningococcus is found in the nasal mucous membrane of persons in contact with cases of meningitis, and in the sick themselves. It is not disputed that the meningococci settle on this membrane, but opinion is divided as to whether it goes at once to the membranes of the brain or first penetrates into the blood. To produce meningitis in monkeys it does not suffice to inoculate the nasal membrane; the meningococci must be injected into the membranes themselves. But so inoculated they escape in part along the nerves of smell into the nose. The virus of poliomyelitis is so active that implantation in the nose does suffice to cause infection. If a monkey is sacrificed about forty-eight hours after an intranasal inoculation, and the brain and spinal cord are removed and then the olfactory lobes and portions of the medulla and spinal cord are separately inoculated into other monkeys, infection is produced by the olfactory lobes alone, since in this brief period the virus has not yet reached other and more distant parts of the nervous organs. Were the virus distributed by the blood, the medulla and spinal cord would have become infective, rather than the olfactory lobes, since they exhibit a greater selective affinity for the parasite. The conclusion, therefore, is unavoidable that the virus ascends by the nerves of smell to the brain, multiplies first in and about the olfactory lobes and, in time, passes, as I believe, into the cerebrospinal liquid which carries it to all parts of the nervous organs. We have already learned that the virus can pass along a large nerve, such as the sciatic, which carries it first to the lumbar cord, whence it ascends to higher levels; we need not, therefore, be astonished to find that it can wander along the olfactory nerves and then descend to

lower levels. The large peripheral nerves are prevented anatomically from becoming infected in nature, while the small olfactory filaments are advantageously placed to act as the means of transportation. Hence the view I desire to place before you, that the nasal mucous membrane is the site both of ingress and egress of the virus of poliomyelitis in man. Support for this view is found also in the study of the microscopic changes in the meninges and the central nervous tissues. Since the virus survives in the dried state it may be carried in dust; and in one instance it has been detected in sweepings from the room occupied by a person ill with poliomyelitis.[12] Its distribution as spray in coughing and speaking is readily accomplished, and by this means both active cases and passive carriers may conceivably be produced. Still one link in the chain of causation of poliomyelitis as here outlined remained to be forged. The clinical evidence is strong in suggestion that human carriers of the poliomyelitic virus exist. The virus has now been detected in the secretions of the nose, throat and intestine of persons suffering from abortive or ambulant attacks of poliomyelitis.[13] The unrecognized examples of the abortive disease play a highly important part in the dissemination of the virus, through which the area of infection is extended, and the number of the attacked increased. A similar part has been accorded by clinical observation to the healthy virus carrier, and the healthy carrier is the last to be detected, and his existence confirmed experimentally. The obstacles in the way of this confirmation are considerable but not insuperable. It is to be remembered that we possess no means of discovering the virus except that of animal inoculation. Should the experimental results arising from the inoculation of the secretions of the nose and throat of such healthy carriers be confirmed the evidence for the mode of infection as here outlined would be complete. The membrane of the nose and throat is far more vulnerable in young individuals, whence arises the greater prevalence during childhood of those diseases the causes of which seek this avenue of entrance into the body. Among them are included diphtheria, measles, scarlet fever and meningitis.

Would the establishment of the respiratory avenue of entrance of the virus exclude all other modes of possible infection? By no means. Plague bacilli are known to be inoculated into man by rat fleas; but the pneumonic form of the plague is admittedly caused by respiratory inoculation. Diphtheria arises upon the mucous membrane of the throat, but can develop in a wound of the skin; the virus of smallpox enters by way of the throat and nose, but can enter by a skin abrasion; the virus of foot and mouth disease is taken in with food, but produces infection when injected into the skin. Hence at the moment while knowledge is still recent and not yet perfect the too absolute adherence to one point of view is to be avoided.

Indeed, the preponderance of cases in the late summer and autumn months early suggested an insect carrier of the infection. House flies can act as passive contaminators, since the virus survives upon the body and within the gullet of these insects. It has not proved possible thus far to infect the common varieties of mosquito and the body and head louse, while success has resulted in one instance in producing infection in bedbugs which were made to feed

[12] Neustaedter and Thro, *New York Medical Journal*, 1911, XCIV., 813.

