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THE NONSPECIFIC FACTORS IN THE TREATMENT OF DISEASE*

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As a natural consequence of the phenomenal advances of the past thirty or forty years in our understanding of disease processes and in what may be termed therapeutics by means of biologic products—advances largely the result of laboratory and more especially immunologic research—medical consciousness, if we may so regard the literature, has rather wholly centered about ideas of specificity, and, taking its cue from the laboratory, has regarded with considerable skepticism and frank disapproval any reference to observations, especially if clinical, at variance with the current trend of thought. And yet one finds a not inconsiderable accumulation of evidence, both from the laboratory and from the clinic, forming in a measure an undercurrent, definitely indicating a much larger share of certain nonspecific and as yet ill defined factors in recovery from disease. While the emphasis placed on certain phases of immunology and specificity, more especially the fruitful antigen-antibody conception of Ehrlich, has been of inestimable value, we rather believe that it has resulted in the neglect of certain perfectly obvious lines of approach to medical problems.

Quite early in the development of the tuberculin therapy it will be recalled that Matthes¹ demonstrated conclusively that to all intents and purposes the reaction considered specific for tuberculin could be produced when deuterio-albumose was used, and showed that whatever difference occurred could be explained by the fact that the tuberculin fraction contained certain toxic peptones in addition. Matthes went even farther, expressing the idea that fever in general was produced by protein split products and suggested the importance of proteolytic ferments in this connection, thus foreshadowing the work of Vaughan in this country and the later German workers in anaphylaxis.

The history of the treatment of typhoid fever with vaccines is quite similar. Fraenkel many years ago demonstrated, in a convincing series of cases, the therapeutic value of typhoid vaccine used subcutaneously. Directly Rumpf followed him with a series of cases treated with a vaccine of *Bacillus pyocyaneus* with equally favorable results. But since the medical pro-

fession could see no merit in a nonspecific method, the entire subject was dropped for a considerable period of time. In this country, too, the controversy occasioned by the Schäfer vaccine is pertinent. Here was a biologic product, which, according to the observation of many competent observers, did at times produce striking results in a variety of infectious diseases; whether or not it was a safe remedial measure, and whatever may have been the defects, is not pertinent in this connection. The very fact that it did do certain things at times should have led to a study of why such favorable changes were brought about. The fact that it was palpably nonspecific, however, was sufficient to warrant the stamp of disapproval by the medical profession.

It is only within the last two years that a certain definite movement away from this rather narrow point of view has occurred, and it is significant to note that Wright,² than whom, of course, no one man has stood out more emphatically for specific therapy, recently made the following statement in this connection:

All those who have had much experience with vaccines will have seen cases where therapeutic effects, lying quite outside the range of the particular vaccine employed, and therefore, as we thought, not quite creditable to science, have been obtained by vaccine therapy.

Schmidt³ is among those who have called attention to the fact that following vaccine therapy of any kind the body becomes resistant to a variety of the commoner infections. So too, it seems that during carcinoma and pregnancy (both, by the way, conditions distinguished by their high antiferment titer) a relatively low "infection index," as Schmidt terms it, is established.

Von Wagner utilized a similar nonspecific method when he obtained favorable results in paretics treated with tuberculin; and only recently Blach⁴ has reported a series of cases of early syphilis treated with tuberculin.

We cite these not to recommend the treatment, because it hardly seems warranted, possessing as we do much more efficient agents, but to indicate the same general phenomenon of a therapeutic effect from a nonspecific method.

It is in the domain of coagulation disturbances that therapy of this nature has received particular attention in the past. The beneficial effect of subcutaneous serum injections in hemophilia is well recognized, although here too the exact mechanism is unknown. Originally the slight leukocytosis was regarded as the potent factor, but for this there is no warrant. Results

* From the Department of Pathology, Vanderbilt University, Medical Department.

