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The Rockefeller University

LOCAL SPECIFIC THERAPY OF INFECTIONS*

SIMON FLEXNER, M.D.

THE specific treatment of infectious diseases has, as you are aware, made great progress during the last two decades. In this time some of the most potent curative agents have been perfected and introduced into practical medicine. However, the achievements of an earlier period in this field should not be minimized. One has merely to allude to the examples of quinine and mercury, to be reminded of the discovery of two of the most perfect drugs for the conquest of specific infections that are still at our disposal. Moreover, these specific remedies date from a period anterior to the present one, in which new remedies are worked out in the laboratories before they are applied to the relief of human suffering. Since the experimental method in medicine is responsible for the recent great advances that have been made, it will be of some interest to refer in passing to the circumstance that the discovery of quinine and mercury was not through magic or intuition but also by experimentation, but in this instance the experiments were conducted upon sick human beings. That is to say, the adoption of these drugs represents merely a selection out of countless hundreds of substances that had at one time or another been tested against the diseases malaria and syphilis.

We are to consider briefly the subject of a specific form of treatment of disease that is distinguished by the peculiarity that it comes to be applied locally to the focus of infection. In order that we may appreciate the purpose of this method, and also the nature of the method itself, it will be necessary to lay before you a few general data concerning the subject of infection and of recovery from that condition.

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In the pursuit of knowledge of the subject of infection, no aspect of the problem has been more enlightening and rewarding than that relating to the reasons for spontaneous recovery from infectious disease. The leading physicians have rarely failed to appreciate the unexcelled power of Nature herself to heal her self-inflicted wounds, and to recognize that many diseases tend of themselves, when not quickly fatal, to progress toward recovery. There resides, therefore, within the animal body, a set of potential forces capable, when aroused, of exercising a highly effective control over disease. You are familiar with the fact that these powers have been traced to a group of substances contained within the blood and passing from the blood into the lymph, where they exert influence on the cells composing the organs and on parasites in the interstices of their tissues.[1] What these substances consist of has already been ascertained in good part, so that they may be classed briefly into soluble, complex chemical bodies, probably of protein nature, that are contained dissolved in the fluids, and of certain mobile white cells, the so-called leucocytes or phagocytes. In virtue of the soluble form and the motility of the cells, these healing substances are able to reach most parts of the body where their special properties may be exerted. Moreover, not only are these curative substances, technically called "immunity principles," preformed in all individuals in which they operate against intending infection, but they

[1] The native curative powers of the blood have been invoked to heal local diseases through the creation of a condition of artificial hyperæmia or congestion. "All organs that functionate are hyperæmic during activity. In every form of growth and regeneration local hyperæmia is present and in a degree corresponding to the rapidity and energy of the growth. . . . . All reactions to foreign substances, whether crude bodies or minute parasites or their chemical products, are associated with hyperæmia. There is no lesion which the body tries to and is capable of removing by rendering harmless, that produces anæmia. Hence if we accept the reactions of the body as useful efforts of Nature, we must admit that hyperæmia is the most common of all autocurative agents" (Bier, Hyperæmia, Translation by G. A. Bleek).

become quickly increased in amount when an infection has been established; and the ultimate issue of the condition in spontaneous recovery or the reverse depends upon the degree of this response to infection and the competency of the curative principles evoked to reach and to suppress the infectious agent.

These principles come to operate equally against all classes of microbic parasites, whether protozoa, bacteria, or that remarkable class the import of which we are just learning—the so-called submicroscopic or filterable organisms or viruses.[2] But the effectiveness of their operation is determined not only by the intrinsic qualities of parasite and of host, 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 a pathological process in the interior of an important organ or part, may be the factor determining whether not only the native curative principles shall gain ready access to them, but whether also extraneous curative agents introduced into the body shall be able to reach the seat of disease.

The parasite, struggling to survive, withdraws, at one time,

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[2] A number of diseases of the higher animals, including man, and one disease of plants (the mosaic disease of tobacco) have, within ten years, been traced to submicroscopic parasites. It is indeed not remarkable that the present microscopes should have failed to define the limits of organized nature. Whether we shall ever invent instruments capable of resolving and rendering visible these minute particles of living matter is a question impossible to answer. Even doubling the potential power of the microscope by the device of employing, for photographic purposes, the ultraviolet rays of the spectrum has failed to bring them into view. Their place in nature is not accurately established. Some, as the parasite causing yellow fever, that passes a stage of its existence in mosquitoes, probably are protozoal; others, as the parasite of pleuropneumonia of cattle, that can be propagated in artificial cultures, probably are bacterial. It can hardly be doubted that they are living organisms, since they are capable of transmission from animal to animal, in which they produce infection, through an indefinite series.

