OBSERVATIONS ON THE HAEMATOPOIETIC HORMONE (ADDISIN) IN PERNICIOUS ANAEMIA *

BY

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The greatest therapeutic advance in recent years has been the discovery of the specific effect of liver and liver extracts in the treatment of pernicious anaemia. The researches of Whipple and Robscheit-Robbins¹ showed the relative haematopoietic values of various foodstuffs in the anaemia of dogs secondary to haemorrhage. Minot and Murphy,² applying these results in the clinic, demonstrated the curative effect of liver and liver extracts in pernicious anaemia. As Davidson and Gulland³ have well said, "the co-operation of experimental and clinical research has achieved an effect which would have been impossible by individual effort."

THEORETICAL AND EXPERIMENTAL EVIDENCE

In 1929 Sharp,⁴ working on an original theory, suggested the use of hog's stomach (ventriculin) in the treatment of pernicious anaemia; Sturgis and Isaacs⁵ demonstrated the truth of the theory, since they found desiccated hog's stomach quite as effective as liver. Independently, Conner⁶ and Wilkinson⁷ also employed stomach tissue in the treatment of Addisonian anaemia.

Achylia gastrica has been one of the cardinal points in the diagnosis of pernicious anaemia for many years. Recently, the alteration of the gastric secretion has assumed greater significance through the researches of Castle⁸ and his co-workers. They have shown that a reticulocyte response occurs when beef muscle digested in normal gastric juice is fed to a patient with pernicious anaemia, whereas there is no reticulocytosis if the beef is digested in artificial gastric juice or in that obtained from the patient ill with pernicious anaemia. They obtained no response from feeding 300 c.cm. of gastric juice daily (without beef) for a period of ten days. They conclude that there is an unknown substance present in normal gastric juice which activates a substance resulting from peptic digestion of beef, and that the absence of this substance in pernicious anaemia is of aetiological significance. They have shown that this unknown substance is destroyed by exposure to a temperature of 40° C. for three days, to 70° to 80° C. for half an hour, and by boiling for five minutes. They have shown that this substance is not pepsin, rennin, or hydrochloric acid. They have also eliminated the salivary and duodenal secretions.

Our studies, begun about a year ago, were based on the theory, predicated largely on the work of Sharp and of Castle, that the normal stomach secretes an haematopoietic substance which, while apparently inert when given by mouth, might, like insulin, prove efficacious if administered parenterally. Our preliminary experiments have been reported elsewhere⁹ and need not be repeated in detail. Suffice it to say that normal human gastric juice, unconcentrated, was found to be practically inert, whereas concentration of the juice by evaporation yielded a preparation of slight activity when injected intramuscularly. When, however, concentration of gastric juice was carried out by distillation *in vacuo*, a highly potent material was obtained, as indicated by reticulocyte

response and maturation of the red blood corpuscles. Following the intramuscular injection, there was also an increase in the number of platelets and of leucocytes, with return to a normal formula.

"ADDISIN"

This substance, present in the normal gastric juice of man, we have found is destroyed by boiling, is dialysable through collodion, and is exhaustible; in addition, it withstands chemical treatment which is known to destroy enzymes. It is therefore probably a hormone, which we have designated "addisin," after the great English clinician Thomas Addison. Through the co-operation of Dr. E. A. Sharp of Parke, Davis and Co., we have been able to study the effect of gastric juice concentrated *in vacuo* from swine, dogs, and cattle, and have been able to demonstrate its presence in all.* It is therefore a constituent of the normal gastric juice of three species, representing omnivora, carnivora, and herbivora. There seems good reason to assume that it is widely distributed in the animal kingdom. The swine juice, obtained from slaughterhouses, has been concentrated to a volume of 3 to 5 per cent., and its activity has been proved by intramuscular injection in patients with pernicious anaemia. But, owing to the inconvenience to the patient resulting from the volume of material required, experiments were undertaken by one of us (J. F.) to concentrate still further, and, if possible, determine the nature of the hormone addisin. Definite progress has been made, we feel, as the following case history will illustrate.

CASE HISTORY

The patient, a male aged 65 years, was admitted to the Medical Service of the Cincinnati General Hospital on May 23rd, 1932. He presented the classical findings of pernicious anaemia. The red cells numbered 1.6 millions; haemoglobin was 50 per cent.; the reticulocytes varied between 0.6 and 1.3 per cent. On June 7th he was given 4 c.cm. of a fraction representing 3 litres of swine juice. (The details of the method of preparing the fraction are to be published later.) On June 8th the reticulocytes rose to 4.4 per cent., on June 11th to 28.8 per cent., and on June 13th to 39.3 per cent. Between June 14th and July 8th daily reticulocyte counts showed fluctuation between 24.5 and 42.9 per cent., after which there was a rapid decline to normal. The maximum reticulocytosis of 42.9 per cent. was reached on June 17th, the tenth day following injection without change in the red cell count. Accompanying the reticulocytosis there was a marked increase in the number of nucleated red cells.