[13] Kling, Wernstedt, and Pettersson, *Zeitschrift für Immunitätsforschung, Originale*, 1911–12, XII., 316.

upon the blood of inoculated monkeys. The virus remained alive within these insects for a period of many days. The inoculation of monkeys with a filtrate prepared from them gave rise to characteristic paralysis and anatomical lesions. This result is significant, since it shows that insects are capable of taking up the virus from the blood where it exists in minimal quantities and in harboring it for a considerable period in an active state; but it does not show that multiplication occurs within them or that in nature they act as the agents of inoculation. A tentative announcement has been made recently by Rosenau[14] that the stable fly (*Stomoxys calcitrans*) can take up the virus from the blood of infected monkeys and reinoculate it into healthy ones which will become paralyzed. The experiment awaits confirmation and, after confirmation, convincing application to the circumstances surrounding infection in human cases of poliomyelitis.

The frequent prevalence of epidemics in sparsely populated country districts has led, moreover, to consideration of domestic animals as sources of the infection. Paralysis of dogs, horses, pigs and fowl has been observed, not uncommonly, but thus far without clear correlation with paralysis in man. Perhaps the most frequently observed coincidental paralytic diseases have been between hens and human beings. Undoubtedly since the wide prevalence of epidemic poliomyelitis, the existence of a paralytic disease among barnyard fowl has been more commonly noted. Possibly the condition has not actually become more frequent, but owing to the circumstance mentioned it has been oftener observed. It appears that the paralysis among fowl is caused not by lesions of the central nervous system, but by lesions of the peripheral nerves and is due to a peripheral neuritis. It has not been found possible to transmit by direct inoculation the paralytic disease from chicken to chicken, or from chicken to monkey, or from paralytic monkey to chicken. However, it has been found possible to develop the paralysis in the laboratory by keeping the chickens in confinement for some time, and by supplying them an unusual and improper form of food. It has proved as little possible to transfer the paralytic affection of dogs from one individual to another by direct inoculation, or from dog to monkey, or from paralyzed monkey to dog, or to set up paralysis in monkeys by inoculating them with nervous tissue obtained from paralyzed pigs, or to produce paralysis in pigs with the virus of paralyzed monkeys. These failures do not, of course, exclude the possibility that a reservoir for the virus may exist among domesticated animals that do not even respond to its presence by developing paralysis or other conditions which could be recognized as resembling poliomyelitis in man. The manner of action of the virus of poliomyelitis in rabbits provides an illustration which shows how necessary it is to avoid general deductions in this field. At first it was strenuously denied that rabbits could be infected at all with the virus of poliomyelitis, and the examples of supposed successful inoculation reported were entirely disbelieved; but it must now be accepted that young rabbits occasionally, but by no means generally, are subject to inoculation with the virus of poliomyelitis, at least after it has passed through a long series of monkeys. Apparently a small percentage only of the inoculated rabbits develop any obvious symptoms, and these die, as a rule, during

[14] Rosenau, communication at the International Congress of Hygiene and Demography, Washington, 1912.

convulsive seizures which come on suddenly. A given virus has up to the present been sent through a series of six rabbits, after which it has failed to be further propagated. From the sixth series it has been reimplanted on the monkey, in which animal typical paralysis has been produced. It remains to add that the rabbits which succumb to the inoculation do not show any characteristic alterations of the central nervous system or other organs, as far as has been determined. The monkey, on the other hand, invariably shows the typical lesion of the central nervous system.

Long before epidemic poliomyelitis had the wide distribution or claimed the attention now accorded it, instances of infantile paralysis were known to every one. Almost every community could point to one or more examples of the condition and no one entertained the suspicion that the cause of the paralysis was an infectious or even contagious disease. Are these isolated cases of paralysis occurring among infants of the same nature as the epidemic paralysis, or has there merely been a confusion of names? We possess means that permit an answer to this important question. Recovery, as you recall, is associated with enduring immunity and the person or animal immune to poliomyelitis carries in his blood principles that neutralize the virus causing the disease. The blood of normal persons or animals lacks this property in any real degree. The test is, therefore, easily made: a mixture of the serum of the blood and virus are prepared, and after being in contact for a time is injected into a monkey. Thus it has been determined that the two diseases are caused by the same parasite, and it has been found that the neutralizing principles are still present as long as twenty-five years after the attack of paralysis and doubtless persist through life. This test has been employed likewise to identify abortive cases of poliomyelitis in which paralysis has not appeared at all.

