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THE LOCAL SPECIFIC THERAPY OF INFECTIONS *

I. THE BIOLOGIC BASIS

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Infection is a contest between two opposing forces: one the invading parasite, the other the resisting host. It is a struggle between two contestants, each displaying great resourcefulness and consummate skill. I propose to lay before you the main facts of this combat in so far as they have been worked out and to draw from them a deduction looking to the better control by improved therapeutic methods of the issue of infection.¹

The properties of living things are not fixed, but are subject to certain and sometimes fundamental fluctuations. What are described as biologic variations arise among the very lowly bacteria and protozoa as among the higher types of plant and animal life.² The character of the variations differs merely because of the minute size and the simplicity of structure of the micro-organisms, while the variations themselves are for the same reasons made more difficult to detect. But they can, nevertheless, be followed accurately both in their cultural qualities and immunity reactions; and it has been found that these variations play a significant part in respect to the specific treatment of disease.³

The microbic causes of disease are subject to a wide play of essential properties, in part spontaneously, as we say, and in part in response to certain definite experimental conditions. The resultants of the changed conditions are new varieties or forms that retain the new characters for indefinite generations and suffice often to constitute new species.

Thus bacteriologists who have occupied themselves with the study of the group of dysentery bacilli or the wider class of colon and typhoid bacilli now find support for the conviction long held that within these groups genetic relationship among the members exists; and while no one has actually as yet succeeded in converting the dysentery bacillus F into the bacillus Y, and while it may still be doubted, notwithstanding the statements

to the contrary, that a typhoid bacillus has been experimentally converted into a paratyphoid bacillus, yet it is nevertheless true that certain colon bacilli regularly undergo changes and develop new special properties quite as fundamental as those that distinguish from each other the types of dysentery bacilli and the typhoid and paratyphoid bacteria.²

Moreover, many bacteria are sensitive to chemical poisons to which they may, however, be adapted; and the new strains produced often retain the power to grow in the presence of the poisons even after long being separated from them.⁴ When it is recalled that the bacteria often pass through many generations within twenty-four hours it will be seen that this quality of chemical resistance is transmissible to an indefinite series of offspring. It also happens that chemical resistance produced to one poison, such as arsenic, may lead to the simultaneous development of resistance to another, such as antimony; and it has further been ascertained that this power of chemical resistance in artificial cultivations may be retained even when the altered bacteria are returned to the animal body.⁵

The bacteria and protozoa show even more fundamental variations in relation to immunity reactions. Inagglutinable strains of bacteria have long been known as occurring in nature, and similar strains have been produced from previously agglutinable ones by artificial methods of cultivation. In nature, moreover, certain micro-organisms, among which may be mentioned the pneumococcus, streptococcus and the trypanosome of sleeping-sickness, exhibit variations of chemical and immunity reactions that serve to separate them into definite classes or types which, as will be shown, play a highly important part in respect to the specific therapeutics of the infections they cause.⁶

We have now seen that variations in properties among micro-organisms may be native or they may be developed by artificial conditions of growth. It remains to add that new varieties also arise among parasitic microbes developing within the body of infected animals. Thus, such micro-organisms as the malarial parasite, the trypanosome of sleeping-sickness and the spirochete of relapsing fever or syphilis, may, as a result either of the processes of spontaneous recovery, or of induced healing by chemical drug or specific serum, suddenly acquire a state of resistance to the curative principles and become no longer subject to their influence. This state of resistance

* This is the first of two lectures which as here presented are based on the Harben lectures of 1912 given before the Royal Institute of Public Health, London, and the Trimble Lectures of the Medico-Chirurgical Faculty of Baltimore of 1913.

1. Flexner: Arch. Pediat., 1908, xxv, 780; The Biologic Basis of Specific Therapy, Boston Med. and Surg. Jour., 1911, clix, 709; The Local Specific Treatment of Infections, Harben Lectures, Jour. State Med., London, 1912, xx, 130, 193, 257.

2. Müller: Bakterienmutationen, Ztschr. f. Induk. Abstamm. u. Vererbung., 1912, viii, 305.

3. Neufeld and Hündel: Ueber Herstellung und Prüfung von Antipneumokokkenserum und über die Aussichten einer spezifischen Behandlung der Pneumonie, Ztschr. f. Immunitätsforsch., Orig., 1909, iii, 159. Ehrlich: Ueber Chemotherapie, Centralbl. f. Bakteriologie, Abt. 1, Referate, 1911, i, Supplement, p. 94.

