Serum Therapy in Therapeutics and Medical Science

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Serum therapy in the form in which it finds application in the treatment of diphtheria patients is an antitoxic or detoxicating curative method. It is based on the view, held by Löffler in Germany and by Roux in France, that the parasites causing diphtheria, the Löffler diphtheria bacilli, do not themselves cause diphtheria, but that they produce poisons which cause the disease to develop. Without this preliminary work by Löffler and Roux there would be no serum treatment for diphtheria.

When the diphtheria poison is rendered harmless within the human organism, then the diphtheria bacilli behave like the innumerable micro-organisms which we absorb without suffering harm every day and like those micro-organisms which correspond morphologically with the diphtheria bacilli, but, from the outset, have no capacity to produce poisons (pseudo-diphtheria bacilli). The poison excreted by the bacilli is the diphtheria bacilli's dangerous weapon against the human being, without which weapon they would be delivered over helplessly to the natural prophylactic power of the living human organism.

The way in which the diphtheria bacilli, after penetrating into the human body, release their poison and how this poison develops its destructive activity has been the subject of many interesting investigations, the result of which can be summed up briefly as follows: In a typical clinical picture of diphtheria in human beings, as summarized for the first time 80 years ago by the Frenchman Bretonneau, the diphtheria bacilli are first localized in the pharyngeal amygdala, which, in all probability, they reach principally via the breath, but also in substances which we take in by way of nourishment. In the niches and small cavities of the amygdala the diphtheria bacilli can multiply as though in an artificial incubator and excrete their poisons. In animals, the organ, called "amygdala" (tonsils) on account of its shape (L. "amygdala" = almond), is missing and this is probably the reason why epidemics of diphtheria are the tragic privilege of human beings. The diphtheria poison gets into the blood stream by way of the lymphatic vessels and starts up inflammatory processes from there in the various organs. The inflammatory symptoms are outwardly visible chiefly in the proximity of the site of production, on the pharyngeal mucous membrane and in the larynx.

If we now introduce the diphtheria serum as an antitoxin into the blood by injecting it under the skin, this antitoxin will reach all parts of the body to which the blood has access. If the injection takes place at a time when the diphtheria bacilli have not yet begun their destructive activity, then the secondary inflammatory phenomena of diphtheria toxicity will not arise. We speak then of immunization or of preventative or prophylactic serum therapy. If, on the other hand, the toxic process has already begun, then the already existing inflammatory processes will follow their natural course, for the anti-toxin exerts no influence, either useful or harmful, on the substrata of the inflammation, on the cells and organs. In this case, all that can influence the already existing disease is firstly to render harmless the poison which has already reached the body fluids, and secondly to prevent the entry of fresh supplies of active poison into the blood stream. It is easily understandable that the diphtheria serum has an abortive action, but it is not the disease which is cut off but the creation of new disease-engendering substances.
It will be seen from this how important *early* use of diphtheria serum is. The longer one delays the injection after the start of the illness, the more existing focal points of inflammation and the more disturbances of vital functions will threaten health and life.

In addition, a certain time must elapse from the injection of the serum until its antitoxic and healing activity in the affected parts of the body can develop. Also, serum injected under the skin does not pass straight into the blood vessels but first into the lymphatic vessels. From here it takes several hours before passing gradually into the blood stream and further time still is needed before it is diffused, not only everywhere in the blood stream, but also into the extra-vascular poison-containing fluids. This interval between injection and detoxification can mean the difference between life and death for the threatened individual and I have asked myself whether, in the interest of the patient, this interval could not be shortened. It can indeed be done if the serum is injected directly into the blood stream instead of under the skin. According to experimental investigations carried out by my erstwhile collaborators, Dr. Knorr and Dr. Ransom, about 8 hours can be saved in this way. Furthermore, it is possible to have a local effect on the poison-producing localities by using dilute serum solution as a mouth wash to rinse the poisoned pharyngeal organs. So that we may recognize the position which serum therapeutics have gained in the treatment of diseases, as compared with other methods in medicine, I hope you will allow me to use one or two technical terms, not only because these have, during the course of time, come to embody a well-known and generally respected concept, but also because these technical expressions, taken from Latin and Greek, are more suited to international understanding than more modern expressions which we might use in their place.