1. Matthes, M.: *Deutsch. Arch. f. klin. Med.*, 1895, xlv.

2. Wright, A.: *Brit. Med. Jour.*, 1915, ii, 629.

3. Schmidt, R.: *Med. Klin.*, 1910, No. 43.

4. Blach, M.: *Wien. klin. Wchnschr.*, 1915, No. 49.

have been obtained with homologous and heterologous serum, and with whole blood; but decisive results depend considerably on the dosage, and marked fluctuations in coagulation time frequently occur following such injections. That such injections do not alter the disease process through supplying directly some deficiency, but rather through stimulating the elaboration of some substance before lacking, would seem to be the conclusion reached by recent workers. This would agree with the stimulating effects observed from injecting serum and whole blood subcutaneously in tuberculosis and pernicious anemia (Esch, Busse, Weber).

The dermatologists have within the past two years had similar results in a variety of diseases, including some cases of psoriasis which had proved refractory to other methods of treatment. As a rule the homologous serum was injected intravenously in these cases.

The therapy of typhoid fever has so far been the chief avenue of approach to the problem. A number of vaccines have been elaborated and used subcutaneously during recent years for therapeutic purposes, and the results have been, in general, very encouraging. It was not, however, until such vaccines were used intravenously that the striking pictures of complete abortion of the disease were obtained. Then Kraus⁵ observed that colon vaccines gave an identical result, while the typhoid vaccine was of marked benefit in certain cases of pelvic infection. Ichikawa⁶ found that his paratyphoid patients recovered with a typhoid vaccine, while Lüdke⁷ went a step farther, using a nonbacterial protein split product—a deuteroalbumose—with equally favorable results, in typhoid fever. The effect of such an injection of secondary proteoses in typhoid fever is shown in the accompanying chart.

Apart from the action of the vaccines, the protein split products, and the effect of both homologous and heterologous serums, observations are recorded of the effect of milk injected intramuscularly (Schmidt), salt solution (Mitlander), dextrose solution, colloidal metals, distilled water (animal experiments) and ferments (including the leukocytic extract of Hiss and Zinsser). It seems probable that the reaction and beneficial effects observed from these substances is based on a similar mechanism in all cases.

SELECTIVE STIMULATION

Latterly the hematopoietic organs have come to be recognized as the chief source of antibodies, a recent

paper by Becht and Leuckhart⁸ demonstrating in a convincing way that the circulating antibodies are not derived from the tissue cells in general, an origin that would presuppose the discharge of these substances into the general circulation by way of the lymph stream. As a corollary of this idea concerning the source of the antibodies, it would seem reasonable to suppose that any disturbance of the hematopoietic system might alter the antibody formation; an observation of Moreschi⁹ quite bears this out. Moreschi noted the persistent absence of agglutinins in leukemic patients suffering from a superimposed typhoid infection.

In view of these facts, it would seem possible that the various agents act as stimulants of the hematopoietic tissue, which, as a consequence, suddenly floods the body with antibodies, thereby overcoming the infection. According to the idea of Wright, vaccine injections

were supposed to be followed by a negative phase, at least as far as the opsonic power was concerned. Contrary to this generally accepted view, Bull¹⁰ has recently shown that this does not hold true following the intravenous injection of a typhoid vaccine in immunized rabbits. Bull noticed that the antibodies were not diminished; on the contrary, they were rapidly increased following the injection. If this is the mechanism involved, it is important to keep in mind that the stimulus itself is not a specific factor, but that the hematopoietic system has been attuned to respond to a nonspecific stimulus with the production of specific substances. Dunklin, working in this laboratory, finds that a marked increase in antibodies follows the intravenous injection of proteoses in immunized rabbits. In a general way this mechanism of recovery would consist of a selective stimulation

of the hematopoietic system by nonspecific substances.

THE LEUKOCYTOSIS

The importance of the leukocytic reaction has been emphasized by Gay and his associates. They believe that the recovery following such intravenous therapy (they worked with a modified typhoid vaccine) is due to a specific hyperleukocytosis. More recently, however, McWilliams¹¹ has observed that this hyperleukocytosis is apparently not specific to the degree indicated by the work of Gay and Claypole,¹² and that even nor-

Intravenous injection of secondary proteoses in typhoid fever: J. S. (City Hospital, courtesy of Dr. McCabe). Illness commenced April 29, one week before admission to hospital; Widal positive on admission; 1.5 c.c. proteoses injected intravenously May 5 (2 per cent. solution); 2 c.c. proteoses injected intravenously May 7 (4 per cent. solution). Protease became positive after first injection. Lipase titer increased from 0.6 c.c. hundredth normal sodium hydroxid, May 5, to 1.9 c.c. hundredth normal sodium hydroxid per cubic centimeter of serum, May 8. Proteoses in the serum increased from 0.1 mg. (nitrogen) per 5 c.c. serum to 0.24 mg., May 8.