4. Marks: Ueber einen arsenfesten Bakterienstamm, Ztschr. f. Immunitätsforsch., Orig., 1910, vi, 293.

5. Seiffert: Studien zur Biologie der Darmbakterien, Deutsch. med. Wchnschr., 1911, i, 1064.

6. Neufeld and Hündel: Ueber Vorkommen und Bedeutung atypischer Varietäten des Pneumokokkus, Arb. a. d. k. Gsndtsamte, 1910, xxxiv, 293. Ehrlich: See Footnote 3. Lamar: Chemo-immunologic Studies on Localized Infections, Jour. Exper. Med., 1912, xvi, 581. Spiess: Die Anwendung von Antistreptokokkenserum (Höchst), per Os und lokal in Pulverform, Deutsch. med. Wchnschr., 1912, xxxviii, 207.

has come to be spoken of as "fastness," and its recognition has thrown a new and penetrating light on the troublesome and often very serious relapses that appear in the course of infectious diseases.⁷

In the healing of infectious diseases by Nature, as we are wont to say, we now recognize that the microbial causes are gradually or even suddenly suppressed through the development by the body of immunity principles capable of bringing about their destruction through dissolution or phagocytosis. When healing is promoted by remedies such as the specific serums, the immunity reaction of the infected body is merely anticipated by the artificial injection of the serum. When, on the other hand, curative drugs are employed, the action is somewhat more complex. Under these circumstances the suppression of the microbial causes of the disease is accomplished partly by the action of the drug and partly through the immunity principles developed from the parasites brought to destruction by the drug.⁷

This interaction of chemical substance and specific antibody, through which the parasites are brought to destruction, is a desirable process, since it insures not only prompt recovery from infection but also security against reinfection. Experience has abundantly shown that Nature's mode of cure of many of the infections is perhaps slow, but, none the less, possesses the great merit of affording an enduring protection against another attack of the same malady. This is the reward of a gradual process of immunization that leaves the restored body amply armed with actually or potentially ready immunity principles that suffice to ward off impending infection.⁸ When recovery is assisted by the employment of artificial immune serums the body, probably, is left in much the same state of preparation, while the effect of healing drugs is determined by the precise nature of their influence on the microbial causes of disease and varies according as the resulting dissolution products are not altered chemically beyond the point at which antibody formation is still possible.

Under the older conditions of the treatment of syphilis with mercury, instances of reinfection were rare and commonly disputed. Under the new conditions of treatment with the far more vigorous salvarsan, reinfection indisputably occurs. This disparity is undoubtedly to be attributed to the different responses by antibody formation to the destroyed spirochetes under the two modes of chemical action⁹; and while at first glance the older method appears to possess advantages over the newer, there are, as a matter of fact, offsetting conditions that quite change the situation.

Not a few infections, and those particularly that pursue a chronic course, are characterized by a tendency to recrudescence or relapse in process of recovery. This condition is commonly observed in malaria, spirochetal infections, trypanosomiasis and tuberculosis. It also appears with less regularity among many other infections. Excluding tuberculosis from present attention because of the lack of knowledge of transformation in type of tubercle bacilli within the body, we may consider what happens when relapses take place in the remaining infections. It is common knowledge that in the course

of treatment of malaria with quinin a state of excessive resistance of the parasite to the drug sometimes arises. In the treatment of trypanosomal and spirochetal infections similar resistances are encountered. Indeed, so commonly has this phenomenon been observed, in the course both of spontaneous or natural infections, so-called, of man and animals and in the experimental ones as well, that the corresponding relapses are now recognized as a characteristic of the clinical characters of the diseases concerned.

Painstaking study has yielded an explanation of the cause of the resistance among the parasites on which the relapses depend. The resistant parasites are variants of the normal species produced artificially in the course of treatment by antibody or by drugs. The variations induced may persist indefinitely and be transmissible. According as the parasite affected is capable of appearing in few or many relapse forms, so-called, the corresponding diseases are attended by few paroxysms, as in relapsing fever, or many, as in malaria or syphilis. Ultimately the complete suppression of the infecting cause is due, when it is accomplished, to the development within the host of as many kinds of antibodies as relapse types of the parasite occur.

