Conquest of pernicious anemia

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THE CONQUEST OF PERNICIOUS ANEMIA

A THESIS

PRESENTED TO THE FACULTY OF
THE COLLEGE OF MEDICINE OF
THE UNIVERSITY OF NEBRASKA
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF MEDICINE

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INTRODUCTION

The year following the close of the decade between 1920 and 1930 would seem a particularly opportune time for a glance in retrospect over the epochal contributions which have so enriched medical science, and which have made this period one of outstanding importance.

In no field of achievement can be found two feats more brilliant or of greater benefit to humanity than the conquest of those dread scourges—Diabetes Mellitus, and Pernicious Anemia. Long treated only by empirical and merely palliative methods, these two diseases had come to be held by both laity and the profession as synonymous with despair and helplessness, as each took its annual toll of thousands while loved ones and medical men were forced to watch, powerless. The announcements of Banting and Best, and of Whipple, Murphy, and Minot thus came as pure light in the midst of what had been comparative darkness, and granted both reprieve to many thousands of sufferers and hope to generations to come. What chapter in any history can rival the discoveries of these few men—either for colorful triumph or for bearing on the lives of those unborn?

The writer has chosen a phase of the conquest of Pernicious Anemia as the subject of this paper, and he feels that this particular phase relates more vividly and succinct
-ly than any other the change in the various aspects of this disease, as viewed during the past decade. The treatment, with which this paper deals, by its revolutionary change in 1926 and the years following, epitomises well the resulting change in our ideas as to prognosis and possible etiological factors to be considered in any discussion of the subject.

Hence, as the writer seeks, both by citing history, experiment, and actual hospital cases, to delineate such changes as have been brought about, it is with a feeling of futility, since words, diagrams, and records are but feeble instruments with which to paint the picture of such long-sought and painstaking achievement. It is only bare justice to say that Medicine owes a great debt of gratitude both to those who brought research on this subject to its recent culmination, and to those unknown ones who, through bygone forgotten years, sought vainly to solve the riddle and in so doing left stones on which their followers might step to reach the higher.
HISTORY

Since this paper is essentially a history of the progress of the treatment of Pernicious Anemia, with a studied endeavor to exclude any other phases of the subject than the one here treated, such as etiology, pathology, symptomatology, or prognosis, any historical mention of treatment would be included under the main discussion of this subject. Hence the writer believes it best to consider the historical data of this paper as bearing on the history of the disease, Pernicious Anemia, as an entity, from the first time at which it came within the ken of the medical world; in so doing it is his purpose to furnish a contemporary historical background for the later consideration of the changes in trend of its treatment. To attempt a resume of the several thousand papers of historical interest on the subject would be out of the scope of this one paper, but, by citing those contributions of outstanding importance, the milestones in the advance of our knowledge may be pointed out.

In 1881 Ehrlich made his discovery of the value of aniline dyes in the staining of blood films, and hematology as a distinct subject may be said to date from this time. Without the benefit of the blood picture it is no wonder that the early accounts of the anemias were confusing and at variance. In the literature which has accumulated on the subject, however, certain contributions stand out above the rest, and the development of
our conception of Pernicious Anemia will be found to run in close sequence with them.

The first paper to hint at the existence of such an entity as an "idiopathic", primary type of anemia, came in 1824 from a Scotch physician, Dr. J. S. Combe. This contained an excellent description of a case of anemia which had come under his care, and would still fit nicely into a modern text-book description. He stated "that if any train of symptoms may be allowed to constitute anaemia a generic disease, the following may be considered an example of it in its most idiopathic form", and suggested that "it is probably owing to some disorder of the digestive and assimilative organs that its characteristic symptoms have their origin".

From this time until 1855, several accounts appeared in the literature of very severe anemias, which, states Gulland and Davidson, were in all probability cases of pernicious type. Barclay, in 1851, was the first to note the presence of glossitis in a patient dying from a severe anemia.

Dr. Thomas Addison, of Guy's Hospital, in 1855, gave an excellent description of a case of pernicious anemia as a preface to his paper on "constitutional and local effects of disease of the supra-renal capsules", the type of severe anemia yet bearing his name. Finding no cause for such anemia, he termed it "idiopathic", but unfortunately his work made little impression on the medical profession in his own country or on the continent. Later however, in 1878, his claim to priority to later
workers was acknowledged by Eichhorst, when he wrote "that this disease was first described in England both in the form of single cases and as a definite clinical disease."

In 1867, and again in 1872, Professor Biermer, of Zurich published papers describing a very severe anemia, which he gave the name of Progressive Pernicious Anemia. His descriptions of the clinical and post-mortem findings were practically the same as those of Addison, but attracted much more widespread recognition than those of the latter. However, while Addison held that the distinguishing feature of the disease was its idiopathic nature, Biermer stated that the absence of clear etiological factors was the exception, and, in short, included under the title of Progressive Pernicious Anemia a group of conditions of which one was the idiopathic variety described by the earlier author. "Hence", to quote Davidson, who quotes Cornell, "it became an international medical pastime to exclude cases from published reports on the basis of purity of type, each of the critics employing his own standard of judgement." From this time on, Pernicious Anemia was known both as Addison's Anemia and as Morbus Biermer.

During the next fifteen years other workers tended to uphold Biermer's view of the disease, among whom were Quincke, Immerman, and Eichhorst. An Englishman, Pye-Smith, was the only one of note to uphold the concept of Addison.

During the two years 1875-6 two independent workers, William Pepper, and J. Cohnheim, both added to the general fund of knowledge of the disease by first calling attention to the
megaloblastic appearance of the marrow of patients dying of this strange anemia. Particular stress was laid by Cohnheim on the disparity between the anemic condition and the increase in the red marrow of such patients.

In 1887, another fragment was added to the clinical picture of the disease by Lichtheim, whose article first called attention to the degenerative changes taking place in the columns of Goll and Burdach during the course of the anemia. At almost the same time, in 1886, Henry and Osler published their paper which dealt with the atrophy of the stomach with the clinical features of Progressive Pernicious Anemia.

