treatment by both tartar emetic and emetine, it has not been possible to obtain similar evidence of cure from the large number of patients which have been treated with Fouadin, and the fact that a far larger quantity of this preparation than is commonly advised possesses the antimony content of the required total dose of tartar emetic has been overlooked.

It would be well if some such scientific investigation could be undertaken in the Union and the relative values of Fouadin, Trystibine and Stibilase properly determined. Until we are acquainted with the proper total dose of any drug, it is unreasonable that it should be widely used by practitioners who are not in a position to collect undisputed evidence of cure.

In any case, anyone who undertakes to treat Bilharzial disease should possess a microscope and follow the effect of his injections upon the blood flukes by carefully examining the escaping ova until they disappear once and for all.

PERNICIOUS ANAEMIA AND SUBACUTE COMBINED DEGENERATION OF THE CORD.

J. J. PRAG.

Review of Literature—

In August 1926, Minot and Murphy recorded for the first time convincing evidence of the therapeutic effect of feeding liver to patients with pernicious anaemia. Since then, their results have been adequately confirmed by a long series of observers, so that today the value of liver in this disease is an accepted and established fact. In their epoch-making contribution, Minot and Murphy clearly demonstrated for the first time (1) that the red blood count of patients with pernicious anaemia could be restored to the normal level by the simple procedure of feeding 120 to 250 grams of liver daily, and (2) that, within a few days after the beginning of the treatment, there is a striking increase in the number of reticulocytes or immature red blood cells in the peripheral blood.

Owing to the difficulty of feeding 250 grams of liver daily to patients who were seriously ill, Minot and Cohn (1927) attempted to prepare concentrated extracts from the whole organ and they demonstrated that the administration of a powder weighing 12 gm. (which they called fraction G, and was derived from 400 gm. of liver) was as effective for blood formation as 250 gm. of whole liver. This fraction G was prepared by the elimination of high percentages of non-essential substances in the liver without impairing its potency. By elaborate chemical procedures, this fraction was further purified until material injected intravenously in doses as small as 0.025 gm. daily would produce a maximal regenerative effect on the blood. General use of this product was not practicable because of its high cost, resulting from the loss of large amounts of active principle during fractionation. In this way, Minot and Cohn gave to the world liver extract for the first time.

Stimulated by the introduction of a new and effective method for the remedy of this otherwise fatal condition, many workers initiated investigations which have thrown important new light upon this disease. One of the first to take advantage of this opportunity was Francis W. Peabody, who
appreciated that a unique opportunity was offered to study the bone marrow by biopsy. By this method it was possible to observe the marrow of a patient during a relapse and again after a remission had been induced by feeding liver. He observed that the bone marrow was red and contained an increased number of megaloblasts during a relapse, and became yellow and fatty during periods of remission. He explained the anaemia of the relapse as due to the functional ineffectiveness of the bone marrow, which results from the failure of the megaloblasts to differentiate towards mature erythrocytes, and he then suggested that the results obtained by feeding liver may be due to some factor in liver promoting the development of red blood cells. In other words, evidence was presented that the anaemia was more the result of impaired blood production than of increased destruction.

This work was followed by Castle, who conceived the idea that pernicious anaemia may be a deficiency disease, but argued that it could not be due to a deficiency of liver in the diet, for it is frequently absent from the diet of unaffected persons. He assumed therefore, that there might be some deficiency in digestion, and this is in accord with our knowledge that all patients with pernicious anaemia, with few exceptions, have an achylia gastrica. To test this theory, Castle fed 300 grams of Hamburg steak to normal individuals and removed the gastric contents one hour later. This was incubated and administered daily to patients with pernicious anaemia. In 8 out of the 10 patients so treated, there was an effect entirely comparable to that of liver. These observations were controlled, either by feeding normal gastric contents, or Hamburg steak alone, to patients with the disease and thereby demonstrated that both materials were ineffective when fed separately. It was concluded that these experiments might indicate some deficiency in the gastric juice of patients with pernicious anaemia, which was related to the cause of the disease. On the basis of this work, Sturgis and Isaacs tried the effect of feeding hog’s stomach (dissicated) in the treatment of pernicious anaemia and demonstrated that it was as effective as liver, if not more so, in inducing a remission of the disease.

As regards the nature of the substance present in the gastric juice which causes the formation of this intrinsic factor, or Castle’s principle, as it is sometimes called, it has been found that it is not present in the hydrochloric acid, the pepsin or the rennin of the gastric juice. It was absent from the normal gastric contents of cases with pernicious anaemia in relapse, and it is present in the otherwise achylia gastric contents of a patient without anaemia and of patients with hypochromic anaemia.

Recently, a further stage in the concentration of the active principle in liver was demonstrated by Dakin and West. The method employed in making the product was that the fraction G was treated with alcoholic calcium acetate to remove inactive material and subsequently concentrated by successive precipitation with ammonium sulphate, Reinecke salt and finally ammonium sulphate again. To this product the name of Anahaeamin has been given. It is a clinically potent light buff coloured granular powder. When prepared from Cohn’s fraction G, a yield of 1% is obtained. The material is soluble in water and dilute alcohol, but insoluble in absolute alcohol and ether. Dakin and West found that on hydrolysis it yielded a number of amino-acids, namely, lysine, arginine, glycine, leucine, hydroxyproline and aspartic acid; purine and pyrimidine bases were absent. The substance was slowly decomposed by pepsin and more rapidly by erepsin. Pancreatic juice had no effect upon it. Intramuscular or intravenous injection of 75 to 150 mgms. have produced maximal reticuloocyte responses.

