PEPTONE THERAPY,

Some Cases and Some Views on the Rationale of the "Shock".

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PEPTONE THERAPY.

Protein shock therapy is a method of employing the split-products of proteins for therapeutic purposes. It is a branch of Non-specific therapy which includes a great variety of different substances of varied application, and is in many respects similar to the use of vaccines without their specific bacterial toxins.

Preventive inoculation was discovered in 1880 by Pasteur and from that time the great 'era of specificity' as it has been called, commenced. The discoveries of Metchnikoff of the chemiotactic influence on the movements of the leucocytes, the observations of Widal in 1896 on the diagnosis of typhoid fever by the agglutination method, the work of Von Behring and Kitasato demonstrating that the serum of animals immunised against attenuated diphtheria toxins could be used for prophylaxis, or therapeutically as an inoculation in other animals, through a specific neutralisation of the toxin of the disease, were purely specific. The work of Koch with his memoir showing six types of bacteria each producing a definite surgical disease and breeding true, the discovery of Kohn a
few years earlier, that anthrax bacilli were the cause of the disease of that name and that a pure culture grown outside the body for a long time could produce the identical disease in many animals, the work of Erlich - his Wassermann test, and his Salvarsan, the work of Borcht on the more physical and serological side - these great workers produced result after result in a short space of time and each of these results contributed to the theory of specificity.

During this brilliant epoch however, there were many minor discoveries - 'cross currents' they have been called, which were hardly noticed at the time because of the rush of progress, but are more evident on retrospection.

It was in 1893 that Eugene Fränkel (1) was treating a series of cases of typhoid fever with typhoid vaccine - subcutaneous injections of typhoid bacilli, when Rumpf (2) attempted to show that a similar series of cases did quite as well when treated in the same way with a pyocyaneus vaccine.

It had been shown earlier by Hans Buchner (3) that other substances in addition to tuberculin could activate resistance to the tuberculous infection, and it was also

demonstrated that animals suffering from tuberculosis were in a condition of sensitisation to other products of bacteria than tuberculin. It was suggested at this time that though the soluble toxins might be specific, there was also a non-specific factor in addition.

It was argued that the tuberculin reaction was caused by the protein split-product content of the tuberculins, and milk was injected to try and produce the same result, and it was in fact shown that the reaction to dentero-albumose was greater in animals infected with tuberculosis than in normal ones.

In 1894 Autoserootherapy - the subcutaneous injection of pleural fluid was introduced, and in animals this produced a leucocytosis. Then came Coley's fluid and Beard's trypsin which both produced what is now regarded as a 'local reaction' and often a 'general reaction subsequent ly.'

McCallum of the Johns Hopkins used diphtheria antitoxin in other diseases than diphtheria. Schafer introduced his mixed vaccines. Colon bacilli were used in typhoid fever. This was called heterobacteriotherapy and it was argued that it was a group reaction; but it was reported by Kraus that good results were obtainable with the Colon bacillus in puerperal fever.

The effect of the circulation of the alleged results of experiments of the nature alluded to had the effect of later causing argument and counter-argument and of calling attention to the matter. Perhaps the best comments on the subject at this stage is a passage from the work of Sir A. Wright\(^{(5)}\) who, as is well known, was for a considerable time one of the leading champions of the strictly specific schools. He says:— "I confess to having shared the conviction that immunisation is always strictly specific. Twenty years ago when it was alleged before the Indian Plague Commission that antiplague inoculation had cured eczema, gonorrhoea and other miscellaneous infections, I thought the matter undeserving of examination. I took the same view when it was reported in connection with antityphoid inoculation that it rendered the patient much less susceptible to malaria. Again seven years ago, when applying antipneumococcus inoculation as a preventive against pneumonia in the Transvaal mines, I nourished exactly the same prejudices. But here the statistical results which were obtained in the Premier mine demonstrated that the pneumococcus inoculation, had, in addition to bringing down the mortality from pneumonia by 85 per cent, reduced also the mortality from other diseases by 50 per cent. From that on we had to take up into our categories the fact that inoculation produces in addition to "direct",

\(^{(5)}\) Lancet, 1919, 1, 489.
also collateral immunisation.

From heterobacteriotherapy the next step was the injection of the components of the bacteria - the protein split-products of the bacterial bodies - then as a seemingly natural sequence came the injection of protein split-products from other sources than bacteria. It was considered at this time - and as will be shown is still by some authors - that the common factor in the administration of the various hetero-substances - vaccines, native proteins, split-proteins such as albumoses, metals, lipoids and enzymes, to enumerate only a few, was the production of a general reaction of a "shock", an "unstimmung" - "von gröers ergotropie".

Hence the term "Protein Shock" has been applied to this form of therapeutics. It will be suggested later that this is a poor term.
In the second of a series of papers on Pyrogenic Therapy (1) Auld recommends the use of Armour's No₂ peptone in a 5% solution. The deciding factor in the effect is the primary proteose content (infra) and Professor Halliburton at Auld's request made some investigations into the amount of this substance present in the brands on the market. There were at the time of writing four such, namely Witte's Peptone, Armour's No₂, Armour's peptone siccum and Fairchild's peptone, and it was found that although in Witte's there was a larger percentage it was too toxic for ordinary use and that Armour's which had a larger denteso-proteose proportion was better. The siccum contained comparatively little of the primary and was therefore not to be employed. He suggested that the pure peptone content was of no importance except when in large amount and then was to be regarded as an impurity. There is now another peptone solution made by Martindale.

As to the mode of preparation, the peptone is dissolved as far as possible by agitation in hot (56°C) normal saline and the reaction to litmus taken which is usually acid. Normal or semi-normal sodium hydrate or carbonate is added

(1) B.M.J. July 20th, 1918.
until solution is faintly alkaline to the litmus. The peptone should by this time be dissolved except for some insoluble residue. The volume is made up with normal saline and the whole is placed in a hot water bath at 56° C for half an hour. It is then filtered while hot through ordinary filter paper and to the filtrate 0.5% phenol is added.

As regards the technique it is better to give the injection early in the day after a cup of tea and a little bread and butter, say, a few hours previously, and it is better to thoroughly empty the bowels. It is suggested that patient should be in bed, as warmth is a comfort should there be a chill, but the author disagrees with Auld in this respect - it is not essential that all cases receiving this treatment should be in-patients at all and in out-patients the doses can be so arranged that no 'chill supervenes, or by the time such a phenomenon occurs or might occur, the patient may be in a position where he could go to bed if advisable. It is also suggested that Adrenalin should be at hand. There is much dispute as to the best route to be employed. The cases shown at the end were injected intramuscularly, a sharp needle with a wide bore being used and the site being either the right or left buttock. The injections were given deeply. Among
those who advocate the intravenous method is Gow (2) who recommends that it be given very slowly and stopped temporarily if the pulse increases 35 beats per minute. He says the patient may complain of giddiness, pain in the stomach, tickling in the throat and may cough. These symptoms disappear directly the injection is discontinued. Auld also advocates this route and has found it is painless. He says that subcutaneous injection causes swelling and pain after some hours. (3) The method advocated by the author does not need such great accuracy of dose as the intravenous, and larger amounts can be given at one time; but there is the disadvantage of putting such a large quantity of fluid into the muscular tissue, and it will be seen in the case of Mrs. C., shown, that an abscess was actually formed. This is not an isolated instance.

At one time peptone was given by the mouth in a condition termed digestive anaphylaxis, 0.5 grms. being given in this way an hour before meals on an empty stomach. This was said by various workers among whom may be mentioned Pagniez Widal and Valery Radot to prevent the symptoms of this disease, - indigestion, flatulence, somnolence, arrhythmia and facial erythema. It was even stated to

(2) Anaphylaxis and Sensitisation. Cranston Low.
(3) B.M.J. July 20th, 1918.
avert attacks of migraine and asthma which might be excited by digestive troubles. The local action was supposed to last for 3 hours and the dose had to be repeated before the next meal. The action was explained by Pavlov on the theory that as peptone contains gastrin - the hormone excitant - given before meals it causes a secretion of gastric juice which acts as a protectant to the mucous membrane and assists in digestion.

Though worthy of mention this matter is not of great present day importance at any rate as far as this description is concerned and will not be again alluded to.

Dosage.

As to the dosage of peptone, the matter cannot be regarded in any rule of thumb method. Various writers have stated their methods - saying that a first dose should be a given quantity of a standard solution and so on. For instance Auld says that in the treatment of Asthma he had been in the habit of using as a first injection a quantity of peptone which equals $\frac{1}{10}$ grain of Witte's - equivalent to $\frac{1}{4}$ grs. of Armour's No. 2 - in actual fact it was mv. of his own solution prepared much as described supra. He would increase this by 2 decimals (approximately m.iii.) until 6 injections had been given. Three or four more injections, he says, should be given, the
dose to be the same as that given in the sixth injection. He admits there are exceptions to this rule. (4) Gow's method of slow intravenous injection was mentioned (supra).

It is best to find out how the patient will react to the "pyrogen" selected, as great variations are encountered, says Auld. Give a small trial dose, and if the reaction is excessive it may be best to select another pyrogen and test it in the same way. It does not matter at all what the pyrogen is, as the action is entirely non-specific. (5) The last statement will be discussed later and it is obvious that to give an enormous dose of any antigen, especially in an intravenous injection, as apparently here the route alluded to, would be dangerous, and so in the author's opinion an infinitesimal dose should be first given. Many workers suggest a diurnal test first, to see if any pronounced effect follows, but however sensible this may seem in theory, in practice it is usually of no avail and the inoculation of various proteins which may or may not produce a skin reaction is subject to the obvious fallacy of their being in the first place native proteins and toxic, and not split-products such as peptone and normal inhabitants of at any rate some of the organs of the body.

(4) B.M.J., July 20th, 1918.

(5) B.M.J., April 24th, 1920.
THE SEQUELAE OF THE INJECTION.

It is unnecessary to deal at any length with the phenomena following the non-specific injection as these are very similar to the happenings after the administration of an autogenous vaccine and well known, although the literature on the subject is very large. First there is the chill, the rise of temperature which in the opinion of many workers and notably Auld, \(^1\) is the vital factor, and because he believes such to be the case he suggests the term 'Pyrogenic therapy'. It will be seen in the reports of the cases and in the author's conclusions that in his submission this is not the case.

Workers have classified the heights of temperature recorded in different diseases and have put them into three groups, but this is obviously of no importance on the grounds of idiosyncracy alone — there are few things more variable than pyrexia as shown by the reaction of children to simple disorders.

The increase of the pulse rate has met with much attention, as has also perspiration, headache and nausea and delirium. It would be useless for the present purpose to say any more about the foregoing as they are merely in the author's opinion the natural response of the body.

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\(^1\) B.M.J. Feb. 16, 1918.

to the introduction of a toxin, which has admittedly been introduced.

According to Scully (3) the systolic blood pressure is increased during the chill, and decreased from 10-25 mm. after the chill is over, the maximum decrease being reached in 6-8 hours returning to normal in about 24 hours. It is admitted that this varies. The drop after the 'shock' is explained by dilatation of the vessels of the splanchnic area.

Glandular activity is increased according to Döllken (4) injections of milk into lactating women has a galactogogue effect.

The nitrogen metabolism is increased from 20% to 30% and becomes normal again after two days - this is set out more fully in Peterson's theory.

The patient is reputed to put on weight which fact is explained by Uddgren (5) as due to loss of "water-balance". There is no renal irritation recorded by the above author who injected milk in 100 cases and according to Döllken (6), in acute diseases with albuminuria and casts, these cleared up after a non-specific injection.

Altered permeability of blood-vessels is dealt with in the theory of Starkenstein but it is worthy of note that in 1912 Luithlin (7) injected ringer's solution into the abdominal cavity of rabbits and afterwards also injected...

the agents of the experiment intravenously and then Sodium Iodide and Potassium ferrocyanide also intravenously and watching the rate of diffusion - found that colloids decreased and crystalloids increased the permeability. Smaller vessels had the permeability of their walls increased with small and decreased with larger doses of protein injection.

The lymphagogue effect is mentioned in the theory of Peterson, and according to him and Davis (8) in a series of experiments on severe intoxications with foreign protein injections, the rate of lymph flow showed an immediate increase which lasted 20-30 minutes, then slowing down and about one hour afterwards showing an increase of longer duration.

They say that this "diphasic curve" is only noted in a severe intoxication - in less severe cases the quickening is less noticeable and lasts a longer time. There is also an added concentration of the lymph proteins.

This increased flow dilutes the blood the volume of which it is said is diminished because of the increased permeability of the vessel walls. These two workers studied the enzymes of the blood and lymph separately after intravenous injections of an heterogenous vaccine (colon bacilli) and their conclusions were that the proteose was increased (this enzyme is described in Peterson's theory)

(8) Protein therapy and non specific resistance. p. 57.
and that the fluctuations in the titre may be simultaneous in the blood and lymph or that the blood may show the changes first - sometimes there is no relationship. They say that there is no known ratio between the protease titre and that of the other enzymes, but that where there are alterations, the lymph and blood are affected usually at the same time. There is no necessity for the enzymes to enter the blood through the lymph channels - it may be direct.

They say that in all forms of 'Shock' the antiferment is increased, i.e. anaphylactic, protein and bacterial, and add also conditions such as serum sickness, fevers and vaccination. "The changes in the antiferment of the blood serum are usually marked and quite uniform in the cases which react favorably to the shock therapy...."

Finally the cases that show no permanent improvement seldom show any increase in the antiferment, indeed almost always present a decrease in the titre following a shock"..

Obermeier and Pick(9) with solution of 5% and 10% peptone found that animals which had been sensitised three months before, responded with increase of precipitins. It was found also in this connection that in horses immunised with diphtheria toxin and then injected with pilocarpin, the precipitin titre was higher after than before

the pilocarpin was administered—this to show that non-specific injections increase the antibody content. Von Beiling showed also that animals sensitised to dysentery formed antibodies to typhoid with only very minute doses of typhoid antigen, subsequently injected—the first immunisation apparently brings the animal to a state of non-specific hypersensitiveness during which it is much more reactive to stimuli of various kinds. On this point Peterson sums up that an animal so sensitised responds with an increase in the antibodies in the serum, and these may come, in a subsequent disease from those formed in the cells but not shed off as Lasson(10) points out. If however they are shed and used up as soon as formed, one cannot expect any increase in this titre during such a disease. According to Dollken there is no increase in the Agglutinins in dysentery with milk injections; but he states that their absence has no detrimental effect on the clinical result. Culver(11) comes to the conclusion that the opsonic index and the amount of bactericidal substances were both increased in his experiments with proteose injections on patients suffering from gonorrhoeal arthritis.