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 agents purveyed by the blood. This is the condition met with in massive inflammations, in abscess formation, and in infections of specialized portions of the body—such as the great serous cavities—that receive normally a modified and dilute lymph secretion.

It is the lymph that carries the protective as it does the nutritive principles for the tissues and organs; and hence this fluid provides the essential safeguard against infection. Moreover, the quality of lymph in the several serous cavities is not the same, but is, indeed, peculiar for each cavity, and the lowest limit of strength is reached by the cerebrospinal fluid —regarded as the lymph of the brain and spinal cord, which is almost devoid of protein matter.[3] As the protein moiety of the lymph carries the immunity principles, it follows that the serous cavities are really less well supplied with them, and the subarachnoid space of the central nervous system the least well of all. These considerations are not without high importance as affecting the provisions for warding off intending infection, and especially for controlling and abating an established infection. Since the anatomical structure decides the quality of the lymphatic fluid in health, it also determines it

[3] The notion that the cerebrospinal fluid is the lymph of the central nervous system is open to discussion. Mott (The Lancet, 1910) suggests that it "may serve as the ambient fluid of the neurons and play the part of lymph to the central nervous system." The fluid arises from the choroid plexus and escaping from the foramina of Magendie and Luschka into the subarachnoid spaces occupies them all and communicates, probably, with a "canalicular system surrounding the cells and vessels of the brain" (Mott). Thus this fluid should provide the most direct path for the penetration of active substances to the nervous tissues; and in fact it has been established by experiment that chemical bodies act upon the nerve cells with greater energy and certainty when introduced directly into the cerebrospinal fluid. The hen, indeed, is not subject to the effects of tetanus toxin injected into the blood, while it suffers from tetanus when it is injected into the subarachnoid spaces (Behring).

in disease, and thus by regulating the composition of this fluid commands the issue of the pathological process. Under such circumstances the parasite that becomes localized in these cavities is insured a potential advantage against the host.

The parasites possess, moreover, an advantage of regulation within themselves to preserve them from extinction—they are capable of altering rapidly, not their form and external appearances, but their chemical reactions and probably chemical structure when too closely pressed and menaced. The change consists in the development of a state of effective resistance, called "fastness," to injurious chemical agents, whether the immunity principles of the blood or other substances. The new qualities acquired have been viewed as the result of mutation among the parasites, and the mutants have been observed to transmit the new characters through an indefinite number of generations. It is precisely this property of mutation that we are learning to hold accountable for the troublesome or dangerous relapses that occur in many of the parasitic diseases, commonly for example in malaria, sleeping sickness, spirochætal infection, to mention only a few.[4] Finally, the so-called chronic carrier of infectious organisms, who is being recognized as a serious menace to the health of society and is sincerely to be pitied, is to be regarded often as the victim of this form of mutation among the micro-organisms which at one time caused him to be ill, but to which he, but not his fellows, has become adapted. In the successful exploitation of specific therapeutic measures account must obviously be taken of the biologi-

[4] This parasitic mutation or "fastness" is more readily developed against serum immunity principles (antibodies) than against chemical agents of the nature of drugs, but once produced, the latter effect is the more difficult to remove. Serum fastness may be overcome by the superinfection of an animal that has recovered from infection with the corresponding "fast" strain, through which reversion to the normal type may be accomplished; while chemical mutation is overcome solely, apparently, through sexual conjugation of protozoal parasites in the body of an appropriate insect host (Ehrlich, Folia Serologica, 1911, p. 697).

cal conditions described as well as others that may in time be discovered.