From 1890 to 1909 one worker who added much to our conception of this type of anemia as a distinct clinical entity, involving both gastro-intestinal and nervous systems as well as the hemopoietic system, was William Hunter. We are told that he strongly criticized Biermer's attempt to group several anemias, etiologically very different, under one heading, and that he maintained Addison's anemia a single entity. Among his many contributions were his observations on glossitis and gastro-intestinal sepsis as related to oral sepsis and a possible but mysterious factor lying within the gut tube as a cause of the disease. However, he failed to include as a factor the very significant changes in the blood and blood-forming organs, on both of which his contemporary, Ehrlich, laid great stress.

While, as stated previously, Pepper and Cohnheim were the first workers to call attention to the megaloblastic type
of bone-marrow in victims of this condition, it remained for
Ehrlich and Lazarus, in 1898, to go a step farther and postulate
that the essential pathological and pathognomonic features of
the disease were "degenerative" megaloblastic bone-marrow types
of change. It is curious that of two men, working at the same
period, one, Hunter, should stress the factors of infection and
hemolysis, the other, Ehrlich, the factor of degenerative change
of the hemopoietic apparatus.

Muir, in 1894, after investigation of bone-marrow
from patients dying of the disease, concluded that the changes
he found there could be interpreted as compensatory to destruc­
tion of blood cells in the portal circulation. Quincke, in
1877, had called attention to pigmentary changes in the liver,
but had attached little importance to his finding.

Further work by many investigators brought the
extreme views of Hunter and Ehrlich closer together, and it
was admitted that the condition of the gastro-intestinal tract
and the evidences of hemolysis were as much a part of the clin­
ical syndrome as the bone-marrow changes. The question of the
primary hemolytic site still remained unsettled, however, Hunter
citing Muir's views as evidence of the secondary importance of
the blood formation in relation to portal hemolysis, and stating
that these changes were most marked when siderosis was present
in the highest degree. Ehrlich and his proponents, however, would
see only the converse, namely that siderosis was most prominent
when the megaloblastic degeneration was at its greatest.
The past ten years has brought further light to bear on the nature of this disease. Achlorhydria has come to be held as one of the cardinal signs of the condition. Pigment metabolism is better understood, recent investigators such as Roux having added to the earlier knowledge given us by Minkowski and Naunyn, and the importance played by extra-hepatic structures, in short, the vast "reticulo-endothelial" system as first proposed by Aschoff-Landau, in the metabolism and disposition of the pigments of the blood has come to the fore. Of especial interest is the view recently propounded by Piney, in regard to hereditary and congenital factors having to do with the disease we are considering. His studies of the bone-marrow in Pernicious Anemia have led him to believe that there is in the victims of this disease a developmental defect by which there is inadequate development of adult (normoblastic) bone marrow, and a compensatory hypertrophy of fetal (megaloblastic) bone-marrow. Through the action of some exciting cause, which may be the broad tape-worm, syphilis, pregnancy, or that which causes the "idiopathic" anemia, with this developmental defect as a weak link in the chain, Piney believes that the signs and the symptoms of Pernicious Anemia are produced.

Finally, the recent revolutionary change in treatment, that of successful therapy by liver, dessicated stomach, and predigested muscle-meats, has hinted to us that our conception of this disease entity should include as etiological factors those of both constitutional element and deficiency,
and we are impressed by the course of the development of our present-day conception of Pernicious Anemia as a clinical entity as we have reviewed the various contributions and the many controversies by which this present-day concept has been attained. Undoubtedly, as severe a menace as it has been since we have recognised the disease as a distinct entity, it had for years beyond number been an obscure cause of death to mankind, and the separation of Pernicious Anemia as a disease for which there is now a rational treatment furnishes bright contrast to what hopeless a picture must have been seen before the condition was even recognised as at present.
DISCUSSION OF TREATMENT

The discussion of the various agents used in the treatment of Pernicious Anemia properly begins with the consideration of the period included between the recognition of such a disease entity and the present time. Many of the older agents of therapy had long been known and used prior to the segregation of this particular type of anemia from the other blood dyscrasias, and are to be mentioned here only in the light of their application to this condition.

Perhaps the two oldest therapeutic agents known in the treatment of those conditions characterized by the clinical manifestations of anemia are blood and iron. The former has been used in therapeutics by uncivilized peoples since time unknown, in the form of fresh blood, dried blood, or dried blood mixed with various dubious ingredients and aided by divers incantations. The latter has been used in therapeutics since the earliest known history of pharmacy, becoming more prominent during the astrological period of that science, when it was inseperably connected with the planet Mars as it appeared in the patient's horoscope. This period reached its height in the fifteenth and sixteenth centuries. The lines of Garth (1706) reveal the esteem in which it was held at that date in the treatment of "the green sickness" (Chlorosis).

"Till the Green Sickness and Love's force betrayed
To Death's remorseless arms the unhappy maid.

Oh, that instead of trash, she'd taken steel!"
Mandel, a French physician of 1804, gave loud acclaim to the virtues of "les boules d'acier de Nancy"—pellets of Iron and Potassium tartrate, recommending them as a sovereign remedy for post-haemorrhagic anemia, chlorosis, and anemia from other causes.

A search of medical literature immediately following Combe's first description of a case of Pernicious Anemia in the year 1824 fails to reveal any suggestions as to its treatment. In Guy's Hospital Reports of 1826, however, Ashwell made certain observations on the treatment of Chlorosis, many cases so diagnosed quite possibly being a pernicious type. His account will bear repetition ---- "I first commence treatment by special attention to the digestive organs and alimentary canal, for I regard the disorders of these as a cause, second only to the peculiarity of constitution already mentioned ******** the deteriorated quality of the blood and its defective quantity may both owe their origin to impaired digestion and nutrition. At first, then, a due evacuation of the bowels must be daily secured; and much will depend on the kind of medicine by which this is effected. If Mercury and drastic purgatives be frequently and largely employed, irritation of the intestines will ensue ******** the best aperients are aloes, rhubarb, sulphate of soda and manna, and, if an alterative be necessary, Hydrargyri cum creta. An injection of warm water into the rectum two or three times a week will work wonderfully as a stimulant to intestinal movement." Among the purgatives which he recommends are the following ---

