TWENTY YEARS OF LIVER THERAPY

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A PERIOD of slightly more than twenty years has elapsed since the introduction of the use of liver for the treatment of the patient with pernicious anemia. It may be of interest and instructive to consider how well the early predictions in regard to the effects of this treatment have been substantiated and to summarize briefly the progress which has been made during this twenty year period.

The intensive and controlled study of the use of liver in the treatment of pernicious anemia which demonstrated its efficacy and assured its general acceptance was begun in the spring of 1925. The results of these studies as carried out on 45 patients were published in August of the following year.[1] Although diets, some including liver, had been previously tried, it remained for this study to establish liver therapy on a quantitative basis as indicated by the following quotation from this first paper: "If liver and similar food is of value, every means must be taken . . . to get patients to eat daily as much as possible, preferably 200 Gm. or more. Failure could be attributed to taking too little of such food."

At the end of another year and after observation of the effect of therapy in 105 patients, it was possible to predict with greater confidence: "Successful therapy of pernicious anemia depends on the treatment being properly carried out for a correctly diagnosed case. With these conditions established, we believe that essentially all patients with pernicious anemia can be benefited, and usually markedly and promptly."[2]

Even though the method of treatment has been greatly changed and simplified since the two statements quoted above were written, the predicted beneficial effect of liver (or its extracts) has been confirmed and the advice contained in them relative to treatment has been found to be as important now with the simplified methods of treatment as it was when whole liver was used. Failure to obtain the best results possible are all too frequently the result of the use of insufficient amounts of anti-pernicious anemia substances or to their use only after irreparable damage has been done—too little, too late.

The stages in the progress of treatment from whole liver to an extract of liver for peroral and finally parenteral administration during this twenty year period are so well known that they need not be here repeated. Although several patients have been well maintained for years entirely with the use of whole liver or extracts for peroral use, the treatment of choice for the great majority of patients is with liver extracts for parenteral administration. These extracts are now fairly well standardized and their potency controlled so that the physician has access to highly potent and refined ones which produce a maximal response with a minimum of inconvenience and discomfort to the patient.

The most rapid and in most instances the most satisfactory response to treatment during relapse has been found to follow the injection of large doses of extract

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supplying a high content of anti-pernicious anemia substances as elsewhere outlined.[3, 4] Thereafter maintenance treatment must be individualized, determined on the basis of its effect on the blood levels and on the neural disturbances if these are present. The amount of liver extract necessary to maintain the best possible state of health varies greatly from one patient to another. The need for adequate therapy cannot be too greatly stressed. In his Nobel lecture made after nearly ten years of experience with liver therapy, Minot[5] made the following statement: "The grave error in treatment is to prescribe too little liver extract or potent substitute. Where there is doubt, more rather than less should be given. It is essential that the individual receive into his body indefinitely and with regularity enough potent material for his given case." Little need be added to this statement in order to condemn an effort to standardize maintenance therapy. It has been demonstrated that the amount of liver extract needed to maintain a satisfactory state of health as determined from observation of a fairly large group of patients[6] is that which supplies 15 units about every three and one-half weeks. The actual intervals varied, however, in this group of patients from one to six weeks. It is obvious from this that one cannot produce the best results if the same dose of extract is given to all patients at the same interval.

The more highly concentrated and refined extracts insure the most satisfactory response with the least inconvenience and expense because of the need for less frequent injections. There is no valid argument for the use of so-called "crude" extracts in the treatment of pernicious anemia even though disturbances resulting from sclerosis of the central nervous system are present. There is much evidence available to confirm the beneficial effect of the concentrated extracts on all of the disturbances characteristic of pernicious anemia including those due to neural damage. No evidence has been presented to show that "crude" extracts are more beneficial in any respect. Furthermore, their use necessitates greater frequency of injection and they are often distinctly more irritating with greater discomfort for the patient. The "crude" extracts contain a greater amount of solids than do the refined which are probably inert; the content of vitamins and other substances which might add to their value has not been found to be greater and some of those used as "crude" extracts are merely dilutions of the refined.