Manifestly, therefore, the bringing of the parasitic causes of microbic diseases under the influence of curative agents will be more readily and certainly accomplished when they are widely disseminated throughout the body than when they are hidden away within an organ or in the interior of a serous cavity. Hitherto the most effective agents of specific treatment have been just those that operated against the generalized infections, of which examples are such drugs as quinine in its action against the malarial parasite, and mercury in its effect on the spirochætal cause of lues. The same result is now being achieved by salvarsan, recently discovered by Ehrlich, in respect to its application to a number of spirochætal affections in man and the domestic animals; while the control of diphtheria by antitoxin, perhaps the most perfect example of all, consists essentially in the neutralization of a universally distributed toxic or poisonous agent that is directly the cause of the serious effects of the disease. When, in generalized infections, the surviving micro-organisms escape from the blood and tissues, as sometimes happens in luetic or other diseases, to aggregate in special situations and local pathological products that are reached imperfectly by the lymph, then the specific drug or other agents assert their curative powers with far more difficulty and far less certainty.

Medicine is now armed with a number of specific remedies for serious diseases, consisting partly of chemical compounds of known composition and partly of more complex serum products of unascertained nature. The number of drugs is potentially greater than the number of sera and is capable of almost unlimited expansion, so that doubtless therapeutics will be greatly enriched by future discovery in this fascinating field. That many immune sera are capable of being prepared artificially is also certain, but the degree of their applicability will need to be worked out in any given instance. It is already clear that the immune sera closely resemble the natural defences against infection and its consequences, so that it follows that

they are essentially non-foreign bodies, and thus, technically, ideal agents with which to combat disease. They are, in essence, so precisely fashioned as to operate exclusively against the agents of infection, and thus to pass over without molestation the sensitive cells of the organs. In fact, their action is less specific than this statement implies, because, as now manufactured, they carry with them in the natural serum of animals certain alien substances that do effect, in some degree, the host himself. A factor that bears upon the production of curative immune sera as well as upon specific drugs is that of fastness or mutation of the micro-organisms within the body. Experiment has already disclosed the high importance of this unexpected phenomenon of infection. In the choice of especially fashioned drugs the two properties that now determine availability for practical medical employment are, first, a low degree of toxicity for the organs of the host, and second, absence of the tendency to produce fast strains of the parasite upon which they exert their influence.

We have still to learn the extent to which specific drug treatment of the infections is capable of altering the state of the acquired immunity to infectious diseases that protects, in some instances, from second attacks of maladies. Important facts bearing on this subject are already appearing in connection with the more energetic modes of treatment recently introduced for the spirochætal infections. It seems that possibly the refractory state in these infections is the result of an enduring sub-infection, the complete removal of which exposes the individual to reinfection.[5] In a similar manner it would appear that in the suppression of microbic agents of disease by the body's forces through a process of immunization, the serum products are more varied and complex than are produced in the

[5] Ehrlich (loc. cit.) explains this phenomenon in a slightly but not fundamentally different manner. He accounts for the decreasing number of spirochætæ, as the disease advances, by a wiping out of the parasites through the action of the successive specific antibodies formed. The fresh outbreaks or relapses, then, are caused by mutants or fast strains that are immune to the antibodies thus far elaborated,

course of artificial immunization of animals that are destined to yield sera to be employed passively, by injection, in the treatment of their corresponding diseases; and that this greater complexity arises from the circumstance that in the suppression of the micro-organisms in the infected body, not only the normal strains but also the mutants are successively overcome, with the result that a series of immune principles, each directed against its particular variety of parasite, is elaborated. Diseases of a relapsing character are accountable for on the basis of the conception that each successive relapse coincides with the appearance of a new mutant of the infecting organism; and the typical disease of this class, relapsing fever, so-called, is characterized by the ability of its spirochætal cause to undergo at most three or four mutations that in turn lead to an equal number of relapses, which, if survived, are followed by an enduring disappearance of the infection. Hence in the artificial production of curative sera we shall have to take account of the mutants or fast strains of the micro-organisms used for immunization purposes. This result is not necessarily accomplished, although it may be promoted by selecting cultures from many different sources. What is required is that we shall learn to distinguish the fast strains or mutants outside the body in cultures and even, indeed, to create them at will so that they may be employed for enriching the sera produced in animals that will thus be better adapted to their purpose of suppressing the parasitic causes of disease.

The successful issue of specific therapeutics, toward which goal our hopes have been eagerly turned by the triumph of experimental medicine, will be secured not only by the production of more perfect instruments for the suppression of the microbic causes of disease, but also through a more effective

and the subsidence of the lesions depends on the production of antibodies for the new strain. During the actual existence of the syphilitic infection insusceptibility to reinfection is secured by the presence of antibodies in the blood to which the strain of spirochætæ, intending to infect, is not immune. But once the disease is actually terminated and all the antibodies have been discharged, reinfection with a normal strain becomes possible.

application of the curative agents themselves to the seat of disease.