A great deal of work has been done in connection with the subject of the effect on the leucocyte; but the

(10) Med. 1919. 11, 332.

general trend of opinion shows that after the injection of native protein, peptone or bacterial protein there is an immediate leucopenia the degree of which depends upon the dose and the agent - with peptone this is produced by the first injection; but with native protein only after sensitisation - and bacterial antigens differ as is pointed out in the author's own theories (infra). On reinfection the leucopenia becomes less marked but of longer duration and Weichart and Greisshammer suggest that the cause is a functional paralysis of the bone marrow. This is followed by a leucocytosis lasting from three to six days or more on repeated injection. They draw attention to the presence of normoblasts, megaloblasts and polychromatomatic red cells to show that the homopoietic system is stimulated, and also state that the leucocytosis is of the myeloid type - "the lymphatic apparatus is usually passive".

Dale (12) in his important work says that the leucopenia is caused by the white cells becoming adherent to the walls of the capillaries and thus not being found in the circulating blood, and Peterson seems to think it possible that the leucocytes are concentrated in the internal organs. Ingestion of the chromocytes by the leucocytes has been observed at the height of the reaction. Other workers who have demonstrated this initial leucopenia are

Gow, who showed that it involved all cell elements, the amounts of each remaining proportional. The work of Nagao(13) is of great interest. He injected non-haemolytic streptococci into guinea pigs. The majority of the cocci were ingested by the leucocytes in 10 minutes. They were found in the circulating white cells for three hours. Both the polymorphonuclear leucocytes and the cocci accumulated in the lungs at once and here the phagocytosis took place. At the same time there was a severe leucopenia and in the spleen the polymorphs were reduced to a quarter of their number. He affirms that there was a similar reduction of leucocytes in the bone marrow. In thirty minutes the lungs were approximately normal and the number of leucocytes in the blood was normal or above and from this time there was an accumulation of white cells in the liver and spleen. In two or three hours there was a marked concentration in these organs of white cells with ingested cocci and an increase in the blood. Present in the serum also were immature leucocytes. Nagao suggests the reason for the appearance of the latter to be "an exhaustion of the leucocyte-forming power of the marrow."

This worker however in the author's opinion cannot but be speculative on the last point. The fact that

immature leucocytes appear in the bloodstream may be due to exhaustion; but in analogy with Hunter's theory of pernicious anaemia it might also be because of an insistent call on the marrow to produce more, the rate of production becoming too rapid for the 'factory' and incompletely cells being 'turned out', and so really a desperate attempt at a leucocytosis of greater degree than Nagao will admit. His work is certainly at variance with that of Peterson and Dale.

Cowie and Calhoun agree with the leucopenia being in reality 'internal leucocytosis'.

The question of white cell response is of great importance and the author wishes to state here in view of his own theory (infra) that the selections of the work done on this subject, quoted above make it abundantly clear, in his submission that any leucopenia there may be after a non-specific injection can be regarded as analogous to Wright's negative phase. It may be of longer duration but the work on this point is vague, or it could perhaps be argued that neither in autogenous or non-specific vaccine was there any leucopenia; but that Peterson and Cowie and Calhoun and Dale are correct, the former two, in their contention as to the internal organs and the latter Croonian lecturer, in his view as to adhesion - if either were

correct the clinical worker would with the ordinary apparatus register a leucopenia. Bull\textsuperscript{(15)} has endeavoured to show by experiment that Wright's negative phase is non-existent; but does not explain the result of injecting a second dose of vaccine too soon after the first, and taking the time factor into account this cannot surely be an anaphylactic phenomenon. The author regards the leucocytic response as of some importance and of considerable interest.

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\textsuperscript{(1)} Protein therapy and Non-specific resistance, p. 99.

\textsuperscript{(15)} J. Exp. Med. XXIII. 419.

The literature on the "mechanism" as the American writers term it, of the "reaction" is enormous. Many of their theories have very little evidence to support them, however ingenious they may be. Peterson(1) gives a lengthy discourse on what he calls "the probable mechanism of the reaction" which is really a synopsis of other theorists' ideas, the whole overshadowed by his and Jobling's ferment-antiferm ent titre work. Among British workers Auld seems to the author to be very much to the fore and his writings are constantly referred to here. To mention briefly some of the leading views:- Weichhardt(2) said that metabolism was increased after the injection of protein split-products and based this statement on experiments with lactating goats - these after administration of the products gave more milk. Small doses, he said, acted as a stimulant to the cardiac muscle and larger doses depressed it. This is much after the action of most toxins. He drew attention to a fact which in the author's submission is of some importance, and which was carried further by others, notably Van Slyke(3) in 1918, that the grouping of the atoms of the protein molecule was a potent factor in its toxicity. The proteins composed of mono-amino acids

(1) Protein therapy and Non-specific resistance, p. 99.
were non toxic whereas those made up of diamino-acids were toxic. When, however, these latter proteins became altered by re-arrangement of their molecule - becoming conjugated proteins, they became non-toxic. He admitted that there were exceptions and sums up "detoxication can take place by synthesis or lysis". Haemoglobin, the pigment of the red blood corpuscles, is a conjugated protein, its molecule consisting of a compound of a protein globin, with a non protein substance, haematin, of unsettled formula, containing one atom of iron and four pyrrol rings in the molecule\(^{4}\). It is non toxic, whereas globin was found by Weichart to be a toxic body. This principle is of importance as paving the way for the detoxication by degradation theory and in a sense leads up to Van Slyke's views, the production of proteoses by autolysis of the body proteins. Schittenhelm\(^{5}\) made the observation that the split-products did not enter the blood stream and suggested that the rearrangement goes on in the cell.

Döllken\(^{5}\) believed in the selectivity of stimulation, that is all proteins do not stimulate the same tissues, much in the same way as tetanus toxin and diphtheria

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\(^{5}\) München med. Wchnschr. 1919. LCVI. 1403.
toxin do not pick out the same structures.

As a result of experiments of the hetero-vaccine type he maintained that pyocyanus vaccines were of use in gummata whereas pseudodiphtheria were not; prodigiosus was of use in neuralgia whereas cholera and dysentery were not. There was no relation between the severity of a focal reaction in these non-specific injections and the ultimate clinical result - sometimes it was in inverse proportion. He thought that all the cells were to a certain extent stimulated; but some more than others and gives a list of these. He drew attention to the beneficial effect upon gout and makes the point that this cannot depend upon bacterial stimulation. Another observation of his was that the rate of sensitisation depended upon the agent employed in the injection.

Paltauf\(^7\) heralded the view which Auld stresses very strongly in his notable papers, that it is the thermogenic substance in the injection which produces the effect. He said that after the pyrexia follows a period of exhaustion and maintains that this is the defervescence and on this point Peterson\(^8\) does not agree as account of the permanence of the fall is not taken. Auld\(^9\) in his work reiterates the point that the rise of temperature is all

\(^7\) Wein, Klin, Wochenschr. 1915. XXVIII, 631.
\(^8\) Protein therapy and non-specific resistance.
\(^9\) B.M.J. April 24, 1920.
important. He objects to the term "Protein Shock" and would substitute that of "Pyrogenic Therapy" - stressing that the reaction is caused by the "pyrogens" of Burdon Sanderson. (10) There must be a high temperature ushered in by a rigor he says. It has been demonstrated by Polly and Meltzer that artificially fevered animals suffering from an infection were influenced favourably by the pyrexia.

Nolf(11) said that as peptone was easy of assimilation and bacteria difficult, the former would assist in the assimilation of the latter and at the same time the peptone would activate the tissues to destroy the bacteria. He says that hexamethylenamin was used together with proteosero therapy in typhoid.

Lindig(12) said that in the serum of pregnant women were proteolytic enzymes which were of importance in preventing infection, these might be derived from the leucocytes or the glands. In excessive doses of protein injection these flood the serum and tissue lysis may occur together with a self-explanatory condition termed "Weichert's protein cachexia". Lüdke(13) stated his ability

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(10) Described 1875.


(12) Arch. J. Gynäk. 1918-19, CX. 545.

to call forth antibodies in immune animals by non-specific therapy and later said that the agglutinin titre was increased in the typhoid cases as was also the germ killing property of the serum. A more interesting theory was that of Lagson (14). Certain bacteria e.g. streptococci and pneumococci are imperfect antigens corresponding to tetanus toxoid i.e. tetanus toxin which has been kept for some time and has lost its toxic property but retained its power of combining with antitoxin. In acute infections these antigens are capable of forming antibodies but these cannot be liberated into the blood stream except by a second stimulus obtainable from the foreign substance injected with them. His conclusion is that the non-specific factor enables the "sessile" antibodies to appear free to combat an infection. He also stated that various agents could act as stimulants to the haemopoietic system, the result being a flooding of tissues with immune bodies and concluded that one could get a specific response to a non-specific stimulus. This opens up fields of speculation and on this point there has been much argument. It is asked why type 1 pneumonia does not produce good results in type 2. Lagson himself asks whether one is dealing with a simple chemical neutralisation of toxin and antitoxin or

(14) Minn. Med. 1919. 11, 332.
antibodies as in the well known diphtheria therapy or perhaps, as has often been claimed, the horse serum alone contains the substances necessary to produce a reaction in pneumonia or in diphtheria.

The recent work of Professor Novy\(^{(15)}\) on this point is of interest. He affirms that normal serum in the pre-clot stage is toxic. This he says is due to a catalytic agent and it is an analogous phenomenon to fibrin formation. The well known retardation of clotting produced by peptone is an expression of this change. When serum is digested with bacterial proteins, agar or Witte's peptone a more intense toxicity is produced which according to Novy is identical with that occurring in the cells and tissues in anaphylactic shock. This effect follows upon the injection of this 'toxified serum', though in the body the toxicity if of short duration. He holds the antigen to act merely as an inducing agent of no toxicity in itself and shows that in the case of agar being used, it is entirely recoverable from the "toxified serum".

Auld\(^{(16)}\) in commenting on this view says that if true there would be very little reason for choosing one substance for injection rather than another, provided the one used could induce this toxic effect after introduction. In rabbits suffering from peptone anaphylaxis there is exophthalmos which does not occur in anaphylaxis produced by any other known agent - this finding was recorded

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(16) B.M.J. Feb. 16, 1918.
earlier by Novy himself - and must show some subsidiary specific action on the part of the peptone.

He goes on to say that in Asthma - Auld's work in the main is limited to the group of diseases that resemble anaphylaxis, asthma, certain skin diseases and migraine - it does not matter what the natural antigen causing the disease happens to be, desensitisation can be effected by peptone as it exhausts the anaphylactic mechanism towards not only itself but towards all other agents. The experiment of Weil\(^{17}\) showed that if egg white were the sensitising agent and during the period of sensitisation a sufficient dose were given, then a subsequent dose of the same substance would be abortive. From this we come back to the much reiterated cry that the desensitisation is non specific in nature. One large dose of peptone may produce a short lived desensitisation but smaller and increasing doses spaced over a considerable time have more effect, being equivalent to a prolonged desensitisation. Starkenstein\(^{18}\) worked with non-specific substances as a group and set one off against another, using fluorescine and noting the colour changes in the eye, and also an artificially produced keratitis he found that some substances produce an increased permeability of the vessel walls and others have the opposite effect. By his second


\(^{18}\) München med. Wohnschr. 1919. LXVI. 205.
series of experiments with the keratitis he observed the accelerating or retarding effect upon inflammation. He concluded that some substances were inflammatory and some anti-inflammatory, that a sub-lethal dose of one poison would protect against a fatal dose of another and also that the central nervous system showed a diminished irritability. This theory is mentioned in reviewing the case of J. B. infra.

Among other observations of interest is one of Pemberton's that in non-specific intravenous injections the metabolism of glycogen is increased and that this is analogous to the improvement he had found in cases of Arthritis treated on a low diet.

Peterson in dealing with the 'probable mechanism of the reaction' says we have to deal with - (1) Pre-formed protein split products which are toxic, toxic owing to the arrangement of their atoms in the protein molecule as it is broken up - this has been dealt with in the theory of Schittenhelm (supra); (2) Protein split-products formed from the bacterium post mortem; (3) Toxic bodies formed during the metabolism of the bacterial cell and excreted; (4) Toxic bodies from the invaded host shed off during the attack. He says the fundamental factor in overcoming

(20) Protein Therapy and non-specific resistance, p.99.
infection, as far as the soluble toxins go, is the digestion of the native protein and its toxic products to their lowest stage of degradation. This means the amino-acids which being normal inhabitants of the blood stream are non toxic. This may also occur owing to synthesis - the building up of conjugated protein, which as has been shown in the case of haemoglobin are also, in many cases, non toxic.

The serum enzymes play a large part in his theories. In the blood stream, he says, we have Leukoproteases, one of which acts as a neutral or alkaline medium and whose effect is to split native proteins to the proteose stage, and another of which will only act in a slightly acid medium but has the same "digestive range". He describes another, an erapsin -like enzyme which will act in neutral medium and can digest more thoroughly. This one can digest native proteins completely, transforming them into amino-acids. The above three are in the view of this writer derived from the leucocytes, hence this group name. Also there is a tryptase which comes from other sources such as the intestine and sometimes from trauma and again a peptidase, the former of which can digest native protein, and the latter the products of protein only, both being active only in a neutral medium. Great stress is laid upon the inhibitory action of antiferment and he considers that this does not interfere with ereptase
which is present in greater amount than the leukoproteases. An increase in the hydrogen ion concentration of the blood will of course favour the action of those that act in acid medium. Applying his theory to the pneumonia focus he points out that the symptoms of pneumonia are due to the ingestion of partial combustion products of proteins, the autolysis causing a rearrangement of their atoms with toxic and non toxic bodies being formed all the time and as an effect of this the pneumococci are killed. The direction of the process is towards the lowest products, which are non toxic. During the "detoxication", leukoproteases are exuded from the leucocytes which are broken up and these together with the other ferments, particularly peptidase assist in the general result as also does the change in reaction.

