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Non specific protein therapy

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NON-SPECIFIC PROTEIN THERAPY.

SENIOR THESIS.

EARL FEIND.
The theory of specificity in resistance to disease processes has largely permeated the medical profession since the discovery by Pasteur that microorganisms are the causes of disease. The work of Koch, Lister, Ehrlich, Von Behring and other careful observers at about the same time firmly established that most diseases were caused each by a specific etiological factor most commonly a microorganism. Out of this grew the theory that if there is a specific causative factor there should also be a specific anti-factor for each disease. This led to the development of vaccines, sera etc. which have been used very extensively in medical practice and with remarkable results.

Naturally enough while such progress was being made along specific lines little or no attention was paid to what work might have been done in other lines of therapeutic experimentation. In fact those working and thinking along non-specific lines at that time were thought to be radical and entirely unscientific. Hence, the work of Frankel, Rumpf, Romer and their followers in the 1890's passed unnoticed or at least was thought to be valueless. Looking back however at the records of these men we notice that Rumpf used with success a vaccine of E. Pyocyanus subcutaneously in the treatment of typhoid fever. In fact the results almost equaled those of Frankel's
who was using the specific typhoid vaccine. Romer at the same time observed that tuberculous animals could be killed by extracts obtained from pneumobacilli and bacillus pyocyaneus just as well as with tuberculin; in other words, the infected animals were abnormally sensitized not only to the specific tuberculin but also to other toxic products. Unfortunately at the time of these observations and their publication the medical profession was witnessing the introduction of diphtheria and tetanus anti-toxins and so the observations were practically ignored.

In 1908 Hiss and Zinsser used leucocytic extracts in the treatment of a variety of infectious diseases. They were unable at the time to account definitely for the therapeutic benefit obtained but thought it to be some form of non-specific reaction.

At about this same time Paton used normal serum and diphtheria antitoxin in the treatment of tuberculosis, arthritis and cerebro-spinal meningitis with apparent therapeutic benefit. He published a small volume detailing his clinical experience along this line in which he made the observation that not only the horse serum used in preparing the diphtheria antitoxin but also sheep and ox sera possessed the same stimulating qualities to which he attributed the thera-
apeutic benefit. A definite fever reaction and leucocytic response was also noted in response to the use of these sera, the temperature rising several degrees for several hours and there being first a temporary leucopenia followed in about half an hour after the injection by a definite leucocytosis.

In 1911 Schafer reported the therapeutic use of a bacterial product with which he had obtained remarkable recoveries in certain infectious diseases. This work was done at a time when many diseases were thought to be caused not only by a single specific organism but in addition a number of secondary invaders, and it was thought that a vaccine to be effective in these conditions must be necessarily a mixed vaccine. This preparation of Schafer's was quite widely used especially in the treatment of arthritis. Unfortunately, however, the preparation fell into the hands of a pharmaceutical house and a country wide exploitation took place resulting in a general disapproval by the medical profession, not only because of the proprietary nature but because careful observation showed it to be of much less value than was at first claimed by Schafer.

Several years later Herescu and Strominger studying morphological similarity in organisms noted that
the meningococcus and gonococcus were strikingly alike morphologically. Working on this basis they used anti-
meningococcus serum in treating gonorrheal arthritis,
gonorrheal ophthalmia, septicemia and other gonorrheal 
complications with considerable success.

Between the years 1905 and 1916 much progress was 
made in the use of vaccines, especially in the treat-
ment of typhoid fever. A group of Argentine physicians 
reported very favorable results from the intravenous 
use of typhoid vaccine, in some cases the disease be-
ing practically aborted, in others terminating by cri-
sis, while in others terminating by lysis shortly after 
the injection.

Krause, an American physician then in Argentine, 
hearing of these results wondered whether or not he 
could obtain the same favorable results by the use of 
other organisms than the typhoid bacillus. He found 
that by using the colon bacillus very similar results 
were obtained.