There is nothing unique in this apparently paradoxical situation. Most, if not all, epidemic diseases prevail at some time as sporadic affections; that is, as diseases of occasional occurrence. This is true of influenza, plague and particularly of meningitis, with which poliomyelitis displays so many affinities. Knowledge is still very imperfect as to just what happens when an epidemic spread of a sporadic disease takes place. Sometimes conditions arise that favor rapid transference of the infecting microbe from individual to individual through which a rise in virulence is accomplished very much as is done every day in the laboratory to enhance the potency of cultures. In respect to poliomyelitis, as seems also to be the case with meningitis, a fresh importation of an already enhanced virus probably occurs and is the immediate cause of the epidemic. The introduction may be at one point or at several points simultaneously, according to where the epidemic arises, and spreads from a single center or from many foci. Finally, sports, or abnormally virulent parasites, appear, prevail actively for a period and then become reduced to an average degree of intensity perhaps never to rise again. Some of the exceptionally severe epidemics of which history tells us may be thus accounted for. Such sports have been encountered in laboratories in regard to both pathogenic bacteria and protozoa.

Are biologically different strains of a poliomyelitic virus known? The evidence at hand is to the effect that different strains or races certainly exist if virulence be taken as the measure. German, Austrian and French pathologists found that

of the human specimens of spinal cords submitted to them for study about one half could be inoculated successfully into monkeys and less than this number could be propagated through successive animals. In America all the original specimens were successfully inoculated, but certain samples were far less active than others. At the beginning many of the inoculated monkeys survived the infection, sometimes with, sometimes without enduring paralysis of leg or arm. Later, fewer survived, and after many passages of the virus from monkey to monkey all became infected and all succumbed. The Swedish virus of 1911 appears to be the most powerful yet studied. This is indicated by the fact that saline washings of the nose and throat and intestine could be inoculated successfully, after removal of all bacteria through filtration, in nearly every instance.[15] In America it has been difficult to procure infection with these materials, from which it has been concluded that the virus displays a degree of infectiousness for monkeys. There are reasons for supposing that similar variations exist for man.

We may not, and probably shall not know certainly whether this variability is restricted to the quality of virulence or whether true types or races of the virus exist until artificial cultivation has been accomplished. Bacteriology has been singularly enriched recently by discoveries relating to biological types of certain microbes; and practical medicine is destined to benefit largely by the strong light which they have thrown upon perplexing questions of specific therapeutics. I am tempted to lead you aside a little way into this subject just because it is so full of suggestion and promise, and not merely with promise, since the fruits of discovery are being already tasted.

[15] Kling, Wernstedt, and Pettersson, *loc. cit.*

The pneumococcus causes many kinds of inflammation and one typical disease that prevails everywhere, namely, acute lobar pneumonia. Not infrequently there attend the pneumonia, and sometimes there appear independently such inflammations as peritonitis, pleuritis and meningitis, caused also by the pneumococcus. Now pneumococci possess in common biological features regarded usually as sufficient to distinguish them; namely, form, staining properties, growth, virulence and solubility in bile salts. But they have another quality that serves to distinguish them more finely, revealing different types among apparently similar organisms. By testing pneumococci from many different sources against an immune serum prepared with a single kind of the coccus, it has been found that the cocci are not all alike but that a predominant type and several subsidiary types occur in nature.[16] Such a serum prepared with a given type of pneumococcus is neutralizing for that one alone, and for no other. The clinical reports on the antipneumococcus serum employed as a curative agent are contradictory, and one cause for this is now apparent.