A great deal of work has been done by this author together with others of the American school on the subject of ferment-antiferment balance. He reiterates his views on detoxication and makes the point that an intoxication is going on at the same time, and that in either case the process is balanced by the antiferment. As an example the healed tuberculous focus is given, which owing to the disintegration of the capsule may become active. This seems to the author a weak example, as it is dealing with a mass action, the liberation of a toxic storehouse
rather than the aggregation of minute changes that Peterson was really discussing. The importance of this balance is very strongly emphasised. As to the nature of this antiferment, it is not an 'antibody', it is composed of highly dispersed lipoids and varies with their amount in the tissues and blood stream. Its amount (titre) is in inverse proportion to the nitrogen output in animals and its purpose may be, among others, "to counteract the increased hydrogen ion concentration consequent upon the heightened protein digestion which takes place in infections in general". The effect of and the application of these theories to the sequence of events following a non-specific infection in many pathological conditions is described by this writer; but for the present purpose the author proposes to be content with the one whose local manifestation has already been alluded to - lobar pneumonia, as it is in this that he is most intelligible. He takes the view that Lobar pneumonia is primarily a lung infection and secondarily a septicaemia. The sharp demarcation between grave intoxication and complete recovery resembles a chemical reaction rather than a biological process. After the injection there is a chill, a slight rise in temperature and then the crisis followed by a subnormal curve for a few hours. There is no change in chest signs but the pulse and "vessel tone" improve. Miller observed 15 consecutive cases treated with 30 mills. doses

of typhoid vaccine. In all was a rise of temperature and in all a leucocytosis. In 9 there was no good result. In 6 a great improvement followed the injection, pulse and temperature returning to normal, cough and pleural pain subsiding, patient being subjectively better. In 3 of these 6, the improvement was only temporary, the previous symptoms returning after some 24 hours unmodified, in 3 it was permanent, but these had a moderate temperature until the time when the crisis would normally have occurred but they were free, says Miller, from any signs of intoxication. It is very improbable that an inert mass throwing out such an abundance of toxin such as the local nidus could be affected by one dose of the heterogeneous vaccine. Peterson says also, and it seems a trite observation, that there would be a difference if the incubation period of pneumonia were of longer duration. In this case the sensitisation of the host to the toxin would have to be considered.

Another point accentuated is the augmentation of the lymph flow as a result of the non-specific infection. This was measured at the thoracic duct by the use of dyes - and also observed at the local focus by the same agency, in the manner that Starkenstein (supra) attempted to differentiate between his inflammatory and anti-inflammatory substances. It has been suggested by McTeague and
Williams (22) that with inflow of the extra lymph, with its antibodies, to a nidus, the healing effect is explained. It should be mentioned here that the concentration of antibodies of the plasma in typhoid fever has been demonstrated to be greater than that of the lymph and augmentation of the latter will therefore ensure a larger quorum arriving at the seat of trouble - to focal site.
Auld's Theories.

During the War this worker was carrying out experiments with colloidal platinum and found that a bottle of this preparation obtained in 1915 produced very marked 'shock' - half an hour after the injection was a rigor lasting 20 minutes followed by a rise of temperature to 104-5° with perspiration, nausea and vomiting, after which the temperature fell to subnormal. This phenomenon occurred whether the patient was normal or suffering from some disease with a small temperature such as sub-acute pleurisy or paratyphoid. He describes the syndrome as "a fit of ague". One case of pneumonia and two of pleurisy are shown, in the former which was refractory to ordinary treatment, the patient a girl of 20, was much improved after an injection of 4 ccs. platinum followed by one of 5 ccs., each dose producing a definite shock. In 1917 he ran out of platinum and could obtain no metallic preparation which would produce the same effects but in 1917 managed to get some colloidal silver, this in doses of 3-5 ccs. caused a marked reaction - more accentuated than that produced by the platinum. In reply to inquiries the manufacturers said that this was protected in a special way. The protective suspension was found when injected to produce the same effects as the colloidal silver, the
same quantities being used, and so he became of the opinion that the protective agent was the real "pyrogen" and tried gelatin with the result that there was no temperature rise but the other members of the syndrome were present. He says that it does not matter whether the agent be metallic, killed bacteria, proteoses or nucleic acid as long as the reaction is produced. It might have been that with the platinum and silver the protective gelatin had undergone hydrolysis with keeping, some toxic body having been formed.

He holds the view that the matrix of the pyrogen is in the blood plasma, that it is always one and the same substance, an anaphylatoxin and that the antigen is merely its evolver and bases this conclusion on the minute quantity of non-specific agent necessary and on the fact that in animals the reaction can be produced by inert substances such as Agar. In a later paper the above worker discusses the effects of induced pyrexia and divides them into two groups which he calls physico-chemical and vital respectively. In the first is included greatly increased transformation of energy, increase in the velocity of the chemical systems with greater activity of catabolic process. The enzyme action is doubled or trebled. Oxyhaemoglobin

has an increased dissociation rate with a greater supply of oxygen to the tissues. Energy is liberated by a lowering of the surface tension. Viscosity of the blood is reduced and its flow rendered easier and dilatation of the bloodvessels makes them more permeable to the serum.

There are other alleged effects but the more important are as above.

The second group he describes as a general expression of powerful stimulation of certain productive capacities of the cells and tissues, and the rapid mobilisation of anti substances. Very similar changes were described by Murphy and Sturm after the application of artificial heat to animals.

In a later work the same author points out that peptone is a toxin and that although present constantly in the stomach and intestines, it can never be absorbed as such into the blood. Even such a small quantity as 0.01 g. introduced produces poisonous symptoms.

A very much disputed subject is the relationship of peptone shock and anaphylaxis.


Vaughan and Wheeler think that protein susceptibility and immunity are different manifestations of the same process. Both depend on the development of a specific proteolytic ferment. When this splits up a living foreign protein (such as a bacterium) before it has had time to multiply, we say that the animal is immune. When cleavage action is less prompt but sufficiently so to split up the living protein before it elaborates a fatal amount of the poison, the animal sickens but recovers. When the action of the ferment is still less prompt, the living protein constructs enough poison to kill, then its liberation causes death. This specific proteolytic ferment is stored up in the cells of an animal as the result of a first injection and remains as a zymogen until activated by a second injection of the same protein. They regard the production of this specific zymogen not as the formation of a new body but as resulting from the alteration of the protein molecule and consequent change of its chemism. (26)

It has been shown by Beidl and Kraus (27) that the

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(26) Vaughan, as quoted Anaphylaxis and Sensitisation. Cranston Low. 1924. (See Ref. 32).

injection of peptone in a dog produces symptoms similar to anaphylaxis, and Kassmer working with guinea pigs showed that in these also the symptoms and post mortem findings were similar, for example dyspnoea, spasms, loss of control of the sphincters, low blood pressure and death from asphyxia, the heart continuing to beat for some time, and post mortem, distension of the lungs, and non-clotting of the blood. Professor Novy's views of the formation of a toxin identical with that found in the cells and tissues of the body in anaphylactic shock when normal serum is digested with Witte's peptone has been referred to above.

Weil showed that when a dog's liver was perfused with peptone the same changes occurred as in anaphylaxis - swelling and capillary congestion. His view is that the shock is due to change in the liver cells produced by the peptone.

The views that something is formed in the animal in anaphylaxis is supported by the existence of "Passive Anaphylaxis" a phenomenon described by Gay and others - the fact that the transference of the serum of a hypersensitive animal into a normal animal will render the latter hypersensitive.

Other workers, among whom were Novy and De Kervyn, claimed to have produced anaphylaxis with a variety of substances which have the quality of being non-nitrogenous in common—among which were pectin, kaolin, starch and histamin. The explanation of this was that the peptone was formed from the blood itself, that these non-nitrogenous bodies absorbed anti-ferment (lipoidal) of the serum leaving the ferment force to proteolyse the serum, which Auld says would be a true autolysis. Jobling and Bronfiner support this view strongly and say that in these cases the blood contains peptone in excess. This however was found not to be the case by Van Slyke. Bayliss says that for such ferment action several hours would be necessary and that anaphylaxis occurs in a few minutes. Auld states that it may be correct to call peptone stock anaphylactic but there is no such thing in nature as the anaphylaxis which we produce with peptone. Clinically anaphylaxis means sensitive. We must regard peptone shock as an "artificial anaphylaxis" which is brought about by the whole protein as antigen.


(30) Anaphylaxis and sensitisation. Cranston Low.

He continues - "The shock produced in artificial anaphylaxis in no way differs from primary peptone shock. This is true of the general reaction and of the local reactions, characteristic of species and extending to microscopic changes. In guinea pigs the bronchial spasm, in dogs the swollen, highly congested liver and in rabbits, the block in the cardio-pulmonary circulation".

Perhaps the greatest authority on this subject, enormous as it is, is Dale, and portions of his work dealing with this point are quoted:-(32)

"In the rabbit the central feature appears to be the failure of the heart. There are in addition certain features common to all species, if the fatal termination is postponed long enough to permit their appearance - flushing and irritation of the skin, loss or impairment of the natural coagulability of the blood, scarcity of leucocytes and agglutination of the blood platelets and rapid fall of the body temperature owing to depression of the metabolism. The differences, however, are very striking and would be puzzling, were it not that the contrasted symptoms represent, in each case, the characteristic reaction of the species to a large class of poisonous

proteins and protein derivatives - peptones, protamines, bacterial proteins, and various extracts of animal organs. During the War this type of action has come to light in a quarter not hitherto suspected, as at least an important factor in some of the conditions loosely classified as "shock" following massive injury of the soft tissues, from which poisonous substances appear to be absorbed into the circulation.

The striking resemblance between the anaphylactic shock and the effects of certain protein derivatives, formed the basis of the alternative theories of the nature of anaphylactic shock, to which a large proportion of the work on the subject has been devoted. These other theories have in common the supposition that a toxic substance or condition arises in the blood, to which the symptoms are immediately due. Some have supposed that the symptoms following the re-injection of the antigen were due to the liberation in the blood of toxic products of protein hydrolysis. In an earlier form of this conception it was supposed that the formation of the complex of antigen and antibody brought the former into relation with a proteolytic ferment in the blood and initiated its rapid digestion. In a more recent form of the theory it is supposed that the formation of this complex removes

(33) Richet. C.R. Soc. de Biol. Vol. 61, p. 1005 (1909);
    Vaughan 'Zeitsche'.

the antitryptic factor present in normal blood, releases the action of the tryptic ferment and thereby initiates an autolytic cleavage of the blood proteins. Another type of theory regards the formation of the complex of antigen and antibody as disturbing the delicate equilibrium of the plasma colloids like contact with a foreign surface, thereby initiating processes analogous to those which precede clotting and imparting to the blood a toxicity similar to that which appears during that process. If we consider the large mass of evidence put forward in support of these plausible and attractive hypotheses, we find that it almost all depends on the possibility of artificially enhancing the toxicity of blood serum in vitro. He goes on to enumerate some of the ways in which this may be done and shows that by injecting this serum, from which the antitryptic factor had been removed, into a guinea pig, the animal dies but the symptoms have only a superficial relationship to anaphylactic shock. Serum rendered toxic by incubation with agar on the other hand, produces no autolysis; but symptoms in the guinea pig much more closely similar to real anaphylactic shock. He continues, "The weakness

of all this evidence, however, seems to me to lie in the lack of clear connection with the conditions of the true anaphylactic reaction. Much of the work seems to have proceeded on the unconscious assumption that the symptom complex was in itself characteristic, and that the appearance of this type of toxicity was sufficient warrant for classing the phenomenon as anaphylactic. We have seen that the symptoms are not characteristic; the essential feature of anaphylaxis is that they are produced by a substance which normally has no such effect. If it could be proved that the injection of the antigen into the anaphylactic animal produced a toxicity in the blood, similar to that imparted to the serum by these various procedures in vitro, the evidence would be strong. But it is just here that it fails. If the enhancement of the toxicity of serum in vitro, by these various substances, really reproduces a process occurring in the blood in the anaphylactic shock, they should be even more effective when injected into the living blood stream."
HISTAMIN SHOCK.

Some authors have attributed the shock effect of peptone to histamin. It was found Wite's peptone contained not more than 0.00335 grms. per 100 grm. peptone and in Auld's hands this gave a skin reaction in many persons but only a very slight effect on intravenous injection of 0.3 ccs. (1 cc. 2% solution = \( \frac{1}{1500} \) mgrm. histamin).

When this solution was mixed with histamin-free peptone, however, there were symptoms of histamin shock such as flushing, headache, salivation, palpitation, cyanosis and dyspnöea. In Auld's view histamin reinforces the action of peptone. The intensity of the reaction depends upon the rate of injection. There is no delay in the appearance of the shock in contradistinction to peptone. There is no rise of temperature in histamin shock.

(2) Arch. Int. Med. 1919. XXII. 69.
As so many of the cases shown are of the nature of rheumatoid arthritis, it is considered advisable to include a short note on the subject of the treatment of arthritis by non-specific therapy.

Gow using proteoses or hetero-vaccines, concluded that benefit could accrue from the intravenous injection of protein more particularly in the type of case where multiple joints are affected and in which no definite septic focus can be found. He urges that it is only to be regarded as an accessory weapon, and not as a 'treatment' in itself.

There have been many workers in this field but perhaps Cowie and Calhoun may be mentioned next. They made a detailed and careful study of a small selection of arthritic cases that had proved intractable to other methods, including arthritis deformans, periartthritis deformans, atrophic arthritis and hypertrophic spinal arthritis. They used typhoid vaccine in doses of 1 billion organisms


(2) Arch. Int. Med. 1919. XXIII. 69.
which often gave a severe 'shock'. Many of the cases they report, showed considerable improvement - considering the changes present. Zimmer using casein intravenously and intramuscularly in doses of 1-5 cc. of a 5% solution in the same type of cases as above (Cowie) came to the conclusion that the best results were obtained when there was a sharp focal and a mild general reaction.

