PYROGENIC THERAPY.

WITH REMARKS ON COLLOIDAL METALS.

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THE term "pyrogen" was first used by Burdon-Sanderson in 1875 to signify a fever-producing substance which he had prepared. Such substances, both protein and non-protein, have since then received ample recognition, though not from the therapeutic side. The subject, however, is one of high practical importance, and in many cases brilliant results may be obtained.

Early in 1915 I began the clinical investigation of various colloidal metals parenterally introduced. They were received from different sources and included those produced by both chemical and electrical methods. The first attempts were limited to subcutaneous injections, gold, platinum, silver, and copper being chiefly used. The results were meagre and uncertain. Sometimes slight elevations of temperature followed the injections. The next attempts were instigated by a consideration of the catalytic action of certain metals in relation to the oxidative processes in the peroxide-peroxidase system. It seemed conceivable that under local conditions of defective oxidation the introduction, if possible, of a new peroxidase might be beneficial, especially if there was some bar to the effective action of the natural peroxidase, which may be regarded as the iron in the haemoglobin and in the tissues. To this end I employed colloidal manganous hydroxide intravenously. The results were distinctly encouraging, and the matter is still under investigation. I also made a third series of trials in view of the well-known catalytic action of platinum, with the design of causing adsorption of toxin-antitoxin on the platinum particle introduced into the blood. If the antigen was not a soluble toxin, it might vice versa be neutralized by adsorbing the platinum. Numerous trials were made in diverse conditions, gold, silver, and copper colloids being also employed, the dosage (intravenous) varying from 2 to 10 c.cm. Favourable results were obtained, more particularly where the injection was succeeded by a rise of temperature, which, however, rarely exceeded 2° F. Cases of pneumococcal and streptococcal infections were influenced in this way, but as to the *modus operandi* it is difficult to conclude, as, except in the case of gases, the interaction of bodies adsorbed on the same surface is not characterized by evolution of heat, at least not to any very appreciable extent. There is, however, another consideration in that the metallic particles might adsorb both active (quadrivalent) oxygen and toxin, leading to combustion of the latter. The infective organism itself might also be destroyed by the active oxygen provided it adsorbed the particle so charged. It is to be remembered also that in a reducing system, as in the case of the liver, the metal would act as a reducing agent.

In the course of these investigations a bottle of colloidal platinum was opened which had been obtained from the manufacturers a year previously (May, 1915). It was perfectly transparent, of a very dark olive colour, and slightly acid to litmus. It was odourless and free from any trace of deposit. When given intravenously in the usual doses (3 to 7 c.cm.) it produced a new and severe reaction. In half an hour there was rigor, lasting for twenty minutes or longer, followed by rise of temperature to 104° or 105° F., with, in the next few hours, perspiration, sickness with vomiting (occasionally) and headache. The temperature then fell usually to subnormal. This reaction occurred alike in normal subjects and in those suffering from diseases characterized by moderate pyrexia, namely, subacute pleuritic and pneumonic conditions, and protracted paratyphoid fever. In these the fall of temperature coincided with a great improvement in the general condition. The entire syndrome exactly resembled the ague fit.

The following cases and charts are given in illustration:

CASE I.—Young woman, aged 20, admitted under me, April 14th, 1916, at the Prince of Wales Hospital, suffering from acute pneumonia and signs of pleurisy in the right side. Temperature 103°, pulse 140, respira-

tions 60. The pneumonia cleared up, but after a week, pus containing streptococci was aspirated from the side. A portion of rib was resected on April 24th and a tube inserted. The temperature then fell to 99°-100°; after five days it rose again to 103°. On May 2nd, when the temperature had temporarily fallen to 99.8°, 4 c.cm. of the colloidal

CHART 1.

platinum was given intravenously (marked by x). This was followed by shivering and rise of temperature to 103.6°, perspiration, headache, and sickness. After six to eight hours, fall of temperature which reached 97.8° next morning, with great amelioration of the symptoms. After four days a second injection of 5 c.cm. was given, followed by rise of temperature to 104.4°, fall to 97.4° with rapid recovery.

CHART 2.

CASE II.—Man, aged 31. Admitted October 7th, 1916, with subacute pleurisy, right side, and pulmonary congestion over lower half of left lung. Temperature on admission 102°, pulse 116, respirations 32. Sputum contained pneumococci, also the fluid withdrawn from the pleural cavity. Temperature remittent. Rapid recovery after the injection (Chart 2, x).