"Second," says Ashwell, "I recommend warm clothing, regular exercise; nutritious animal diet and a mild malt liquor will be productive of benefit. The improvement of the digestive organs indicated by the return of appetite and the healthier condition of the bowels is evinced by their natural daily evacuation. At this crisis, some of the preparations of Iron may be exhibited, and the sulphate is probably the most efficacious, and possesses more specific qualities than any of the rest. If the order of procedure, now pointed out, be reversed --- If the iron be used before the bowels have been freely evacuated and their functional action improved, or while the tongue is loaded and foul, aggravation of the symptoms will be produced; while if there be only the peculiar debility and pallor then the iron may be most beneficially used. Occasionally the effect of the iron is almost magical, especially where it does not confine the bowels or induce febrile heat. The following forms may be prescribed:


Quinine, Sarsaparilla, Gentian, and Zinc are all remedies also of acknowledged power". Thus, from the type of treatment set forth in this paper, almost a century ago, we may see what were then the prevailing ideas as to the treatment of anemia, a conglomerate term, with little distinction as yet made between its various types.
From this time until 1877, despite the early controversies in regard to the entity of Pernicious Anemia, little or no advance in its treatment appears. At this time Dr. Byrom Bramwell, an English physician, announced the cure of a case of Pernicious Anemia by the use of Arsenic. It is debatable as to whether or not this was a true case of this disease, as the study of the dye-stained bloodfilm did not begin until the discoveries of Ehrlich, several years later. However, due to the discussions of Addison and Biermer and their respective adherents, such an entity as a distinct Pernicious Anemia was recognized, advance in treatment to the contrary.

The year 1880 brought one advance in therapy in the form of the first blood transfusion performed on a case of Pernicious Anemia, by Starr, an American physician ———- a method of treatment which was to remain as one of the sheet-anchors until the advent of modern therapy. However, in the same year, the prevailing methods of treatment were again reflected in a paper by Taylor, an Englishman. A short list of medication used by him is of interest, and indicates the trend to alteratives and symptomatic measures ——-

Try Tr. Ferri Perchlor. m xv., Inf. Quassiae ½ tid.
Try Ale, 01 daily.
Try O1. Phosphorati mi., Aq. menth. pip. ½, Mucilage ½ tid.
Quinine, digitalis, and Aromatic Spirits of Ammonia were also used in various cases by this writer.

Two years later, Pye-Smith, a pupil of Addison, published a report of a case treated by him, in which the medication leaned on the effects of Arsenic and other alteratives for its effect. A list of agents used in this case is of interest, as it
seems to be a good example of the medical armamentarium against
Pernicious Anemia at this time, excluding the newly introduced
agent of blood transfusion.
R. Phosphate perles tid.
R. Liq. Arsenicalis m v, Tr. Chlorof. m xv., Aq. ad ʒi. tds.
   pip. āā ʒiv. Ter die sum.
R. Ol. Morrhuæ, ʒii tds.

This list of medicaments, making use of Arsenic, Iron, Phosphorus, and Ol. Morrhuæ in truth represent the half of therapeutics
of Pernicious anemia almost to the present time, but by their alter-
erative nature betray the dearth of any type of treatment for a
recognisedly specific disease.

While by the year 1890 a great deal had been written pro
and con as to the nature, etiology, and prognosis of this disease, I
have found no instance in which the writers have attempted to de-
part from time-honored means of treatment and work out a rational
method, coupling etiology and treatment in their reasoning, until
William Hunter, who first published a paper on Pernicious Anemia at
this time. Up until the present time no worker has given more imp-
-ventus to the study of this subject than he, and his papers in the
British Medical Journal are worthy examples of careful thought and
painsstaking effort. The theory of a gastro-intestinal toxin as a
factor in the production of Pernicious Anemia, propounded by him,
has greatly influenced thought on the subject to the present day,
and has, so far as I know, never been disproven. Also praiseworthy
was his stand with Addison, against the German school, namely that
Pernicious Anemia should stand as a pathological and clinical entity in itself, and not be classified among other types of so-called Progressive Pernicious Anemia. His summary of treatment, while rather long to be quoted verbatim, shows such sound reason and so reflects the change from empiric to rational thought that I venture to quote it in full in this paper. "The Object of my investigations into this disease has been by elucidating its true nature to establish a basis for its rational treatment. There are, I believe, two indications—first, to remove the cause, with the attendant gastro-intestinal conditions favoring its operation. This indication of treatment can only be successfully fulfilled when the local conditions favoring its operation can also be removed. Cases belonging to this group are those where recovery has rapidly followed the removal of worms—Bothriocephalus latus and Anchylostoma duodenale—from the gastro-intestinal tract. The most important point, therefore, to be attended to in diagnosis, after the true (hemolytic) nature of the anemia has been recognised, is to determine what the favoring condition is. In the hope that it may be an unhealthy condition of the stomach or intestinal mucous membrane, induced by the presence of intestinal worms, free movement of the bowels should always be encouraged in the earliest stages of the disease. Where it is recognised to be of a more permanent character—for example, Gastritis, Atrophy of mucous membrane of stomach—the problem of treatment becomes more difficult. It is in such cases that the advisability of washing out the stomach will have to be considered. Such a treatment was first suggested by Sandoz on the view that certain of the symptoms
were those of indigestion, and that the products formed as the result of indigestion might in this way be removed. I have shown that these products are of an entirely different character from those had in view by Sandoz, and further, that they are formed not so much, if indeed at all, in the contents as in the wall of the stomach itself. How far such a plan of treatment will prove successful under such circumstances may be open to doubt. It is one, however, which I conceive might be adopted with advantage in the earlier stages of the disease, at least. ******** Whether neither the cause nor the favoring condition can be attacked directly by methods such as the foregoing, it is still possible to effect the object indirectly. The beneficial action of Arsenic in cases of Pernicious Anemia, first pointed out by Dr. Byrom Bramwell, has now come to be generally recognised. In some cases (and the foregoing is one of these) it altogether fails. Its mode of action has hitherto been usually conceived to be in accordance with the views prevalent as to the nature of the anemia, by stimulating blood formation. I conceive that its action in such cases may be more simply explained as an entirely local one on the mucous membrane of the stomach or intestine, but especially of the latter. ******** Any beneficial action Phosphorus may have in certain cases is probably to be similarly ascribed to its local action.