I have alluded to the circumstance that the infectious agent may be strengthened in its attack by confinement within the organism, through which confinement it is preserved from injury by the defensive principles in the blood and lymph. Now no group of infections is in position better to secure this protection than that located within the membranes surrounding the brain and spinal cord, the fluid contents of which are so poor in defensive principles; and for this reason, and for the reason also that the subarachnoid spaces in these membranes are in such intimate association with the peri-cellular spaces about the sensitive nerve-cells, the consequences of meningeal infections are highly serious. To endeavor to reach the infections seated in the membranes by means of the general blood and lymph circulation is futile because of the established fact that not only are the large protein molecules, which include the immunity principles, not secreted within the membranes, but also because highly diffusible salts tend as well to be excluded. But what cannot be thus accomplished by indirection can, in this important instance, be achieved by direction. No operation is simpler in competent hands than lumbar puncture, so-called, which came into use originally to provide cerebrospinal fluid for purposes of diagnosis and now promises to be of far greater value in affording the means of local specific treatment of meningeal infections. How valuable this route may be for the introduction of curative agents is illustrated best at the moment, perhaps, by the convincing results that have been obtained in the treatment of epidemic cerebrospinal meningitis by the antimeningitis serum. This therapeutic agent is utterly without effect on the local infection when introduced directly or indirectly into the blood, but it has proven of unmistakable value when injected into the seat of the disease by lumbar puncture. The latest figures relating to its employment are, and should be, the most favorable to its action, since the methods of production and administration have been improved through experience; and, therefore, it is

a source of gratification that in the recent French epidemic of meningitis the gross mortality among cases treated by serum injections begun in the first three days of illness fell below 10 per cent.

The results secured in epidemic meningitis have suggested the extension of the method of direct local specific treatment to still other kinds of infection of the meninges. Meningitis is now known to be caused by a number of micro-organisms, including the streptococcus, staphylococcus, pneumococcus, the bacillus of tuberculosis and of influenza. Generally speaking, all these inflammations are highly fatal in character. There is still doubt whether recovery from tuberculous meningitis ever takes place; the number of recoveries from pneumococcus meningitis is surely very few; and while we are just learning the extent to which influenzal meningitis prevails, we can already predict that the infection is not only not infrequent, but it is highly fatal in character. Many cultures of influenza bacilli have slight or non-appreciable action on animals, and cannot, therefore, be employed for purposes of artificial immunization; but cultures obtained from cases of influenzal meningitis not only can be used for preparing an immune serum, but also produce, when injected into monkeys, a form of meningitis that in its nature, course, and fatal effects cannot be distinguished from the spontaneous human affection. This experimental fatal disease, like epidemic meningitis, can be controlled by the intraspinal injection of an anti-influenzal serum. The degree of applicability of this serum to the treatment of spontaneous disease in human beings is still to be determined; but in view of its highly fatal character it should be tried. Undoubtedly, it will be necessary to apply the serum early and by repeated injection to secure beneficial results; and the early application will be dependent upon prompt bacteriological diagnosis, which can be made by immediate microscopical examination of the cerebrospinal fluid.[6]

Influenzal meningitis, as it occurs spontaneously or is produced experimentally, is attended by an invasion of the blood

[6] See Wollstein: Jour. Exp. Med., 1911, xiv, p. 73.

with the influenza bacilli which sometimes appear there in large numbers. It is important, therefore, to consider the consequences of the bacteræmia, as it is called, upon the local treatment of the meningeal infection. Now, fortunately, the difficulties surrounding the passage of the antiserum from the blood into the cerebrospinal fluid are sharply contrasted with the ease with which the antiserum escapes from the meninges into the blood. This discrepancy is explained by the fact that while the fluid on entry is in the nature of a secretion from the choroid plexus, the escape is by way of the veins in the membranes themselves.

While, therefore, it is impractical to bring the antiserum into the meninges from the blood, the reverse effect is readily accomplished; and thus it comes about that in such secondary infections of the circulation with bacteria as are being here considered, the suppression of the local development not only stops the eruption of bacilli that causes the blood infection, but the passage of the antiserum from the membranes into the blood arrests their development there.