I. Chikawa, a German worker, in 1914 made similar 
discoveries independently and made the observation also 
that those patients suffering from paratyphoid were 
helped by the administration of the ordinary typhoid 
vaccine intravenously.
These last two observations, namely the startling results from the treatment of typhoid fever with colon bacillus vaccine and the treatment of paratyphoid fever with typhoid vaccine together with Krause's further observation that puerperal infection could be treated favorably with colon vaccine, were observations that the most skilled immunologist or specific therapist could not explain away as being due to faulty experimentation or group reaction. Thus the theory of strict specificity so long harbored by the medical profession and so splendidly proved in the laboratory had to admit, because of actual clinical demonstrations, that there was also a non-specific reaction of definite clinical value. Thus we found a relatively simple explanation of what was before obscure and unexplained clinical phenomena.

With this as a background we come to the more recent development and experimentation of non-specificity in therapy. It might be well to mention here that it is not the purpose of this paper to discredit specific therapy and supplant non-specific in its place for there is no question but that many conditions respond to specific therapy in a manner not to be surpassed. However, there likewise seems equal proof that a very definite value may be resultant from the use of non-specific agents.
How then shall we explain the value or mechanism of action which so favorably results in therapeutic benefit? It is well known that the immediate effect of foreign protein injection is a rise in temperature, chill, sweating and an increase in circulating leucocytes in the bloodstream. It is also known that a rise in temperature often favorably influences a preexisting disease process, a chill often a favorable sign in a septic case, a severe sweat frequently relieves the symptoms of many diseases, and a leucocytosis, an indication of a satisfactory tissue response. Are then these things the reactions responsible for the beneficent result? Certainly we can say that they play a very important role. However, it has been found that the use of foreign protein therapy is much more effective early in the course of disease processes rather than late and that there is greater benefit if the reaction is more severe than if it is less so. Also late in disease processes the response to injection is much less severe and likewise much less efficacious. It seems therefore that perhaps there is something more than simply fever, chill, sweating and leucocytosis.

Weichardt, while working with protein intoxication in Germany described the reaction as probably one due to the stimulation of all the cells of the organism to great-
er activity. This increased activity resulting in either the production of specific antibacterial substances or simply increasing the general resistance by speeding up the mechanism of detoxification and aiding in the elimination of the toxic products. To this type of reaction Weichardt applied the name "Plasmaactivation," indicating a universal cellular response. He believes that there is not an alteration of cellular function but rather an increase in functional activity. No new agencies or methods of defense are brought into use. There is simply a cumulation of the normal defense agencies of the organism. It is logical to conclude then that no therapeutic benefit can be realized when once the organs are completely exhausted and incapable of increasing their function regardless of the stimulation applied. However, Weichardt believes that differences in reaction exist between normal individuals and individuals that are sick or sensitized to the particular foreign substance to be used and that this accounts for the wide variation in the reactions studied. This theory explains the observation—that after repeated stimulation with non-specific agents the organism fails to respond as favorably as upon first stimulation—on the basis of cell exhaustion or fatigue.

Contrary to Weichardt's theory of universal cellular activation, Dollken believes in selective stimula-
tion, i.e. certain non-specific agents stimulate certain organs or groups of organs while others stimulate other organs. To support his contention he calls attention to the fact that vaccines made from prodigiousus organisms were effective in treating neuralgias while vaccines of cholera and dysentery were practically valueless and that pyocyaneus vaccines were effective in treating gummas, while pseudo-diphtheria vaccines were ineffective. He describes other similar instances of differences in reaction and concludes that certain non-specific agents have specific organs or tissues upon which they act, hence the term selective stimulation. The organs being stimulated to the greatest extent being the liver, spleen, kidneys and bone marrow, while to a lesser degree there is often decided effect on tissues of joints, eyes and glands.

Faltau, Saxl, Weiss and others have supported the theory that the non-specific agents injected contain thermo-genic substances and these stimulate the heat regulatory mechanism resulting in an increase in temperature which they believe to be the primary factor. The leucocytosis etc. being secondary manifestations. They believe that following such stimulation the heat regulatory center becomes exhausted and hence there is a drop in the temperature below that existing prior to the injection.
Wright believes that immune bodies are produced chiefly in the tissues about the area involved in disease processes and that the injection of non-specific agents in healthy tissues distant to the site of infection stimulates then to antibody formation which therefore increase the resisting power of the organism to the existing pathology.

Starkenstein, a brilliant clinical observer, believes that the benefit of protein therapy lies in a change in vessel permeability as a result of injection. This change in vessel permeability hastens the inflammatory process, speeds the elimination of toxic substances and, thus relieves the organism much more rapidly than if only the natural methods were left unaided.