Pneumococcus meningitis can be produced in monkeys by injecting subdurally, by lumbar puncture, a virulent culture of pneumococcus; it is invariably fatal. Antipneumococcus serum alone injected subdurally can change the outcome very little. But this infection is subject to combined chemo- and serum-therapy in which the chemical agent consists of sodium oleate that alone attacks and dissolves the pneumococcus. Acting separately, in the body, sodium oleate can accomplish little; it re-

[16] Neufeld and Händel, *Zeitschrift für Immunitätsforschung, Originale,* 1909, III., 159; *Arbeiten aus dem kaiserlichen Gesundheitsamte,* 1910, XXXIV., 293; *Berliner klinische Wochenschrift,* 1912, XLIX., 480.

quires the assistance of the immunity principles. Acting together the two agents quickly bring the infection under control and recovery follows. This happens even after the pneumococci have entered the blood stream and begun to multiply there. The effects of the soap and serum compound are, however, restricted to the type of pneumococcus represented by the immune serum in the mixture.[17] When the type of microorganism and serum differ absolutely no therapeutic action follows. This obstacle to the practical employment of this method of specific treatment will doubtless be reduced or even wholly set aside by preparing a true polyvalent immune serum that will represent not many cultures of the pneumococcus taken at random, but the several types or races occurring in nature. We already know the number to be few.

It has become the custom to speak of these types of microbes as resistant or "fast"; but the term is relative merely. The fact and degree of fastness will be revealed by the source of the test-serum. But within a given microbic species this quality of resistance may well appear against chemical bodies as well. Pneumococci, for example, vary in properties by gradual gradations in the direction of the streptococcus, which besides differing in still other biological properties chances not to dissolve in bile. The gradients of pneumococci approaching the streptococcus are progressively less acted upon by sodium oleate. The trypanosome of sleeping-sickness is less subject to the therapeutic action of certain organic arsenic compounds in some regions in Africa than in others. The antimeningitis serum suppresses the growth and multiplication of most meningococci, but not of all. This quality of fastness is not alone innate but can be developed artificially as a mutation, both against serum principles and chemical drugs and may persist. Infectious diseases showing a strong tendency to relapse in course of recovery are caused by microbes tending to flourish as races or types. Relapsing fevers that pass three or four exacerbations on the way to recovery are attributed to spirochetæ assuming a corresponding number of distinct forms. Infections tending to many relapses, of which lues is an example, are attributed to parasites capable of flourishing in many such types of which one part is innate and the other the result of mutations under the influence of curative serum or drug. Fortunately, there appears to be no parasite capable of performing indefinite mutations; and experience is teaching that the more precise, specific and vigorous the means employed to control infection, the smaller the risk of mutation and the greater the probability of suppression of the parasitic agent of disease.

In 1886 Theobald Smith[18] first clearly pointed out that the injection of dead bacteria conferred active immunity to subsequent inoculation with virulent materials. Now the employment of dead bacteria is widespread both for preventing and for healing disease. Wright[19] especially is to be credited with the general application of the method to therapeutics. While the limits of value of inoculation, as it is termed, are not yet defined and it promises, theoretically, more for the subacute and chronic than for the acute infections, I am inclined to the belief that to be really effective attention will need more and more

[17] Lamar, *Journal of Experimental Medicine*, 1911, XIII., 1; 1912, XVI., 581.

[18] Salmon and Smith, *Proceedings of the Biological Society of Washington*, 1884–86, III., 29.

[19] Wright, *Proceedings of the Royal Society of Medicine*, 1909–10, III., Supplement, 1.

to be accorded to the question of specific type in the infecting bacteria.

In pursuing the devious courses of infection, of which examples have just been given, the fact has emerged that the effectiveness of curative means will be determined not only by the intrinsic qualities of the parasites but also in a high degree by the manner of location and distribution of the parasites themselves within the infected host. Whether they have a general distribution throughout the blood and tissues or whether they are confined within an important organ or part may be the factor determining the ease with which they can be reached not only by the natural curative principles of the body but also by artificial curative agents introduced into the body.[20]

The parasite, struggling to survive, withdraws, at one time, into situations to which the curative substances gain access imperfectly and with difficulty, causing thereby local infections more or less cut off from the general circulation and the curative substances purveyed by the blood. This is the condition met with in focalized inflammation and in infections of specialized portions of the body, such as the great serous cavities that receive a modified and dilute lymph secretion carrying reduced quantities of the protective principles contained within the blood. The quality of lymph in the several serous cavities and in the various tissues is not the same, and the lowest limit of strength is reached by the cerebrospinal fluid that functions as the lymph of the brain and spinal cord. The exclusion of dissolved substances from the cerebrospinal liquid is a provision of great importance, but is not an unmixed good. For while it affords protection to the sensitive nervous tissues from injurious chemicals, it deprives them also of curative principles. Happily this deficiency has now been superseded by a method of direct local treatment by injections that has given excellent results in meningitis, but is now being employed in luetic affections of the meninges and central nervous organs with encouraging results.[21]

