A Paper

ON

THE USES OF NON-SPECIFIC PROTEIN THERAPY*

BY

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Non-specific protein therapy has now been in use for a sufficient number of years to allow us to form some idea of its value and uses.

PROPER PLACE OF THERAPY

At one time it was thought that in every infection there was a corresponding specific reaction, and that in order to combat successfully any disease by inoculations the corresponding specific serum or vaccine must be employed. There are, however, many indications that this is not the case. In the infectious fevers, for example, there is a common factor in the sickness, malaise, rise of temperature, skin rash, etc., and the specific factor, which is characteristic of each disease and which enables it to be distinguished. Of the two factors, provided the disease is in an early stage and toxins as yet not fully developed, the common factor is the important one from the point of view of combating and shortening the duration of the infection. Non-specific protein treatment is used to assist the reactions which are common to all infections and conditions in which sensitization has occurred, and so enable the individual to desensitize or immunize himself. It is well known that an attack of one disease often has a very beneficial effect on another entirely different disease from which the patient may be suffering at the same time.

If a patient with psoriasis or a chronic eczema develops pneumonia or other disease with a temperature which lasts several days, the skin disease will usually improve enormously or even disappear. There is also the well-known fact that an attack of erysipelas on the top of lupus vulgaris may cause an extraordinary improvement in the lupus. Reactions at one time thought to be absolutely specific are now known not to be so—for example, tuberculosis of the skin reacts to injections of trichophytin, milk, and many other substances in the same way as to the specific tuberculin. It is also known that a skin which has become sensitive to one particular irritant also becomes more sensitive than it was before to other irritants as well.

Therefore, although on first consideration it might be thought that non-specific therapy is illogical and unscientific, the above facts and many others point to its being a form of treatment based on rational and scientific foundations. When a foreign protein is introduced into the system, certain reactions follow, with rise of temperature, alterations in the blood, etc. Hence this form of treatment has been designated protein shock or pyrogenic therapy.

METHODS IN USE

A large number of methods have been used to produce this shock effect. They may be divided into the following groups:

1. Blood and serums (a) normal—for example, human, horse, sheep, ox, goat, or chicken; (b) antitoxic—for example, anti-diphtheritic, anti-streptococcal serum, etc.; (c) fluid from blisters, pleural effusions, cerebro-spinal and joint fluids.
2. Milk (cow's) and preparations made from milk—for example, aolan, caseosan, and lactin.

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3. Tissue extracts, both human and animal—for example, spleen extracts, tumour extracts, and autolysates, and skin-scale extracts.

4. Vegetable extracts—for example, pollen extracts; seed extracts—for example, millet and alfalfa.

5. Bacterial proteins of all kinds—for example, non-specifically used vaccines and tuberculins of all kinds, pure or in mixture, Coley's fluid.

6. Split proteins—for example, proteoses, deuterio-albumoses, and peptones.

7. Chemicals, such as turpentine, injected so as to produce a "fixation abscess" causing a breaking down of tissue, and, by absorption, a protein shock effect.

8. Artificially induced diseases—for example, malaria.

It is also a question whether the administration of drugs such as mercury, iodides, arsenicals, colloid metals, etc., does not act by breaking down inflammatory tissues with a resulting protein absorption. X rays, radium, cauterization, diathermy, freezing with CO₂ snow, ultra-violet light treatment, cupping, and Bier's congestion treatment might also reasonably be included as indirect methods of protein therapy. But in this discussion I do not propose to stress the interpretation of protein therapy to include them. It is also doubtful whether substances such as spleen extracts should be included. Several observers (Birke, Vallery-Radot and Blamoutier, Paul, and Gaté and Charpy) used injections of spleen extracts in urticaria, eczema, pruritus, and dermatitis herpetiformis, etc., with good results in some cases. As the extracts were disalbuminized, it is doubtful whether the results are due to the spleen enzymes or are really a form of protein therapy.