Ungley, Davidson and Wayne (1936) investigated the treatment of pernicious anaemia with the Dakin and West liver fraction (Anahaeamin) and came to the following conclusion:

By the 3rd to the 6th day there was, in most instances, a marked subjective improvement which was less marked or delayed in patients with red blood count above 2 million per cmm. One remarkable result of this experiment was that the soreness of the tongue which occurs in pernicious anaemia is promptly relieved by the end of the first week by Dakin and West’s liver fraction. This is more remarkable in that the chemical nature and mode of preparation is unlikely to contain any of the known vitamins and is interesting in view of the theories of Hutter, Middleton and Steenbock and of Groen, who suggest that the tongue changes in pernicious anaemia are due to deficiency of some portion of the vitamin B complex.
The gastro-intestinal symptoms such as epigastric discomfort, vomiting and diarrhoea usually cleared up in the first ten days with the treatment of AnaHaemin. The use of the Dakin and West's principle thus resulted in production of reticulocyte response, increase of red blood cells and clinical improvement. It is thus highly active for blood regeneration in pernicious anaemia.

It might be asked why, when potent preparations are already available, intensive research is still required into the purification of the active principle. There are at least three reasons why investigations in this direction are necessary:

1. Increased concentration should permit the use of smaller quantities and longer periods between injections.

2. Until the material is obtained in its pure state there is no possibility of its synthesis, a process which might lead to a marked reduction in the cost of treatment.

3. There is the obvious desirability from the scientific point of view of investigating the influence of the pure substance not only upon blood formation, but also upon certain neurological and other phenomena associated with the syndrome of pernicious anaemia.

As soon as the remarkable effect of liver in restoring the red blood cells to normal in patients with pernicious anaemia was discovered, the question immediately arose concerning the relation of treatment to the lesions in the spinal column. This is of great importance because 80% of patients suffering from pernicious anaemia have involvement of the nervous system, although in many instances it is trivial and consists only of a rather mild paraesthesia of the hands and feet. Sometimes there is evidence of a widespread spinal cord lesion, with definite indication of injury to the posterior and lateral tracts, such as is present in the disease known as subacute combined degeneration.

**Introduction**

It has been shown by Suzman (1931) in an investigation of 100 cases of subacute combined degeneration over periods of time varying from 25 to 55 months that distinct and often remarkable improvement can be brought about by intensive liver therapy. The following table is a summary of the effects of liver treatment on the nervous system in 100 cases of subacute combined degeneration of the cord, compared with 61 control cases.

<table>
<thead>
<tr>
<th></th>
<th>No Liver</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>Not improved</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Deaths</td>
<td>-61</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>100</td>
</tr>
</tbody>
</table>

From a study of the literature it is seen that (1) pernicious anaemia may occur without subacute combined degeneration; (2) subacute combined degeneration may occur before pernicious anaemia; (3) pernicious anaemia may occur before subacute combined degeneration; (4) pernicious anaemia may improve while subacute combined degeneration remains stationary; (5) subacute combined degeneration improves before the pernicious anaemia; (6) there may be a relapse into subacute combined degeneration without pernicious anaemia; and (7) a relapse into pernicious anaemia may occur without subacute combined degeneration.

These facts point to the absence of two factors, the one responsible for pernicious anaemia and the other for subacute combined degeneration. By the feeding of brain, Ungley demonstrated an improvement in the subacute combined degeneration without an improvement in the pernicious anaemia; actually the blood condition was aggravated. The question thus arises whether there is more than one factor in the stomach—one responsible for pernicious anaemia and the other for subacute combined degeneration. If, in the gastric juice of a patient with subacute combined degeneration without anaemia there is present the intrinsic factor, then subacute combined degeneration cannot be caused by the absence of the intrinsic factor and, therefore, it may be due to the absence of some other factor.

**Method**

The theory propounded in the above paragraph led to an experiment conducted by the Department of Medicine to find the effect of feeding a patient suffering from pernicious anaemia alone, without any nervous lesion, with beef digested by the gastric juice from a case of subacute combined degeneration without anaemia and to ascertain whether or not the gastric juice from the case of subacute combined degeneration contained the intrinsic factor.

40 ccs. of gastric juice, found to contain hydrochloric acid and pepsin, were daily taken from the patient suffering from subacute combined degeneration. 200 grams of beef
muscle was incubated for 2 hours with 4 grams of pepsin and 75 ccs. of distilled water and enough hydrochloric acid to give a pH of 3.0. The liquefied mixture was then neutralised to pH 7.0 and to it the gastric juice of the patient with subacute combined degeneration was added. This was then submitted to a further incubation of two hours. The resulting product was administered daily to the patient suffering from pernicious anaemia. Reticulocyte counts, red blood counts and haemoglobin percentages were taken twice daily on this patient for a period of 14 days.

**Results**

There was no rise in reticulocytes, red blood cells or haemoglobin percentage. One thus concludes that the gastric juice of the donor (subacute combined degeneration) did not contain Castle's intrinsic factor.

Subsequently it was discovered that the patient suspected of having subacute combined degeneration was in reality suffering from a spinal cord tumor. It is strange, therefore, that no reticulocyte response resulted, for there is reason to believe that the gastric juice of the donor (subacute combined degeneration) was normal.

The probable explanations are (1) Faulty technique in the preparation of the beef-gastric juice digest. (2) Insufficient dosage. The recipient (pernicious anaemia) subsequently responded to liver therapy in the ordinary way, so there is no reason to suppose that there was interference with the absorption of the digest from the stomach of the pernicious anaemia patient.

**Conclusion**

Great caution should be exercised before diagnosing a case of subacute combined degeneration when the blood formation is essentially normal.

**Acknowledgement**

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**BIBLIOGRAPHY:**


