DISCUSSION.

Lieut.-Colonel T. D. YOUNG stated that the City of London Public Health Department presented a good example of the collaboration between the medical and veterinary officers. Dr. Collingridge, with keen foresight, recommended some years ago that the officer in charge of meat inspection should be a veterinary surgeon, and the City Corporation adopted his suggestion. The appointment was followed by the issue of by-laws to regulate the hours of slaughter; any killing proposed to be carried out after regulation hours was to be notified by the butchers, and no carcass or offal was to be removed until inspected. Statistics showed the marked results as to efficiency. Following the improvement of slaughterhouses came the more scientific inspection of pig carcasses, whereby £50,000 was saved in 1915 in the central markets, and the Departmental Committee on Meat Inspection recommended the adoption by local authorities of similar by-laws and the same system of examining pig carcasses as to their fitness for human food. Colonel Young gave instances of the finding of dead animals in lairages, the rapid examination of the blood, and the diagnosis of anthrax, whereby danger to slaughtermen and drovers was prevented. Dr. W. J. Howarth, the medical officer of the City, was not less anxious that progress should be made in all matters relating to the purity of meat and milk supply. In the speaker's opinion no public health department was complete without a veterinary officer collaborating with the medical officer in controlling and supervising meat inspection, inspection of cows and cowsheds, contagious diseases of animals, and the care of the authorities' horses. The salary (paid by the various committees) would be well spent in the interests of the public; he urged the reintroduction of the Cattle Tuberculosis Order and the sterilization of all milk or milk products to calves and pigs, as is done in Holland and some other countries. Figures were given showing the splendid results obtained.

THE SCIENTIFIC BASIS FOR NON-SPECIFIC PROTEIN THERAPY.*

BY

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THE clinical successes obtained with non-specific protein therapy have attracted great attention, particularly in America and Germany. Unfortunately the scientific foundations for this method of treatment are very uncertain. The present paper is an attempt to collect the available scientific evidence showing the nature of the effects produced by non-specific protein therapy. It is important to remember that this method of treatment developed along purely empirical lines from specific treatment with serums and vaccines. The minds of clinical workers were strongly prejudiced in favour of the view that such treatment to be effective must be specific; nevertheless, in spite of this preconception, it was established that in many cases non-specific vaccines and serums were as active as specific, and it was discovered that a large assortment of proteins and products of protein breakdown produced the same effects as vaccines; intravenous administration, moreover, was found to be a particularly effective method of administration.

Non-specific protein therapy has been recommended for the majority of known diseases, but there is fairly satisfactory evidence that it is of benefit in the following classes of cases.

1. *Acute general infections*—for example, typhoid fever; here, after an initial exacerbation of the fever, it frequently causes it to terminate abruptly by crisis.

2. *Chronic infections* with local lesions; in this case the injection causes a febrile reaction, which is followed by a secondary phase in which there is a feeling of bodily well-being. The local lesions during the febrile reaction show acute inflammation, and subsequently healing is accelerated in many cases.

Non-specific protein therapy has been particularly successful in the treatment of arthritis, both acute and chronic, in gonorrhoea, in typhoid fever, and in anthrax.

The reaction obtained in non-specific protein therapy depends upon the agent administered and the manner in which it is administered; the general characters of the febrile reaction appear to be essentially the same whatever agent is employed. The effects following the hypodermic administration of typhoid vaccine are familiar to all, and may be taken as a type.

The intravenous injection of vaccines produces a more rapid and more severe response than the hypodermic administration. Peptone administration produces a less violent reaction than vaccines, and it is much easier to get peptones of standard activity than vaccines of standard activity. Purified proteins are usually given by intramuscular injection; they produce a mild reaction after a delay of some hours.

Reagents Used in Non-specific Protein Therapy.

(*a*) Proteins—for example, purified casein (caseosan, aolan).

(*b*) Mixtures containing proteins—for example, milk, normal serum.

(*c*) Products of protein breakdown—for example, purified proteoses, commercial peptones.

(*d*) Other preparations containing products of protein breakdown—for example, some commercial preparations of colloidal metals, polyglandular extracts, etc.

A febrile reaction similar to that produced by protein therapy often follows a large number of other therapeutic measures, and Bier[1] is of opinion that any measure which causes breakdown of body proteins produces therapeutic results similar to the injection of proteins. According to this view the following procedures may be classed under the same heading:

(*a*) Intravenous injections which produce alterations in the blood proteins—for example, hypertonic and hypotonic solutions, protein precipitants such as mercury perchloride, and many other disinfectants.

(*b*) Radium, *x* rays, and the cautery and other procedures which lead to the destruction of body cells.

The Action of Non-specific Protein Therapy on Infections.