BIOLOGICAL EFFECTS

Many different routes have been used to introduce proteins into the system. Injections may be given intravenously, intramuscularly, cutaneously, and subcutaneously. The intramuscular route is very often preferable to the intravenous because the technique is easier. Many recent observers have stressed the superiority of the cutaneous as against the subcutaneous route, but except with vaccines, where the quantity injected is small, the intracutaneous route is impossible if large doses are to be administered. Whilst usually the injections are given at a distance from the lesions, proteins have also been injected locally into, under, or around the lesions. Time will not allow a discussion of details in the technique of administration of each kind of protein and the intervals at which the injections are usually made. Those of us who have used these methods are all quite familiar with them. The principle which underlies the treatment is the administration of a quantity of protein at short intervals of from two to four days. If the intervals between injections are too long there is a risk of anaphylactic reactions. The dose must be sufficient to cause a moderate general reaction. If the reaction is too severe, symptoms of intoxication appear and more harm than good will result. When a protein is introduced into the system, products of protein breakdown are thrown into the circulation, producing effects very much like those of surgical shock from trauma or the shock seen in extensive burns. What the mode of action of protein therapy exactly is, is still undecided. Clark gives a very good summary of the changes that take place in protein therapy. He states that "the active agent is a product of protein decomposition. The washing of tissue fluids into the circulation produces changes in the blood such as leucopenia followed by leucocytosis; increase in young and atypical erythrocytes and platelets; increase in fibrinogen, globulin, thrombokinas, and blood sugar, in the non-protein nitrogen content, and in the proteolytic

ferments; and, finally, an increase in the permeability of the cell membranes and capillaries."

Many observers emphasize the importance of the proteolytic enzymes which are liberated after the injections. Weichardt thinks that, in addition to the stimulation of the body cells to anti-bacterial activity, there is a stimulation of the internal secreting glands and the bone marrow. Hermann contends that specific antibodies are liberated by these non-specific injections, and Larsen thinks that sessile antibodies are thrown off into the circulation, and so healing is promoted. Most observers are agreed that a leucopenia followed by a moderate leucocytosis in two hours or so occurs in protein therapy, but recently Burgess and others have doubted this. They think that the leucocytosis is no more than the normal fluctuation seen after food, etc., so that it would appear that Spiethoff was correct when he stated that the leucocytosis is not responsible for the results obtained. Similarly, a rise of temperature is not essential for a successful result. Many cases which do excellently on protein therapy show little or no rise of temperature. Therefore, which of the many changes occurring after protein injections are essential is still in doubt.

I think it will be practical to take each disease separately and describe what results have been obtained by the different non-specific methods. In that way a good idea will be obtained of the value of the treatment in each disease.

DISEASES IN WHICH NON-SPECIFIC THERAPY HAS BEEN USED

Urticaria, including Angioneurotic Oedema and Urticaria Papulosa.—In urticarias and angioneurotic oedema, where the cause cannot be found, non-specific therapy is sometimes a very useful method of treatment. C. S. Wright, out of forty-nine cases treated with auto-haemotherapy, had twenty-three absolute cures, eleven which improved but relapsed, and fifteen failures. Vallery-Radot and Rouquès recommend peptone therapy, and if that fails, auto-sero- or auto-haemotherapy. Many others also report good results with auto-serum and auto-blood. Schulmann emphasizes the importance of continuing the injections for some weeks after the disappearance of the eruption. O'Leary, Fordyce, and Ullmann, however, had disappointing results by these methods. G. T. Brown, after trying sterilized milk, auto-blood, distilled water, and horse serum, unhesitatingly recommends, as producing the best results, a 33½ per cent. peptone solution, given at first intradermally for the smaller doses, and later subcutaneously. Linser cured fifteen out of eighteen cases of chronic urticaria with injections of healthy normal human serum, and in twenty-four cases of urticaria papulosa in children all were cured after one or two injections of the mother's serum.

Eczema and Dermatitis.—In eczema in adults non-specific therapy on the whole has worked fairly satisfactorily. Out of twenty-eight different observers, whose records I have looked up, twenty-one report good results either on the way of cure or marked improvement of the condition; three found very slight benefit, and four report definite negative results. All methods have been used. The most frequently used method was auto-sero- or auto-haemotherapy. But turpentine injections seem to give just as good, if not better, results. Milk, and milk preparations, such as aolan, have given less satisfactory results. Vaccines (typhoid, staphylococcus and streptococcus) have also been used, but less frequently. Personally I have used peptone and milk injections in a few cases of chronic eczema which failed to respond to other treatment, with, on the whole, rather disappointing results.

There are very few records of the treatment of infantile eczema. Linser and McDonell both report good results with auto-serum, and Ullmann in two cases of generalized infantile eczema found no result from auto-serum treatment alone, but exceptionally rapid improvement when local treatment as well was instituted. I have repeatedly tried giving small doses of peptone by the mouth half an hour before food in cases of infantile dermatitis, but without the slightest result.