Many other theoretical explanations have been suggested as being the basis for the reaction all of which have factors in them which seem quite logical and quite effectively proven.

May we say then that perhaps the reaction is one that in its entirety does not fit any one of the above theoretical observations but is one of such a wide or diffuse character as to embrace a number of factors. At least we must say that at present the best we can do is to treat the reaction as being somewhat empirical
until further definite proof can be presented. (18).

In the study of the more recent application of non-specific protein therapy it is believed that wherever an increased resistance might be of use, non-specific proteins will be of great value. It would seem therefore that the main field of such therapy would be in the treatment of infections. The increased activity produced in the liver helps to eliminate the toxic substances absorbed from the local site of infection and since the protein injections bring about a vascular dilatation as well as a functional stimulation of all the splanchnic organs, we have increased absorptive power and detoxifying action.

There is at present a wide variance of opinion among clinicians as to the efficacy of non-specific treatment. Some refuse to recognize it as being of any great value while others use it extensively and almost with impunity. The ease of use of the hypodermic needle which makes possible the parenteral introduction of proteins into the body has led to a widespread and, perhaps at times, uncritical use of this method in the treatment of all types of diseased conditions, and to the drawing of clinical conclusions without consideration of the natural course of the disease or other factors which might influence its course. In fact in some instances of re-
ported therapeutic results, clinical claims have been advanced far beyond laboratory and controlled experimental evidence. It is a question then whether or not clinical evidence can stand on its own merits without laboratory or experimental confirmation. That the injection of foreign protein produces profound changes in the body is shown both by laboratory tests and clinical observation. The question to be answered is not whether such changes occur but whether they are of advantage to the patient and if so whether the advantage affects any possible disadvantages. It must also be determined whether such improvement as is noted is actually due to the remedy or whether, in the disease in question, similar improvement may occur spontaneously. (5)(7).

As previously mentioned non-specific therapy has been used in the treatment of almost every known disease in some with much more benefit than in others. It would be practically impossible to study the reaction and results in each disease in which the treatment has been used. However, a study of the usual reaction in those conditions in which non-specific therapy is more commonly used is herewith presented.

The usual reaction manifests itself as a prodromal phase and in two further phases a "negative" and a "positive" phase, generally considered to be distinct. The
period just after the injection is given and before the temperature begins to rise, is the procromal phase consisting of what may be called a prechill and a chill period. Then there begins the negative phase, that period from the onset of the rising temperature to the point of maximal temperature. The second or positive phase extends from the height of the fever to the return of normal temperature. Occasionally a secondary chill and fever occur the following day. During the negative phase there are inaugurated certain phenomena, some of which seem deleterious to the patient's well being and which, if long continued, would militate against the usefulness of the treatment. There is in general however, a sharp reversal of these phenomena at the beginning of the positive phase and during this reversal the processes of healing are markedly stimulated. (6).

Ferdinand Hoff outlines the reaction as follows:

Phase 1.

1. Rise in temperature.
2. Leucocytosis (myelocytic).
3. Decrease in alkali reserve (acidosis).
4. Increase in basal metabolism.
5. Increase albumosis.
6. Increase blood sugar.
7. Decrease of cholesterol in the blood.
8. Hyperactive sympathetic nervous system.
9. Increase in thrombocytes (blood platelets) and their destruction.
Phase 2.

1. Drop in temperature.
2. Drop in leucocytosis with a tendency to a lymphocytosis.
3. Increase in alkali reserve.
4. Minus basal metabolism.
5. Less albumosis in the blood.
6. Decrease blood sugar.
7. Increase in the quantity of cholestrin.
8. Hyperactivity of the parasympathetic nervous system.
9. Thrombocytes return to their normal proportions.

Phase 1 is determined one-half hour after the injection. Phase 2 is determined two hours after injection.

"While the nine points of the table are all important when employing foreign protein injections only some are very essential, as well as practical as a routine; whereas others are more technical and employed as checking the other routine tests so that numbers 1, 2, 3 and 9 are employed at regular intervals, whereas number 4 should be determined at the beginning and again within two weeks. The other tests which are all based on blood chemistry should be done at the beginning and at such times when these other tests would indicate some sharp changes. At a glance one might consider this an unwieldy method of treatment, however, as practice shows, it is not the case."