5. Kraus, R.: Wien. klin. Wchnschr., 1915, p. 29.

6. Ichikawa, S.: Ztschr. f. Immunitätsforsch., Orig., 1914, xxiii, 32.

7. Lüdke, H.: München. med. Wchnschr., 1915, lxii, 321.

8. Becht, F. C., and Leuckhart, A. B.: Am. Jour. Physiol., 1916, xl, 366.

9. Moreschi, C.: Ztschr. f. Immunitätsforsch., Orig., 1914, xxi, 410.

10. Bull, C. G.: Jour. Exper. Med., 1916, xxiii, 419.

11. McWilliams, Helen: Jour. Immunol., 1916, i, 259.

12. Gay, F. P., and Claypole, E. J.: Specific Hyperleukocytosis, Arch. Int. Med., November, 1914, p. 662.

mal rabbits respond with a marked leukocytosis to the intravenous injection of typhoid vaccine. This coincides with our own experience. We must keep in mind, too, the fact that in typhoid fever particularly, the normal course of recovery is not marked by a leukocytosis; on this ground alone we might be justified in seeking the influence of some other factor or factors in the recovery following intravenous therapy.

THE HYPERPYREXIA

It is a common clinical experience that in some diseases, among them subacute joint diseases, neuralgia, diabetes, pernicious anemia, certain dermatoses, sarcoma, etc., distinct beneficial results follow at times on some intercurrent febrile condition. Is it possible, therefore, that these varied agents influence the course of the disease by producing a high temperature?

A long list of investigators, among them Walther, Hildebrand, Englehardt, Rolly and Meltzer, have reached the conclusion that a high temperature (from 40 to 42 C. or 104 to 107.6 F.), artificially produced, has a favorable influence on an established infection. Lower temperatures, on the other hand, as recently noted by Winslow and his associates,¹³ would seem to retard the formation of immune bodies. Inasmuch as a very sharp febrile reaction almost invariably follows the intravenous injections, the importance of this phase of the subject cannot be overlooked. In our own cases we have at several times observed a reaction temperature of 107 F. within one-half hour following a proteose injection (in typhoid patients); unaccompanied by a change of the pulse rate of any moment or other untoward symptoms.

THE MOBILIZATION OF FERMENTS

We have already¹⁴ pointed out that in experimental animals the intravenous injection of bacteria, kaolin, protein split products and trypsin is almost invariably followed by more or less marked mobilization of serum protease and usually of lipase (esterase).

In the patient a similar reaction occurs following the intravenous injection of vaccines and proteoses, but not to the same degree nor with the same regularity as in animals. In considering the possible effects of such a mobilization of ferments, both protease and lipase, we must keep in mind that a variety of reactions may occur. The serum protease, as other tryptic ferments, is without effect on bacteria; but if we consider the source of the intoxication occurring in the diseased organism as primarily due to protein split products, then such a mobilization of protease may be of considerable importance in the process of detoxication, in that the toxic fragments are hydrolyzed to lower and nontoxic forms. We have discussed this possibility in detail in its relation to pneumonia.¹⁵

As a result of this effect the diseased organism would rid itself for the time being of the toxic substances circulating at the time of the injection, although the disease process itself, and the infecting organisms, would possibly continue in existence capable of further injury. This would seem to be the explanation for the clinical picture obtained after intravenous therapy in such instances in which only an incomplete or transitory effect results. In all these cases the patients present a considerable improvement, both subjectively and

objectively, on the day or days following the injection, despite the fact that the temperature may recur or even continue uninterruptedly.