Dermatitis of External Origin.—I can find only two records of such cases being treated by protein therapy. Hajos treated ten cases of occupational dermatitis, where the cause could

not be found, with injections of turpentine with good results. Grimes noticed that an acute dermatitis due to *Rhus toxicodendron* cleared up within thirty-six hours after a road accident in which the patient fractured his thigh and suffered from extensive extravasation of blood. Later he treated twenty cases of *Rhus toxicodendron* dermatitis with injections of the patient's own blood. In all, the acute dermatitis cleared up very rapidly.

Light Dermatitis.—In 1925 Castle reported a cure of dermatitis solare with four injections of peptone. In the last few years I have treated seven cases of dermatitis solare with peptone subcutaneously. Two of these cases I have been unable to follow up. In two there was no benefit, in one marked improvement in light tolerance occurred, and in two definite cure resulted. One of these cured patients remained well for two seasons so that she could go out in the sun with impunity. In the third year the sensitiveness returned, but on receiving another course of six peptone injections she was again cured. Apparently in such cases the desensitization only lasts for about two years. In none of my cases was there any haematoporphyrinuria. They all belonged to what Barber has designated the adult group of dermatitis solare as distinct from the juvenile group of hydroa vacciniforme. Castle's case was one of this type. I also treated a case of dermatitis due to heat rays. This dermatitis occurred after exposure to any kind of heat. A course of peptone injections had no effect upon it.

Neurodermatitis: General and Local Pruritus.—Good results with auto-serum and auto-haemotherapy in cases of pruritus have been recorded. Milk and milk products have also been employed with satisfactory results. Appel found turpentine injections, on the whole, were successful in general pruritus, but in some cases relapse occurred and treatment had to be repeated. As all forms of neurodermatitis are usually very stubborn, these results with non-specific methods seem to be satisfactory.

General Exfoliative Dermatitis.—The only records I can find on this condition are of two cases. In 1916 Engman and McGarry treated a case with typhoid vaccine intravenously. The result was very satisfactory. The eruption paled rapidly and soon disappeared. McDonell also reports a similar cure with auto-serum injections. In 1924 I recorded a spectacular cure of exfoliative dermatitis with milk injections. Since then I have employed milk injections in seven other cases. In six the results were negative, and in one, which was an exfoliative dermatitis on the top of a psoriasis, the result was extremely good, the eruption rapidly disappearing but leaving the psoriasis unaffected.

Pemphigus.—Pemphigus chronicus has been extensively treated with protein. Auto-serotherapy has given astonishing results in a few cases. Praetorius reports complete cure in a case of two years' duration. Many cases were improved but some unaffected. Auto-haemotherapy has also been frequently tried. Breda treated three cases, and in all the eruption disappeared completely. In the majority of the cases, however, improvement only was noted, and in some cases the result was negative. Fischer had an apparent complete cure in a case of chronic pemphigus from the use of injections of human blood together with neosalvarsan, and Perry reports marked improvement after injections of normal horse serum. Milk injections were used by O'Leary and Ambrosoli with only temporary result. Holobut and Lenaskowicz and Don Giovanni obtained improvement by the subcutaneous injection of fluid from the patient's own blisters. Turpentine injections were also given by Klingmüller and Gewalt with good results.

Pemphigus Foliaceus.—One case treated by Passini with intravenous vaccine showed no result, and Linser found improvement in one case treated with normal human serum.

Pemphigus Vegetans.—Gougerot, Civatte, and Blum record a complete cure after auto-haemotherapy together with 914, and Ruete reports improvement with an auto-vaccine. Capelli and Signorelli, using a cholera vaccine, noted improvement, but Passini had no result with an intravenous vaccine in one case. Therefore, in all forms of pemphigus, which is such a chronic and serious disease, non-specific protein therapy, although it does not hold out the prospect of

permanent cure, except occasionally, is a method worthy of trial.

Dermatitis Herpetiformis.—Auto-serotherapy, hetero-serotherapy, auto-haemotherapy, intravenous typhoid vaccine, and intravenous deuto-ro-albumose, have all been used in the treatment of dermatitis herpetiformis. In nearly every case improvement or a complete disappearance of the eruption has occurred for a shorter or longer period, but invariably this is followed by a relapse. This agrees with my own experience of auto-haemotherapy in this disease.

Pregnancy Dermatoses.—Auto-serum has been used by Stümpke in the treatment of herpes gestationis with good result. Linser, Rubsamen, Veirl, and Mayer each record a case of cure of herpes gestationis with injections of serum from normal pregnant women. By the same method Linser and Mayer have also cured cases of urticaria occurring during pregnancy. Similarly Mayer and Rongy each record cures of general pruritus occurring during pregnancy. In no case had the injections any ill-effect on the pregnancy.