The American school has done considerable work with typhoid vaccine, perhaps Miller and Luck might be mentioned. They conducted two series of experiments on cases of arthritis, treating the first class with proteoses or typhoid vaccine and the second with pollen extracts or proteose, or smaller doses of typhoid. They came to the conclusion that with proper care the results would be the same whether the typhoid vaccine was employed or not. In this series were 45 cases of acute arthritis and 29 are reported to have recovered promptly, pain, swelling and redness disappearing in about five days or under; eight are reported to have benefited considerably; six derived slight benefit, and nine had a recurrence.


As to the rationale of this form of treatment in the various forms of arthritis, it is interesting to recall that Terc\(^5\) treated a large number of cases with bee stings and obtained often a typical reaction, but Dold\(^6\) has failed to sensitise animals to the poison of the bee. Torwey says: "the lack of result with sera and vaccines, unless the administration is followed by a definite febrile reaction, and the good result following such reaction, no matter what agent is used, indicates that a non-specific agent alters bodily conditions materially ......... more reason exists for the view that the change affects the toxic expression of the infection and that, while the organisms are still retained in viable form, their presence or products do not excite response by marked tissue change. There is probably a prompt detoxicating action exerted in the blood or tissues by the allergic response to the introduction into the blood stream of a foreign protein". He goes on to advocate the intravenous route "where the protein is put into the blood unmodified by passage through other tissues and unaltered by membrane or cell selection".\(^7\)


\(^{(6)}\) Ztschr. f. Immunitätsforch 1917. XXVI. Orig. 284.

We know that the non-specific injection produces often a focal reaction. Whether as a result of the reaction the local tissues become immune to the toxic effect of bacteria still within the joint or whether it merely means that there is an increased tolerance to the autolytic products set free at a distance and to which the local tissues were formerly hypersensitive (8) it would be interesting to know.

(8) Prof. Therapy and Non-Specific Resistance. Peterson.
With such a plethora of detail as to the events following the non-specific injection and with such varied interpretations put upon these happenings, it is difficult to formulate any sort of theory which does not either coincide in some essential particular with one of the standard views already alluded to, or else become merely a summary of several of them. Taking the injection of Armours No. 2 peptone 20% solution prepared in the way set out above, and introduced by the intramuscular route, there would appear to the author to be one or two points of immediate interest. The amount of local pressure exerted will naturally depend upon the dose - the administration of 6 ccs. must necessarily cause a certain amount of damage to the delicate individual muscle cells of the area by a purely physical force, and this tissue breakdown will have the effect of liberating protein products in various states of chemical combination. Not only does this apply to the split products of the protein molecule but also some carbohydrate and perhaps fat also. This being the case there will be as an immediate sequel a pro-
cess of synthesis and re-grouping of atoms, with the formation of either less toxic products such as conjugated proteins or proteins in a further stage of 'degradation', or of more toxic substances. For the purpose of this analysis or synthesis, the 6 ccs. of peptone introduced would be also available. Now the toxic substances liberated in this way, and it is not claimed that this would be anything but a very localised and restricted item, would assist materially in setting in motion the process of inflammation with its concomitant phenomena and particularly the migration of antibodies and cells to the site by chemiotactic influence. These, as has been alleged in the theory of Peterson (supra) would exude their leukoproteoses which with the assistance of the other ferments attracted, might be expected to assist in the 'detoxication' already incepted. There would on the other hand be the presence of antiferment; but Peterson's views on the flooding of a local site with leukoproteoses, ereptose, proteose and the other enzymes, might explain the alteration of the ferment-antiferment balance to the reparative side. In considering this point one must remember the dilution of the tissue fluids and a possible alteration in the reaction favouring the enzymes of one class while inhibiting those of another.

Taking the inability of the ordinary striped muscle cells in an intact state to digest protein or to alter the
chemical composition of any intermediate products of
digestion to the amino-acid stage as a fact, the time
factor would be all-important. The process of absorption
into the lymph and blood stream certainly commences and
proceeds before the detoxication process has got very far.
This is a basal fact, because otherwise there would be
nothing except amino-acids absorbed and these being
natural inhabitants of the blood, could not act as antigen
and could cause no reaction. The altered permeability of
the vessels (Starkenstein), the lymphogogue effect (Peterson
and Davis), the peripheral leucocytosis and the decreased
coagulability of the blood could not be observed, being
necessary factors the secondary process of inflammation.
The objective manifestation of the above theory is the
almost constant phenomenon of the "local reaction".
Assuming these various combinations of protein atoms, toxic and non-toxic to be absorbed into the blood and lymph, the same sequelae are observed as in the case of any toxin introduced into the body, and which for practical purpose may be grouped under the heading of fever. The rigor, the perspiration, the leucocytosis, the increased nitrogen metabolism, the alterations in blood pressure, and the like phenomena, all seem to the author to be the well known manifestations of any toxic disturbance. Of course all the signs are not present in all fevers - in some there is a continued leucopenia, in some there is usually a greater degree of pyrexia than in others; but this principle is of paramount importance in the study of all morbid conditions, and depends upon the nature of the antigen and the idiosyncracy of the patient among other factors. In the disease produced by the injection of peptone there are phenomena alleged to occur, which are present in some cases and not in others and a given sequel might be more in evidence in this reaction than in that produced by, say, a typhoid heterogenous vaccine; but one named symptom is more evidence in scarlet fever than in diphtheria or typhoid or pneumonia, which fact does not contraindicate their classification as fevers.

The mechanism of fever is far from being understood and it would naturally follow that the relative importance
of such facts as increase of lymph flow, altered coagulability of the blood, ferment antifermant balance and absorption of particles by the antigen antibody complex, or their correct interpretation is also, except in the minds of the particular theorists, also far from clear.

It will be noted that Auld called the process Pyrogenic therapy and insisted that the vital factor was the production of fever. Professor Novy went one step further and declared that it did not matter what substance was used as long as there was a sufficient rise of temperature.

The author does not admit that this pyrexia is of the importance that these workers suggest, and in several of the cases appended there were no "shock" reactions in the accepted sense, and yet clinical improvement was observed of quite as great a degree as would be expected in the particular type of case, the period of treatment and the lengthy histories being taken into account.

In order to understand the reason why there should be a rise of temperature after an injection of peptone in some cases and why in other seemingly similar ones there should not, and the mechanism which effects such a rise, instead of delving into the inter-relation of minute biochemical changes in the cell, the matrix of the plasma, the central nervous and homopoietic systems, it seems for
the present purpose better to deal with broad principles and to pursue the fever analogy somewhat further.

In zymotic diseases such as diphtheria, scarlet fever and tetanus, we have local foci disseminating toxins of unknown chemical composition into the blood stream and the lymph and these circulating in some form or other and producing the cardinal fever syndrome - the fact that certain tissues are selected more than others may be neglected for the moment to preserve clarity. In peptone therapy we have artificially introduced a toxin which also circulates in some form or other and also produces in many cases the same picture, this time called "Shock".

Both these unknown toxins whether dilute or concentrated are in close association with the heat-regulating mechanism of the basal ganglia which is apparently thrown out of tune. That damage to this structure can do this is well recognised as a result of the observations on routine haemorrhages.

The other signs are merely surely either a reaction to the causative factor - the introduction of the poison, or to the effect on the heat regulation. The latter explains the sweating, nausea and general malaise and increased katabolism and the former, the leucocytosis, antibody mobilisation and obscure pain, often in the back.
The fact that, as shown in the cases, there is no rise of temperature in some, even with large doses, does not, it is submitted, impair the analogy. The reaction to antigen is so very much a question of idiosyncracy that different subjects cannot be expected to 'answer' identically. It is impossible to state the degree of pyrexia which will be attained in a case of early scarlatina - it may be a very high one or it may not, and yet according to general belief the toxin is the same whether it be high or low, and it would be impossible to prognose whether a child with tuberculous meningitis would 'run a temperature' or not, - and yet the toxin is the same. And so with peptone. Perhaps it would be as well here to risk the accusation of labouring the point ad nauseam and to hint at another possible explanation of the varying degree of reactivity.

We do not know the chemical composition of toxins and although we assume them to be true to type, our only grounds for this assumption, is their standardisation by effect, and the same applies to peptone.

We are told by various workers, as has been shown, that a process of autolysis occurs producing the so-called detoxication by the breaking down and building up of the tissue products at the focal site. Now during this rearrangement it seems feasible that the antigen is altered as well, and that it, in its new form, or partly changed
together with the intermediate products of which it has caused the production, is the real pyrogen — a totally changed substance from the original peptone.

Some similar change may, it could be argued, take place with regard to other unknown toxins and to reach the point at issue, although a causal agent may be tested on an animal and found to have a certain effect, it might in other hosts be altered in different ways either to become more toxic or less toxic and might produce corresponding results.

As to the focal reaction. It was suggested (infra) by Weichart that the non-specific reaction resulted in omni plasma-activation and by Döllkin that there was also a selectivity. On broad principles if all the tissues were stimulated by peptone to an equal extent it would be difficult to understand why a focal reaction is possible. In the cases however where peptone is given therapeutically in contradistinction to experimentally, there is some focus where disease is present — in the cases dealt with here, the joints, the lungs or the skin; and if we assume this general stimulation to take place, it appears rational to suppose that its effect would be greater on tissues already the seat of inflammation or in some way damaged. In these tissues there is a greater receptivity for toxins than there is in the case of intact tissue. The effect might be the same as was suggested in the local reaction,
the toxin being brought into contact with the focus and at first adding to the morbid process already going on and then acting as an extra fillip to the immigration of the anti-inflammatory substances.

This in rheumatoid arthritis, it is submitted, might be held to in some way explain the 'lighting up' of the joints after such an injection and the consequent benefit to the joint in those cases in which bony change is not evident; and in asthma, the temporary appearance of rhonchi so often noted followed by disappearance of these and of cessation from attacks for a longer and shorter period.

The permanent defervescence of the fever, with the disappearance of malaise and the temporary discomfort merely means the elimination of the antigen and detoxication of its products and of those which have been produced by its agency. The whole effect of a 'Shock', the term being a misnomer and applied here to include the cases without rise of temperature, is in the author's opinion an isolated event and may or may not be a step towards recovery; but it is not claimed here that that step having been taken any subsequent benefit can accrue without a
As to the much disputed question of whether it is an anaphylactic phenomena, it does not seem to matter very much, although it is a subject of great scientific interest, and more work is necessary before a definite conclusion can be formed. Dale's view however probably holds the field - that peptone shock is not identical, at any rate with anaphylaxis.

**CONCLUSIONS.**

1. The mechanism of the reaction is not yet understood. Many of the following phenomena take place during the reaction syndrome.

(a) Autolysis at sites altering the arrangement of the atoms of the protein molecule and thereby the formation of more toxic or less toxic substances and their absorption.

(b) Alterations in the ferment titre.

(c) Alterations in the ferment-antiferment balance.

(d) Alterations in the blood pressure, the coagulability of the blood, the rate of the lymph flow, the permeability of the vessel walls, leucopenia followed by leucocytosis.

(e) Other minute biological changes.

2. The inter-relation of these and their effect in producing the result is not yet understood.

3. The term 'Shock' is a misnomer, as is 'pyrogenic' - it is not necessary to have a rise of temperature for the production of benefit, this applies especially to cases of
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3. The term 'Shock' is a misnomer, as is 'pyrogenic' - it is not necessary to have a rise of temperature for the production of benefit, this applies especially to cases of
4. The question of dosage is one of experience with injections as a whole and no rule of thumb doses are likely to be a success.

5. It is best to begin with an infinitesimal amount and to increase very cautiously or if the response is sharp, to repeat the last dose.

6. The route of the introduction is a matter of individual selection.

7. Whatever may be said as to the absence of any need for care in selecting the particular pyrogen, as long as its effects are pyrogenic, and however much it may be reiterated that this form of therapy is entirely non-specific - it seems to the author that in selecting the agent it would be best where possible to choose one that is likely to cause a response and also exert other beneficial influence as well and it is therefore suggested that when possible an autogenous vaccine will do better than any non-specific agent - by reason of its specific bacterial toxin. Wherever this cannot be done - or is unsuccessful peptone appears to be a safe and efficient pyrogen.
CASE 1. Rheumatoid Arthritis. Duration 2 years.

Mrs. C. Age 38. 2 years ago the right elbow became painful, stiff and swollen. The right wrist also became swollen and stiff but not so painful. The elbow became flexed to a right angle in which position it has remained since.

A year later the right knee became stiff, painful and swollen and patient ultimately was unable to walk. This joint however has never pained her as much as the elbow. The right ankle was also painful but never became swollen.

Family and personal history showed nothing of note.

On examination the right elbow was seen to be flexed as mentioned above, slight swelling was present.

The right wrist was slightly dorsiflexed, fixed and swollen. The fingers of this hand demonstrate enlargement of some of the joints.

The left shoulder moved freely, slight creaking being elicited.

As regards the right leg the hip joint was normal, the knee was flexed at an angle of 30° but could be actively moved to a right angle. The joint was swollen.

As to the other systems: there was no pyorrhea but the lower teeth were carious - an upper denture. There was slight pulsation in the neck with forcible heart sounds. Otherwise there was nothing to mention.
Treatment was begun on August 29th 1923 with light diet and rest and on September 1 an intramuscular injection of Armour's Ni. 2 peptone 2%, the dose being .2ccs, was given at 7 p.m.

At the time the injection was given the temperature was 98°, the pulse 88 and the respiration 22. Within four hours the temperature dropped to 97°, the pulse was then 80 and the respiration 24, and four hours later the temperature had risen to 98.2°, the pulse had increased to 100 and the respiration was still 24. There was no focal or general reaction.