Probably recovery from any local bacterial infection is not wholly accounted for by the several activities of blood-serum and phagocytes that are usually invoked to account for the phenomenon. This restricted view leaves out of consideration certain definite chemical substances that are always present in a focus in which tissues and cells are disintegrating. That some of these substances are injurious to bacteria we now know. While the nature of the so-called stabile bacterial substances yielded by extraction of the somatic cells is still doubtful, it would appear that among them are certain soaps yielded by disintegration of the neutral and higher phosphorized fats contained within protoplasm. That soaps are injurious to bacteria has been abundantly proven; so that the view should be entertained that the degeneration of leucocytes and tissues which results from a local bacterial infection may not be entirely to the advantage of the parasitic agent, but is also of use to the body in assisting it to overcome the bacteria, since the cells brought to death and disintegration by the parasites yield

chemical substances that themselves exert a destructive action upon the infecting bacteria.

The application of these considerations to the treatment of a typical pneumococcus infection, such as the experimentally produced pneumococcus meningitis in the monkey, has been rewarded with significant results. We are still ill-informed of the factors which control resistance to and recovery from a local pneumococcus infection. The decrease in number of the organisms that takes place as recovery progresses in lobar pneumonia, for example, has not been shown to depend either on phagocytosis or on serum solution of the bacteria. It is a highly suggestive fact that the pneumococcus differs from most bacteria by reason of its solubility in chemical solutions, such as those containing bile-acids and, as has been recently discovered, soaps. The effect of soap is peculiar in that exposure of the pneumococci to its weak action merely modifies the texture without altering the growing properties in cultures, so that when the soaped pneumococci are next exposed to blood and serum, and especially to an antipneumococcus serum, they suffer complete dissolution. These conditions are, indeed, present in a local pneumococcus infection since soaps are produced there, and during its progress immunity principles appear in the blood and lymph.[7]

By employing a suitable combination of sodium oleate and antipneumococcus serum, experimental pneumococcus infections of the meninges can be controlled and abolished. Through this means monkeys that would surely have succumbed have been repeatedly restored to health. But the successful employment of the soap and serum mixture rests upon the overcoming of the property that the soap possesses of uniting with the protein of the antiserum and thus being rendered inert and withheld from acting upon the pneumococcus. This obstacle is the common one on which so many high hopes of the chemical suppression of infections, by what is termed "internal antisepsis," have been wrecked. Luckily, in this instance, it has been proven that the soap portion can be kept apart from the

[7] See Lamar: Jour. Exp. Med., 1911, xiii, p. 1.

protein moiety of the serum by introducing a second protective chemical body, itself innocuous, into the mixture. When minute quantities of boric acid are thus introduced, the soap is isolated and left in condition to exert its injurious action upon the pneumococci, for which organisms it appears to have a greater affinity than for ordinary protein matter. Whether among the products of local tissue disintegration a similar separation of the soap and serum elements is secured has not been ascertained; but we should consider factors that possibly suffice to overcome this initial impediment to the bactericidal action of the soaps, among which are the proximity of the bacteria to the nascent fatty acids and soaps and the natural occurrence within the exudate of chemical bodies that have the effect of removing the protein inhibition.[8]

The antisera and the chemical disintegration products of cells do not exhaust the list of defensive agents that operate against infection, for there remain the living leucocytes themselves. Certain bacterial infections that have not thus far been made to respond to the dissolved immunity principles may still be subject to influence by the white cells of the blood. Hence the effort has been made, and with an encouraging degree of success, to control experimentally produced tuberculous pleurisy in the dog by the repeated injection of living leucocytes;[9] and the observation made upon this condition has been extended to include experimental tubercular meningitis produced likewise in the dog, the course of which it has also been found possible to affect in a favorable manner.[10] In the pneumococcus and tubercular infections just considered, as in the influenzal bacillus affection already mentioned, the general infection of the blood and organs has been suppressed or much reduced by the local specific treatment.

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[8] The fatty acids and soaps are yielded by the dissolution of the neutral and the higher phosphorized fats contained within the cellular protoplasm in which other colloidal bodies of a protecting nature may well be stored.

[9] See Opie: Jour. Exp. Med., 1908, x, p. 419.