Local reactions to the injections are usually not severe. There may be considerable swelling at the site
of injection, this is especially true when a pyocyaneus vaccine is used. Alexander reports a case wherein he used foreign protein therapy that caused such a reaction and destruction of the mastoid as could not have occurred from the disease itself, and it made it necessary to operate much earlier than intended. However, such reactions are very rare and very few can be found in the literature. (13)(10).

Various factors influence the reaction; the kind and degree of the patient's illness; the method of administration, type and freshness of the protein used, the size of the dose, and the response of the patient. Reactions to the proteins are essentially the same regardless of the variety used. When the substance is given intramuscularly, reactions are minimized and delayed. When it is given intravenously reactions are sharper and more prompt. The ability to produce fever and other phases of the reaction vary also with different preparations of vaccine, i.e. fresh vaccines give a more prompt reaction than old vaccine and consequently should be used in smaller doses. Preparations of milk or sulphur are used quite extensively but perhaps typhoid vaccine has been used most widely. Typhoid vaccines made by state boards of health, the United States Army and commercial houses
are generally considered as standard. It is generally given intravenously but occasionally some use it intramuscularly. Frequency of dosage and amount of vaccine used with each dose vary considerably. Some advise the administration of foreign protein not more often than once a week; others every second day. Usually it is given twice a week unless untoward reactions develop. In the case of typhoid vaccine the initial dose is usually from 15,000,000 to 25,000,000 bacilli; subsequent doses are 50,000,000, 75,000,000 or 100,000,000 and so on gradually increasing according to the response of the patient and severity of the reaction. (4).


In the field of Gynecology foreign protein treatment has been used most extensively and with undisputed beneficial results in many cases. The protein most commonly
used here is whole sterile milk. This is put up in ordinary test tubes in 15cc quantities, stoppered with sterile cotton and sterilized by placing in a water bath and boiling for ten minutes; the tubes of milk to be kept in ice until used. The site of injection is, preferably, the gluteal area, and a long, thin, very sharp needle is used. When the needle is well in the muscle it is then withdrawn for a very short distance to be sure that the point is not in the lumen of a vessel. The injection is made quite slowly and with but little pain, although the bulk of the milk injected may cause momentary discomfort. The initial dose is usually 5cc, sometimes only 3cc being used if the patient is very weak or whenever any of the special conditions to be mentioned later among the contraindications. The second and third injections are given after an interval of one or two days or after the reactions of the former doses have subsided. Usually after a series of three injections the patient's response to the treatment is observed for two or three days before beginning another series. During this interval a pelvic examination is made, a blood count, and in many clinics a sedimentation determination made. The patient should be kept in bed and the symptoms treated symptomatically.
Yates and Davidow make the following report of their experience with non-specific therapy in gynecology:

"The use of sterile milk injection was begun by us in 1924 and up to the present time over 1,200 patients have received this treatment while in-patients of the hospital, and approximately another 1,000 cases have been treated in the out-patient department. In all there have been at least 8,000 injections given including those hospitalized and those seen in the out-patient clinic. In not a single instance has abscess occurred."

"The types of case treated among the 1,200 hospitalized patients may be classified as follows:

<table>
<thead>
<tr>
<th>Case Type</th>
<th>No.</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute salpingitis</td>
<td>447</td>
<td>37</td>
</tr>
<tr>
<td>Subacute salpingitis</td>
<td>374</td>
<td>31</td>
</tr>
<tr>
<td>Chronic salpingitis</td>
<td>217</td>
<td>18</td>
</tr>
<tr>
<td>Fibroids with acute infection</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Septic abortions</td>
<td>72</td>
<td>6</td>
</tr>
<tr>
<td>Pelvic abscesses</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Bartholin abscesses</td>
<td>25</td>
<td>2</td>
</tr>
</tbody>
</table>

"Among the chronic salpingitis patients were found cases of chronic pyosalpingitis with low sedimentation rates which were found at operation and diagnosed from the pathological specimens removed."

"The majority of these patients, therefore, fall under the head of acute cases and the total percentage may be listed as 82 per cent or 990 cases."

"In 80 per cent of these cases the patients showed
a reaction of $100.4^\circ$ temperature or more, in at least two
injections in their series of three. Of the remaining 20
per cent who did not show this reaction the majority were
cases of chronic salpingitis as proved by operation" (24).