Hence in considering the problem of the therapeutics of infection we must take into account the fact that the parasites possess an advantage of regulation within themselves to preserve them from extinction, through which they alter rapidly, not their form and external appearances so much as their chemical characters, when too closely pressed and menaced. And this change consists in the development of a state of resistance or "fastness" to injurious chemical bodies, whether the immunity principles of the blood or still other substances.

It is true that the active termination of infections through the unassisted elaboration of specific protective principles by the infected body probably oftener secures to the host an enduring immunity than does the more quickly induced passive termination through the operation of artificial healing substances; for in the first instance the variety of antibodies evolved may equal all the possible number of normal and fast strains to which a given microbe is subject and thus a more perfect protection be secured. A specific treatment that destroys the parasites, not at one blow, but successively may, however, bring about a similar result, since, although each succeeding group of parasites yields less easily, yet in succumbing it gives rise to a new variety of antibody. Against the advantages of producing by a slow process an enduring immunity or recovery, however, must be weighed the danger of fast strains arising that may prove impossible of destruction with any known means whatever. From the point of view of effective therapeutics it is thus clearly desirable to terminate the infection quickly and diminish the risk involved. To accomplish this result several factors must cooperate: the specific chemical or serum must not only be suitable but also come to act on the parasitic causes of disease in such degree of concentration as to insure the maximum effect. It has been shown for trypanosomal, meningococcal and streptococcal infections that the higher the concentration of the specific immune serums about the corresponding parasites the greater is the assurance of their complete destruction.¹⁰

7. Ehrlich: Ueber Chemotherapie, *Centralbl. f. Bakteriol.*, Part 1, Referate, 1911, I. Supplement, p. 94. Rosenthal: Experimentelle Untersuchungen über das Wesen und die Genese des Rezidivs Ztschr. f. klin. Med., 1913, lxxvii, 161.

8. Flexner: The Biological Basis of Specific Therapy, Boston Med. and Surg. Jour., 1911, clxv, 709.

9. Schilling, von Krogh, Schrauth and Schoeller: Die Wirkung organischer Quecksilberverbindungen bei Spirochäteninfektionen, *Ztschr. f. Chemotherapie, Orig.*, 1912-13, I, 21. Anton: Sieben Fälle von Reinfektion syphilitica und Betrachtungen über schwere salvarsan-Intoxikationen, *Deutsch. Med. Wochenschr.*, 1913, xxxix, 508.

10. Ehrlich: See Footnote 7. Flexner: A Serum-Therapy for Experimental Infection with *Diplococcus Intracellularis*, *Jour. Exper. Med.*, 1907, ix, 168. Flexner and Tobling: An Analysis of Four Hundred Cases of Epidemic Cerebrospinal Meningitis Treated with the Antimenigitis Serum, *Jour. Exper. Med.*, 1908, x, 690. Neufeld and Kundla: Beitrag zur kenntnis der "antilaggressiven" Serum. *Arb. u. d. k. Gesundheitsamte*, 1912, xl, 1.

There is still another consideration that merits attention. Hitherto we have employed curative serums or drugs separately, and not in conjunction, to support and supplement each other. Since in the course of their curative action the specific drugs are assisted in the destruction of parasites by antibodies, the artificial combination of specific drug and specific antibody should offer definite therapeutic advantages. One of the advantages to be gained by enlisting more than one antagonistic agent against the pathogenic micro-organisms results from the circumstance that an antibody or drug will operate with greater effect against an already injured than against a normal parasite, and, next, because mutation in several directions is less readily achieved than in the one direction. Hence a fortunate union of serum antibodies and suitable chemical substances affords, in theory at least, a favorable means of suppressing infection. That this is not merely a fancy, but has already been verified by experiment, it will be part of the next lecture to show. But just as the availability of every chemical substance is determined by the manner of its distribution in the body, and that in turn is decided by facts of chemical and physical affinity for particular tissues and cells, so will the utilization of combinations of different therapeutic agents depend on the completeness with which they can be made to act together in the manner designed. This requirement might be met either by happy accident, once the joint bodies are introduced into the blood and allowed of their own affinities to seek together the places at which their action is to be manifested, or by intent, when they are introduced purposely directly into the seats of disease.