CASE III.—Man, aged 40, seen September 30th, 1916, suffering from left-sided pleurisy with effusion, of a subacute type, with signs of consolidation. Sputum abundant, containing pneumococci. Effusion diminished, but patient continued ill, temperature 99° to 101° F. After

CHART 3.

about three weeks (on October 18th) he received an injection of 5 c.cm. The temperature rose to 104° F., but instead of falling to subnormal in the usual time, fell to 99.8°, with a secondary rise to 101° F. on the following day. On the third day it became subnormal, and a speedy recovery ensued.

During the cold stage the blood pressure rises from 10 to 20 mm., and thereafter during the hot stage it falls to about the same extent below its normal level. The temperature reaches its height in two to four hours. Leucocytosis sets in during the rise, and may continue for forty-eight hours. After the critical fall in temperature the pulse-rate and respirations may show a sharp drop in frequency, but sometimes the decline is gradual. Facial herpes may follow the treatment. These reactions were not obtained in the acute stage of pneumonia or pleurisy, nor was benefit derived. Instead of a rise, a fall in temperature of several degrees may take place (negative phase), with subsequent return to the original level, or nearly so.

At the same time as these results were obtained, Jobling and Petersen,¹ and some others in the United States were employing the method of intravenous injection of typhoid vaccine which had been introduced in 1914 by Kraus and Ichikama in the treatment of typhoid fever. To Kraus, however, belongs the credit of showing

that precisely similar effects were obtainable by the use of *B. coli* vaccine, and that therefore there was nothing specific about the treatment. Miller and Lusk² reported striking results in arthritis, and Engman and McGarry³ in certain skin diseases by means of the vaccine, the reaction being in every respect identical with that which I had obtained with the colloidal platinum. "Non-specific vaccine therapy" and "protein shock therapy" were applied to the procedure. I can certainly add my testimony to the remarkable effects of the treatment in cases of recent arthritis.

When the supply of active colloidal platinum I had been using was nearly exhausted I was unable to obtain any colloidal metallic preparation capable of producing the reaction. It was not until September, 1917, I obtained a specimen of colloidal silver, which, in doses of 3 to 5 c.cm., acted with particular intensity, even more so than the platinum colloid. Being informed by the manufacturers that this silver was protected in a special manner, I requested them to send me the protective suspension exactly as used, which they willingly did. On trying it clinically, I was somewhat surprised to find that it reproduced very faithfully the effects of the colloidal silver itself, bulk for bulk. The protective used was given as veal peptone 0.4 per cent., with 1 per cent. glucose. It gave a violet biuret reaction. The veal "peptone," of course, was the active agent, as the effect of the glucose alone was nil. The result was surprising also in view of the fact that I had frequently given larger doses of peptone intravenously without reaction. Such a discovery naturally led me to suspect all the colloidal metals supplied, as they all contain some albuminous substance as protective. Most of those I had used, including the very active platinum, were protected by gelatin. The gelatin protective was also prepared for me and on injection it certainly produced symptoms such as headache and malaise, but without the rise of temperature found in the active platinum. Whether this latter preparation owed its properties to an unusual state of dispersion of the platinum particles, or to some accidental impurity such as hydrazin, or to some toxic body formed by hydrolysis of the gelatin after prolonged keeping, is difficult at present to decide. Examined under the ultra-microscope, the platinum was certainly in a very fine state of division, and showed active Brownian movements. Although doubt is thus thrown on the colloidal metals, it cannot be affirmed that they are clinically inactive, as they may certainly produce results which are not accompanied by high temperature reactions. It is, however, very desirable that they be issued in a purer and more standardized form.

If the pyrogen which produced the reactions was not colloidal platinum it matters little therapeutically, as all pyrogenic substances in appropriate doses produce the same effects, whether killed bacteria, proteoses, nucleic acid, or protected colloidal metals, to mention only a few.

How is the reaction brought about? This is a disputed point. The minute quantity of certain of the pyrogenic substances necessary, and the apparent possibility of producing in experimental animals similar symptoms by such inert (non-protein) substances as kaolin and agar, would seem to favour the view which has recently been elaborated from a large number of experiments by Novy and De Kruif,⁴ that the matrix of the pyrogen is in the plasma; that it is always one and the same substance, namely, anaphylatoxin, and the antigen merely serves to evolve it. This is the reverse of the split protein theory of Friedberger and Vaughan.

