William P. Murphy - Nobel Lecture

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Pernicious Anemia

During the twenty-year period following 1849, in which year Thomas Addison first described the diseased condition, which he designated as "idiopathic" anemia, reports of similar cases were published by such men as Barclay, Wilks, Bristowe, Lebert, Habershon, and others.

Further interest was aroused, both on the Continent and in America, by Biermer's discussion of a group of patients with severe anemia of varying etiology, in a paper published in 1872. As a designation for these cases he suggested "progressive pernicious" anemia, a name which became more generally used than "idiopathic" anemia, suggested by Addison. Biermer also called attention to the frequency of retinal hemorrhages and the occurrence of fever in his cases.

Even as early as 1878, Eichhorst published a 375-page monograph on Progressive Pernicious Anemia, and five years later Laache of Christiania published his monograph on anemia, which consisted of 256 printed pages together with many graphs and plates illustrating the blood changes. He described particularly the presence in the blood of large, deeply coloured corpuscles. Quincke had previously called attention to the variations in shape of the red blood corpuscles - the poikilocytosis.

Even these early papers had presented the clinical picture of pernicious anemia essentially as we see it today. Various theories as to the etiology were discussed but perhaps the one of most interest, when viewed in the light of knowledge available since the era of liver therapy, is that presented in 1880 by Fenwick in his book *Atrophy of the Stomach*. Fenwick wrote: "indeed most of the symptoms are not the immediate result of the atrophy of the stomach, but arise from the deficiency of the blood produced by it" And again: "it will be readily conceded that the anemia that accompanies atrophy of the stomach is the result of the imperfect secretion of the gastric juice consequent upon it".

Since the earliest use of liver in the treatment of pernicious anemia, however, new fields of observation have been made available both in the clinic and in the laboratory. We have been allowed the thrill of watching the patient through a few days of depression following the institution of liver therapy until remission occurs with its often sudden and almost unbelievable sense of well-being simultaneously with the maximum increase of the reticulocytes or new red blood cells. Then we have followed this remission through to completion, until the blood

becomes normal, with a normal red blood cell level - that is 5,000,000 or more cells per cubic millimeter of blood. Perhaps even more dramatic has been the improvement in the disturbances of locomotion resulting from nerve damage. But all of this has been described in our early papers, so that further details need not here be recited.

Observations of the patients at intervals in the office or hospital blood clinic, and attention to the important details of treatment have made it possible for us to regularly maintain our patients in a state of economic efficiency and with reasonably good health. Forty-two of the forty-five patients originally treated and discussed in our first paper of 1926 have been kept under observation. Of this number, thirty-one, or approximately three fourths, are living and well after almost ten years of treatment. Eleven have died from various causes other than pernicious anemia.

The problem which, during the past few years, has particularly interested me, as a practitioner of medicine, has been the practical one of making treatment more bearable for the victim of pernicious anemia, who must necessarily continue treatment indefinitely in order to maintain a satisfactory state of health. For this purpose treatment must be simplified, its efficiency increased and its cost decreased. Definite progress has been made in this direction through the development of a liver extract for parenteral use. At the Peter Bent Brigham Hospital we have, for over three years, used an extract of uniform potency for intramuscular injection which is so concentrated that 3 cubic centimeters is prepared from 100 grams of liver, and represents the potency of fifty times the amount of liver from which it is prepared. Or, in other words, the injection intramuscularly of 3 cubic centimeters prepared from 100 grams of liver is equivalent in its effect to that of 5,000 grams of whole liver when taken perorally.

Because of the concentration of the extract and its uniform and high potency, it is possible to bring about improvement most rapidly and with confidence, to maintain a normal blood level and state of health with infrequent injections, perhaps three cubic centimeters every two to four weeks, and at a minimum of expense to the patient. A rough comparison of dosage and cost of treatment by the various means may be of interest. It is estimated that 5,000 grams of whole liver, 84 vials of liver extract for peroral use (prepared from 8,400 grams of liver) and 3 cubic centimeters or 1 vial of liver extract for intramuscular injection (prepared from 100 grams of liver) will have essentially similar effects. The liver may cost $5.50, the liver extract for peroral use $17.00 and the liver extract for intramuscular use $1.17, a striking difference.

Not only has this liver extract for intramuscular injection proved its value for pernicious anemia;it has also, which is perhaps of even greater importance, displayed its ability to stimulate the production of leucocytes. The fact that the granulocytes may be practically doubled in number within from six to eight hours after a single injection, recommends its use in many of those diseased states accompanied by granulocytopenia, such as pneumonia, influenza, agranulocytosis of Schultz, and even in some instances post-operatively.

Again, we find it effective in enhancing the rate of hemoglobin formation in the hypochromic anemias treated with iron. Perhaps its effects here is in producing the stroma or envelope in which the hemoglobin may be more quickly and normally stored.

So there will continue to be found more and more uses for this highly potent material and, with even greater concentration in the near future, it will further lighten for the patient the burden of continued treatment. During the next few years many important problems in the general field of the blood dyscrasias will also be solved as a direct result of the introduction of liver therapy for pernicious anemia.

Rather than enlarge further upon the details and results of the treatment of pernicious anemia, I shall now present, with your permission, a motion picture which will illustrate many points more clearly than I could discuss them here.

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