Since earliest times, in that sphere of medicine which is responsible for the analysis of the symptoms of disease, their cause and natural or artificially induced conquest, namely pathology, humoral and solidistic pathologists have been in opposition to one another. In the last century the solidistic pathologists won the upper hand and the form which Virchow has given to the solidistic pathology by the foundation of *cellular* pathology is now so firmly established that the old humoral pathology can probably be regarded as having been finally laid to rest. With the victory of solidistic *pathology*, however, there has now arrived, pari passu, in the teaching hospitals a solidistic and cellular *therapy* of which one cannot speak so highly as in the case of the cellular *pathology*.

In the treatment of wounds, solidistic trend in therapy expressed itself more in salves, balsams, alteratives, which were supposed to influence the diseased body elements in ill-looking wounds to new and different activity. As you know, this aspect of solidistic therapy has vanished from medicine since Lister, with epoch-making success, laid down the principle, which he taught us to follow down to the smallest detail: "Keep fingers away from wounds, leave the cells as much as possible undisturbed, but take care that noxious agents from outside are kept away from wounds and cells".

In internal medicine, however, solidistic therapy remained "faute de mieux". New remedies were constantly coming on to the market and into use in practice which were supposed to curb, with antifebrins, the vigorous activity of the cells aroused by fever, encourage the will to live and alter the misdirected cell activity. I do not need to quote instances when I maintain that we were all reared in the solidistic- and cellular-therapy dogma according to which the morbid manifestations of life are and must remain the subject of internal therapy. A glance at any Government-sanctioned Pharmacopoeia will show that even now medicaments are classified against a background of this viewpoint.

The detoxicating, or as it is also called, the antitoxic serum therapy, is, on the other hand, *humoral* therapy. Just as little as it has any direct influence on the diphtheria bacilli, is it able to have any direct action, whatever, on the living body elements of the patient who either has, or is threatened
with, diphtheria. The detoxicating process acts exclusively in the body fluids, in the blood, in the lymphs and in the pericellular lymphatic areas. I must emphasize this especially, because many authors take the view that the diphtheria anti-toxin can also neutralize the poison which has penetrated into the body cells and become established there. My own experience runs entirely contrary to such a view.

Serum therapy in the treatment of diphtheria is, therefore, humoral therapy in the strictest sense of the word. It leads us back to the supposedly long-abandoned crasis theory which attributed an important role in the development and overcoming of disease to the peculiarities of the mixing of the substances solved in the body fluids. As long as there is active diphtheria poison in the body fluids, then a dyscrasia exists. After inactivation of the diphtheria poison, or in other words after the detoxication of the body fluids by the addition of diphtheria antitoxin, the dyscrasia is overcome; in its place appears, so to say, a eucrasia. I do not object if someone tells me that the process of disease does not consist in a faulty mixture of fluids, but in the abnormal functioning of living body elements, the solids of the whole organism. In this sense, there can, in fact, only be solidistic pathology or cellular pathology, and never humoral pathology since, indeed the lifeless, inert body fluids cannot be attacked by any or illness. In so far, however, as the diseased function of the living body elements is, in the main, conditioned by the incorrect mixture of body fluids, I find the linguistic inconsistency of the use of the word humoral pathology no worse than if one speaks of pathological anatomy, although the subject matter of this discipline concerns cadaver anatomy and cannot really be attributed to cadavers. However this may be, no one doubts any more of the existence of a humoral therapy since antitoxic diphtheria therapy has found an assured place for itself in medicine.

I must add another important epithet to the word serum therapy in order to characterize its position in medicine. It is aetiological therapy in contrast to the symptomatic therapy just described. As in the case of the Lister treatment of localized wound infections, serum therapy also, in the treatment of general infections, holds to the principle "leave the cells in peace and simply take care that noxious agents from outside are kept out, or, if they once get into the body, are removed". The internal anti-infectious therapy would appear to have the more difficult task, and as long as it was thought that anti-infectious activity could only be carried out by killing the living disease germs, the pessimists appeared to be justified in making the discouraging statement that "internal disinfection would always remain impossible". If now an internal disinfection has, nevertheless, been achieved, this is not thanks to speculation or change of doctrine, but thanks to the fact that Nature herself has been taken as a guide. I doubt whether it will ever be possible to establish artificially the antitoxic principle of serum therapy in diphtheria, without the aid of vital organization and secretion faculties. It is one of the most wonderful things imaginable to see how the supply of poison becomes the prerequisite for the appearance of the antidote in the poisoned living organism, how then the antidote in the blood reaches a state of almost unbelievable antitoxic energy through the systematic increase of the poison supply, how the bearers of this energy, the albumins and globulins of the blood, show no sign of any chemical change whatever, how the newly-won energy is so elective that we have no other means of proving its existence than solely by the diphtheria poison.