The next dose.4 ccs of the same solution was given by the same route on the 4th September at 5.30 p.m. At that time the temperature was 97.2, the pulse 98° and the respiration 24, and at 7 p.m. the temperature had advanced .1 degree, the pulse had increased to 100 and the respiration was still 24. Four hours later the temperature had risen .2 degrees, and the pulse and respiration had dropped slightly and in another four hours the temperature was still at the same level (97.8°) the pulse had increased a few beats and also the respiration. At 7 a.m. - four hours after the last observation, the temperature had gone up .3 degrees, the pulse increasing 2 beats and respiration rate decreasing as many, while at 11 a.m. - that is eighteen hours after the injection the temperature had dropped 1.2 degrees with a quickening of the pulse 8 beats and a decrease in the respiration rate of two rhythms. There
This rather lengthy description of the temperature, pulse, respiration relationship is given here to demonstrate that in small doses, the time factor is unreliable. With large doses there is exceptionally a delayed reaction but in the cases where minute amounts are injected there is frequently a slight drop in the temperature before any rise and even when the small increase takes place the pulse is sometimes slower than before. This can be seen on the 3rd here at 3 and 7 a.m. and on the 4th at 7 a.m. and 11 a.m. A slight decrease before any rise in the temperature curve is seen with first injection on September 1st and can be explained by the preliminary leucopenia mentioned above - or the time factor necessary for the elaboration of the pyrogen - in this case it seems especially of interest because it was the first dose.

The next injection of 1 cc. was given at 11 a.m. on September 8th. This was followed by a moderate reaction. the temperature rising in 16 hours from 97° to 100°, the pulse following to a limited degree and it may be noticed here too that after a drop of 2.2 degrees the pulse was slightly more rapid than at the height of the 'shock'.

On this occasion patient complained the next day of more pain and stiffness in the joints and particularly in the left elbow. Thirty-two hours after the administration there was a slight rise of temperature in which neither the pulse nor the respiration participated. After the
reaction had subsided patient did not notice much difference as regards the condition of the joints. Objectively there was no alteration.

A further dose of 2 ccs. was given at 8 p.m. on September 16th followed by an ideal reaction.

Within 4 hours the temperature shot up from 98.4°F to 102.2°F, the pulse rate increasing by some 12 beats. During the next four hours the temperature dropped 2.2 degrees, the pulse following, only to go up again to 100.6, four hours later with concomitant pulse increase. During the succeeding lysis the phenomenon alluded to above as regards to pulse, temperature ratio will be noticed.

On the morning after the injection patient complained of general soreness, pain in the back and right knee which was also stiff. The fingers were not affected. There was a marked local reaction with considerable pain.

On the next day - the 17th - the knee was still stiff and there was slight pain, but generally she was feeling much better. The pain at site of injection in the buttock was still severe.

Four days later when the 'shock' had completely subsided patient thought there was slight improvement in the movements of the wrist.

On September 22nd an injection of 4 ccs. was given
at 7.20 p.m. followed by a pronounced "shock", the temperature dropping .2° in the succeeding 8 hours and then shooting up from 97° to 102.4° in the next 8 with increase in pulse rate of some 54 beats and a slight increase in the respiration rate. The temperature immediately dropped to 99.2°, the pulse and respiration following, only to rise again in four hours to 100.4° and then to 100.6° - this time the pulse and respiration not following, and then on the next reading to fall 2.1°, afterwards assuming a lytic character for 12 hours. It is to be noted that when the temperature was 100.6 at 3 p.m. on the 23rd, the pulse was 96 and subsequently on the 24th when 98.4° was registered the pulse was 104. On the 22nd patient had a very restless night but not very much pain. Profuse perspiration was noted with morning nausea. There was little change in movement of the joints.

The next occasion on which Peptone was given was at 8.10 p.m. on the 29th. September when a dose of 4 ccs. was given, and at 11 p.m. a temperature of 103 was registered. Four hours later it had risen 1° and at the next reading it had fallen to 99°, the pulse following. There was then a rise to 101.4° followed by readings of 99.4°, 98°, 101.4°, 100°, 99.6°, 98.8°, 99.6°, 99.4°, 100.6° at four hour intervals followed by a rapid drop to 97°. Here again the pulse did not respond to the fluctuations.
At 11 a.m. on the 30th the temperature was 104° and the pulse 118 and at 7 p.m. the same day the temperature was 98° and the pulse 134.

On the night of the 29th patient was restless and complained of a feeling of heat with profuse perspiration but there was no change in the joints.

This injection produced an abscess in the buttock which had to be drained and so probably part of the 'reaction' was really septic absorption from this. After drainage, there was considerable improvement.

The final dose of 6 ccs. was given on October 12th at 3.15 p.m. with a satisfactory reaction, the maximum temperature on this occasion being 102.8° falling rapidly and slightly rising 20 hours later - the pulse following the initial peak. The whole 'shock' effect took 36 hours approximately.

Four hours after the injection there was no nausea or headache, but some throbbing at site of injection in the buttock with an area of swelling. There was a rigor at 7 p.m. and another at 8.30 p.m. Patient spent a very restless night with profuse perspiration. The buttock was very painful especially on movement. Complained also of pain in the small of the back and of flatulence. At 10.30 a.m. the patient was looking very tired and paler and complained of severe pain in buttock.
After this there was gradual improvement at site of injection and in two or three days she was able to move with comfort.

No more injections were given and on the 17 October the knee was put in plaster after being straightened.

On the whole there was a little improvement in this case with the course of injections. The wrist became more mobile but the elbow and knee did not improve very much, and patient will never be more than a cripple; but before treatment was begun the condition was far advanced.

It was thought well to describe this case rather more fully on account of the four typical 'shock' effects and the two questionably delayed reactions on September 1st and October 2nd. The seeming lack of relationship between the temperature and pulse during the shock periods has been alluded to ad nauseam perhaps but it occurs throughout the cases and is in the author's submission of slight interest though granted there are many factors at work any of which might produce it.
MRS. CLUMIE
38 yrs.

Notes of Case

Day of Dis.

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Printed and Published by Wadderson & Co. C. & Co. 58, Street. Lincoln's Inn.
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Printed and Published by Woodruff & Co., 6 Gate Street, Lincoln Inc.
CASE 2. Rheumatoid Arthritis.

Fanny H. Aet. 49. Charwoman. History extended over 2½ years. At that time patient noticed that her upper arm on the right side became swollen and very painful so that she was unable to continue at work. Her wrist on the same side also troubled her but not so much as the arm. About the same time the right knee became swollen, painful and stiff - so much so that she was unable to walk. Pain was constant but varied in intensity from time to time.

Personal and Family history were not helpful.

On examination: Right shoulder showed no limitation of movement and there was no creaking. Elbow joint was normal. The right wrist was swollen and very tender with limitation of movement in all directions but mainly in flexion. Joint showed slight dorsiflexion.

The right knee was very tender with swelling at posterior aspect of joint and marked restriction in flexion. The left knee was very slightly swollen - not tender - movements in this joint were free in all directions.

As to the Other Systems:-

Gums were healthy with both dentures. Flatulence was a source of trouble. Urine on admission contained occasional pus cells.

As to general treatment, free elimination was relied upon, together with symptomatic measures.
Intramuscular injections of Armour's No. 2. peptone (10%) were given commencing with a dose of .2 cc. on September 1st, 1923 - that is five days after admission to hospital.

The temperature at 7.10 p.m. when the agent was administered was 98.2°. There was a subsequent rise to 99° at 3 a.m. followed by a drop to Normal at 7 the next morning. The pulse quickened a little reaching 104 beats per minute at 3 a.m. Otherwise the reaction was not evident.

The next injection was given on the 8th September at 11 a.m. and on this occasion the slight rise of temperature that there was seems to have been slightly delayed. During the first four hours there was a rise to 97.6° followed during the next four by a drop to 97° with a subsequent rise four hours later to 98.8°, falling back to normal.

On September 9th at 8.10 a.m. an injection of 1 cc. was given followed by a rapid rise of temperature to 100.4° in 4 hours and remaining at that level for the same period and again dropping to 98.6°. Neither the pulse nor respiration showed much increase.

On the 16th September at which date on the general chart will be seen a rise of temperature to 100° the pulse and respiration being slightly increased, patient complained of considerable pain in the right knee joint and increased pain on pressure over medial aspect. The
posterior swelling was not as great as on admission but there was some thickening above the patella. There was no alteration in the condition of the wrists - slight tenderness but no pain.

There was some inflammation at site of last injection. This may possibly have been a delayed reaction from last dose - 5 days previously.

On the next day, the 17th, the knee joints were still stiff and painful on movement, but patient was subjectively better. On the 18th there was still slight stiffness in the knee, and on the 19th she was feeling well except for a little pain in the knee - movement at night wakened her up. There was still some tenderness. On the 20th there was still very slight stiffness on extension and flexion. No tenderness.

On September 23rd 1 cc. was again given at 2.30 p.m. with slight reaction, the temperature rising to 99.4°, and on the day following there was again increased stiffness, there was no pain and no tenderness.

At this stage some 20% solution was obtained and substituted for the 10% On September 29th 2 ccs. of this was administered with a long drawn out reaction, the temperature rising to 99.4°, within eight hours from 99.8° to 98.4° and then rising within 4 hours to 99.4°, remaining at that level for 4 hours and in another four dropping to 99°, and rising again in the same period. to 99.8° The pulse showed
On the night of the 29th pain was complained of in the right knee, extending up the thigh. The following day headache with a continuation of the pain in the knee. Appetite was very poor and there was slight nausea in the morning. Also slight pain in the finger joints was present. The other joints were unaffected. There was profuse perspiration. The pulse was weak and irregular in force and time.

On the next day, the temperature was still swinging slightly and the pain was still present shooting up to the right hip joint from the knee. There was still headache and general malaise. Patient slept very poorly.

The next day (Oct. 2) the temperature was showing a wider swing and the most noticeable point in addition to those symptoms of the previous day, which were on this date less severe, was the weakness of the pulse.

On October the 6th 4 ccs. of 20% were given at 7.45 p.m. followed by a drop in the temperature from 99° to 98.9° at 3 a.m. and then a gradual climb up to 100.2 at 11 p.m. followed by a drop to 98.6 at 3 a.m. the next day.

Slight tenderness was complained of at the buttock (local reaction). The knee was very painful at night - swollen, hot and tender.

Three days later the knee was very much better and the pain had given way to a stinging sensation. The foot
could be put to the ground.

On October 14th a dose of 5 ccs. was given at 12.15 a.m.

At 7.30 p.m. the temperature was 98.6, pulse 86 and respiration 24. Patient was then feeling rather upset and looked very tired but did not complain of headache or sickness. There was considerable pain on the right side - knee and thigh.

At 11 a.m. the next morning, there was great improvement - temperature was then 98.4°, pulse 68 and respiration 20. She had had a good night. There was stiffness locally.

On the 16th further improvement was noted. There was now no pain in any joint except the right knee which was also stiff. Great progress had been made in respect of the wrists which moved much more freely.

She was discharged on October 19th very much improved.

This case has been reported rather more fully as being in many respects a typical one, showing the relation between pyrogenic effect and focal and local and general reaction which is a most variable one. Here we see a marked focal and general reaction without on any of the occasions a very high temperature.

On September 8th, September 23rd, particularly on the 29th and on October 6th the 'time factor' which is alluded to more fully in the case of Mr. C - is demonstrated.
Name: **Fanny H.**
Age: 49
Disease: **Rheumatoid Arthritis**
Result:

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**In Hospital:**

**September 1923.**

**Day of Dye**
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**Temperature (in Centigrade) (continued)**
- 42°
- 41°
- 40°
- 39°
- 38°
- 37°
- 36°
- 35°

**Pertone H.**
CASE 3. Rheumatoid Arthritis.

Woman, A.K. Aged 34 years. There was a long history extending over some eleven years, but the symptoms had been progressively worse during the last two. At first a swelling was noticed in the right wrist with some tenderness, and six months afterwards the other wrist became swollen, painful and stiff - the swelling had been intermittent, and continued so for some nine years off and on until both wrists were to a considerable degree ankylosed. For the two years preceding treatment the disease spread to the right ankle and left knee with considerable pain, and during the last year both joints had become swollen and remained so, interfering with walking and thus preventing her attending her place of work. There was no previous history of any relevancy except irregular action of the bowels and a consequent tendency to dyspepsia.

The teeth were good (upper denture) and gums healthy. Wrists were found to be much swollen, especially the right where oedema extended on to the hand, and both were almost completely ankylosed and the left knee showed marked swelling, and considerable grating was elicited.

Blood Count showed nothing abnormal.

Otherwise there was nothing to record.

As to general treatment, patient was given light diet, iron and arsenic, sodium salicylate and sodium bicarbonate, and also the colon was washed out frequently.
On September 15th intramuscular injections of Peptone were begun and on that date .1 m. was introduced (x) on chart) without any ascertainable reaction, except a slight rise of temperature on the four hour chart which is not more than is of constant occurrence and probably was not related to the injection.

On September 18th another dose of Peptone was administered .3 gms., again without any reaction. A third dose .6 gms. on the 22nd September showed a slight rise of temperature and the pulse increased some 10-12 beats per minute, and there was a very slight increase of respiration on the night of the 23rd. On September 25th 1 gm. Peptone was given in the same way with less reaction even than the time before, with the exception of the respiration rate which showed a very slight increase. Again on September 29th another dose of 1 gm. was given with more effect, the temperature for the first time, with the exception of the day after admission, reached the normal level, and it will be noticed that the pulse on the night of the 30th showed a greater increase than heretofore, and that the respiration was also slightly increased. No further injections were given in this case for a fortnight and on October 13th a dose of .5 gms. was given in the same way with a marked reaction, the temperature soaring to 102.6 in the course of some 4 hours and dropping to 99.4° 8 hours
later only to rise again to 103.8 some 8 hours afterwards — "overshooting the optimum" as Auld describes it. It will be noticed that the pulse followed the temperature to a limited extent, its greatest number of beats during this period being 120. On the day of this injection and on the succeeding days the quantity of urine passed did not show the diminution from the daily amount just before, that one would have expected with the hyperpyrexia. The explanation of the marked reaction to a smaller dose of the antigen, a fortnight after the last larger injection, can only be explained by reverting to the theories which have been alluded to supra.