The presence of special micro-organisms as an essential factor in such cases naturally suggests the use of drugs having antiseptic properties. The one I have tried, and the one I believe the best suited for internal use, is beta-naphthol. It possesses in a special degree the two properties essential for an intestinal
antiseptic, namely, great disinfecting power, with, at the same time, great insolubility in water; its antiseptic power is three times that of iodoform. I used it in the foregoing case during the latter few weeks of the patient's illness, too late, however, to derive any benefit from its action. It can be given in doses of Gr. v., tid, suspended in mucilage.

The second indication is to combat the symptoms. The most important of these is the excessive destruction of blood induced by the absorption of the poisons. It is the continual drain on the blood thus brought about that causes the intense anemia and the excessive weakness. The best way of combating this--apart from the removal of the cause----I conceive to be, by regulation of the diet, with a view to diminish blood destruction as far as possible. The most important factor regulating the amount of blood destruction in health I find to be in the nature of the diet, a nitrogenous diet causing a much greater destruction than a farinaceous or fatty one. The blood destruction which occurs in this disease so greatly exceeds, however, that of health, and depends upon the operation of such different factors---the formation and absorption of specific poisons of the nature of Ptomenes---that the difference between a nitrogenous and a non-nitrogenous diet may be of comparatively little moment. Nevertheless, the results obtained in the present case suggest that such is not the case. The patient was placed on a more farinaceous diet on March 10th, his previous diet having been made up of beef-tea, extracts of meat, etc. The effect of this treatment was at once noticeable, and was evidenced at once by an entire disappearance of blood pigment granules from the urine, and
by the subsequent improvement in the patient's general condition. After his attack on April 20th, I placed him on a purely milk diet. The disease was, however, too far advanced to permit of successful treatment. I deemed it desirable, in the results obtained after a change of the diet in the present case, to obtain some further data as to the effect of a more exclusively farinaceous diet on the change occurring within the intestine. The method adopted was to determine the relative excretion of free and aromatic sulphates in the urine on (1) a mixed diet, and (2) on a more exclusively farinaceous one. While on a mixed diet the ratio of free to aromatic sulphates (conjugated with phenol, indol, skatol, and cresol) was on the average as 9 to 1, the effect of a more farinaceous diet was to reduce the excretion of aromatic sulphates (representing the amount of putrefactive loss occurring in the food within the intestinal canal) by more than one-half, with an average ratio of 15 to 1. The result may be expressed in this way—that with an almost equal quantity of food of both kinds, the amount of loss due to putrefactive changes within the intestinal tract diminished by more than one-half by the use of a more farinaceous diet; at the same time there was an increase in body weight. It is on these grounds that I believe good results may be expected from a more exclusively farinaceous diet in cases of Pernicious Anemia.

Thus, in this carefully thought-out summary of treatment, in which Hunter endeavored to swing the tide from the empiric to the rational, two new angles of attack are added to the therapy of this disease——Intestinal antisepsis, and Dietary regime. While the
idea of disinfecting the intestinal tract has since been proven fallacious, and the farinaceous dietary proposed by Hunter has been placed at variance with the modern dietetic regime, this one contribution represents a well-planned line of treatment in the light of Hunter's conclusions, and stimulated thought along the line of the importance of foods in the treatment and possible cure of this disease. It is, however, regrettable that Hunter, in his zeal to prove that the disease was primarily due to a hemolytic factor, neglected to consider seriously the significance of the stained blood-film and the characteristic bone-marrow changes so emphasized by his contemporary and critic, Paul Ehrlich.

Regardless of the amount of data published by workers of the German school, during the period of the Hunter-Ehrlich debate, it is significant that we do not find in the literature any new advances of any importance which come from the Teuton. However, the careful study and speculations advanced by this group, having to do with the marked changes in the hemopoietic organs in this disease, emphasized another very important part of the whole picture, and further stimulated thought down to the immediate present.

Hale White, connected with Guy's Hospital, was the next to publish a summary of results of treatment of a number of cases, all diagnosed as Pernicious Anemia. Quoting him in brief--- "We thus learn that although several patients have been known to recover from their first, or even their second attack, nevertheless even then almost invariably they soon relapse and die, and that generally within a year. Most of the cases that have been benefitted have taken Arsenic."
The next advance in treatment was suggested by Fraser, a physician in Edinburgh, who instituted the feeding of marrow to patients. His first case was cited briefly as follows--- "In 1893 this measure was first tried. Ox and calf bone-marrow, not cooked, were given by mouth to a patient who had failed to respond to Ferrous Chloride and Liquor Arsenicalis daily. At the beginning of the marrow feeding the red cell count was 843,000, and the hemoglobin percentage 18. After three weeks with Arsenic, Iron, and the Marrow, the red cell count had risen to 1,800,000, and the hemoglobin percentage to 35. Arsenic, Salol, and Marrow were then given over a period of 26 days, at the end of which time the red cell count came to 2,470,000, and the percentage of hemoglobin to 55. For a further period of 32 days the patient received Ox and calf bone-marrow with Salol, gr. xxx daily. At the end of this time the red cell count was 4,100,000, and the hemoglobin percentage 75."

While later critics have questioned these results on the ground that the marrow was not given alone to determine its effect, and that this was possibly not a pure case of Pernicious Anemia, it is significant that in this regime of treatment we see combined the results of both Hunter's and Ehrlich's views, in the use of an intestinal antiseptic and of specific dietary measures, and in the recognition of a possible marrow deficiency or abnormality.

Five years later, in 1898, Coupland, in Allbutt's System of Medicine, summarizes the then accredited agents of therapy in dealing with Pernicious Anemia. These were --- Rest; Diet of a predominantly farinaceous type, to which might be added peptonized
foods, pounded raw meat, and bone marrow; Iron, best given in the form of the perchloride; Arsenic, the sheet-anchor of treatment, given as Fowler's solution or as Liquor arsenici hydrochloricus; Intestinal antiseptics, such as Salol, Beta-naphthol, or Bismuth Salicylate; Transfusion; and Gastric Lavage. In conclusion, he states — "Pernicious Anemia, then, tends ordinarily to run a downward course, often uninfluenced by any treatment used; frequently, when marked improvement has followed use of certain remedies, a relapse has occurred in which the same means are no longer successful." This one provision, coming at the end of a long list of therapeutic agents, serves well to reflect the efficiency of all treatment known to the best medical men of the time, and to show the well-nigh hopeless attitude adopted in regard to the disease both by the laity and the profession.