By those using sterile milk injections fairly uniform
symptoms occur in the patients' reaction to the injection.
There is a general reaction which consists of a chill fol-
lowed by a rising temperature that reaches its maximum in
from six to ten hours after injection and subsides usually
within twenty-four hours. The chill usually varies in
length from a half minute to forty-five minutes, even the
longer chills having no apparent injurious effects on the
patient. The temperature ranges from 5 to 7 degrees above
normal depending largely upon the acuteness of the disease,
the greater rise being in the more acute cases. Sometimes
there is in addition to the chill and fever, nausea, vom-
itting, headache and general malaise but these usually
subside within a short time and are not of great signifi-
cance except for the temporary discomfort to the patient.

Within twenty-four hours after the injection the gen-
eral symptoms usually subside and the patient feels much
better. In fact so much better that they frequently de-
scribe the feeling as one of euphoria. This feeling of
well being is more common in those cases having the more
severe reactions. They feel definitely better, the pain is relieved, appetite and general appearance are improved and frequently the patients declare themselves cured. It is this last factor which although very pleasing to the patient makes the treatment somewhat difficult because the patient feels so much improved that she insists no further treatment is necessary and leaves the physician, improved but not cured.

Those cases definitely proved to be of gonorrheal origin have showed the most striking beneficial results. However, cases of septic abortion and pelvic abscess have been treated similarly and in many cases definitely benefited. (15).

Kleemann in a series of over sixty cases of bilateral adnexal inflammations of gonorrheal origin with tumor masses varying in size from 2 to 10 cm in diameter, and with occasional temperature, menstrual disturbance-pain, bleeding etc., used milk injections and found the results to be very favorable. Convalescence was established much sooner than with the ordinary local or expectant treatment. The local tumor masses being reduced in size and the general condition of the patient much improved. In no case did he find any ill effects or any injury from the treatment, and in over 200 injections given there was no ac-
cess formation resultant.

Fuchs believes that the non-specific treatment is of very definite gynecological value, even in the treatment of early adnexal inflammation accompanied by acute symptoms and much pain and profuse hemorrhage. The pain diminishes after the second injection, menstruation becomes normal after the next period and the adnexal swelling is reduced. The fact that this can all be accomplished in an ambulatory patient is of decided advantage.

In an attempt to prove that the results he obtained were the results of the use of foreign protein and not natural processes alone, Murray selected a group of twenty-two cases and handled them in the following manner: No patient was given milk injection until five to seven days of conservative treatment had failed to reduce the temperature or afford subjective relief. Each case was put on conservative treatment on admission; absolute rest in bed, elevation of head of bed, ice bag to abdomen, low simple enema daily and hot alkaline douches morning and night. This routine is usually sufficient to reduce temperature and effect clinical improvement in from five to seven days. The twenty-two cases studied were those that had failed to respond to such treat-
ment and were then given milk therapy. The benefit derived therefrom can be considered directly as being due to the milk therapy because of the test of routine therapy proving ineffective.

From the study of these twenty-two cases, Murray concluded that:

1. "Milk injection is a valuable adjunct in the conservative treatment of pelvic infection.
2. It is without uncomfortable local or systemic reaction except in a very small percentage of cases.
3. Marked increase in the total leucocyte count and a corresponding increase in the polymorphonuclear is the rule; in 75 per cent of cases the temperature promptly returned to normal after milk injections.
4. Definite clinical improvement was noted in 60 per cent of the cases." (15)

Clinicians uniformly agree that the response to protein injection in pelvic disease is of much greater advantage in the acute than in the chronic cases. Operation in the chronic cases reveals that a great deal of fibrous change has taken place as a result of the inflammatory processes. It is believed that this fibrosis hinders the healing process induced by foreign protein whereas the simple exudates of acute inflammatory processes respond more favorably.