Having accomplished so much we must look forward as a next step to the greater perfection of immune serums themselves. By taking into account the natural types or races of pathogenic micro-organisms, each with its definite specificity, and perhaps also the fast strains artificially produced, new and more effective bactericidal serums may be produced. In the past an effort has been made, but imperfectly, to develop polyvalent serums by employing for immunization purposes many different strains of a given micro-organism; but increased knowledge has shown that this method may or may not succeed, according to whether in the choice of cultures racially dissimilar strains have or have not been secured; for an immune serum prepared with one racial strain will be effective against all samples of that strain and wholly ineffective against all members of another strain, and vice versa. The problem, therefore, is first to adapt the serum or chemical to the particular strain of infecting micro-organism and then to insure its maximal effect by direct application to the seat of infection.

It should now be apparent of what high importance in respect to the specific treatment of microbial disease is this phenomenon of variation among micro-organisms, which earlier I compared to mutation among the higher plants and animals. The variations among the bacteria and protozoa occurring in external nature, or produced in test-tubes, or appearing under the influence of drug or antibody acting within the infected animal, arise often with startling rapidity. They are therefore in essence identical with those alterations of character that constitute mutation among the higher living organisms. But there remains, possibly, still another way in which this phenomenon may operate to cause disease. The realm of microbiology includes the subject of epidemiology or the science of the nature of the causes accountable for epidemics of disease. The data of epidemiology, because of their inherent complexity, are still few and uncertain.

Now I wish to suggest that those remarkable and often sudden accessions of virulence in micro-organisms that determine devastating epidemics may have their origin in mutational modifications affecting particularly their pathogenic or disease-producing power. We have recently witnessed manifestations of sudden accession of disease-producing power, which have resulted in pandemics of meningitis and poliomyelitis, that within ten years have twice encircled the globe; and, in a somewhat more restricted field, severe outbreaks of milk-borne streptococcus infection prevailing in Baltimore, Boston and Chicago and claiming many victims. Imperfect as our knowledge is of the relation between cultural conditions and the rise of virulence, nevertheless evidence exists tending to show that plague bacilli¹¹ in artificial culture may suddenly take on a heightened pathogenic power, and streptococci growing in milk as suddenly assume the cultural peculiarities of the special micro-organism responsible for the epidemics of so-called streptococcal septic sore throat.¹²

Turning now to another aspect of our theme, namely that of local therapy, it should first be stated that the idea of specific treatment of disease is not a new invention, although the significance of the term to-day is wholly different from that previously current. The discovery of specific drugs for combating disease is not a new achievement. Cinchona bark and its alkaloidal constituents and the compounds of mercury are as specific therapeutic agents as the latest product of the biochemical laboratory. But the manner of attacking the problem of the cure of disease is wholly different to-day from what it was in the past. The place of chance and empiricism which ruled the earlier quest has been taken by knowledge, in many ways and cases accurate and full, concerning the nature of the causes of the infectious diseases and the means of their suppression. It is, indeed, to the acquisition of this fund of knowledge that we owe the more rapid advances being made and the hopefulness with which the immediate future of discovery in the domain of specific therapy is being viewed. Having now considered some of the shifts adopted by the parasites to accomplish the ends of infection we may turn with profit to an examination of the means employed by the animal body in resisting their effects.

Immunology and experimental therapeutics have established the chief factors on which recovery from infection rests. All are in last analysis chemical reactions that are performed with varying reagents consisting of antibodies, phagocytes and specific drugs, acting separately or together. Probably the antibodies and phagocytes always cooperate and in many instances certainly, if not in all, the antibodies, phagocytes and drugs as well. Recovery from infection, therefore, is brought about through suppression of the microbial causes either by biologic antibodies evoked within or by drugs introduced from without the body. The antibodies, it is well known, consist of several sets of definite substances named cytolytins, agglutinins, precipitins, opsonins, etc., beside which are to be placed the essential leukocytes or phagocytes whose part in the drama is not less conspicuous. You are aware, moreover, that at best the antibodies are but slightly represented in the healthy body and are produced anew either wholly or largely in the infected one; while the quality of the phagocytes is not noticeably

11. Gotschlich: Allgemeine Morphologie und Biologie der pathogenen Mikroorganismen, in Kollé-Wassermann: Handbuch der pathogenen Mikroorganismen, 1911, 1, 167.

12. Davis: Bacteriologic Study of Streptococci in Milk in Relation to Epidemic Sore Throat, THE JOURNAL A. M. A., June 15, 1912, p. 1852.

altered, although their number is often increased and their activities are frequently excited through new antibodies, such as opsonins, which are elaborated.