Until 1913 no new ideas of treatment of any importance were advanced, and at this time both Bramwell and Boggs began the use of Salvarsan on cases coming under their attention. Bramwell treated 11 cases in this manner, 4 of which seemed cured, 2 showed marked improvement, 1 slight, 2 giving no indication of improvement, and 2 succumbing. Boggs likewise treated 11 cases, 9 of whom were reported as improved, 2 succumbing.

Hobart Hare, summing up the measures of therapy in 1918, comments on the addition of dilute Hydrochloric acid to the list, and concludes as follows — "In Pernicious Anemia, splenectomy and repeated transfusions are to be considered, and very pronounced, but unfortunately only temporary good results follow the free use of Arsenic by mouth or its hypodermic employment in the
form of Sodium cacodylate. Diet is an important part of the
treatment of anemia. The food should be good, well-flavored, and
varied, as well as easy of digestion. It should contain as far as
possible the remedies needed by the system, such as bone salts and
iron, and its ingestion may be accompanied by some red wine, such
as port." Surely no significant advance of thought here!

Willson and Evans, analysing the clinical histories
of 114 cases of Pernicious Anemia treated in London Hospital from
1909 to 1919, found that, dating from the time of admission, within
3 months 31.2% of these patients were dead, within 6 months, 43.9%,
and within 9 months, 52.6%. At the time this paper was published,
in 1928, only 1 of the original 114 was living. Surely a pitiful
result for all of the years of research and controversy as to
the etiology, nature, and treatment of this disease!

Sir Rendle Short, in his "Index of Prognosis and End
Results of Treatment", published in 1922, takes inventory of all
the measures previously cited, and makes the following significant
statements --- "As regards medicine, no drug can yet be said to
compete seriously with Arsenic, and an important element in prog-
nosis is the way the patient responds to it. I do not
believe Salvarsan or Neo-Salvarsan to be of value save for such
febrile reaction produced by it. Iron does harm rather than
good in most cases of Pernicious Anemia, but is sometimes good in
the course of recovery, when the color index is low. Any
benefit derived from the administration of Anti-Streptococcus
serum from the serum reaction, not from an anti-streptococcus
element. Blood transfusion is a measure usually reserved
for desperate cases. Practically all patients are improved for a longer or shorter time; in several cases a remission followed, though the subsequent history of the disease was not influenced. Splenectomy has often been performed as a treatment for Pernicious Anemia; but, while the initial risk is great, the subsequent history of the cases which have been followed up is not such as to encourage us to adopt the procedure. One of the remarkable features of the disease is the occurrence of remissions. They sometimes begin quite abruptly, even though severe symptoms are present, and their occurrence is often attributed to the exhibition of medicines which had no part in bringing about the improvement. Not only is the chance of a remission greater after a first than after a subsequent attack, but after a first one there is a much greater likelihood that, if a remission occurs, it will be more complete and more prolonged than after a second or subsequent relapse. These almost nihilistic statements serve well to indicate the skepticism of this writer as he surveys the woefully inadequate means of treatment at his command with which to combat this baffling malady, and illustrates the general feeling in the medical world at this time.

Medicine now stood on the threshold of the period of discovery which was to change the whole aspect of treatment of Pernicious Anemia. During the same year in which Sir Rendle Short wrote so despairingly of any valuable treatment, an American, Fitch, had the secret within his grasp, but, failing to comprehend the significance of his idea, did not get it across to the prof-
ession at large. In his work on Dieto-therapy, he recommends that bone-marrow, liver, and spleen be included in the dietary of the sufferer from Pernicious Anemia, but justifies his statement on the ground that these foodstuffs are rich in nucleoalbumins containing iron. He further proves that he does not appreciate the significance of his statement by remarking--- "the life of the patient may be prolonged and a reasonable degree of comfort secured through careful supervision of digestion and elimination, though there is no specific evidence that diet per se modifies the course of the disease."

However, for the previous several years another American worker, Whipple by name, and his associate, Robscheit-Robbins, of Rochester, had interested themselves in the effects played by various diets in influencing blood regeneration in animals rendered anemic by hemorrhage, and it was through this beginning that the great discovery was to be made which was to conquer the disease which for so many years had baffled Science.

"These observers, working with dogs, in 1920, had determined for each animal the 'available red cell pigment' by observations of the hemoglobin percentage and the blood volume. They then produced a uniform degree of anemia by the removal, on each of two successive days, of one-quarter of the already determined blood volume. The time taken for the available red cell pigment to return to its previous level was then observed, and the influence of a variety of dietetic factors noted. On an ordinary diet of mixed table scraps the time taken for a complete return to normal was four to seven weeks. On a liberal diet of meat and beef heart
however, the time was only three to four weeks, while with cooked liver it was even less (two to four weeks). Watery liver extract had a distinct, but very slight, influence on blood regeneration, but of course the dosage may have been insufficient. Commercial meat extract was found to be inert. It was found that the active foodstuffs could be given either alone, or in combination with other foods, and that they 'would stand the severe test of promoting definite blood regeneration when administered after long limited-diet periods unfavorable to blood regeneration.'"

"Studies on blood regeneration were also reported by Jencks in 1922. Regeneration was found to be more rapid 'with protein than with either carbohydrate or fat, when fed as a sole nutrient, and a diet of vitamine-rich food gave somewhat more speedy regeneration than any other diet containing only one food factor.' The foregoing quotation is taken directly from an essay on The Treatment of Pernicious Anemia by Dr. J.G. McCrie, as quoted by Goodall and Davidson, and summarizes briefly but successfully the earliest reports on successful dietetic treatment. The writer has gone over the articles summarized personally, and believes this as excellent a resume as could be used within the scope of this paper.

In 1925, Whipple and Robscheit-Robbins reported further work along this line, in which they had produced a constantly maintained severe secondary anemia, in place of the single post-hemorrhagic anemia of their previous experiments. They maintained the hemoglobin level of their dogs at between 40 and 50 percent by repeated bleedings of estimated amounts, and used the blood obtained to estimate the total hemoglobin present, and from these figures
were able to follow the rate of blood regeneration. Also, the maintenance of the constant hemoglobin level kept a more constant stimulus to blood regeneration, and thus the sudden initial stimulus of a single hemorrhage did not have to be reckoned with as a possible confusing factor in the interpretation of the results of the dietary therapy. By this method they found that while in the previous short, immediately post-hemorrhagic anemias beef muscle, heart, and liver were equally efficacious in treating the more severe type of anemia produced by repeated hemorrhages the maximal effect was obtained by the feeding of beef liver, beef heart being less valuable, and beef muscle still less. The final conclusion reached by these workers was that "Liver feeding in these severe anemias remains the most potent factor for the sustained production of hemoglobin and red cells. This favorable and marked reaction is invariable in our dog experiments, no matter how long-continued the anemia level, no matter how unfavorable the preceding diet periods may be, and regardless of the substances given with the liver feeding."