Psoriasis is the disease in which non-specific therapy has been most frequently used. It would serve no purpose to enumerate the results of each observer, as many of them refer to only a few cases. Auto-serotherapy, auto-haemotherapy, intravenous vaccines (chiefly typhoid), and milk and its derivatives have been extensively used. The majority of observers found benefit from these methods, but a few obtained no result. The consensus of opinion seems to be that, whilst in an occasional case a striking result can be obtained by injections alone, in the majority of cases the only result is to increase the susceptibility to local treatment, especially with chrysarobin, and so hasten the cure. I think that those of us who have tried this form of treatment will agree with this conclusion.

Lichen Planus.—Although comparatively few cases of lichen have been treated non-specifically, on the whole the results have been encouraging. Payenville and Troabas had a case of almost universal lichen which developed diphtheria, for which he received eight injections of anti-diphtheritic serum. In sixteen days the lichen had completely disappeared. Whether this result was due to the diphtheria or to the serum is not quite clear. Stümpke and Gottheil and Satenstein using auto-serum, Kren and Ambrosoli using milk injections, and Cadbury using typhoid vaccine, all noted improvement and in some cases rapid disappearance of itching and eruption. The best results, however, were obtained by Klingmüller with turpentine injections.

Staphylococcal Infections.—Weirauk treated twenty-six cases of carbuncles with milk injections, and in twenty of these the lesion subsided or only required simple incision. Pospelow, Ambrosoli, and A. Kraus also had satisfactory results in furunculosis with the same method. Auto-haemotherapy has proved useful not only in promoting rapid healing in furunculosis, but in clearing up recurrent cases. Auto-serum has not proved so successful. Intravenous vaccines have produced slight benefit in carbuncles and poor results in furunculosis. Turpentine injections (Levin and Rose, Appel, Becher) have also given good results in boils and pyoderms. In sycosis, Gawalowski did not find the benefit from milk injections which he obtained in tinea barbae, but Pospelow claims some successful results. O'Leary reports only fair results with intravenous typhoid vaccine in sycosis, and Capelli and Signorelli complete failure in a case of lupoid sycosis. The only really satisfactory results which are recorded are two cases of Wright's, both of which were cured and remained well after two injections of turpentine.

Streptococcal infections have seldom been treated non-specifically, with the exception of erysipelas, in which milk and its derivatives, such as aolan, have proved very successful even in desperate cases. El Sayed and Turnheim stress the benefit of injecting the milk near or round the lesion. Hoff and Heesch used auto-blood, and Pines reports recovery in a very bad case in an infant after injections of the father's blood. Basset obtained cures in from two to six days with a polyvalent antiserum. Anti-diphtheritic serum has been used with excellent results. Campani and Bergolli obtained better results with anti-diphtheritic serum than with the specific anti-streptococcal serum.

Ringworm.—In deep-seated trichophyton infections of the skin and beard very good results are reported. Milk, aolan, and lactin produced rapid involution of the lesions, and turpentine was used with marked success. Löwenfeld and Pulay compared the effects of trichon (specific), tuberculin and turpentine (non-specific), and obtained the same good results with all three preparations. Loeb, using a mixed staphylococcal vaccine, found that deep-seated tinea barbae healed fairly rapidly, but the results were not so good in superficial ringworms. The only unsatisfactory report is by O'Leary, who used bacterial vaccines and other non-specific methods without much benefit.

Lupus Erythematosus.—In its subacute and chronic forms, lupus erythematosus responds fairly well to desensitization methods. Klingmüller and Wright used turpentine, A. Kraus milk injections, and Engman and McGarry typhoid vaccine with benefit. MacCormac had a good result in one case with injections of normal saline.

Lupus Vulgaris.—Klingmüller showed that cases treated with turpentine injections gave focal reactions in the lesions. Appel also found that turpentine had the same effect as tuberculin injections. Marked local and general reactions occurred. In lupus cases so treated the inflammation disappeared from the lesions in all cases and sometimes also the lupus nodules.

Erythema multiforme, purpura, scurvy, prurigo, herpes zoster and simplex, parapsoriasis, impetigo, erythema, erysipeloid, acne, actinomycosis, pityriasis versicolor, pityriasis rosea, alopecia areata, leprosy, aphthous stomatitis, Darier's disease, warts, and mycosis fungoides are some of the other diseases in which non-specific protein therapy has been used in a very limited number of cases.