Uniform clinical and laboratory findings are noted in the acute cases of gonorrhea. The average temperature before treatment in the acute case varies from 100° to 102°
and the average blood count varies from 12,000 to 15,000 white blood corpuscles per cubic centimeter. The average leucocyte count determined shortly after the height of the fever is usually from 15,000 to 20,000 and cases are reported in which it reached as much as 20,000. The average temperature change following injection of milk in a series of cases reported by Yates was:

<table>
<thead>
<tr>
<th>Injection</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st.</td>
<td>101.8°</td>
</tr>
<tr>
<td>2nd.</td>
<td>103.2°</td>
</tr>
<tr>
<td>3rd.</td>
<td>103.6°</td>
</tr>
</tbody>
</table>

The highest temperature noted was 107° and no ill effects noted.

During the past several years much importance has been laid on the determination of sedimentation time of the red blood cells in selecting the type of treatment to be used in pelvic infections. In the acute cases the average sedimentation time is from 15 to 20 minutes and in the chronic cases 75 to 100 minutes. This test is of importance in that it shows the presence of infection and pus even after the blood counts and temperature have become normal. It is a means therefore, of determining whether the relief obtained from the treatment is recovery or is merely localization requiring surgical intervention. The use of sterile milk injection also markedly shortens the time necessary for preoperative
treatment in that it hastens localization. Before the use of sterile milk patients with acute infection required 14 to 28 days of conservative symptomatic treatment preoperatively whereas since the advent of milk therapy only 7 to 14 days are required.

After a careful study of his cases Davidow summarizes the gynecological use of protein therapy thus:

1. "Should cellular repair depend upon the increase of leucocytes and their activity, then it would seem that protein therapy is rational.

2. It is not a specific but should be used as supplementary to other recognized measures.

3. Acute cases of adnexal disease are those most adaptable to its use.

4. The sedimentation of the red cells has been a great help in the selection of suitable cases for this treatment.

5. Those patients who have had repeated infection, with resulting fibrosis, receive little or no benefit.

6. In none of the patients have the reactions done harm where contra-indications were adhered to.

7. In 3,000 injections no abscess has developed at the local site." (24)

It is evident, therefore, that there is a very definite value in the use of foreign protein in treating gynecological cases. This same type of therapy has been used in many other fields with results of a very similar nature but perhaps not as extensively. The reaction
in most cases is practically identical with that previously described and each will not be discussed independently. May it suffice to merely mention some of the fields and conditions in which this therapy has been used.

In the field of otomnolaryngology foreign protein has been used in treating:

3. Postoperative mastoid disease both after simple and radical mastoid.
4. Postoperative sinusitis, both after simple or conservative and more radical operations.
5. Atrophic rhinitis.
6. Chronic tonsillitis and pharyngitis.
7. Chronic laryngitis and tracheitis.
8. Bronchiectasis.
10. Fistulas about head and neck. (2).

In each of the above mentioned conditions favorable reports have been obtained.

In the treatment of asthma, Nelson and Porter have found that small weekly doses of broth in high dilution given to an asthmatic person have an extremely marked effect on the course of their attacks, even when these attacks are very bad and recurring frequently and have resisted all other attempts to modify them. Where the patient is relatively slightly affected, especially in children, the results for the most part are dramatic and
immediate. But it is equally clear that if the weekly
dose of protein is discontinued within anything less than
six months to a year or even longer, the attacks reoccur
and are sometimes as severe as before any injections
were given. The treatment is then not strictly curative
but in reality prophylactic in nature. However, the re-
lief produced has made it a decidedly worth while proce-
dure. (17).

The use of foreign protein injections in treating
diseases of the eye especially iritis and in children,
conjunctivitis has met with considerably popular favor
and many encouraging results have been reported.

Colitis has been decidedly benefited by such treat-
ment in many cases and in cases of peptic ulcer some
very interesting observations have been noted. Muller
demonstrated that aolan had a spasmyotic effect upon
contractions of the stomach. This was done by having
a patient suffering from peptic ulcer swallow a small
rubber balloon and then by inflating this balloon and
attaching the end to a Kymograph the contractions were
traced. Ten cubic centimeters of aolan were given in-
tramuscularly after a preliminary tracing was made. It
was found that the contractions ceased immediately fol-
lowing the injection and that the pain subsided syn-
chronously with the cessation of the contractions. It was concluded therefrom that by such treatment definite rest could be afforded an otherwise spastic ulcerated area and thus healing aided materially. From the above observation it was also supposed that perhaps such treatment relaxes enterospasm and that this relaxation may be the basis for the effectiveness of such treatment in colitis. The effect of the injections on the bleeding ulcer is also a very interesting factor. In a series of four cases of severe bleeding as shown by stool analysis, Meyer and Kartoon found that blood disappeared entirely from the stools during and after the treatment in all the patients except one and this one later proved to be carcinomatous. It is thought that the relative flaccidity induced by the protein injection is the basis for the cessation of hemorrhage. It would seem from the above observations that protein therapy is a valuable adjunct to the standard method of caring for gastric ulcer and spastic condition of the intestine. (19)(14).