One other piece of work which was reckoned as bearing on the possible application of such a dietary to the treatment of Pernicious Anemia in humans was a group of experiments performed by Baker and Carrel, in 1925. These investigators found that lipoids, both those occurring naturally in serum, and those extracted from various tissues, had an inhibitory action on the growth of fibroblasts in vitro. Koessler and Maurer, two other American workers, in 1926, had also emphasized the importance of a possible connection between Vitamine A and blood regeneration, after conducting
a series of feeding experiments on rats rendered anemic by repeated hemorrhage, and recommended a balanced diet containing necessary vitamins in the treatment of primary and secondary anemias.

Repeated animal experiments by the foregoing group of workers have furnished significant hints as to the possible successful application of a Liver and Vitamin Rich, Low Fat diet in the treatment of Pernicious Anemia. Minot and Murphy, in Boston, have become interested in this information and have determined to test out its value in cases under their observation, and the stage is set for an announcement which will be received by the world as one of the greatest advances in treatment ever made.

In August, 1926, Minot and Murphy made their first report on the treatment of Pernicious Anemia by the new dietary. A series of 45 cases were reported as having received a diet rich in liver and red meat, relatively poor in fat, and containing an abundance of fresh fruit and vegetables, for periods varying from six weeks to two and a half years. This diet consisted of, daily, 120-240 gm. of cooked calf or beef liver; 120 gm. of red meat; not less than 300 gm. of vegetables; 250-500 gm. of fruit; 40 gm. of Fat; an egg if desired; 240 gm. of milk; dry crusty bread; potatoes; cereals----to give a total calorific value of 2000-3000 (340 gm. carbohydrate; 135 gm. of Protein; not more than 70 gm. Fat). Sugar was used sparingly; grossly sweet foods were prohibited.

A few, at first, had been unable to take the full diet, and in them liver alone was "pushed". Within a week to ten days
all were able to take the diet and exhibited a "ravenous" appetite. The bowels became more regular. Four of the forty-five died, but all of these were so ill from the beginning that they could take no liver. The remainder all improved, irrespective of the length of time the disease had lasted before the treatment was begun, and all were pronounced "well" at the time of publication. By the end of the first week of treatment the reticulated red cells of the blood had risen markedly, returning to a normal level by the end of the second week, and at this time the red cell count and hemoglobin percentage were beginning to show noticeable improvement. The rate of improvement was found to be greatest in those who had the lowest initial counts. After four to six months of treatment no patient had less than 3,500,000 red cells, 81% had 4,000,000 or more, and 30% had over 5,000,000. The icterus index had usually fallen to below normal by the time the red count had reached 2,500,000. Those patients who were most careful in taking the full amount of liver improved more quickly than those who were careless in this regard. Three of the patients relapsed, but it was shown that they had not been taking their diet as they should have, and marked improvement followed the institution of the proper dietary schedule. In their conclusions, Minot and Murphy called attention to the well-known phenomenon of natural remissions in the disease, but pointed to the regularity, measured by reticulocyte increase, with which the remission in their cases had commenced within a week after the beginning of the treatment. They also called attention to the fact that each natural remission tends to be
less complete than the one before, and in contrast to this point out the fact that in their series of cases they had many patients who had had previous remissions, during none of which had their red cell count reached the high level which it attained under the new dietary regime. As the experiment had been carried further, these workers found that the low fat content in the diet, prompted by the earlier researches of Baker and Carrel, was of minor importance to the high protein diet constituent. In a paper issued at a slightly later date these workers made public sample menus that had been successfully used by them.

Save for the work of Banting and Best on Diabetes Mellitus, no medical announcement in the last three decades has aroused more of a furore. Physicians all over the world eagerly seized this new method of treatment, hopeful that it would not prove another false hope, while thousands of sufferers from the disease which it combatted took hope. For the few months following this announcement every medical journal bore reference to its possibilities, and soon reports came drifting in from other workers who had met with success with the use of the new diet. The long-sought-for specific treatment for use against Pernicious Anemia seemed to have been found.

At this juncture medical men began to speculate as to what might be the factor contained in this Liver diet which was responsible for this miraculous change in cases treated. Was it the fact that some substance within the liver fed supplied material for the stroma of the red cells, allowing a normal number
of these to be formed? Was it the Vitamin content of the material ingested? Was it Vitamin A, as suggested by Koessler? Or was it some as yet unthought-of factor?

A possible explanation of the action of Liver was advanced in April, 1927, when these same workers demonstrated that rats, when fed with iron in the form of ferrous salts, were unable to assimilate it properly in the absence of Vitamine E, and soon developed deficiency symptoms, while the substitution of ferric salts or the addition of Vitamine E to the diet resulted in the normal utilization of iron by the body. Ergo, reasoned these workers, perhaps the beneficial action of liver in Pernicious Anemia is due to the fact that the liver fat contains considerable Vitamin E, and the liver itself contains an appreciable amount of iron. They pointed to the fact that the beneficial effects of the diets used by Koessler, and attributed by him to the presence of Vitamin A could just as probably have been due to the action of E.

In the same month Murphy published a further account of his results with Liver therapy in ten cases. In this paper he called attention to the reticulocyte crisis, the fall in the icterus index, the rise in the red cell count and hemoglobin percentage, the fall in color index, the increase in the numbers of circulating leukocytes and platelets, disappearance of abnormal forms of red cells, rise of corpuscular and whole blood volume, plasma volume remaining constant, the constant level of non-protein nitrogen and
protein nitrogen in the plasma, and the increase of circulating protein to an extent accounted for by the increased quantity of hemoglobin.