Remote as some of them may seem, the considerations to which I have called your attention have a bearing more or less vital upon the problem of a specific and effective treatment of poliomyelitis. Poliomyelitis is not a disease with a very high mortality; its chief terror lies in its appalling power to produce deformities. When death does occur it is not the result, as in many infections, of a process of poisoning that robs the patient of strength and consciousness before its imminence, but is caused solely by paralysis of the respiratory function, sometimes with merciful suddenness but often with painful slowness, without in any degree obscuring the consciousness of the suffocating victim until just before the end is reached. No more terrible tragedy can be witnessed.

I have already laid before you certain facts regarding immunity in poliomyelitis and it remains to be added that the employment for treatment of the immune serum, taken from monkeys or from human beings, exercises a definite if not very strong protective action upon inoculated monkeys. Either the disease is prevented altogether or its evolution is modified in such a manner as to diminish its severity. When the virus used for inoculation is highly adapted to the monkey and thus very virulent it is more difficult to control the result than when it departs less from the original human type and is less active.

[20] Flexner, Simon, *Boston Medical and Surgical Journal*, 1911, CLXV., 709; The Harben Lectures, *Journal of State Medicine*, 1912, XX., 130, 193, 257.

[21] Swift and Ellis, *New York Medical Journal*, 1912, XCVI., 53. Wechselmann, *Deutsche medizinische Wochenschrift*, 1912, XXXVIII., 1446.

The immune serum has thus far acted best when it was injected into the subdural space on several successive days. This is in conformity with the fact that however introduced into the body the virus establishes itself in communication with the cerebrospinal liquid where it propagates for a time. Later the virus localizes in the nervous tissue itself and becomes accessible not from this liquid only but, probably, from the general blood also. The serum introduced into the subdural space soon escapes into the blood; and thus a double action is secured: on the one hand, it reaches the nervous tissue directly from the cerebrospinal liquid, and on the other indirectly with the blood. An immune horse serum at first gave disappointing results but latterly its employment by intramuscular injection has given more promise. But none of the sera mentioned can be regarded as having more than touched the fringe of the problem of a cure for the disease.

Such brilliant success has been recently recorded in respect to the specific chemical therapeutics of infection that an effort has been and still is being made to attack the problem from this quarter. Here also only a starting point has been secured and the subject merely opened to further experimentation. The point of departure, which we have adopted, is the drug hexamethylenamin (urotropin) which possesses a degree of antiseptic action in the body and is known to be secreted into the cerebrospinal liquid. When the drug is administered by mouth it can be detected by chemical tests in the liquid in a short time. When inoculation of virus and administration of the drug are begun together and the administration continued for some days afterward, the development of the paralysis is sometimes but not always averted. Hexamethylenamin lends itself to modifications by the addition of still other antiseptic groups to its molecule. We have tested a large number of such modifications and have found certain ones to exceed the original compound in protective power, and others to promote the onset of paralysis. This is the common story of drugs. None are wholly without some degree of injurious action upon the sensitive and vital organs of the body. But manipulative skill has already succeeded in eliminating the objectionable and improving the valuable features of certain drugs so that they exert their action but little upon the organs and severely upon the parasites when they become useful as therapeutic agents. This process may be called sundering the organotropic and parasitotropic effects. Whether this can be successfully accomplished with this class of compounds can not be predicted. But if not, the quest will be transferred to still other drugs. When it is accomplished the victory will be won. By whom will the victory be won, and when? Ours is the office of story-teller and not the vision of the prophet!

In giving Huxley to science the Charing Cross Hospital School of Medicine conferred a great benefit upon the world. In imbuing him with the ideals of biological science it performed an especial service for America. For in 1876 Huxley journeyed to Baltimore to deliver the address at the formal opening of the Johns Hopkins University, at which time he outlined in essence the plan of medical education which, twenty years later, was adopted and put into practise at the Johns Hopkins Medical School. The example of this wise foundation, inspired by Huxley, has acted far and wide throughout the United States as a regenerating force upon medical education.

Simon Flexner