VENEREAL DISEASES

Syphilis.—All stages of syphilis have been treated with non-specific injections either alone or in combination with some form of drug treatment. Milk injections, or a combination of milk and auto-haemotherapy, were used in primary syphilis by Ahlswede. He thinks that all cases of early syphilis, especially where the Wassermann reaction is already present, should have a combined treatment with non-specific therapy and drugs. Greenbaum and Wright obtained partial or complete involution of secondary and tertiary lesions with injections of milk without the aid of any drugs. Beume reports a case of syphilis which did not clear up with several courses of neosalvarsan, mercury, and bismuth. This man had an accident which resulted in extensive haemorrhage into and round the knee and ankle-joints. The syphilitic eruption rapidly disappeared and the Wassermann reaction became negative, even although no further drug treatment was being given. This must be looked upon as a case of auto-haemotherapy. Bernucci, in early syphilis, found improvement with milk injections, but the final results were unsatisfactory unless drugs were also given. Tuberculin injections have been used in secondary syphilis by Bloch and Biach, typhoid and cholera vaccines by Ersettig, Capelli and Signorelli, Engman, Jorsted and Engman, and Kemp and Stokes. In some cases primary or secondary lesions disappeared, but the results were not satisfactory unless drugs were also used. This corresponds with the experimental findings of Kolmer, who treated early testicular syphilis of rabbits with T.A.B. vaccine, but failed to get a cure. An attack of malaria has been known to influence beneficially cases of syphilis even in the early stages. Kerl found that artificially induced malaria had no effect on primary syphilis, but that it did good in the later stages (two to six years). Vonkennel also found induced malaria combined with drug treatment in primary and secondary syphilis not strikingly superior to treatment with arsenic and bismuth alone. On the same lines Schamberg and Tseng treated cases of secondary syphilis with very hot baths daily to induce a temperature, and obtained improvement or even disappearance of the skin lesions.

It therefore is evident that all forms of protein shock treatment, especially if a temperature is induced, will influence the early stages of syphilis beneficially, but not to such an extent as to warrant their adoption generally, either alone or in combination with drug treatment. The position is quite otherwise, however, in the later stages of syphilis, and especially

in neurosyphilis. Within recent years malarial therapy has been very extensively used in the treatment of neurosyphilis, and especially in tabes and G.P.I. The results have, on the whole, been very satisfactory, due consideration being given to the fact that anti-syphilitic drug treatment alone is usually unsatisfactory. The malarial treatment, however, has certain disadvantages. It may not be easy to obtain a donor, and some individuals, especially in the coloured races, have an immunity to malaria, so that the malarial attacks die out spontaneously and prematurely. Once the attacks are established, their severity cannot always be controlled. In addition, there has been a certain mortality from this treatment. For these reasons other easier and safer methods of producing a temperature reaction have been experimented with. Bornstein obtained good results in neurosyphilis with milk injections combined with arsenic. Schacherl in 1914 used tuberculin injections combined with mercurial treatment. In tabes dorsalis typhoid vaccine has been used by Nelson, Kemp, and Stokes; other bacterial vaccines by Fischer and Dollken. In many cases an improvement and remission of the symptoms has resulted. Recently Gibson and Gordon treated cases of tabes with hot baths of a temperature of 106 to 110° F. for forty-five to fifty minutes daily till the patient's temperature rose to 106 or 107°. These were continued every day for about nine months, with very striking improvement in the condition.

General Paralysis.—Typhoid vaccine has been used for this, and the results were just as good as with malarial treatment. Jakow and Joachim similarly used injections of old tuberculin to produce a temperature reaction in these cases. Von Jauregg used a staphylococcal vaccine and obtained remission of symptoms in 74 per cent. of the cases which were in the earlier stages of the disease.

Non-specific protein therapy also has a definite effect on the Wassermann and other serological reactions of syphilis. This is to be expected, as there is a definite general tissue reaction following such treatment. Milk, peptone, vaccines (typhoid, cholera, tuberculin), together with drug treatment, have all been noted as influencing the Wassermann reaction favourably. Uddgren and Schreiner both found that the Wassermann reaction became more rapidly negative after milk and peptone injections together with drugs than was the case when drugs alone were used. Schamberg and Tseng also noted slight improvement in the Wassermann reaction in secondary syphilis in patients treated with hot baths. A few observers, however, have seen no effect on the Wassermann reaction from non-specific therapy.