The favourable effects (which in a considerable percentage of the cases means the termination of the disease by crisis) have been variously ascribed to leucocytosis, to rapid mobilization of antibodies, to stimulation of the non-specific ferments of the serum (protease and lipase), and alteration in the ferment-antiferment titre. Teague and McWilliams⁵ in an experimental investigation have not been able to confirm these as causal agents. They suggest an active passage of bacteriolytic substances from the blood into the lymph spaces which traverse the local area or areas of infection. Doubtless various factors are at work, but without the pyrexia there is no benefit.

Under present conditions, typhoid vaccine is probably the best pyrogen to use. Nucleic acid (2 per cent.) is not always available in a reliable form, and the same applies to albumose. From fifty to two hundred and fifty million

of killed typhoid bacilli are injected intravenously, according to the strength of the patient and the existing state of the temperature. In apyrexial cases, as in many of the arthritics, the dosage should be greater than in cases of pyrexia. The treatment is specially adapted to sluggish cases of localized infective diseases, with low or moderate pyrexia. Little benefit results unless the full reaction is induced, and rarely more than one injection is necessary. An overdose is indicated by dyspnoea, cyanosis and diarrhoea. The injection should not be given while the temperature is high. Heart disease, high blood pressure, and rigid arteries are contraindications. With care in the selection of cases, the treatment is not dangerous and it is not necessary to produce "shock," nor is the expression "shock" therapy in my view desirable. As an antidote to this, I have used the prefix "pyrogenic."

It is a pleasant duty to acknowledge my indebtedness to Professors Bayliss and Donnan of University College, who have kindly granted me opportunities of consulting them in respect of certain problems presented by colloids and electrolytes.

REFERENCES.

- ¹ *Journ. Amer. Med. Assoc.*, June 3rd and August 7th, 1916, pp. 1753 and 515. ² *Ibid.*, June, 1916, p. 1756. ³ *Ibid.*, December 9th, 1916, p. 1741. ⁴ *Journ. Infec. Diseases*, May and June, 1917. ⁵ *Journ. of Immunology*, February, 1917, p. 167.

TREATMENT OF WOUNDS OF THE CHEST,

WITH SPECIAL REFERENCE TO INFECTED
HAEMOTHORAX.

BY

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At the beginning of the war we were interested merely in the question of diagnosis of a haemothorax and whether or not aspiration of the blood was worth while. Fortunately it did not take very long to settle this latter point, and aspiration very quickly became a routine procedure. Simple aspiration was very soon followed by replacing the aspirated blood with oxygen in order to do away with the disagreeable symptoms sometimes produced by the rapid removal of a large quantity of blood from the pleural cavity. Thus, as far as the treatment of a simple haemothorax was concerned, perfection was reached; but there were other and more serious problems to be solved, and it was in the solving of those the most striking advance was made during the past year.

The problems with which we were confronted were three in number: how to deal with an open pneumothorax; how to deal with an infected haemothorax; how to deal with a foreign body in the lung. During the three years of the war a great deal of work has been done on these problems, and I am glad to say they have been solved.

In the treatment of wounds of the chest four classes must be distinguished.

I. A Non-infected Haemothorax or Pneumo-haemothorax.

The treatment of a simple non-infected haemothorax or a pneumo-haemothorax consists in merely aspirating the blood from the pleural cavity. This should be carried out in all cases in which more than two fingerbreadths of dullness can be made out. In my series of 450 cases 368 were aspirated; in the remainder there was not sufficient fluid to warrant it. The aspiration is done by means of the ordinary aspirating apparatus, but there are one or two practical points which, if carried out, make the procedure easier both for the patient and the surgeon. A local anaesthetic should be injected into the skin, muscles, and pleura in order to make the aspiration as painless as possible. After the injection of the anaesthetic a tiny incision should be made through the skin so that the round cannula will not be gripped by it. In the next place it is important to use a fair-sized trocar, as small needles are very easily blocked; another advantage in using a trocar is that when the sharp obturator is removed the blunt cannula can be moved about the pleural cavity without damaging the lung. If during the aspiration the patient begins to suffer pain in the chest and shortness of breath, the trocar can be disconnected