[10] See Manwaring: idem, 1912, p. 1.

Although the treatment of these tuberculous affections with leucocytes is still in the experimental stage and is not yet ready for application to medical practice, it has been described in this connection in order that there might be brought under review the diverse means that are at present invocable in the efforts to determine the conditions that underlie the therapeutic control of varied infectious processes.

Finally, the application of the principle of the local treatment of infections holds out hope of some measure of therapeutic control, at least, of that serious and menacing disease, now in the foreground of interest for physicians and public alike, namely, epidemic poliomyelitis. The propagation of the disease in monkeys has led to the elucidation of its cause and pathology, while at the same time it has exposed it to therapeutic experimentation. The cause of the malady is an exceedingly minute parasite—submicroscopic and filterable—which probably gains access to the spinal cord and brain by way of the meninges and through the lymphatic connections that surround the olfactory filaments that terminate in the nasal mucosa and are in direct communication with the subarachnoid spaces. The lesions of the meninges constitute an important effect of the infection, and especially of those prolongations of the meninges about the veins and arteries that enter the spinal cord and bulb and support the perivascular lymphatics. The lymphatics and, indeed, the subarachnoid spaces in general, comprise a system of communicating channels charged with cerebrospinal fluid that extend to the pericellular spaces and therefore penetrate to the nerve-cells. Consequently a parasitic or toxic agent that gains access to the cerebrospinal fluid is capable of ready transportation to all parts of the nervous system; and by utilizing the same route it is obviously possible to distribute what may prove to be a soluble antagonistic and therapeutic agent.

Recent experiments have shown unmistakably that spontaneous recovery from poliomyelitis is brought about by a set of immunity reactions that involve the formation in the blood of soluble principles or antibodies for the parasitic

virus. Similar principles are formed in inoculated monkeys; and they can be used successfully, up to a certain point, when injected into the spinal canal by lumbar puncture, in preventing the development, after an intracerebral inoculation of the virus, of experimental poliomyelitis. This effect has not yet been accomplished by the introduction of large quantities of immune blood into the circulation, a result that was predictable in view of the location of the pathological process that leads to the paralysis in the meninges.

It is not excluded that epidemic poliomyelitis may be subject to effective treatment by drugs. There is, indeed, one drug—urotropin, or hexamethylenamin—that does exert some action even when administered by the mouth, since it presents the exceptional instance of a chemical body being excreted into the cerebrospinal fluid.[11] But its powers are limited. However, as the drug is constituted in a manner that permits of many modifications of its composition without the sacrifice of its central structure through which formaldehyde may be liberated, it has been found readily possible to prepare a number of derivatives far exceeding urotropin in activity, some of which have been applied to the treatment of experimental poliomyelitis with a hopeful measure of success. These new compounds, it should be added, require to be injected into the spinal membranes and act best in conjunction with an immune serum.[12] They are subject to rapid dissociation, upon which phenomenon probably their high activity depends; and

[11] See Crowe: Bull. Johns Hopkins Hosp., 1909, xx, p. 102.

[12] The advantage to be secured against the parasites by employing more than one antagonistic agent results, first, from the circumstance that an antibody or drug will operate with greater effect against an already injured than against a normal parasite, and second, because mutation in two directions is less readily effected than in one direction. Hence a fortunate combination of serum antibodies and a drug offers, theoretically, a favorable means of overcoming an infecting micro-organism. Ehrlich (loc. cit.) recommends the simultaneous employment of two curative substances, one of which is especially chosen to injure the protoplasm and the other the nuclei of the parasites.

the dissociation proceeds somewhat more slowly in the presence of the colloidal constituents of the immune serum that itself carries a small amount of healing substances. This is obviously no more than a beginning in the effort to accomplish therapeutic control of this protean and serious disease, the natural history and significance of which are just beginning to be appreciated; but the outlook for its conquest is at the moment made hopeful through the utilization of the method of the local specific treatment of infections.

The arguments that have been presented and the examples adduced would seem to possess not only theoretical but also established value in justifying the further pursuit of the measure of opposing local infection by local specific remedies. In the effort to combat the infectious processes account will have to be taken, in any given instance, of the peculiarities of the infecting parasite, as well as the particular anatomical and physiological adjustments of the infected parts, that together constitute the foundation upon which effective specific therapeutic effort must ultimately come to rest.