Ulcus Molle and Complications.—A great many cases of soft sore and the accompanying buboes have been treated with milk injections. All observers emphasize the very beneficial effect of the milk injections on the buboes. If unburst, the glands nearly always diminish rapidly in size, and heal without requiring to be opened: if discharging, rapid healing takes place. The soft sores themselves also healed promptly in nearly every case. Becher reports excellent results with turpentine injections and Spiethoff with auto-serum. Treubel, and Bussalal and Devoto saw rapid healing of ulcers and glands with auto-haemotherapy. Almkvist had similar good results with injections of tuberculin. Mariani, who used all kinds of protein therapy, concluded that in soft sore hetero-proteins, especially peptone, give better results than hetero-serums or vaccines. Therefore, in soft sore and buboes, all non-specific methods can be relied on to give satisfactory results.

Gonorrhoea and Complications.—As in the previous disease many methods of treatment have been adopted. Milk injections have been used with satisfactory results in both gonorrhoeal urethritis and its complications. Spiethoff recommends auto-serum for gonorrhoeal prostatitis, and Bussalal and Devoto and Mariani report equally good results with auto-haemotherapy in all forms of gonococcal infection. With turpentine injections Krebs found the duration of a urethritis was shortened, and there were fewer complications than usual. Becher also found turpentine injections very useful in posterior urethritis, epididymitis, prostatitis, and arthritis. Normal horse serum has also been extensively used. L. D. Smith found it just as good as an anti-gonococcal serum. R. A. Brown, in gonorrhoeal epididymitis, obtained almost equally good results with anti-diphtheritic serum as with normal

horse serum, but the anti-diphtheritic serum, in addition to a smaller dose being required, was preferable, as it was more efficient in ameliorating the symptoms. Culver reports good results in gonorrhoeal arthritis with injections of *B. coli* vaccine and of deuterio-albumose. Apparently, any of these non-specific methods give just as satisfactory results in the treatment of gonorrhoea and its complications as the specific gonococcal vaccines and antisera.

CONCLUSIONS

The foregoing results, therefore, show that non-specific protein therapy has a very wide field of application in skin and venereal diseases. Practically all the conditions which benefit are conditions in which sensitization is either definitely known or is suspected to occur. Many of them are acute or chronic infections of known or unknown origin, and injection of proteins, by stimulating the protective mechanism, leads to rapid cure.

Although there is less risk of anaphylactic reactions than is the case with specific desensitization, there are certain dangers connected with the treatment. Anaphylactic shock reactions have only been reported in two cases (Sachs, Oppenheim). They both occurred from milk injections after the second and third injections respectively. In both cases the preceding injection had been given seven days before. Both patients recovered. In using milk injections care must always be taken not to introduce the milk into a blood vessel, otherwise fat embolism results—as occurred to me on one occasion. In auto-serum and auto-blood injections, there is no risk such as is always present when foreign serums are used.

There are certain contraindications to the use of protein therapy. The patient should always be in fairly good condition. Injections should also be given as early as possible. One should not wait till the condition is desperate and the powers of reaction are exhausted. Alcoholism is an absolute contraindication. Several cases are recorded in which delirium tremens developed during a course of protein treatment, and one case ended fatally. Pregnancy is given by Petersen as a contraindication, but that cannot be so, as pregnancy dermatoses have been successfully treated without any effect on the pregnancy. The most important factor is the condition of the myocardium. Patients with chronic myocardial changes and advanced arteriosclerosis should not be treated by these methods. Valvular heart disease is not a contraindication unless there is a very gross lesion and the heart is in difficulties. Lindrig and Uddgren think that diabetics should not be treated, but Kemp and Stokes consider it safe if the patient is carefully watched. Pulmonary disease, especially tuberculosis, may show focal reactions, and care must therefore be exercised in these cases. Marked degrees of focal infections may also be aggravated by non-specific injections. Old age and infancy, provided the general condition is good, are not to be considered as contraindications.

Thus, bearing in mind the foregoing contraindications, non-specific protein therapy may be considered a very useful and safe method of treatment for many diseases. It should not be used to replace specific therapy where that is possible. It may be used as the sole means of treatment, but the best results are obtained in combination with suitable general or local drug treatment. It is not very important which form of protein is used. Auto-haemotherapy, milk, turpentine, bacterial vaccines, etc., all give almost equally good results. The important point is to so regulate the dosage that an appropriate and not too severe reaction is produced. More than one method may be used in the same case if the first method tried is unsuccessful. It is not a treatment to be used as a routine, but is very useful in many conditions where all other methods have failed to give relief.