The antibodies, or immunity principles, as they are also called, are detected in the blood, although produced in the bone-marrow, spleen and lymphatic tissues generally. The quantity existing in the blood is taken as a measure of their potency, although in a few known instances efficient immunities exist without the presence of demonstrable corresponding antibodies in the blood. The immunity principles, however, and the phagocytes that act along with them in defense of the integrity of the organism, pass from their sources of production in the organs into the blood, from which they endeavor to reach the special locations of the infective microbes which they are designed to overcome.

In identical manner the curative serums prepared artificially in animals and the specially fashioned specific drugs that are introduced into the body from without are so placed as to reach as directly as possible the circulating blood, which is to become the purveying medium to the rest of the body. We are obliged, therefore, to take account not only of the nature but also of the manner of distribution of parasitic micro-organisms within the infected body, either as they occupy the blood, when they can obviously be brought immediately under the influence of the curative agents, or as they are confined in the tissues or segregated in a remote cavity where they cannot be reached so directly. In the latter instances they can at best come under the influence of the lymph that in process of being separated from the plasma of the blood carries away from the latter part of its various dissolved ingredients.

It is the lymph which contains the protective, as it does the nutritive, principles for tissues and organs, and hence this fluid provides the essential safeguard against infection. The protective principles are not known in the pure state, but there are excellent reasons for regarding them as protein in nature and as composed of compounds of high molecular size. Hence they partake of the physicochemical and osmotic limitations of this class of compounds.

Their relation to the lymphatic fluids is of high importance as affecting the problem of infection. We know that the perfected antibodies do not persist indefinitely within the blood. When they are introduced passively by injection the quantity begins to diminish until at the expiration of a few weeks or months, and more quickly in the case of injected foreign (heterologous) than of native (homologous) serum, they have wholly disappeared. The manner of their disappearance is still undetermined, but little appears to be excreted unchanged, while the greater quantity would appear to be metabolically transformed. On the whole, assuming the principles to be protein matter, it is remarkable that they should resist the metabolic processes so well. Their capacity to pass into the lymph is of even greater significance. Since they partake of the nature of the proteins, we should expect them to be similarly affected by the varying compositions of the lymph in different regions of the body. It is common knowledge that the quality of the lymph in the serous cavities and in the cellular tissues is not equal. While the lymph taken from a large lymph-vessel or cavity of the spermatic cord may approach in protein content that of the blood, the lymph yielded by the serous cavities is more dilute than blood-serum, and, moreover, the fluids of the several cavities vary among themselves within wide limits. In one indi-

vidual and under identical conditions of production a lymphatic transudate in the pleura may show in a thousand parts twenty of protein, in the peritoneum eleven, and the cerebrospinal membranes six. Whatever the anatomic conditions are on which this difference depends, its physiologic significance is at once apparent. We have only to discover that relationship exists between the protein and the antibody content of the several fluids to arrive at the important deduction that the chemical composition of the lymph is a deciding factor in the issue of infection.

Our knowledge of the quantity of immunity principles present in the lymphatic fluids as compared with the blood of the same individual is still imperfect, and yet its meaning is unmistakable. We can take as indexes of the general content in protective principles the amounts of agglutinin and hemolysin that have been shown to occur in different transudates. Under conditions in which the agglutinin for the typhoid bacillus exists in the blood it has been found absent from the lymphatic fluids in the peritoneum, pleura and pericardium.¹³ Hemolysin, antihemolysin and complement have all likewise been ascertained to be absent altogether or to be present in diminished and fluctuating amounts in the several transudates and exudates occurring in these cavities; and it is highly exceptional for any at all to exist in the cerebrospinal liquid.¹⁴ Furthermore, a relation has been established between the total nitrogen, as determined by the Kjeldahl method, and the quantity of immune bodies present in the fluids, a circumstance that in itself shows how intimately these substances are bound to the protein moiety of the lymph.¹⁵

It is known that the substances which cause agglutination offer a certain resistance to diffusion *in vitro*; and in the living organism it is certain that the phenomena surrounding diffusion are far more complex than in dead membranes, and the passage of different dissolved elements of the plasma into the humors and secretions is not explained solely by simple dialysis. The very fragile barrier of the placenta is sufficient to arrest the passage of agglutinin from the mother into the fetus. The mechanism that provides for the secretion of the tears, saliva and urine permits little or no agglutinin to pass; while that which brings about the secretion of milk secures at the same time the passage of immunity principles of varied sorts and in quantities that approach or even equal the amounts existing in the blood.¹⁶