An attempt has been made to make a comparison between the method of action of the antitoxic serum albumin on the poison molecules with other compensating and inactivating processes. In my first work, I myself used the non-prejudicial expression "rendering the poison harmless", replacing it later, following Ehrlich*, with the better sounding expression "poison destroying". But I gave up this expression as well when I realized that I was being credited, on account of it, with the assumption that the poison molecule would be, to a certain extent, demolished and so become non-poisonous. I began then to speak of "neutralization", but right from the start I secured myself against the opinion that the antitoxic and the toxic protein combine in a way which resembles the formation of salts from acid and alkali. Now I prefer to use the word "detoxication" which makes
no reference to the method of action. But if I want to indicate roughly how I imagine this
detoxicating process, then I speak of "inactivation". I imagine, in fact, that, as regards chemical
analysis, the antitoxic and the toxic protein stay exactly the same after detoxication as before; what
changes is simply the activated condition; in the same way as the conductors of positive and
negative electricity, before and after compensation of their active conditions, remain the same
substances in terms of chemical analysis. Perhaps, at some later date, work in the physico-chemical
border territory which you here see represented by such illustrious names as van't Hoff and
Arrhenius will bring us to the point where we can refer to active protein without the need of talking
in parables!

With this example of antitoxic diphtheria therapy, I have attempted to enumerate for you the chief
characteristics of serum therapy as a novum in therapeutics and as a progressive step in medicine.

It is a humoral therapy, because its activity develops only within the fluid and solved components of
the individual who is ill or threatened with illness. It has an anti-infectious action brought about by
internal disinfection, but is, in this respect, in contrast to the anti-bacterial disinfectant treatment
methods which, for example, can be carried out in laboratory experiments with the aid of the R.
Pfiffer's bacteriolysin; because its activity is only detoxication, we call it antitoxic. Because it does
not influence the substrata of the diseased manifestations, the cells and organs, but only the cause
of the disease, I call it aetiological therapy, which comes to approximately the same thing as the
therapeutic endeavours which are referred to in other quarters as causal, radical, abortive, etc.

Now I must speak on a special subject in which serum therapy takes its place with those methods of
combating infectious diseases such as Jenner's smallpox vaccination, Pasteur's anthrax prevention,
Pasteur's hydrophobia treatment, and Koch's tuberculin therapy.

These kinds of treatment can be indicated as isotherapeutic methods because they treat the
infectious diseases with media which are of the same kind as the disease-causing, infective
substances. Briefly expressed, serum therapy works through anti-bodies, iso-therapy through iso-
bodies.

You know that by treating horses with an iso-body, the diphtheria poison, we obtain the curative
anti-body. In explaining the nature of isotherapy, I would like, however, to start with an example
where, for me, the isotherapy is not just a means to an end, but an end in itself. This is the case in
the experiments which I have been carrying out for a number of years in Marburg with the purpose
of combating tuberculosis in cattle.

As you know, tuberculosis in cattle is one of the most damaging infectious diseases to affect
agriculture. It causes premature death in affected animals, damages nutrition and milk production
and is the cause of inferior meat. Furthermore, it is feared as being a carrier of tuberculosis to
humans, although admittedly R. Koch recently disputed this.