The next step toward solving the question of the role played by the Liver in treatment of anemia was made by Cohn, who, later in this same year, prepared a water-soluble fraction from whole liver which had a beneficial effect comparable to that of Liver itself. This fraction was insoluble in ether (proving that its action was not due to the content of Vitamin E, which is not soluble in water, and is soluble in ether), was precipitated by alcohol, and contained no lecithin or any of the ordinary lipoids. Murphy and Minot, using this extract on their cases, reported that patients responded quite favorably to its use. This disproved the postulate that liver acted by furnishing some absent material for the red cell stroma, since it would not be contained in a mere aqueous extract.

At this time favorable results were reported from the feeding of large quantities of kidney to Pernicious Anemia patients, but this was not deemed as efficient as the liver diet. However, it did point to one significant fact, namely, that the therapeutic agent was not contained in liver alone.

Also during the year 1927 another quite pertinent question was raised by Peabody. This worker had shown that during the stage of relapse in Pernicious Anemia the bone-marrow was crowded with primitive myeloid cells, megaloblasts, the first differentiated form of the erythrocytic line. In the stage of remission, however, he found that the predominating erythroblastic cell was the
normoblast, and that the appearance of the marrow was nearly, if not entirely normal. These findings prompted Peabody to reach the very sensible conclusion that the vital factor involved was quite probably in the nature of a stimulus to normal erythropoiesis, which, in the case of the patient with Pernicious Anemia, was lacking.

In September 1927 Minot and Murphy published a report on further cases, including, in all, 105 cases which they had treated with the Liver diet, some of whom had been under observation for three years. Of these, three had died, but in no case was death due to the Pernicious Anemia. Of 90 patients who had started treatment when the red count was below 2,700,000, 10 who took the diet badly averaged 3,500,000 after 4 to 6 months; the remainder all averaged 4,790,000; and 44 had a red count of over 5,000,000. These workers emphasized the need for a maintenance diet of Liver after the blood count had reached its normal level if the patient were to remain well. Patients who had had repeated previous transfusions had not responded so well as those who had not, and the presence of complications such as infection, or cirrhosis of the Liver, also mitigated against the maximal desired response.

The improvement in the state of the patients was described by Minot and Murphy. Beside the points remarked on in their previous papers, they called attention to the following: the disappearance of fever; a pink flush to the cheeks; early loss of weight from the disappearance of oedema; increased appetite and sense of wellbeing; disappearance of glossitis and gastric symptoms; in spite of the continued absence of free hydrochloric acid
in the gastric juice); the diminution in size of the liver and spleen, if previously enlarged; the clearing up of scaliness, pigmentation, purpura, and other skin lesions; and the disappearance of cardiac pain in those patients who had exhibited this rather uncommon symptom. There was no evidence of renal injury, attributable to the liver diet, nor was there any hypertensive trend. In a few cases Bursitis had developed, while in others a pre-existing arthritic condition had been improved. In regard to neural signs, no case showed further progression of symptoms, while some, especially those who had been afflicted with earlier signs, such as paraesthesias, had actually undergone improvement. Patients who had received no Hydrochloric acid had improved equally as well as those who had. Excess of Fat had not been found, as was first thought, to inhibit the rapid improvement in the condition of the blood. Finally, these workers claimed that the success of this mode of treatment was such that, if a case showed little improvement after six weeks of treatment, the diagnosis of Pernicious Anemia was probably wrong.

During the following year many reports are to be found in the literature of successful cases under Liver therapy. Many Biological and Pharmaceutical houses began the manufacture of the liver extract isolated by Cohn, and in 1928 he and his co-workers succeeded in still further purifying the extract by a precipitation method with Phosphotungstic acid. From this work, a fraction has been produced which will produce a typical response if given in a dosage of 0.6 gm. daily, and at the present time nearly all the leading Pharmaceutical houses have a reliable brand on the
market. This extract is of especial value in the treatment of Pernicious Anemia in patients whose stomachs are upset and who cannot tolerate whole liver. It should be used in all cases in which renal damage exists with concomitant increase in blood urea. It is, therefore, valuable in that type of Pernicious Anemia associated with pregnancy, as some of these cases show albumin and casts in the urine; and it to be used in all other cases of Pernicious Anemia in patients for whom a low protein diet is indicated, since it contains only a trace of protein, as well as sulphur and iron.

During this same year (1928) Ordway and Gorham tabulated the results of liver therapy published in every country. These authors included no case which started treatment during the period of a remission, and hence their list excludes many hundreds which might rightfully be included. They found that 578 cases had at this time started treatment with Liver or Liver extract with an average red count of 1,500,000 and had finished with an average of 4,000,000. Attention was called to the fact that the average should have been higher, but that many cases felt so well by the time their red cell count had reached 3,500,000 or 4,000,000 that they would leave the hospital for their homes, where blood tabulations were difficult to obtain. Seyderhelm, during the same year, collected 150 publications dealing with 2000 cases. All of these had benefitted by Liver treatment, only 20 failing to give the desired response. What a world of contrast exists between these two summaries of treatment given above and the summary of Panton and Valentine of cases treated prior to the advent of Liver therapy, previously
In June, of the following year, Castle published an article in the British Medical Journal, dealing with certain experiments by which he had determined that the stomach of a normal person secreted a substance which would develop a blood-maturing principle from meat ingested. Quick to recognize the potentialities of this discovery, Sturgis and Isaacs, of the University of Michigan, decided to test the activity of gastric tissue itself in the treatment of Pernicious Anemia. These experiments were later carried out with Dr. Sharp, of the Parke Davis Research Laboratories. Fresh whole hog stomach was used by these workers, and it was so dessicated that 30 grams of the dried product was equivalent to 218 grams of fresh tissue. By extracting the fat from the residue with petroleum benzine, the marked concentration was made possible. This product had very little odor or taste, and was substituted for liver extract in the treatment of 3 cases of Pernicious Anemia. From the quite favorable results obtained from these 3 patients it was concluded that this dessicated stomach extract, or Ventriculine, is more active than liver, as smaller amounts of it had been needed in order to produce a remission. Sturgis and Isaacs stated at this time --- "The question of the origin of the active principle is being tested. There are several possibilities. One is the presence of an enzyme, or similar substance, which may act on protein present in the stomach tissue during the period that elapses after the organ is removed and before it is dried. (This agrees..."
to a marked extent with the conclusion reached by Castle.) Another possibility is that there may be a supply of the active hematopoietic principle itself present in the stomach wall, as it apparently is in the liver and kidney. We are not certain as to whether this is in muscularis or mucosa, or both. The observations so far are in accord with the idea that those suffering from Pernicious Anemia have evidently lost, or never had, the ability to secrete a substance in their stomachs which has the power to produce a blood-maturing material from food."