As it is the protein, and in particular the globulin fraction of the lymph which carries the immunity principles, it follows that the several lymphatic fluids will determine the degree to which the serous membranes and other parts are supplied with them, and that the subarachnoid spaces of the central nervous system will be least well supplied of all. This consideration must be of high importance as affecting the provision for warding off and later controlling and abating an infection. Since the anatomic structure decides the quality of the lymphatic fluid in health it also determines it in disease; and by regulating in the first instance the composition of the fluid and, in the next, the extent of the lymphatic interchange, it commands the issue of the pathologic process.

13. Levy and Gissler: Untersuchungen über Typhusserum. München. med. Wchnschr., 1897, xlv, 1435.

14. Strauss and Wolf: Ueber das hämolytische Verhalten seröser Flüssigkeiten. Fortschr. d. Med., 1902, xx, 1, 209. Lüdke: Ueber Hämolysine und Antihämolysine in menschlichen Transsudaten und Exudaten. Centralbl. f. Bakteriol., Orig., 1907, xlv, 268.

15. Archard and Bensaude: Sur la présence de la propriété agglutinante dans le plasma sanguin et divers liquides de l'organisme. Compt. rend. séances de l'Académie des sc., 1896, cxviii, 504.

Under such conditions parasites which have become localized in inaccessible or not readily accessible regions are insured a potential advantage against the host; and this advantage is strengthened by the circumstance that, as they multiply within a confined area to which the lymph has not ready access, they exhaust the immunity principles originally present. Hence the sufficiency of the immunity principles is determined not only by intrinsic qualities of parasite and host, but also, in high degree, by the manner of location and distribution of the parasites themselves within the infected host. Whether the parasites have a general distribution throughout the blood and tissues, or are confined within a pathologic process in the interior of an important organ, may be the factor deciding not only whether the native curative principles shall gain ready access to them, but also whether or not extraneous curative substances introduced from without into the body shall be able to reach the seat of disease.

In the course of the struggle for survival, therefore, the parasites withdraw at times into situations which are reached imperfectly and with difficulty by the lymph, and thus they produce local inflammations more or less cut off from the general circulation and the curative agents purveyed by the blood. This is the condition encountered in massive inflammations, in abscess formation and in infections of the serous cavities receiving a modified and diluted lymph secretion.

Manifestly, therefore, the bringing of the causes of microbial diseases under the influence of healing substances will be more readily and certainly accomplished when the parasites are widely disseminated throughout the body than when they are hidden away within an organ or in the interior of a cavity. Hitherto the most effective specific curative agents have been just those that operate against the generalized infections, of which quinin in its action against the malarial parasite affords an example; while the control of diphtheria by antitoxin, perhaps the most perfect example of all, consists essentially of the neutralization of a universally distributed poisonous or toxic substance that is directly the source of the serious effects of the disease. When in generalized infections the surviving micro-organisms escape from the blood to aggregate in special situations and local pathologic products that are not readily reached by the lymph, then the specific drug or serum asserts its curative power with far more difficulty and far less certainty.

Special aggregations of this kind, more or less inaccessible to the circulating healing principles, are gummatous formations and the still other special localizations of the syphilitic virus that occur in locomotor ataxia and possibly in paresis, the trypanosomal cause of sleeping-sickness when confined in the central nervous system, the pyogenic bacteria contained within large collections of pus-cells, tubercle bacilli enclosed in caseous foci, and many other instances that suggest themselves. When obliterating disease of the arterial system exists, as in certain tuberculous, syphilitic and other focalized lesions, the ability of the healing principles to penetrate into the pathologic lesion is still further diminished.