Within a week following the injection there was remarkable subjective improvement. At the end of two weeks increase in the number of red cells and percentage of haemoglobin was first noted (1.8 million red blood cells and haemoglobin 55 per cent.). Thereafter there was a steady rise in both red cells and haemoglobin till September 21st, when examination of the blood showed 4.5 million red cells and haemoglobin 93 per cent. The patient received no further treatment after the original injection.

CONCLUSIONS

The chief points to which we wish to draw attention in the foregoing case report are: (1) the small volume of material injected; (2) the prolonged and sustained reticulocytosis (duration thirty-four days); (3) the maturation of the red cells which eventually took place; and (4) the fact that a single injection produced such a sustained response. Technical difficulties are being encountered in the concentration of swine juice, but in time it is felt that these can be overcome so that material may be available for extensive clinical trial. Our results with human gastric juice have been confirmed by Conner¹⁰ and by Zerfas.¹¹

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* Experiments with bovine juice are as yet not completed, but activity has been reported by Wearn of Cleveland.

The absence of addisin in the gastric juice in pernicious anaemia is the cause, we believe, for the reversion to a megaloblastic marrow in this disease. The lack of a satisfactory test for the presence of addisin in concentrated gastric juice, save its injection into a patient with pernicious anaemia, is a handicap, as it has been in the case of liver extract and ventriculin. Experiments are under way, both biological and chemical, to try to overcome this difficulty. The observations we have made up to the present time indicate the probability that addisin is the physiological hormone which maintains the normal state of the blood in health.

The therapeutic effect of intramuscular injections of addisin in secondary anaemias is under investigation.

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AN AMBULATORY DISTRACTION SPLINT FOR LEG FRACTURES

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The splint illustrated consists of two lateral distending rods, bearing on an upper transfixion pin passed through the tibial tuberosity, and a lower one passed through the tibia and fibula just above the ankle-joint. Each rod has a central segment, the ends of which are turned with right- and left-hand screw threads respectively, which, engaging in corresponding sheaths, can lengthen or shorten the whole rod.

The terminal parts which engage the transfixion pins are connected with the rod by universal joints to rectify any deviation in the axes of the pins. A rectangular cross-bar, with movement in two planes, connects the upper segment of one rod with the lower segment of the other rod, and so corrects the internal rotation of the lower bone fragment, which is produced by the transfixion pins lying in different horizontal planes; the lower pin passes from without inwards and forwards, whereas the upper pin passes directly from side to side. The steel pins, about 3/16 inch in diameter and 7 inches long, are "square-tapered" at one end to facilitate penetration of the bone. Care is taken that the points are not softened by overheating on the lathe, as the cortex of the fibula is very hard and is apt to turn the steel point, while a long taper, about 3/4 inch, is less likely to split the brittle fibula.

TECHNIQUE AND RESULTS

The leg is x -rayed in two planes. The patient is then taken to the theatre and, preferably, given a general anaesthetic: local anaesthesia does not control the jarring at the site of fracture. The lower pin traverses the fibula first, driven through with an ordinary heavy carpenter's hammer. The distraction splints are then threaded over the pins and extension secured by turning the middle

segments with a key. Correction of lateral angulation and final adjustment of the bone fragments is done under the x -ray screen on the following day, after which the patient is made to walk. The internal-rotation deformity of the lower fragment is corrected by clamping on the cross-bar, while antero-posterior angulation is controlled

FIG. 1.—The splint applied.

FIG. 2.—X ray showing position.

by stretching a well-padded bandage between the two splints. Although early full correction of bone displacement is desirable, such manipulations can be repeated as often as is found necessary during the course of the first four or five weeks, no anaesthesia being needed. In the three cases—one Tamil and two Chinese coolies—treated by this method (all closed fractures), union between the fragments occurred suddenly—that is, within the space of two to four days at about the end of the fifth week. The pins are removed and the splint discarded after six weeks (actually forty-three days in the above cases). The method is suitable for any case in which the line of fracture does not encroach upon the terminal two inches of either end of the tibia.

Ulceration of the superficial tissues occurs around the pin-holes, more so above, where it may reach the size of a sixpence, and where a small slough of deep fascia may separate, after which the small cavity so formed fills up with clean granulations while the patient continues to walk about on the pins. It must be admitted that early progressive ulceration with a purulent discharge caused by a dirty-looking pin transfixing the leg rather strains one's confidence in the capacity of the body tissues to survive surgical insults; but provided the

Diagram of apparatus.