The superiority of parenteral extracts over other forms of therapy is in part due to the careful follow-up control of the patient, made possible by his return for injections at regular intervals. The pernicious anemia patient is subject to the same weaknesses of the flesh as are we all. As his condition improves with peroral therapy there is a great temptation to neglect treatment and the check-up visit to his physician; the result in too many instances is hematologic and neurologic relapse. The relatively frequent visits for injection have improved the physician-patient relationship so essential to the most satisfactory control. The importance of this is emphasized by Minot,[5] also in his Nobel lecture when he cautions: "The physician, however, must do more for his patient than prescribe a proper amount of liver, stomach, or the like; he should attend to all aspects of the case and not neglect attention to the individual's problems of thought and action."

Were it possible for all patients with pernicious anemia to receive treatment

sufficiently early in the course of their disease and in accordance with the principles demonstrated to be most effective, the cause of death would rarely be recorded as that of pernicious anemia. The causes of death have changed somewhat in respect to frequency of occurrence as the average age of the patient has increased in consequence of the liver treatment. Hypertensive cardiovascular disease and malignancy account for a rather high percentage of deaths as might be expected in a control group of comparable age.

The incidence of malignant disease in patients with pernicious anemia is not known. In the author's[7] series of 578 cases followed during the first twelve years of liver therapy, 29 instances of malignancy involving some part of the body were observed, an incidence of 5 per cent. During that same period malignancy of the stomach caused death in only 4 cases. Two more involving the esophagus were noted. During the twenty year period 50 instances of malignant disease have been observed. Twenty of these involved the stomach and in all but 1, still living, was the cause of death. Whether or not this indicates a higher incidence of gastric carcinoma than occurs in a group of patients of comparable age without pernicious anemia has not been determined. It is quite likely that this is not the case.

The recent synthesis of folic acid[8] and its demonstrated beneficial effect on the blood levels in pernicious anemia[9] has stimulated renewed interest in the therapy of the disease. Although this new development may be an important step toward solving several questions concerned with the mode of action of liver or its extracts and although the preliminary reports of its use in the treatment of pernicious anemia are encouraging, it must be remembered that its use is still in the experimental stage. Many of its possible effects are yet to be determined, as for example, the amount necessary to initiate a satisfactory remission during relapse, the amount needed to maintain over a period of years normal blood levels and whether or not that is possible in all patients. Its possible toxic effects are not known and its value in preventing or bringing about improvement of the neural disturbances remains to be seen. Evidence has already appeared to indicate that it does not control these and that it is not a complete substitute for liver or its extracts in the management of pernicious anemia. It is to be hoped that the medical profession will not be stampeded into the use of folic acid as a substitute for liver substances by glowing reports of its value made, particularly in the lay press, by irresponsible writers who do not have at heart the best interests of the patient with pernicious anemia.

Much more study is needed before folic acid can be accepted as a safe and effective substitute for liver and liver extracts. Efforts to side-step a definite decision in this regard by combining folic acid with liver extract merely increase the cost of treatment without definitely adding to its effectiveness. One may confidently say in the light of our present knowledge that liver will do everything that folic acid will do and more for the patient with pernicious anemia.

Finally it may be stated with confidence that results of the use of liver or its extracts in the treatment of pernicious anemia during the twenty years justify the early optimism in regard to its value.

Some of the patients included among the first group of 45 treated and more of

those who were included in the group of 105 reported the following year are alive and well insofar as their pernicious anemia is concerned. Except for the complications which have appeared as the result of increasing age and not related to the anemic state, many more of these original groups would now be living. Few of those who partook of sufficient liver to bring about a satisfactory remission have died from pernicious anemia either as the direct or indirect cause.

Not only have these persons been kept alive but they have been maintained in such good physical condition that it has been possible for them to carry on their normal occupations as housewives, merchants, teachers, lawyers, physicians, etc. The distressing, and often incapacitating, disturbances resulting from damage to the central nervous system have been controlled or completely avoided.

Before the introduction of the liver treatment, the number of deaths from pernicious anemia in the United States alone had risen to about 10,000 per year. It may, therefore, be estimated that 200,000 persons with this disease in this country alone have had their life span increased by at least ten years and that there are 100,000 persons now living with this disease who would not be except for their use of liver or its extracts.

In closing this brief resume of the experiences in the treatment of pernicious anemia with liver and its extracts during this first twenty year period one cannot better express the outlook for the future than did Minot[5] in the closing words of his Nobel address: "It seems to me that one may expect in the future more information to be obtained which, directly or indirectly, will follow as the result of these observations. Thus, upon the foundations laid by previous investigators, do medical art and science build a structure which will in its turn be the foundation of future knowledge."

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