The orthodox theory of anaphylaxis might be said to partially account, this being the first time in the course of treatment that there had been a sufficient time between the injections to constitute the "Latent period" of ten days as originally laid down by Richet. On the other hand this was not the second dose but the sixth and the processes of immunisation should have by this time taken some effect; as Auld terms it "the effect of prolonged desensitisation". A dose of .3 gms. was given on October 20th, with a moderate reaction — not the "temperature between 102-3° which Auld says is the object of the injection (supra), but enough to activate the "protective
processes."

A final dose of .3 gms. was introduced on October 29th with a satisfactory result, the temperature rising in the course of eight hours to 102.2°, falling in 4 hours to 99° and thence to subnormal, and again rising 12 hours later to 99° - then to drop to normal for the individual. In this particular reaction the pulse followed the temperature, again to a limited degree, and the respiration showed a slight increase, reaching rather more 'rhythms' per minute than in any previous dose. Patient was very much improved with treatment - both general and Pyrogenic, and when she left hospital was able to walk with moderate ease at any rate.

Emphasis has been laid in this case on the temperature reaction - because it is alleged without it there is no real benefit (Auld. supra). There were, of course focal and local reactions, but these will receive due stress in a succeeding case. The point of importance here seems the necessity for more or less prolonged treatment even if there is no "reaction" at once - there must be, and it has been alleged that there is, "a time factor", in the elaboration of the poison, be it anaphylatoxin or not, and it appears possible that this time factor may vary in different individuals. Another point in the author's submission is that it is vital to start with very
small doses and to proceed in increasing them very cau-
tiously. Had a marked addition to the initial amount
been used in the second or third injection in this case,
the temperature curve would have been different probably,
but the symptoms would also possibly have been alarming
and the benefit to the patient negligible.
HOUR CHART.

DISEASE.

Time
Bowels
Urine

Temperature (Fahrenheit)

97°
98°
99°
100°
101°
102°
103°
104°
105°
106°
107°

13 14 16 17 20 21 23

Day of Dis.

Pulse.

Sept 15th 16th 18th 19th 22nd 23rd 25th

Date

Entered at Stationers Hall
Printed and Published by Wedderspoon & Co. 8, Wate Street, Kingsway w.c. Goulds Clinical Chart

A.K.

Agnes King
Agnes King

Book No.

Notes of Case

34 years.

Temperature (Centigrade)

Sept 1923

Date of admission

Result
Name: Agnes King  Age: 34  Disease:  Result:

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</thead>
<tbody>
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</table>

Temperature (°F):

- 107°
- 106°
- 105°
- 104°
- 103°
- 102°
- 101°
- 100°
- 99°
- 98°
- 97°

Day of Dis.

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|---|

SEPTEMBER 1923
CASE 4.

George C., aged 42. Case showed long history of pain in the feet and ankles extending over some 16 years. In 1922 ankles began to swell slightly and in 1923 he developed pain in the knees, back and shoulders, and began to experience stiffness so that it became difficult for him to change position and when he sat up he experienced pain over the lower abdomen. Condition altered little from this time until admission to hospital 23rd October 1923.

On examination of the left foot the metatarso-phalangeal joint of the great toe was markedly enlarged and formed a prominence on the medial border of the foot. There was no movement in the joint. The interphalangeal joint of the digit was also enlarged. The second toe was a "hammer" and the third was displaced dorsally but was fairly movable. The third, fourth and fifth toes were crushed together.

In the right foot, the metatarso-phalangeal joint of the great toe was enlarged but movable. In the second to the first phalanx was displaced backward. The other digits of this foot were normal.

The ankle joints showed good movement. On the left side slight creaking was observed. The leg muscles were flaccid and showed wasting.

The knees showed no swelling, tenderness or heat. On the left side hyperextension caused pain over lower border of patella, in the popliteal space and up the front of thigh. Some creaking was elicited.
On the right there was some creaking but the joint was less affected than the left.

The left hip joint showed limitation of movement in all directions. On active or passive movement pain was complained of extending from a point midway between the posterior-superior spine of the ileum and the great trochanter, round to the groin and down the medial side of the thigh. The muscles of the thigh were prominent and demonstrated occasional fibrillary twitchings.

On the right side there was slight limitation of movement, both active and passive, with pain in the groin - there was no fibrillary twitching.

As to the shoulders, hyperextension of the left joint was restricted and pain was caused in the deltoid region.

X-ray examination showed that in the metatarsal and phalangeal joints there was evidence of serious toxic arthritis. Knees showed early arthritic changes.

It should be mentioned that patient had had an attack of gonorrhea fourteen years before admission, and that he was at the time of treatment suffering from iritis of the right eye, attacks of which he had had for the last ten years occurring about every three or four months, sometimes in one eye and sometimes in the other.

The blood count showed little abnormal and the Wassermann test as regards the blood was negative on October 26th,
as also was the gonococcal complement fixation test on November 3rd. The cerebro-spinal fluid showed a faint trace of globulin the cell count being 2 per cubic centimetres and the stained film revealed a few small lymphocytes. It was Wassermann negative. On November 24th the gold colloid test was negative.

Treatment with intramuscular injections of Armour's No.2 peptone (10% solution) was commenced on November 11th 1923, on that date a dose of 1 cc. at 11.50 a.m. followed at 1.20 by a series of rigors and headache - the former ceasing about 2 p.m. As will be seen from the four hour chart the temperature rose to 100° within some 6 hours, the pulse and respiration showing some increase, and patient reported that movement was easier.

On the 14th November patient was much easier and could evert both feet and flex legs with less pain.

On November 15th 1.5 cc. of the same solution was given by the same route with rise of temperature to 102.4 with marked increase in pulse and respiration rates. The rise and fall on this occasion was very rapid.

On November 20th the general condition of the joints had much improved.

On November 21st a dose of 2 cc's was given with rise of temperature to 101.2 with concomitant effect on the pulse and respiration.
On the 26th November 3 ccs and on December 2nd 4 ccs were given with shock effect in each case (see 4 hour charts).

On discharge on December 9th the condition of the joints was much improved. Patient was able to walk fairly well with some comfort on the level but had difficulty in getting up and down stairs - stiffness but little pain.

This case shows the pyrogenic effect fairly well - the effect without which Auld says there can be no benefit and the result in it was certainly more marked than in some of the other ones shown where there was no visible reaction.

It must be here reiterated that however advantageous a marked "shock" may be, it is not necessary in order to obtain benefit - although in suitable cases it may be a perfectly safe and desirable procedure. Some of the effect is possibly of psychic nature.
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Temperature (Fahrenheit)

Normal Temperature of Body

Day of Dis.

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CASE 5. Rheumatoid Arthritis.

Annie M., age 52. This case showed a history of some 30 years duration with swollen joints and acute pain at intervals most marked in elbows and shoulders. Sixteen years previously was treated in hospital for 6 weeks with 6 weeks subsequent convalescence and greatly benefited by this. Nine years before present treatment gained some relief at Harrogate.

One year ago the arms became worse and she was unable to arrange her hair at the back because of pain and stiffness in shoulders and elbows. Was able to walk about all the time. Vaccine treatment was tried with little good result.

About 10 weeks ago the condition became worse and she was sent to hospital.

Previous history showed that at 14 years patient had a swollen knee, the condition then being similar to the present condition of the knees. Family history showed a tendency to rheumatism.

On examination shoulders were limited in movement more marked on the right side but on neither side could the arms be raised to a right angle. Extension in both was limited but there was little or no limitation of flexion. Rotation was markedly limited in all directions, on the right side more than on the left. There was grating elicited on moving the head of the humerus in the glenoid cavity on the right side.
As regards the elbow joints, there was marked deformity with thickening. Thickening marked between olecranon and humerus and round the lateral epicondyle of the humerus on both sides. As to movements, extension was impossible on either side. When fully extended the angle formed was about $160^\circ$ on the left and $150^\circ$ on the right. On both sides flexion was slightly limited. Supination was impossible. There was no grating; and no pain during examination. Patient was most comfortable with arms extended.

The wrists were markedly deformed, thickening being present at the distal end of ulnar and radius, more marked on the left side. Carpal bones were displaced. Wrists were fixed in position of pronation. There was marked muscular wasting.

The hips showed only slight impairment.

The knees were markedly deformed, on the lateral aspect of the left joint the capsule protruded through the soft parts. Flexion was possible to a little beyond a right angle, and grating was present. There was marked muscular wasting of thighs and lower legs.

Occasional swelling was present in the ankle joints.

Apart from frequency of micturition there was nothing to note in the other systems. The duration of this symptom was about one year.

Treatment was by hot air baths and guaiacol carbonate grs.x. t.i.d. and some general improvement was noted.

On November 2nd 1923 patient had a bad night with
severe pain in the shoulders, and on November 6th the left elbow caused her much suffering, and on the succeeding night she was unable to sleep because of elbows and shoulders.

These facts point to the case being one unlikely to benefit from peptone therapy. The vaccine given previously was not a success and at that time conditions would presumably be much more in favour of this type of treatment. The intense toxicity over a long period as shown by the wasting of the muscles and bony change together with the subjective manifestation made hesitation in embarking upon anything but conservative treatment a necessity.

On November 12th patient was given ml v. of a 20% solution of Armour's No. 2. peptone intravenously and showed, as was expected, a marked hypersensibility with rapid rise of temperature from 97.2° to 101.2° in 4 hours, dropping again rapidly to 97°. Subjectively patient had a very bad night, severe pain in the joints, shivering and headache; but was better the next morning.

An herpetic condition of the lips arose as a result of this injection.

On November 16th the same dose was again administered in the same way with a marked "shock". The temperature rose from 97° to 102° in 4 hours, the pulse following and also the respiration to a lesser extent. Again patient had a bad night aspirin and bromide being necessary - severe pain in the joints and profuse perspiration being noted. Another
crop of herpes appeared on the lips. Patient was better the next day; but as a result of this second injection the tongue and gums were painful, which caused some distress.

There was recorded general improvement in this patient but not more than would be expected with the rest, diet and regime and baths.

The interest here is in the marked response to small dosage - it may be that in such a toxic individual the treatment is contra-indicated - at any rate in anything but infinitesimal doses to begin with.
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**Notes of Case**

Annie Morgan

Age: 52 yrs.

Date of admission: NOV 2nd

Date of discharge: 1923

**Temperature**

- Normal Temperature of Body: 98°F
- Day of Dis.: 96, 84, 88, 88, 86, 92, 84, 90, 74, 80, 82, 80, 76
- Date: NOV 2nd, 3rd, 4th, 5th, 6th, 7th, 8th

**Pulse**
- 20, 18, 22, 20, 22, 20, 22, 20, 20, 22, 20, 20, 20

**Resp.**
- 20, 18, 22, 20, 22, 20, 22, 20, 20, 22, 20, 20, 20
Annie Morgan

52 yr.

Book No.

Notes of Case

Hour Chart.

Disease.

Temperature (Fahrenheit)

Normal Temperature of Body

98°

Day of Dis.

Date of admission

Pulse: 78 82 80 84 80 84 80 84 80

Resp.: 22 22 20 20 24 22 20 20 20

Date: Nov. 23rd

Entered at Stationers Hall. Printed and Published by Wedderspoon & Co. 6, Gate Street, Kingsway W.C. Goulds Clinical Chart.
CASE 6.  Urticaria Pigmentosa.

A.B. Age 52. (Female). Eruption appeared at the age of 17 when menstruation commenced, as a crop of real blotches on the outer aspect of the left arm, not itchy or hot and disappearing on pressure. These faded away between the menses, a fresh crop, at the same site appearing each month. This lasted some 32 years. About 5 years before treatment commenced, after a period of worry and strain - there was a rigor, followed the next morning by an eruption over both arms, gradually spreading over the chest, of the same character. Three years later this was present also on the ankles, and a year later also on neck and hands. The condition was then progressively getting worse - great irritability and burning at night being experienced.

When treatment commenced, there was present all over the body except face, bright red, slightly raised wheals, not disappearing on pressure - a brownish pigment being left. The size of this was about $\frac{1}{4}$ - $\frac{1}{2}$ inch in diameter, but over triceps, especially on the left side there was a tendency for them to coalesce. The general character of the skin was dry, there was lack of subcutaneous tissue and no desquamation.

Apart from advanced otosclerosis and slight pre-
menstrual dysmenorrhoea, there was nothing further in this case to report - the other systems were more or less healthy.

The general treatment was, eliminative, rest, light diet and symptomatic. This was begun on November 21st, 1923.

On December 4th 1 c.c. Peptone (Armours No.2. 20°) was injected intramuscularly without any visible reaction being produced and on December 7th, 2 c.c.s. of the same solution produced a similar effect. Another injection of 3 c.c.s. on December 10th also was without result. On December 13th a dose of 4 c.c.s. was administered with some reaction - the temperature going up to 100° in the course of a few hours with some increase in pulse rate (20 beats per minute). The next day patient showed a general reaction - not feeling well, cramp in the right leg and complaining of cold and sickness, followed by pain right side of body lasting a day. No focal reaction was evident. On December 16th a dose of 1 c.c. of same strength as the previous solutions was given by the same route followed by a moderate reaction with rise of temperature to 99.6° and an increase of some ten beats in the pulse rate. There was here also a general reaction with pain on the left side of the body "from leg up to ear" but a headache, which had been present on the previous day had
It is interesting to note that this reaction was nearly as marked as the previous one three days before which was induced by four times the dose. Whether the slow sensitisation of the previous three progressively increased doses without any visible result had taken effect, or whether it required the 4 ccs. on the 16th to, so to speak, light up the mechanism or to produce the anaphylatoxin, it would be interesting to know. On December 19th, 1 cc was again given with very slight temperature reaction and on the 22nd 2 ccs. with similar result.

On the 28th December 3 ccs. were given with apparently no reaction at the time, except a small rise of temperature on the four hour chart to $98^\circ$, falling again to $97^\circ$ and rising on the 31st to $102^\circ$, the pulse increasing some 20 beats and the respiration also showing slight quickening. This "optimum" was not sustained, a fall by lysis taking place in some three days. That a general reaction was present, was demonstrated by a sore throat and headache, the former continuing for a day or two with considerable severity.