In different countries, or in different regions of the same country, the disease does not always strike
with the same violence and frequency. Thanks to the support of Count Zedlitz, the Lord-Lieutenant
of Hesse-Nassau, I have been in a position to ascertain some remarkable statistical facts in this
connection. As a result of many thousands of tuberculin inoculations in two areas of the province of
Hesse, I at first thought that the question of breed played an important part. It appeared, namely, that
in the heavy, high milk-yielding strains (Dutch, Friesian and Swiss cattle) 30 to 40% showed a
tuberculin reaction, whereas in an exceptionally pure breed of red cattle, raised in Hesse, the so-
called Vogelsberger cattle, there was less than 1%. However, comparative infection experiments carried out ad hoc in Marburg showed no differences in susceptibility, and extensive research led finally to the explanation that the number of cattle reacting to tuberculin is, in the main, dependent upon whether any or few cattle are kept permanently in the same stalls. It appeared that, quite independent of hygienic feeding and living conditions, in almost every case the cow-houses with 20 and more cattle were heavily vitiated, whereas the small-man's cows kept in small stables only very occasionally reacted to tuberculin. The large cow-houses were nearly all occupied by heavy, high milk-yielding strains and the small ones by red cattle. And when, in the neighbouring area of Giessen-Gutshofen, the Vogelsberger cattle, which were in large numbers kept together in one building, were submitted to tuberculin tests the proportion of animals which reacted was also very high.

When making these observations, attention was also paid to whether, in those areas which had been pointed out to us by the authorities as being suspected breeding grounds for human tuberculosis, an especially large number of cases of bovine tuberculosis was present. But such a coincidence was definitely not found to exist.

One could feel inclined to use this observation (which I passed on to the Lord-Lieutenant at the beginning of this year in an official report) as corroborative evidence for the view expressed by R. Koch that the tubercle bacilli are different in humans and in cattle. My own observations, however, point more to the view that spontaneously occurring cases of cattle tuberculosis are no more caused by passing contact than is the case with humans, but that rather cohabitation of long duration is required if infection leading to tuberculosis is to be passed from individual to individual.

In my experience cattle are on a relatively low susceptibility plane with regard to tuberculosis infection. In a series of cases, I introduced tuberculosis virus, from pearl nodules containing tubercle bacillus, under the skin direct from animal to animal, achieving in this way nothing more than a local tuberculosis with extensive proliferation of bacilli, which after existing for months completely disappeared. After intravenous injection of the emulsified pearl nodules I observed a general feverish condition lasting for weeks, but which also cleared up spontaneously. Many of these spontaneously cured cattle I later infected together with fresh control cattle in such a way that the latter died of acute miliary tuberculosis in 4-6 weeks, whereas those which had recovered earlier were quite healthy again after a short indisposition.

If there is to be any certainty of cattle dying after a single, arbitrary infection with tuberculosis virus, it is essential that consideration be given to the following main factors:
(1) origin and special composition of the virus;
(2) method of application;
(3) dosage.

I can confirm absolutely Koch's statement that many tubercle-bacilli cultures of human origin are no more dangerous to cattle than Arloing's homogeneous bacilli culture is to guinea-pigs.

In my own experiments with tubercle bacilli of human origin which were avirulent to cattle, cultures were always used which had been cultivated for years in the laboratory. If, however, I used human cultures for cattle infection which had only recently been cultivated from tubercular sputum, they proved by no means unharmful. In the same way, those human bacilli which had become avirulent to cattle through long-continued culture in the laboratory can act again with considerable virulence in cattle if they are first used to infect goats and then, after the death of the animals, are cultivated from the carcases. I have a strain of human-goat tubercle bacilli which, after culture, is probably the most virulent of all to cattle.
There is more probability that cattle-virulent cultures can be obtained without first being passed through goats if the culture stock is obtained from the body of the cattle. Even here, however, I have gained the impression that a long period of cultivation on artificial nutrient medium curtails the disease-causing activity in cattle.

It is very noteworthy here that one must certainly not conclude that the loss of disease-causing activity for cattle necessarily means a decrease in virulence for other animals. The Pasteur Anthrax studies establish, in fact, that there is a definite scale for the decline in virulence. A weakened anthrax strain no longer fatal to mice is not fatal to any other kind of animal either, and one which is virulent for rabbits proves always extra virulent for guinea-pigs and mice. It would be very surprising indeed and would strain credulity if anyone were to report an anthrax strain which is virulent for rabbits, but not for mice and guinea-pigs. There is a firm scale here in accordance with which all anthrax strains, wherever and however they may be obtained, act with greater disease-causing energy in mice than in guinea-pigs, and with greater energy in guinea-pigs than in rabbits.