The influence of the fat-splitting ferments mobilized is as yet obscure. In the ultimate analysis, of course, we must turn to ferments of this nature for the attack on the invading organism, because it is more than probable that the actual surface of the bacterium consists largely of lipoids, or intimate lipoprotein combinations, for the destruction of which fat-splitting ferments are essential. In certain infections with lipid-rich organisms, such as tubercle and lepra bacilli, the clinical demonstration of the association of a high lipase titer in the serum, with a favorable prognosis, has been well established. At present, however, the subject is still one in which only diligent inquiry will furnish definite knowledge.

THE INCREASE IN ANTIFERMENT

When discussing the low "infection index" observed during the course of certain conditions, among them carcinoma, pregnancy and following vaccine therapy (Wright emphasized the latter finding particularly in his report on the antipneumococcus vaccination at the Premier Mine), we called attention to the fact that during such states a relatively high antiferment index is a well recognized accompaniment. The question arises whether this is a mere coincidence or whether there is some causal connection between the antiferment increase and the increased resistance to infection.

We have previously shown that the antiferment power of the serum depends on the amount of unsaturated lipoids present in a highly dispersed state in the serum.¹⁶ Consequently, any factor that will tend to increase these lipoids, be it by increasing the supply or by decreasing the utilization (as when the lipase in the serum is decreased) by injuring tissue cells and causing them to discharge such lipoids to the blood stream, will increase the antiferment titer; while conversely, any influence decreasing these lipoids, their dispersion or their unsaturation, will tend to decrease the titer.

It is particularly the state of dispersion of these lipoids that is ignored by most investigators of their physiologic properties. Serum lipoids in coarse dispersion are inactive as antiferments as well as in the mechanism of coagulation, a fact that should be kept in mind when the effects of lipemia are considered.

Wright worked with saprophytic and serosaprophytic organisms, and noted that the addition of antiferment to the culture medium completely checked the growth of the serosaprophytic bacteria, and found that even the saprophytic bacteria grew less luxuriantly when no trypsin was added. In view of the results obtained by Rettger, Berman and Sturges,¹⁷ showing that the ordinary infectious organisms are not able to derive their protein requirement from native or even partly hydrolyzed proteins, but probably solely from the lowest degradation products, the direct influence of the antiferment cannot be so simple as Wright would assume. The antiferment inhibits only the action of the tryptic and not the peptolytic and ereptic ferments. Of course, when we are dealing with a definite tryptogenic organism it becomes apparent that an increase in antiferment would offer an increased factor or resistance against its growth.

13. Winslow, C. A.; Miller, J. A., and Noble, W. C.: *Proc. Soc. Exper. Biol. and Med.*, 1916, xiii, 93.

14. Jobling, J. W., and Petersen, William: *Bacteriotherapy in Typhoid Fever*, *THE JOURNAL A. M. A.*, Aug. 7, 1915, p. 515.

15. Jobling, J. W.; Petersen, W., and Eggstein, A. A.: *Jour. Exper. Med.*, 1915, xxii, 568.

16. Jobling, J. W., and Petersen, William: *Jour. Exper. Med.*, 1914, xix, 459.

17. Rettger, L. F.; Berman, N., and Sturges, W. S.: *Jour. Bacteriol.*, 1916, i, 15.

An increase in the serum lipoids affects bacterial growth, however, in another way, since an adsorption of lipoids occurs at the surface of the bacteria. The relation of this adsorption, seemingly a nonspecific and purely physical process, to the phenomenon of sensitization, is as yet not clear. It is reasonable to suppose, however, that the metabolic exchange of the bacterial limiting membrane is markedly influenced by increased lipoidal adsorption on the surface, resulting not only in influencing the metabolism unfavorably, but possibly preventing the excretions of substances protective for the bacterium (leukocidins, virulins, etc.).

The immediate effect of the vaccine and proteose injections is not an increase, but a distinct decrease in the antiferment titer for a short period of time, followed later by a rise. It is probable that the decrease is due to the chill which occurs after the injections, the increased metabolic demands of the organism being met in part by the rapid utilization of the serum lipoids.