No part of the body is, as has been seen, so isolated anatomically and physiologically from the contents of the blood as are the subarachnoid spaces of the central nervous system, in consequence of which pathologic states affecting the meninges and the adjacent central nervous tissues that depend on the fluid contents of these membranes for food and protection are especially difficult to bring under the influence of curative substances. It has been found far easier, for example, to abolish by

specific drugs the trypanosomal cause of sleeping-sickness in the blood and lymph-nodes than in the cerebrospinal liquid. And we are just learning that in tabes, and shall probably learn that in paresis also, it is the special localization of *Spirochaeta pallida* in the central nervous tissues in situations accessible to the cerebrospinal fluid, rather than to the blood, that has so largely determined the failure of almost every effort to combat these now established syphilitic affections by the usual antisyphilitic remedies.¹⁶

Without entering into discussion of the question in how far the cerebrospinal fluid constitutes the lymph of the central nervous system, we may yet consider with Mott¹⁷ that it completely occupies the subarachnoid spaces and communicates with a canalicular system surrounding the vessels and nerve-cells of the brain and spinal cord. This liquid should therefore provide the most direct path for the penetration of active substances to the nervous tissues. Pharmacologic tests have demonstrated the existence of such a system of communication. Thus, while it has been abundantly shown by experiment that many active substances present in the blood are successfully excluded from the cerebrospinal fluid, it has also been found that when they are introduced into it directly the effects produced on the nervous organs are particularly severe. Many examples might be given in illustration, but only one will be cited.

Behring found the hen not subject to the effects of tetanus toxin injected into the blood and highly subject to its action when it was injected directly into the subarachnoid spaces. Of the many different drugs tested certain nitrites pass in small amounts the barrier of the chorioid plexus to gain access to the cerebrospinal fluid, while hexamethylenamin (urotropin) alone passes the barrier freely. It appears that after the intravenous, but not after the intramuscular, injection of salvarsan detectable quantities of arsenic appear quickly in this fluid and as quickly disappear.¹⁸ The intact chorioid plexus therefore exercises a high degree of control over the composition of the cerebrospinal fluid. The fluid itself readily escapes into the general blood and apparently by way of direct anatomic communications existing between the subarachnoid spaces and the veins. Evidence is lacking of a similar direct communication with the lymphatic system.¹⁹ From this it follows that while the composition of the cerebrospinal liquid is little subject to influence through the components of the blood, it readily yields to the blood all that it contains. When the meninges and the chorioid plexus are acutely inflamed, the cerebrospinal fluid receives from the blood an increase of protein matter and thus probably any associated immunity principles which the blood contains. It appears, however, that the principles remain in the meninges only a short time and exert little neutralizing effect on poisons or microbes.

It must now be evident that the solution of the problem of specific treatment of disease is bound up in no small way with the problem of the segregation of the parasitic causes of infection in relatively inaccessible portions of the body. Hence, the recommendation which I bring forward is that of a more direct mode of attack

16. Swift and Ellis: The Direct Treatment of Syphilitic Diseases of the Central Nervous System, New York Med. Jour., 1912, xcvl, 53. Wechselsmann, Ueber intralumbale Injektion von Neosalvarsan, Deutsch. med. Wchnschr., 1912, xxxviii, 1446.

17. Mott: The Oliver-Sharpes Lectures, On the Cerebrospinal Fluid, Lancet, London, 1910, II, 79.

18. Sclard and Bloch: Perméabilité menagée à l'arsénobenzol, Compt. rend. Soc. de biol., 1910, lxi, 624.

19. Dixon and Halliburton: The Rapidity of Absorption of Drugs Introduced into the Cerebrospinal Fluid, Proceedings of the Physiological Society, Jour. Physiol., 1912, xlv, p. vii.

on the local processes of infection that are not readily, or at all, to be reached by the introduction of curative agents into the blood. It is patent that a method enabling the healing substances to be delivered in and about the seat of disease and made to exercise their effects on the parasites, not through a diluted lymph secretion, but in such a state of concentration and combination as experiment and experience proves in given instances to be useful, offers high hopes of success. So far as the surfaces of the body are concerned the method of local treatment, generally considered, is time-honored; but even with the infections of these surfaces it has been too little practiced. In the second lecture I shall present evidence bearing on the advantages that may be gained from a wider adoption of the practice of specific local therapy.

I have now briefly and, I fear, inadequately presented the main facts that have to be taken into account in the working out of a system of specific therapy of the infectious diseases. If I have inspired a depressing sense of hopelessness in the quest I have failed in my purpose. It is indeed true that while we have been fascinated with admiration for the wonderful forces possessed by the higher animals for warding off and abating infections, we have perhaps been slow to realize that the parasites themselves must be provided with correspondingly perfected adjustments with which to resist these mechanisms. These adjustments have now been, in part at least, uncovered. The result is that we enter on the task of the perfection of artificial means of strengthening the body's defenses and power of overcoming parasitic micro-organisms not with a lessened, but with an increased, feeling of confidence in the issue. To phrase such a problem too simply is to court failure and discouragement; to clothe it in all the facts, without regard to their complexity, is to inspire hope and perchance to win success.