This case did not show great benefit from the treatment but is interesting showing the time factor in producing the shock and also - perhaps? the variable dose necessary to induce a visible reaction, though the increased permeability of the vessels, the alteration in the ferment-
antiferment titre and the inauguration of anaphylactic mechanism together with the other phenomena already dealt with in the theory of the subject, may have been set in motion by the doses which had a less dramatic effect though perhaps not to the same degree.
Hour Chart

Disease

Amelia Ballingall

52 years

Tea Book No

Notes of Case

Date of admission

1923

Entered at Stationers Hall

Printed and Published by Wedderspoon A.C. 26 Gate Street, Kingsway W.C.2

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CASE 7.

James A. Aet. 45  Commenced with dislocation of right shoulder two years before admission to hospital. Reduction was affected the same night and treatment was continued for some weeks because of inability to raise the right arm more than 40°, without any benefit.

Family history showed nothing worthy of comment and personal history an attack of gonorrhoea at the age of 19.

On examination the right shoulder was found to be longer than the left and there was on inspection a bony prominence corresponding to the acromio-clavicular joint. On palpating the joint tenderness was elicited, most marked near this prominence and pain present at this site on movement of the arm. The limb could be abducted to a right angle but not more. Movements at the elbow were good. This was the only joint affected.

An x-ray report stated there was definite rheumatic change especially over the head of the humerus.

Armour's No. 2 Peptone (20%) was given by intramuscular injection, the first three doses of 0.5 cc. and 1 cc. producing no visible reaction of any sort. A repeated dose of 1 cc. produced no 'shock' effect but patient complained of a restless night and more pain on pressure over the joint.
A fifth dose of 1.5 ccs. on the 12th August produced a feeble response (see chart) and on August 14th patient was able to abduct with more ease.

On the 19th 2 ccs. produced a moderate temperature reaction in which the pulse participated slightly, patient had a broken night, slight stiffness with increased limitation of movement.

On 26th 3 ccs. produced no visible reaction and patient slept well and complained of slight increase of stiffness in the joint.

On September 2nd. 4 ccs. produced apparently no effect as did 5 ccs. A final injection on the 16th September of 17 grms. was given with subsequent restlessness, local tenderness but no stiffness.

This seems another case of benefit without any marked 'shock'. The focal reactions were here present to a more marked degree than usual and there were symptoms of general reaction without any real pyrogenic effect in the sense understood by the authorities.
CASE Rheumatoid Arthritis.


Complained of stiffness and pain flitting from joint to joint - worse in damp weather and on resting; but relieved on exercise. Starting pains present at night. The pain was boring in character over left scapula. There was also difficulty in walking. On left hand there was swelling of the tissues of first phalanx but no limitation of movement and no redness. In the right hand there was thickening of the tissues over metacarpo-phalangeal joints - and also no limitation of movement. In the left foot there was talipes with limitation in all directions - no swelling or creaking on movement.

In the right foot was talipes equino-varus with limitation in all directions - without swelling or limitation.

X-ray report: Knee joints very average. Lateral plate shows traces of Rheumatoid Arthritis. There is a loose body in Anterior-Posterior position. The hands showed trace of change in the index finger in the carpo-phalangeal joint on the right side. Ankle joints and tarsus practically unaffected - trace of pipping in the left coronoid process - right less marked than left. Traces present with radii. Hip joints not affected.
There was nothing to note beyond this system.

Beyond light diet and purgation, peptone was the only treatment in this case.

Treatment commenced on November 23rd, 1923, with the injection of 1 cc. 20% Peptone (Armour's No.2.) without any visible reaction, followed on 27th by 2 ccs. also without any result. On December 4th, 3ccs. were administered with very slight reaction and on 7th 4ccs. with even less. On Dec. 10th, 5ccs. produced no result but on 13th, 6ccs. produced marked reaction with rise of temperature to 101.6 with marked increase in pulse rate and concomitant increase of 6 rythms in respiration. There was a subjective reaction with malaise and increased pain in the affected joints.

On the 16th, 1 cc. was given with rise of temperature to 101°, increase in pulse rate and slight increased rapidity of respiration, and on the 19th, 1 cc. was again given with no reaction, as also was 2 cc. on the 22nd. On 28th, 3 ccs. was administered with very slight result except the presence of malaise and on 1st January, 1924, 5 ccs. produced a sharp 'shock' - temperature soaring to 100°, respiration following but not the pulse. Weight had been lost during this time - patient decreasing from 7 stone 10½ lbs. to 7 stone 8 lbs. There was no great improvement but very little could be expected as will be seen from a perusal of the X-ray report - some bony changes being present.
It seems in this case that it needed a large dose of peptone to set the mechanism into action - 6 ccs, and 5 ccs. Admitted the reaction was marked with 1 cc. on 16th December, but the explanation there might be that the "Shock" dose two days before had so altered the ferments, the permeability of the arteries and the whole protective processes that they were at the time of the subsequent injection in an unstable state and would easily "flare" up - this may be very much against the orthodox theory of a "negative phase", but in this case there had been six previous injections, all of which were sensitising doses and 'inducing' agents.

An example of idiosyncracy to toxic agents and on Starkenstein's theory, one poison injected might give rise to others formed in the body as result of the introduction of the first, and the changes produced by either might increase the tolerance or the sensitiveness of the host to the other.

John L., aged 51. History of sudden onset of pain in the right groin 6 months before treatment. Pain was of shooting character, worse at night. Began to lose weight during the last 3 months - 2 stones.

Previous history showed malaria and dysentery in 1918 from which he had intermittently suffered; but not for the last 18 months.

Right hip was the only joint affected. There was no swelling and no effusion - very little limitation of movement, but pain on abduction, adduction and rotation. There was no muscular wasting and no crepitation. X-ray report showed slight lipping round the acetabulum.

As regards the other systems with the exception of carious teeth there was nothing to note.

General treatment embraced guaiacol carbonate, dental and balneological therapy - this was begun on August 25th 1923. On September 2nd a dose of Armour's No. 2, 20% solution of Peptone was injected intramuscularly (0.2 gms) with no general reaction and no visible focal effect. On the 4th of the same month 3 gms was given in the same way with similar result and on the 24th 4 gms with as little visible effect as before.

After the second injection patient got up (September 6th) and the pain gradually subsided and there was considerable increase in the powers of walking. Weight increased under treatment from 11 stone. 11 lbs. on admission to
12 stone \(\frac{1}{2}\) lb. on September 18th to fall again at discharge on October 3rd to 11 stone, 12 lbs.

The improvement in this short time was greater than is likely to be accounted for by the general treatment.

It seems probable that the three increasing doses had set in motion the desensitising mechanism without any 'pyogenic' effect. With the lipping round the acetabulum it would be too much to expect very great improvement.

It might be correct to assume that the mobilisation of the anti-inflammatory substances could exist to a limited extent without any marked pyrogenic effect.
Name: John Linton  Age: 51  Disease:  

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Other Observations:  
- Weight: 110 lbs
- Pulse: 60
- Resp: 18

September 1923

Printed and Published by Wodderspoon & Co., 65 Gate Street, Lincoln's Inn.
CASE 10. Subacute Rheumatism.

George N., aged 32. History of 5 weeks duration. Caught a chill with cough and two days later pains in the back and shoulders with some stiffness in the latter. Pain then spread to the knees particularly the left with considerable sweating. Since then had never been free from the pains, which flitted from one joint to another.

Previous history showed rheumatic fever while in the Army, which caused him to be classed C₂ instead of A₁, as formerly.

On examination there was no swelling, tenderness or heat noted in either of the shoulder joints, movement however in both was limited in extension and abduction.

The knees were slightly swollen and the right one showed increase of temperature. There was no limitation of movement and no creaking.

Swelling was also seen in the right hand in which movement was almost impossible. Wrists also were slightly swollen.

Fingers were swollen, most marked in the right middle finger, so much so that hands could be closed only to about half their normal extent.

There was no muscular wasting except in the legs from disuse.

The other systems showed nothing of interest except a mitral systolic murmur.
Blood Wassermann was negative.

Treatment was during the acute stage confined to Sodium salicylate, light diet, aspirin and rest, and it will be seen from the early chart that the temperature fell by lysis during the first week. This treatment was continued for about 6 weeks.

On December 21st 5 cc. of a 10% solution of Armour's No. 2 Peptone was given intramuscularly without any result, followed by 1 cc. on the 26th, 1.5 cc. on the 31st, 2 ccs. on the 5th January 1924, 2.5 ccs. on the 11th and 3.5 ccs. on the 16th.

None of these injections had the slightest result either generally or focally, and the improvement in the condition was ascribed to the general specific treatment.

This case is mentioned to show that acute or subacute cases do not do well with this type of treatment. It has been pointed out above that pneumonia, pleurisy and the like have shown good results from protein therapy but it is against all theory and in the author's submission, all practice also. The details are set out in Miller's experiments in pneumonia and Auld's comments thereon (Supra). The whole of the charts are reproduced here to show the slight variations after the initial lysis.
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**Notes of Case**

** Entered, at Stationers Hall. Printed and Published, by Wodderspoon & Co., 6, G. Gate, Street, Kingsway, W.C. Goulds Clinical Chart.**
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**Notes of Case**

- **Temperature**: 107°F
- **Pulse**: 80, 76, 78, 72, 76, 76, 84, 70, 84, 76, 72
- **Resp.**: 22, 22, 22, 22, 22, 22, 22, 22, 22, 22
- **Date of Admission**: December 12, 13, 14, 15, 16, 17, 18

**Entered at Stationers Hall.**

**Printed and Published by Wedderburn & Co. 6, Gate Street, Kingsway, W.C.**

**Gould's Clinical Chart.**
## Hour Chart

### Disease

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### Bowels

- 1703
- 1989
- 11420
- 1845
- 1845
- 1760
- 1561

### Urine

- 8
- 8
- 8
- 8
- 8
- 8
- 8

### Time

- 107
- 106
- 105
- 104
- 103
- 102
- 101
- 100
- 99
- 98

### Temperature (Fahrenheit)

- 97° 98° 99° 100° 101° 102° 103° 104° 105° 106° 107°

### Normal Temperature of body

- 98° 99°

### Date of Discharge

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- December 19th
- December 20th
- December 21st
- December 22nd
- December 23rd
- December 24th
- December 25th

### Notes of Case

- George Nicol
- 32 yrs.

---

*Entered at Stationers Hall.* Printed and Published by Wedderspoon & C. 8. Gate Street, Kingsway w.c. *Goulds Clinical Chart*
### Disease

**Notes of Case**

- **George Nicol**
- **32 yrs**.

**Temperature (Fahrenheit)**

- **99°**
- **98°**
- **97°**

**Day of Dis.**

- **14**
- **15**
- **16**
- **17**
- **18**
- **19**

**Pulse.**

- **82**
- **76**
- **80**
- **74**
- **80**
- **84**
- **78**
- **86**
- **76**
- **88**
- **84**

**Resp.**

- **20**
- **20**
- **20**
- **20**
- **20**
- **20**
- **20**
- **20**
- **20**
- **20**
- **20**

**Date.**

- **January 2nd**
- **3rd**
- **4th**
- **5th**
- **6th**
- **7th**
- **8th**

**Entered at Stationers Hall**

**Printed and Published by Wodderspoon & Co. 63, Gate Street, Kingsway W.C.**

**Goulds Clinical Chart.**
Hours Chart.

Disease.

Notes of Case of Admission

George Nicol 32 yrs.

Book No.

5.

(X).

Entered at Stationers Hall. Printed and Published by Woddenspoon & Co. 6, Gate Street, Kingsway W.C.
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**Temperature (Fahrenheit)**

- 97°
- 98°
- 99°
- 100°
- 101°
- 102°
- 103°
- 104°
- 105°
- 106°
- 107°

**Day of Dis.**

- 64
- 65
- 66

**Pulse.**

- 72
- 76
- 76
- 72

**Resp.**

- 20
- 20
- 20
- 20

**Date.**

- January 23rd
- 24th
- 25th

Entered at Stationers Hall.

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Goulds Clinical Chart.
CASE 11. Rheumatoid Arthritis.

Mary B., aged 20. This case gave a history of some two years' duration, the first symptoms being stiffness and undue tiredness after walking, the sensation being most noticed in the back, legs and arms, and being severe enough to make patient go to bed for three or four days at a time. This state of affairs went on for some twelve months, at the end of which time it was noticed that the left thigh was the focus of maximum trouble. During the two months preceding treatment all joints became affected and occasional swelling was noticed in the ankles - necessitating her giving up her work as a lift attendant.

There was also a 6 years history of stomach trouble culminating in an operation for duodenal ulcer the year before treatment for the present trouble was begun and she still had symptoms of a dyspeptic nature - this is mentioned in relation to the aetiology of the rheumatoid arthritis.

Previous History showed nothing of importance, and family history a rheumatic tendency in the father.

The teeth and gums were in good condition with the exception of an upper left premolar and a right upper molar. Creaking was elicited in both hip and knee joints and especially in the left hip, which joint showed restriction of movement both as regards flexion and extension, even passive movement causing pain. There was no muscular wasting.
With regard to general treatment - milk diet - Sodium salicylate and Sodium bicarbonate and washing of the colon were relied upon together with free purgation.

Peptone was administered intramuscularly at regular intervals for one month, all the doses being the same - \(\frac{1}{2}\) cc. 20% solution of Armour's No. 2., and with the exception of the dose given (No. 7.) on Feb. 7th 1924, there was no temperature reaction and even this time the 'optimum' of Auld was not reached, and neither the pulse nor respiration followed; but the latter varied a great deal during the course of treatment and could be no guide. After each injection there was some local reaction at site of puncture and some focal reaction in the joints, but not a great deal. When treatment was discontinued there was some improvement in the joint condition and most notably an increase of 3½ lbs weight.

This case was complicated by the gastric trouble and the neurotic nature of the patient who persisted in having a walking stick or crutch near the bed end and is included to show that some progress may be made without any dramatic reaction which suggests that the term 'Pyrogenic Therapy' is not the best one, nor is 'Protein Shock'.