It may be stated at once that there is very little evidence that protein therapy has any effect upon the course of infection in laboratory animals. As a whole the laboratory evidence fails to confirm the clinical evidence.

For example, Bingel[2] treated 471 cases of diphtheria with diphtheria antitoxin and treated an equal number of alternating cases with normal horse serum, and found that there was no difference in the mortality rates. Meyer[3] found that normal horse serum only saved 33 per cent. of guinea-pigs from a minimal lethal dose of diphtheria toxin, and Cowie and his co-workers[4] showed that the mild protective effect produced by horse serum was due to its containing traces of diphtheria antitoxin, and that other serums had no such effect. This, therefore, is not a case of non-specific protein therapy.

Normal ox serum has been used extensively in anthrax, and Kraus[5] found that it protected laboratory animals from anthrax, but other workers[6] have had negative results. Weichardt[7] obtained favourable results by treating mice infected with pneumococci with non-specific proteins, but Kross[8] had completely negative results with this treatment in rats infected with mouse typhoid.

One common criticism may be made of most of the above-mentioned results—namely, that the protein reaction varies greatly in different species, and that since rabbits, rats, and mice are peculiarly insensitive to protein shock they are unsuitable material upon which to test the results of protein therapy.

The Substance Producing the Protein Reaction.

Since injections both of proteins and of products of protein breakdown and the destruction of body cells all produce a similar reaction, it appears probable that the common active principle is a product of protein decomposition.

Vaughan has shown[9] that the heating of protein with alkali in alcohol produces an intensely toxic product of which 0.5 mg. is sufficient to kill a guinea-pig. This substance appears to be a proteose; it gives the biuret reaction, it diffuses slowly through collodion membranes, and it is freely soluble in absolute alcohol, although insoluble in ether. When proteins are hydrolysed the higher cleavage products are toxic. The toxic effects produced by such preparations as Witte's peptone are well known, but it is important to note that so-called peptone poisoning is produced by proteoses and albumoses, and that proteins, when broken down completely to peptones, have very little toxicity.

Commercial peptones contain various bodies soluble in alcohol which have interesting pharmacological actions on isolated organs, but these substances are not highly toxic; heating with acid or alkaline alcohol produces, however, a strong poison which has all the characters of Vaughan's soluble protein poison. This substance was named "vasodilatin" by Popielski.[10] I measured the toxicity of peptones

* A paper read before the Section of Therapeutics and Pharmacology of the Royal Society of Medicine.

by intravenous injections into mice, and found that 1 gram of Witte's peptone yielded about 0.3 gram of vaso-dilatin, and that the minimal lethal dose of the peptone was 4 mg. per gram of mouse, while the minimal lethal dose of the vaso-dilatin was 0.1 mg. per gram. This experiment shows that the vaso-dilatin cannot be preformed in the peptone, although it appears to be formed more readily from peptone than from protein.

The base histamine produces effects similar to peptone poisoning, and it has been suggested that the toxic actions of peptones are due to histamine. Hanke and Koessler[11] showed that the content of Witte's peptone in histamine was not more than 3 mg. per 100 grams. I found that histamine was practically non-toxic to mice, which survived intravenous doses up to 0.3 mg. per gram. Histamine cannot therefore be the active principle of vaso-dilatin or of peptones.

The effects produced by peptones, protein poison, and histamine are very similar, although the reactions in different species of animals vary greatly. These varying effects in all cases closely resemble the symptoms of anaphylactic shock. The chief features of the reaction produced by these products of protein breakdown are as follows:

(*a*) A rise of temperature associated with an increase of nitrogenous metabolism.
(*b*) Contraction of plain muscles.
(*c*) Increased secretion of glands.
(*d*) Increased permeability of the capillaries, particularly of the liver capillaries.

The effect of intravenous injections of peptones in dogs is to cause a rapid fall of blood pressure, associated with a great swelling of the liver and rise of portal pressure. The peptone appears to act as a poison to the liver capillaries, and thus causes the liver to be engorged with blood; this prevents a proper return of blood to the heart, and consequently a fall of blood pressure, and at the same time a great increase in the lymph flow. The blood becomes non-coagulable and the animal is rendered immune to a subsequent injection.

Peptones have only a slight toxic action on rabbits, rats, and mice, and have no strongly toxic action on guinea-pigs. Vaughan's soluble protein poison produces the same effects as peptones in cats and dogs, but also acts as a strong poison to the other animals mentioned. Histamine has the same general action as peptones, but it does not render the blood non-coagulable, does not increase nitrogen metabolism, and does not produce immunity. Maunter and Pick[12] found that peptones and histamine produced engorgement of the isolated liver of the cat, dog, and ape, but had no such action upon the livers of rodents. The action of these poisons on skin capillaries can be demonstrated very easily by applying them endermically, when they produce wheals.