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OVERRESPONSE TO AFFECTIVE STIMULI FROM STATIONARY CORTICAL LESIONS

WITH REPORT OF A CASE*

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An investigation of sensory phenomena resulting from lesions occurring at any level of the nervous system is ordinarily of much interest and is attended with difficulties which in many instances are not easily surmounted. I believe that symptoms resulting from disturbances of the various components of sensation are the hardest symptoms in medicine to interpret, and consequently are the least understood.

After the sensory impulses undergo a regrouping at the first synaptic junction in the spinal cord they ascend in tracts according to quality. All impulses of a painful and thermal character cross over immediately, enter the contralateral spinothalamic tracts, and ascend in secondary fibers of the spinal level.

Those impulses evoking sensations of postural recognition and spatial discrimination ascend in primary fibers of the peripheral level in the ipsilateral dorsal tracts are regrouped in the spinomedullary nuclei, cross over and ascend through the brain-stem in the contralateral mesial fillet.

Impulses evoked by tactile stimuli traverse the cord in the ipsilateral dorsal tracts and the contralateral spinothalamic tracts. It is for this reason that unilateral cord lesions do not cause a loss of tactile sense over any part of the body.

We thus see that the various components of sensation are grouped in the spinal cord and brain-stem and traverse, according to quality, separate paths. On reaching the optic thalamus they are all of whatsoever quality grouped together in the external nucleus. In this organ they undergo a characteristic and definite regrouping. Those which evoke in consciousness sensations of pleasure and discomfort pass by fibers of the thalamic level into the gray matter of the thalamus in the internal nucleus. After acting on the essential center of the thalamus, sensory impulses are conducted by fibers of the cortical level, in five main groups, through the internal capsule and sensory radiation to that portion of the cortex between the precentral convolution and occipital lobe.

Head groups these sensory impulses as follows:

1. Those which underlie postural recognition and the appreciation of passive movement. On this group depends the secondary faculty of judging the differences or identity of two weights placed on the unsupported hands.

2. Impulses which underlie the recognition of tactile differences or the power of appreciating those qualities of touch other than contact and roughness. To this group we owe the faculty of recognizing the increase or diminution in weight of a test object, and of distinguishing the difference between two weights placed on the supported hand.

3. Those on which depend spatial discrimination (compass points applied simultaneously) and its allied faculty, the recognition of size and shape.

4. Those impulses which enable the patient to recognize the spot stimulated (localization). They carry with them the power of appreciating the double nature of two points applied to the surface one after the other.

5. Thermal impulses. On this group depends the possibility of recognizing those degrees of temperature which necessitate a comparison with the consequences of some previous sensation.

We recognize two masses of gray matter or sensory centers in which impulses tend to evoke that psychic state called a sensation. One of these is situated in the internal nucleus of the optic thalamus, the other in the parietal region of the cerebral cortex. Anatomically, the optic thalamus is very complex and plays a threefold part in the fate of all sensory impulses. It contains the termination of all sensory paths. The gray matter forms the center for certain fundamental elements of sensation and is under control of the cortex through the corticothalamic fibers which terminate in the external nucleus, and its activity is checked and regulated by corticothalamic impulses.

Roussy,¹ Holmes and Head,² Edinger³ and various others have correlated the symptomatology with the anatomic findings at necropsy, in lesions of the optic thalamus, and Roussy in 1907 formulated the thalamic syndrome, which is as follows:

1. A persistent loss of superficial sensation of one-half of the body and face. This loss to touch, pain and tem-

1. Roussy, G.: *La couche optique*, Paris, 1907.

2. Holmes, Gordon, and Head, Henry: *A Case of Lesion of the Optic Thalamus with Necropsy*, Brain, 1911, xxxiv, 255.

3. Edinger, L.: *Gibt es central entstehende Schmerzen?* Deutsch. Ztschr. f. Nervenhe., 1891, I, 202.

* Read in the Section on Pathology and Physiology of the American Medical Association, at the Sixty-Fourth Annual Session held at Minneapolis, June, 1913.