Also is demonstrated here the fact that idiosyncrasy must play a great part in the "Non-specific reaction". Here the initial dose of \(\frac{1}{2}\) cc. 20% Armour's No. 2. would in many patients have produced a sharp 'shock' or this result would
have been produced by a second or third dose. Here we seem to have detoxicated, but it probably would have been easy by different management to have altered the re-grouping of the components of the focal autolysis and synthesis, and also ferment balance, reaction etc., and to have produced more of an intoxication.
Arthur A., aged 51. This case showed a history of some 6 years duration, the onset being quite sudden - patient noticed lameness of the left leg, which for 3-4 days seemed to improve and then to return and he has been lame since. A month later pain was noticed in the hip joint on this side, slight at first but gradually getting worse until about one year before treatment the leg became stiff and painful unless kept extended. When flexed a sharp stabbing pain was experienced. The right leg also had by this time become painful, on flexion there was no stiffness. Previous history showed operation for hydatid cysts.

Family history showed a "rheumatic diathesis" in the mother.

On examination there was found prominence of the great trochanter on the left side with some atrophy of the gluteal muscles. Anteriorly the limb was slightly flexed, and externally rotated. There was no voluntary movement but passively a slight degree of rotation could be obtained. The knee is a little stiff, but free movement is possible. There was no limitation of movement in right hip.

As to the other systems it is important to note pyorrhoea alveolaris was present to a marked degree.

Patient was admitted to hospital on September 1st 1923 and was treated by intramuscular injections of Armour's No. 2 Peptone (20%).
In all three injections were given without any general reaction, though focally there was increased pain temporarily and also increased mobility. On September 24th 0.2 grms were given, followed by 0.4 grms on the 30th and 0.6 grms on October 7th. On the last occasion it will be noticed on the four hour chart that the temperature did, in fact rise to 98.4 some sixteen hours after the injection.

It was realised that owing to the bony changes there could be no marked improvement in the left hip; but during his stay in hospital there was considerable improvement in mobility. There was an increase of 1 lb. in weight.

This seems another case of improvement without 'shock'.
Hour Chart.

Disease.

Arthur Anderson
51 yrs.

Book No.

Notes of Case

Date of admission

Result

Entered at Stationers Hall
Printed and Published by Wedderspoon & Co., 50 St. Street, Kingsway W.C.

Gould's Clinical Chart.

Jessie V., aged 41. Case showed a long history of 13 years, starting with bronchitis, wheezing and breathlessness worse at night, lasting a fortnight. After this there were no further attacks for a year when she wakened up suddenly one night, fighting for breath - this occurred in the spring and lasted off and on for a fortnight, relief being obtained with morphia. Attacks now occurred regularly in summer and autumn but not in winter for some seven years until in 1918 patient was a victim of the epidemic of influenza of that year and after being very seriously affected by this plague became much worse as regards the asthma - attacks being more frequent and sometimes following close upon one another and at others patient being free for two or three months, as compared with the four month intervals previously. About a year before admission to hospital she was always wheezy and the attacks were still more frequent though not so severe but because of their number, patient became worn out. At this time they appeared to be brought on by cold or any form of excitement. Hay or flowers, cheese and bacon, exertion, digestive disorders, menstruation, nasal catarrh, were all inducing agents.

Family history showed asthma in one sister which began at age of 28 - she died aged 56 of cardiac failure - phthisis in one brother, together with a highly strung temperament in the father.
Apart from influenza as mentioned supra and Nasal Polypi there was nothing of importance in the personal history. On examination patient was found to be breathless and during the times when she had bronchitis there was occasional hemoptysis. There was little or no emphysema and percussion note was good. Breath sounds were harsh, vesicular and accompanied by sibilant rhonchi scattered over the chest and heard during the expiratory phase. During this portion of the cycle were also audible many coarse bubbling râles. There was considerable dyspnœa, amounting at times to orthopnœa.

Sputum contained diphtheroid bacilli and staphylococci. Apart from idiosyncrasy to certain "inducing" agents, constipation and menstrual dysmenorrhœa, there was nothing to note in the other systems.

Blood count on admission was red blood corpuscles 5,700,000 and white blood corpuscles 12,400 and hemoglobin 72%.

Treatment was commenced on July 31st 1923 and on August 13th a laryngeal swab was taken which on culture grew streptococci and micrococcus catarrhalis and from this a vaccine was made containing approximately per cubic centimetre 100 million streptococci and 400 million micrococcus catarrhalis and on the 19th of August the initial dose was administered of .1 cc. There were in all 19 doses of this vaccine given, varying between .1 cc and 1 cc. at
usually three days intervals and from the accompanying
temperature charts it will be seen that there was in no
case any appreciable general reaction, nor was there any
outstanding subjective phenomena. As to focal reaction,
the tables show that after the first three doses there were
less attacks each twenty-four hours; but that it was neces­sary to administer more adrenalin to relieve each than
before. After the fourth dose - the amount of vaccine had
been the same after each injection - the attacks ceased
altogether for 15 days to reappear again, fewer in number
than at the beginning of treatment but again requiring a
larger dose of adrenalin than initially. During the next
24 days the attacks continued and during that time eight
doses of 1 cc. each were given. When the next dose was
given there were no attacks occurring, but for the next
three days patient was affected once each night and then the
attacks became more frequent in spite of the last two in­
jections - about as many in each twenty-four hours as before
treatment commenced. It was never possible now to control
the spasm with three minims of adrenalin as it had been
before the vaccine was started.

On second of November a course of Peptone was begun,
Armour's No.2. 20% solution administered by intramuscular
injection.

On this date .5 cc. of this solution was given,
followed on the 4th by 1 cc. and on the 7th by 2 ccas., and
on the 11th by 3 ccs., on the 15th by 4 ccs., on the 19th by 5 ccs., and although there was in no case any general reaction, there was on the other hand during these seventeen days no asthmatic attack, and with the exception of one slight nocturnal paroxysm the day after the last of the above doses she was perfectly free for the remainder of her time in hospital, that is for 25 days - not one real remission since the peptone was commenced. After the 19th November one more dose was injected - 6 ccs., and this was the only injection of either specific or non-specific nature to induce any reaction. On this occasion, the temperature rose for the first time since treatment to 99° falling the same night to its previous level.

This case may be another example of benefit without "shock". It was noticeable that a very small dose of the vaccine controlled the attacks, after 2 doses, whereas a dose 10 times as great failed to do so after they had recommenced even after six doses - It is true that when 1 cc. was first given there were none, but there had been also none just prior to this and also that on the day when peptone was begun there were none also; but this was apparently an isolated occasion. It is interesting in noting the entire absence of attacks after peptone administration to consider the application of arson's sessile antibody theory - non-specificity necessary for exfoliation. (Supra). Also of interest in this type of case is a consideration of the
formation of the anti-anaphylatoxin by different antigens both specific and non-specific and a combination of the two. The sole reaction on the 23rd November may have been due to the size of the dose or to the stage reached in the complex alterations in vital processes which have been enumerated above, culminating with formation of a substance sufficiently toxic to act as a pyrogen, or simply to prolonged sensitization.

Case shows the value of having specific and also non-specific remedies and the advantage of combining them or selecting one or the other after due consideration.
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Name: Jessie Veitch  Age: 40 yrs.  Disease:...

Printed and Published by Wodderspoon & C. & Gate Street, Lincoln's Inn.

July 1923 - August 1923.
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**Result:**

- **Name:** Jessie Vielch
- **Age:** 40
- **Disease:**

_Case of Case_

_August 1923_
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**September 1923**
Name: Jessie Veitch  Age: 40  Disease:  

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November 1923.

J. B., aged 24. Showed a history of some twelve years, the first attack following bronchitis and subsequently recurring about every fortnight and later every week. Different climates had been tried with no beneficial result. During an attack the patient was usually ill three or four days. About two years before the present treatment was begun he was in hospital and the protein cutaneous tests were applied and showed purely negative result. Vaccines were administered and had apparently the effect of prolonging the free intervals but not of shortening the attacks.

Family history showed no asthmatic tendency.

On admission to hospital the chest was found to be emphysematous, though not fixed. There was slight dyspnea. Movement was good and equal on both sides, the percussion note hyperresonant and the breath sounds harsh vesicular with no adventitious sounds. The vocal resonance showed slight decrease. Otherwise there was nothing to note. General eliminative treatment was commenced on January 22nd 1924 and on January 35th a dose of .5 cc. of 20% solution of Armour's No. 2. Peptone was injected intramuscularly with a slight rise of temperature from 96.4° to 98.4° there being no acceleration of pulse or respiration. Another dose of the same solution 1 cc. was similarly administered on January 30th with no visible reaction, except a headache the same evening which responded to Acid acetyl-salicylic grs x.
Patient left hospital earlier than advised but during the eleven days there was no sign of an asthmatic attack - in the ordinary course of events he would have been due for two, and it seems possible that these at least were aborted. This was without any marked "shock" effect and is another example in the author's submission, of that class of case in which benefit may occur where the patient does not show many signs of reaction at the time.
Notes of Case

Name: James Bellamy, age 24

Disease

Result

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</tr>
<tr>
<td>100° 300° 101° 201° 104° 100° 3°</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Temperature (Fahrenheit)

[Graph showing temperature fluctuations over time]

Day of IEx

Pulse: 20 22 20 20 20 20 20 20 20 20

Respiration: 25 24 25 26 27 28 29 30 31 1

January 1924
NOTE:—It is thought well to include one or two more charts showing 'Shock' with the provoking doses of Peptone without a description of the case, except a brief reference to its nature.

CASE 15. Rheumatoid Arthritis.

Robert M., age 59. Included to show the two 'reactions' with doses of Armour's No. 2. Peptone intramuscularly introduced at 3:30 p.m. on March 12th and .2 ccs. at 9 p.m. on March 18th.

In the first case there was a rise of temperature from 97.6° to 100.2° in 8 hours with quickening of pulse beat and temperature, and in the second 'shock' a rise of temperature from 97° to 99.8° in 8 hours, without any response on the part of either the pulse or respiration.
Notes of Case

Date of admission, (suit

M. A. —

Pulse.

Resp.

Day of Dis.

Result

Entered at Stationers Hall. Printed and Published by Wodderspoon & C. G. gates street, Kingsway w.c. Goulds clinical Chart.
<table>
<thead>
<tr>
<th>Time</th>
<th>Bowels</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Temperature (Abnormal)</th>
<th>Normal Temperature of Body</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>98°</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day of Illness</th>
<th>Pulse</th>
<th>Resp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Printed and Published by Wodderspoon & C. E. Gate Street Lincoln's Inn.

Name: Robert Miller  Age: 59  Disease:  
Result:  

May 1923.
Name: Robert Millar  Age: 59  Disease:  

<table>
<thead>
<tr>
<th>Time</th>
<th>1</th>
<th>1</th>
<th>1</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>4</th>
<th>2</th>
<th>2</th>
<th>3</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>0</td>
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</table>

Temperature (Fahrenheit)

<table>
<thead>
<tr>
<th></th>
<th>97°</th>
<th>98°</th>
<th>99°</th>
<th>100°</th>
<th>101°</th>
<th>102°</th>
<th>103°</th>
<th>104°</th>
<th>105°</th>
<th>106°</th>
<th>107°</th>
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</table>

<table>
<thead>
<tr>
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<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
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<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse</td>
<td>80</td>
<td>87</td>
<td>95</td>
<td>89</td>
<td>88</td>
<td>62</td>
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<td>94</td>
<td>57</td>
<td>60</td>
<td>65</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Resp.</td>
<td>24</td>
<td>23</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>22</td>
<td>20</td>
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<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>
CASE 16. Acute Arthritis of right hip following injury.


On Aug. 1st at 8 p.m. with no reaction.

On Aug. 5th 2 ccs. at 8.20 p.m. with a similar result.

On Aug. 10th at 8.45 p.m. with a typical 'Shock'; pulse and respiration participating.

On Aug. 17th 1.5 ccs. with moderate reaction, pulse and respiration again taking part.

On Aug. 26th 2 cc. at 9.15 p.m. with slight reaction.

On Sept. 2nd. 3 cc. at 7.15 p.m. with the often noted preliminary fall of temperature, in this case without any subsequent rise beyond the point at which injection was given.

On Sept. 9th 5 ccs. at 8 p.m. with a good reaction, pulse taking part.

There was no good result; but it was considered that in view of the state of the hip joint, none was to be expected.

Case points to the time factor necessary for the elaboration of the necessary mechanism and variability of the host from time to time in its response, or the agent in its toxicity.
## Notes of Case

**Date of admission**, **Pulse**, **Resp.**, **Date**.

**Case Book No.**

**Name**: James Adams

**Age**: 29 yrs.

**Date entered**: at Stationers Hall

**Date published**: 1923

**Gould's Clinical Chart**.
CASE 17. Asthma.

James Allen. age 49. This patient, a highly neurotic individual, suffered from frequent asthmatic attacks, sometimes as many as twelve occurring in the course of 24 hours. Adrenalin had very little effect in relieving the spasms, but Pulv. Stramonii gave considerable ease.

On the 20th December 1923, that is 5 days after admission ten different native proteins were introduced by the dermal method and in no case was there any reaction but as will be seen from the chart appended the temperature immediately rose and with the exception of a small remission continued to do so for three days, reaching an 'optimum' of 102°, the pulse and respiration following. During the next 9 days there was a lysis, with wider diurnal variations than normally, for the first 3 days of this phenomenon. During this time - the whole 9 days, the patient was subjectively in a state of 'Shock' - perspiration at intervals, pains in the joints, there were considerably more rhonchi in the chest than before and there was also much general malaise.

Each protein was later tested singly by the same method and in no case was there any reaction.

On January 11th 1924 .5 cc. Armour's No. 2. Peptone 20% was injected intramuscularly without, as will be seen, any "shock".

The case is shown as it is submitted it is an unusual
one and serves to show that it may be possible to provoke a true "shock" effect by using small amounts of different proteins (native) in this way. Singly they produced no result - and their mass action may be due to a larger dose of foreign protein being absorbed - or to the counter-action that Starkenstein described, or to some totally different toxin or anaphylatoxin being formed from the ingestion of a combination of the ten substances.