In the case of tuberculosis things are different. I have studied with special care in this direction three tubercle bacilli modifications: tubercle bacilli from human beings (Tb-Hu), tubercle bacilli from cattle (Tb-Ca) and tubercle bacilli weakened according to Arloing (Tb-Arl). Tb-Hu and Tb-Ca remain, with great obstinacy, virulent to guinea-pigs and rabbits, but behave differently, in so far as Tb-Hu loses its Ca-virulence more quickly than Tb-Ca. Tb-Arl are harmless to human beings; in rabbits and horses, when injected intravenously, they cause severe illness which can quite soon end in death with symptoms of pneumonia.

For my tuberculosis strains, therefore, I have a quite different virulence scale, according to the kind of animal which is being taken as standard. The reaction of horses is quite exceptionally striking. In these animals the tubercle bacilli obtained from cattle show the lowest degree of virulence.

As regards my methods, I test the disease-causing energy in cattle in three ways: through infection from the subcutaneous tissue, through intravenous injection of the emulsified tuberculosis virus, and through intra-ocular infection. With my assistant, Dr. Römer, I have found that intra-ocular infection is the most effective. I was led to this method of infection by a study of the work of Professor Baumgarten of Tübingen and I now use the intra-ocular infection method to determine the degree of artificially achieved tuberculosis immunity in my cattle. Next I use intravenous infection and lastly subcutaneous infection.

Even when using the tubercle bacilli most virulent to cattle, the culture dose must not be too small in the case of intravenous infection if it is required to cause an illness severe enough to lead to the death of the animal. As an average dose for this purpose, I take 0.04 g from a culture not more than 6 weeks old. The quantity of bacilli contained in this dose corresponds approximately to 2 cm$^3$ of tuberculosis bouillon culture. With intra-ocular infection, a much stronger action is achieved with a much smaller quantity of bacilli. Here the propagation rate in the eye itself is very considerable.

After observing several cases of spontaneous recovery in tuberculosis-infected cattle, the thought occurred to me that the tubercle bacilli modifications which were only slightly active in the case of cattle behaved in the same way as the vaccines to the destructive virus. I then undertook an experiment aimed at systematically rendering young cattle immune to tuberculosis with living tubercle bacilli. An exact description of these immunization experiments, with detailed records and temperature curves, will most probably follow in March of next year in my "Beiträge zur experimentellen Therapie". At this point, I should like to emphasize the following results: in the case of cattle, I forego the subcutaneous preliminary treatment and use instead exclusively the intravenous injection. As immunization vaccine I use a little Ca-virulent Tb-Hu (3267), then go
over to Tb-Ca (Nocard) and, finally, I use nothing stronger in the way of tuberculosis virus than a goat-passage culture.

I have also made experiments using an originally strong tuberculosis virus which has then been dried under vacuum conditions at room temperature and left standing for a long time, whereby its disease-causing potential is greatly reduced. Where pure cultures on artificial nutrient media were concerned, I was not very satisfied with the results; the experiments with dried pearl nodules and tubercular organs from cattle turned out better.

If, on account of the preliminary treatment, a cow became immune to Ca-virulent Tb-(cultures), then there was also an immunity against Ca-virulent Tb-Hu (goat-passage) and vice versa. This does not appear to confirm that Tb-Hu and Tb-Ca are different in kind.

After my Marburg experiments showed the possibility of tuberculosis immunization for cattle, we were now faced with the task of finding out, by research through special experiments, in how short a time and with what minimum of detriment to the animal to be immunized and financial sacrifice, tuberculosis protection for cattle could be achieved in practice. In order to carry out these investigations, I procured for myself living space and grazing ground for a large number of cattle and I am hoping to use the large money award which has come to me through the Nobel Foundation to show the possibility and practicability of fighting tuberculosis in cattle along the lines of Pasteur's protective inoculation to a larger extent than up to now. It would give me much honour and pleasure if any among you would care to inspect my Marburg work and installations on the spot and see, at the same time, how I am using my best endeavours, in accordance with the intention of the noble founder himself, Alfred Nobel, to promote the common good.

I need hardly add that the fight against cattle tuberculosis only marks a stage on the road which leads finally to the effective protection of human beings against the disease. Here, however, it has been my intention to report on facts, not hopes. And it is as a fact that I think I am able to report the immunization of cattle against tuberculosis to you.

*As far as I can ascertain, the expression "poison destruction" appears for the first time in the Abrin study by Ehrlich in the year 1891 (Deut. Med. Wochschr. 1891).

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