Non-specific protein therapy has recently found its way into the treatment of functional mental disorders. The treatment is still very elementary in nature but a number of cases have been reported. The observation that mental symptoms of the psychotic are ameliorated after
a severe physical shock was the basis for this type of treatment. The cases reported were those suffering from chronic schizophrenia. A typhoid vaccine of a concentration of 1,000 million organisms per C.C. with 0.5 per cent phenol as a preservative was used. Injections were given intravenously at intervals of from four to eight days and the initial dose given in the majority of the cases was fifteen millions. The dosage was increased rapidly except in those having very severe reactions until the maximum dose of one billion bacilli per injection was reached. Each patient received ten injections. In those developing high temperatures a liquid diet and an ice cap to the head were used. Of the twenty-seven patients treated four apparently recovered fully, one was greatly improved, nine slightly improved and the remaining thirteen showed no change but none becoming worse mentally or physically. Eighteen of the patients showed an increase in weight ranging from one to thirty-eight pounds and two remained stationary while the remainder lost small amounts varying from one to nineteen pounds. The immediate effects were chill, fever, headache and temporary loss of appetite. Following the acute symptoms, however, appetite increased and the above noted results took place. From the above series it is impossible to
draw any definite conclusions or determine the real merits of the treatment but the results at least warrant further observations along this line. Some other workers have reported fifty per cent showing remissions after the treatment. (9).

In the organic neurological disorders especially in neuro-syphilis everyone is familiar with the improvement following non-specific therapy. The use of sulphur injections and more commonly malarial therapy has proved beyond question to be beneficial in many cases. It has been the experience of many observers and investigators that the beneficial results of malaria is roughly proportional to the height of the fever produced. The importance of obtaining the highest possible fever is, therefore, obvious. With malaria the temperature averages about 104° and peaks at 105° or 106° during the attacks. By using ordinary bacterial proteins the temperature produced is distinctly lower. Nelson thought then that if he could work out some means of obtaining temperatures of around 105° or 106° by using bacterial proteins he could do away with the disadvantages of infecting the patient with the plasmodium. He proceeded to use a typhoid vaccine as follows: Two daily intravenous injections of the vaccine properly spaced as to time were given. The
first dose is given at any selected time and is of a size calculated to produce a slight fever; the second is given during the height of the fever produced by the first usually at the end of the second or third hour. The second dose seems to have the effect of "exploding" the charge supplied by the first and in this way relatively small doses are capable of producing fevers as high as 107° F. One of Nelson's cases is herewith presented to illustrate this type of treatment:

A woman, aged forty-eight, presented the evidences of an asymptomatic neurosyphilis. Two years ago she had been started on malarial therapy but for some reason this was stopped in the middle of the course. Spinal fluid examination showed: cells, positive Wassermann, and positive colloidal benzoin reaction. She was given the following treatment:

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose of Vaccine</th>
<th>Highest Temp.</th>
<th>(Prelim. trial with old method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov. 28.</td>
<td>100 Million</td>
<td>102.6</td>
<td></td>
</tr>
<tr>
<td>Nov. 29.</td>
<td>20 Million</td>
<td>99.4</td>
<td>25 Million</td>
</tr>
<tr>
<td>Nov. 30.</td>
<td>25 &quot;</td>
<td>99.8</td>
<td>50 &quot;</td>
</tr>
<tr>
<td>Dec. 1.</td>
<td>10 &quot;</td>
<td>99.0</td>
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<td>&quot; 3.</td>
<td>30 &quot;</td>
<td>?</td>
<td>225 &quot;</td>
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<tr>
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<td>65 &quot;</td>
<td>99.0</td>
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<td>&quot; 5.</td>
<td>75 &quot;</td>
<td>99.0</td>
<td>125 &quot;</td>
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<tr>
<td>&quot; 6.</td>
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<td>&quot; 7.</td>
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<td>&quot; 10.</td>
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A spinal test following this treatment showed no es-
sentinal change in the fluid but subjectly the patient was improved. This serves to illustrate, however, that by proper size of dosage and by proper spacing almost any desirable temperature may be obtained. If it is the temperature then that is of greatest benefit the above treatment should be very effective. Not all observers will agree that the height of the temperature determines the effectiveness of the therapy so again we must refrain from hasty conclusions.