CONCLUSION

It seems probable that the fundamental change on which the majority of the above described biologic reactions are based is one of colloidal dispersion, in that the injections bring about a less dispersed state affecting not only the serum proteins but also the serum lipoids. Such an alteration is sufficient to account for the fluctuations in the ferment-antiferment balance, and in the coagulation mechanism, as well as in the opsonic and complement powers of the serum, although it does not at present explain the increased antibody titer. With this as a basis we can understand that so many and diverse substances can bring about a reaction almost identical clinically and therapeutically. But here, as in so many other biologic problems which have to do with that most complex of tissues, the blood, it seems probable that no single factor can be identified as responsible for all the changes which occur, but that a whole train of events is inaugurated when the equilibrium of some of the delicate serum balances is disturbed, all of which tend toward a condition favorable for recovery from infection.

THE TREATMENT OF ARTHRITIS BY THE INTRAVENOUS INJECTION OF FOREIGN PROTEIN *

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During the past year attention has been called to the value of intravenous typhoid vaccine in the treatment of typhoid fever. The early reports by Penna, Kraus and Mazza of Buenos Ayres, and the independent investigation by Ichikawa, demonstrated clearly that by this method of treatment a certain percentage of typhoids might be brought to an immediate termination. Kraus and somewhat later Lüdke were able to show that similar results could be obtained with a vaccine made from colon bacilli, this showing definitely that the reaction was not due to a specific vaccine. Lüdke later was able to show that a solution of albumose would accomplish the same results.¹

During the past summer we used the intravenous typhoid vaccine, 200,000,000, in the treatment of typhoid. Later, following the suggestion of Lüdke, we thought it might be of interest to compare these results with a series treated with albumose. We were unable to obtain any of Merck's albumose, but through the courtesy of Drs. Jobling and Petersen of Vanderbilt University we secured some proteose which they had prepared for their experimental work. By giving from 1 to 2 c.c. of a 4 per cent. solution of this proteose, we obtained the same results as with the typhoid vaccine, 20 per cent. of the treated cases terminating by crisis after a single injection. In addition, in about an equal number following the injection there was a termination by rapid lysis, and in a third group, which again equaled approximately 20 per cent., following a single injection, the continuous fever was changed to a very irregular type, which continued until the termination of the disease. The remaining cases, while reacting with a chill and rise in temperature, continued their febrile course in an uninterrupted manner. As stated, the proteose, in its chill, temperature reaction, leukocytosis and percentage of cases in which the course of the disease was modified, gave the same results as the typhoid vaccine.

These results are simply confirmatory of those already recorded, making it quite apparent that the sudden termination of the disease is not due to the specific character of the vaccine, but probably to the action of a foreign protein. It was decided to apply this method of treatment to another infection, and we selected for this purpose acute, subacute and chronic arthritis. In the selection of our material, the patient after entering the hospital was kept in bed for two or three days without special medication for observation as to how much improvement might follow simple rest. It was quite surprising to see how many patients with acute arthritis, after two or three days' rest in bed, were so much improved that we did not consider them suitable subjects for testing out the value of a therapeutic agent. Selecting, then, only those cases for study in which the disease was of a persistent type, we gave a 4 per cent. proteose solution, in doses of 2 c.c., intravenously. The patient reacted by a chill, rise in temperature and moderate leukocytosis. The day following the injection there was a moderate but definite improvement in the joint symptoms.

As our supply of proteose was limited, and as we believed that the reaction was due solely to the foreign protein, a typhoid vaccine was substituted for the proteose. This vaccine was prepared from the Rawling's strain, killed by heating to 55 C. and preserved by 0.5 per cent. phenol (carbolic acid). In the preliminary cases a dosage of 150,000,000 was given intravenously. The reaction was the same as when the vaccine was given to a typhoid patient except that the leukocytosis was much more marked, in two instances reaching 52,000. Immediately following the injection there was a moderate leukocytosis which increased slightly until the chill, which usually occurred in from five minutes to one hour. During, or immediately following the chill, there was a rapid drop in the leukocytic curve, resulting either in a normal count or a leukopenia, followed promptly by a rapidly developing leukocytosis which reached its maximum usually at the end of four and occasionally at the end of twelve hours, gradually returning to normal in from twenty-four to forty-eight hours.

* From the Medical Clinic of Cook County Hospital.

1. For complete references to the literature the reader is referred to the paper by Frederick Gay, *Journal of Laboratory and Clinical Medicine*, 1915, 1, 13.