The Mode of Action of Protein Therapy.

The evidence considered makes it easy to understand why a large number of different procedures, all tending to introduce into the blood products of protein breakdown, should have a similar pharmacological effect. It is more difficult to understand why such reactions should produce therapeutic benefit.

There is no doubt that an excess of protein breakdown products is violently toxic. Besides the evidence from animals, we have the clinical evidence regarding traumatic shock, which appears to be caused by protein breakdown products. Whipple, moreover, has shown that the toxaemia produced by acute intestinal obstruction is due to the absorption of toxic proteoses.

All who have studied non-specific protein therapy emphasize the necessity of grading doses correctly, and agree that an overdose is extremely dangerous in its immediate effects, and does damage in its ultimate effects. The reaction, therefore, will only produce benefit if it is of a certain strength.

Weichardt[13] explains the effect of protein therapy by saying that it causes "omnicellular plasma activation." Other observers state that protein therapy establishes a condition of vagotonia. In this connexion it is interesting to note that Rosenthal and Holzer[14] and Freund and Gottlieb[15] found that protein therapy caused an increased sensitivity to adrenaline and pilocarpine in experimental animals. There appears to be no obvious explanation for this phenomenon.

The Blood Changes Produced by Protein Therapy.

The most important effect of protein therapy appears to be to produce an immediate negative phase with increased permeability of the capillaries, followed by a positive phase with decreased capillary permeability. The chief effect of the increased permeability is an increased lymph flow which washes into the blood stream a large variety of products of cell metabolism. Heidenhain first showed that peptones and various proteoses caused increased lymph flow, and numerous writers have confirmed this. Petersen[16] showed, for instance, that in a dog typhoid vaccine induced increased lymph flow. Starkenstein[17] studied the rate of excretion of fluorescein into corneal ulcers, and concluded that non-specific protein therapy at first caused increased permeability of capillaries and later decreased permeability. Luithlen[18] measured the rate of excretion of iodides and ferrocyanides into the peritoneal cavity in the rabbit, and concluded that protein therapy caused decreased permeability of the capillaries. Starkenstein[17] and Döllken and Herzger[19] found that protein therapy diminished the toxicity of strychnine to rabbits.

There is no doubt that the protein cleavage products have a strong lymphagogue action and produce increased permeability of the capillaries, particularly in the liver and in the skin. The last effect is shown by the readiness with which they produce urticaria. Whether the capillaries really become less permeable than normal during the positive phase of the reaction appears to the writer a little doubtful. The blood changes observed are as follows:

(*a*) Immediate leucopenia, followed by leucotyosis (Gow[20]); during the latter stage an increased number of young and atypical red cells and an increased number of platelets are present (Cowie and Calhoun[21]).
(*b*) There is an increase in the fibrinogen, globulin, thrombokinase, and blood sugar content in the blood.
(*c*) The non-protein nitrogen content of the blood is raised considerably (Van Slyke and Whipple[22]).
(*d*) The proteolytic ferments in the blood are increased (Jobling and Petersen[23]).
(*e*) The antibodies in the blood are increased.

There is a general agreement as to the occurrence of these changes, but the relative importance of the changes is a matter of dispute. Jobling considered that the alterations in the content of the blood in proteolytic ferment was of great significance, but this is denied by Teale and Bach.[24] The increase in antibodies only occurs if an animal has been previously immunized. Apparently new antibodies are not formed, but antibodies present in the tissues are washed back into the blood.

The anaphylactic state depends upon the presence of antibodies in the tissues and their absence from the blood, and it is interesting to note that peptone injections cause a temporary desensitization in sensitized animals (Kellaway and Cowell[25]). Observations on typhoid patients show that only a slight rise in agglutinin content of the blood is produced by protein therapy, and most observers agree that it is quite insufficient to account for the beneficial effects produced by protein therapy in this disease.

The diphasic action produced by protein therapy is confirmed by Dresel and Freund,[26] who found that in cats caseosan injections caused at first the appearance of a dilator substance in the blood, and that after a few days a vaso-constrictor substance appeared. A vaso-constrictor substance can be obtained from blood platelets, and the platelets probably furnish the vaso-constrictor substance which appears when blood clots; but vaso-constrictor substances can be obtained from most tissues of the body, and therefore the origin of the substance found by Dresel and Freund is uncertain: it is certainly unnecessary to assume that it is a product of platelet breakdown.

These changes observed in the blood are of great interest, and the bulk of the evidence points to the fact that non-specific protein therapy causes a washing out of the tissue fluids into the blood, and that this process causes a number of changes in the composition of the blood. Unfortunately the evidence at present available is insufficient to indicate which of the changes observed is really of chief clinical importance.

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