Unusual reactions to foreign protein although quite rare must be considered in a discussion of this nature. When one considers the profound response to the injections untoward effects might be expected much more frequently than they actually occur. In a series of 2,500 cases receiving over 10,000 injection, Hench reports unusual clinical phenomena subsequent to only twenty injections and in only fourteen cases. They occurred seventeen times in the treatment of twelve patients with arthritis and three times in the treatment of patients having occlusive vascular disease. The unusual reactions were: Acute and subacute, appendicitis, cholecystitis, enteritis, pleurisy, pericarditis, iritis, glaucoma, adenitis, extensive vascular thrombosis and renal insufficiency. In arteriosclerotic vascular disease, acute thrombosis is the occasional possibility. In arthritis
and other diseases the reactions are variable. The reactions are believed to be related to the injections on the basis of flare-ups of underlying disease rather than incidental complications due strictly to the protein injections.

In Hench's cases death occurred in three instances, a mortality rate of 0.12 per cent. This constitutes a very small risk but one that must be taken into account and one that may possibly be avoided by careful selection of patients to be treated.

Unsuspected latent or quiescent focal inflammation and infection may be stimulated. Except in certain conditions, of which pulmonary tuberculosis is one, the known presence of latent or quiescent foci should not act as a contra-indication to protein therapy. In fact part of the value of such treatment lies in the possible demonstration of suspected or unsuspected foci otherwise undemonstrable at the time. In that way the unusual reaction may be beneficial rather than detrimental. Dosage seems to be of variable significance in the production of undesirable reactions. Untoward reactions have been observed after very small doses administered intramuscularly as well as intravenously. Likewise frequency of dosage seems to have little or no bearing upon the pro-
duction of unusual reactions. The possibility of protein sensitization must always be borne in mind when giving such injections, and there must always be adrenalin handy to help combat such a reaction.

There are certain contra-indications to non-specific therapy which must be borne in mind. No patient should be subjected to injections which produce severe shock unless there is definite evidence that the patient is a good clinical risk and able to bear the strain imposed upon him by such injections. If non-specific therapy is desired in some of the more uncertain cases some of the less severe methods can be employed with lesser risk such as intramuscular or subcutaneous injection rather than intravenous. Also it must be remembered that the completely fatigued patient is no longer capable of responding to stimulation and, therefore, protein injection is at best valueless in such cases. Before using proteins we must take particular care to obtain a history or nervous instability, epilepsy, serum sickness, hypersensitivity, urticaria, or angioneurotic, edema because in such cases only the more benign forms of protein shock can be used without seriously endangering the life of the patient.

Chronic alcoholism has developed into definite de-
lirium tremens following non-specific reactions and is considered an absolute contraindication.

Diabetics, because of the tendency to vascular changes are not to be given protein injections.

In patients with cardiac lesions great caution must be employed because of the danger of the added strain, produced by the therapy, resulting in cardiac failure. The cardiac lesions to be feared chiefly are: valvular lesions, sclerosis, hypertension and myocarditis.

The danger of waking latent foci in pulmonary tuberculosis brand this disease as a contra-indication. Also in the more severe acute diseases when the patient is extremely toxic or septic shock therapy is not to be used.

Some consider pregnancy also as a contra-indication because of the added strain produced by such therapy.

We can see then that non-specific therapy does require judgement in selection of cases and careful attention and bedside study of the patient perhaps in greater measure than ordinary therapeutic procedures. It cannot be considered as a routine method of treatment but must be adapted or individualized to each patient. The size of the dosage, the type of preparation and the time of application must vary according to the disease, its in-
intensity, duration and the condition of the patient. It is not to be considered a cure all, but rather a valuable adjunct to other therapeutic measures when properly used. When so used, it should prove to be one of our most useful measures in combating both the acute infectious diseases and the more chronic inflammatory lesions.
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