As a result of these announcements, various clinicians at once tried the efficiency of Ventriculin the treatment of cases then under observation, and since that time many controversies have been held as to the respective merits of liver extract and the newer dessicated stomach preparation. Anderson, in 1931, cites several cases which came under his care, which did not respond nearly so well to liver therapy as they did to Ventriculin. Several charts have recently been circulated by the producers of the latter, which give a graphic illustration of its superiority over liver extract. However, this still remains a moot point as far as therapeutic effect is concerned.

While Minot, in 1929, demonstrated that a rapid remission in Pernicious Anemia could be brought about by the intravenous injection of an extract of liver, and Castle and Taylor reported favorable results in a case which had not responded to orally administered liver, it has not been until the last year or so that such a preparation has been placed on the open market. At least one leading pharmaceutical and biological house in the
United States now has both an Intra-muscular and an Intra-venous extract for general use. These solutions are refined by a process which eliminates toxic nitrogenous substances that might produce severe constitutional reactions if injected. The dosage of such an extract, especially of the intra-venous type, is small compared with the amount needed for oral therapy under similar conditions. The parenteral administration of such extract would seem to be especially adapted to cases that show an increasing exhaustion of the bone marrow and do not respond readily to the average dosage of the oral preparation; also to the requirements of patients whose digestive function is so impaired that the antianemic substance when given orally is only imperfectly assimilated. In addition, it is claimed by those who have used the intra-venous extract, that, after an individual's red cell count has been restored to normal, an average of one ampoule by vein per month is sufficient to keep it up. Compare such magical results with the hopeless therapy of the period ending five years ago!

During the recent two or three years research and speculation as to the nature of the vital factor contained in these extracts has been marked. Davidson and Gulland believe it to be a poly-peptid or a nitrogenous base. Others have the conception of a hydroxy-glutamic acid. Whatever its actual composition, the fact that it is present in the normal stomach, in meats digested by the normal stomach, in the liver, and, to a lesser extent, in the kidney, suggests the nature of a hormone,
an amino-acid complex, or an amino-acid, as yet unknown to us, the lack of which, whether due to a congenital tissue debility or to other factors, results in a perverted stimulus to the hemopoietic tissues, and causes the clinical condition which we know as Pernicious Anemia, a deficiency disease.

Both experiment and clinical experience have proven that if the patient expects to sustain permanent remission from symptoms he must ever afterward continue the use of the vital principle in some form or other. Since the expense of the diverse preparations to the patient, as well as their availability and convenience, must be considered, the following data obtained from Parke-Davis and Company, are worthy of note. The maintenance dose of Liver Extract is 3 vials daily; that of Ventriculin is 1 vial daily. Going at a maintenance rate, the patient would pay $67\frac{1}{2}$ per day for the Liver Extract, and $26\frac{3}{4}$ or less daily for Ventriculin. Respectively, this would come to $20.10 and $7.80 per month, the Ventriculin being by far the more within reach of the average patient. However, the new ampoules of Intravenous Liver Extract, of which one per month is estimated as sufficient to maintain the red cell level at its normal, cost only $2.00. To what a degree this mode of treatment will displace the other two previously considered remains to be seen. However, it is, from these quotations, quite evident that the necessary therapy to regain and maintain health is within the reach financially of practically every individual.
PRESENTATION OF CASES

Case I.

This case, while not presented completely as far as the laboratory findings are concerned, is one of especial interest to the writer for two reasons — first, because it illustrates clearly the hopeless efforts of therapy prior to institution of liver diet, and second, because it was observed from beginning to end in the writer's own family.

The patient, a woman 53 years of age, first complained of weakness on exertion and shortness of breath after unusual exercise such as walking out-of-doors. Soon after this she noticed numbness and tingling of the lower extremities, and had some difficulty in walking because of spasticity and uncertainty as to the position of her feet. At this juncture the patient had the misfortune to fall, severely spraining an ankle. After all the swelling and pain had left this member and almost two weeks had passed she tried to begin walking again, and found that she was unable to do so without maintaining her balance by clinging to nearby articles of furniture. At this time the attending physician took a blood count and suspected Pernicious Anemia. The patient was brought to Omaha, and placed under the care of two of the city's best internists. While I do not know the laboratory data obtained, I know that the tentative diagnosis of Pernicious Anemia was confirmed. During her three weeks stay in the Omaha
hospital she received the usual medication of the day, consisting of dilute Hydrochloric Acid, Fowler's solution, and some Iron compound, as well as two transfusions of 500 cc. each. She was sent home little improved, and from then until her death, three weeks later, rapidly declined. Evidence of progressive cord changes was present, with almost complete loss of sphincter control, and lassitude and cachexia increased until the exitus. The rapid and inexorable progress of the disease, unchecked by the efforts of proficient physicians, shows how inadequate was the treatment of the day, and offers a pitiful and ironic sort of contrast to the results obtained by the Murphy-Minot diet, which was made public just three months later.

Case 2.

This case, while coming under the attention of a competent physician after the Murphy-Minot diet was generally accepted, is illustrative of the somewhat hopeless plight of the sufferer from unrecognized Pernicious Anemia who became the victim of an acute infection calling for the mobilization of body reserves which were already sadly depleted.

The patient, a woman 33 years of age, who had been in a somewhat "run-down" state for several months, was brought to a local Omaha Hospital under the care of a capable internist, with the clinical diagnosis of lobar pneumonia. On entry, the blood-picture was as follows; R.B.C. 2,240,000, Hb. 30%, Color Index .6. W.B.C. 4,480, granulocytes 58%, lymphocytes 42%. There was a marked anisocytosis and poikilocytosis, with much polychromato-
philia. The temperature fluctuation was between 96 and 104 degrees, and the pulse rate varied from 80 to 100, with moderately accelerated respiratory rate. In spite of all possible supportive and stimulatory treatment, the patient showed only slight resistance to the pulmonary involvement, and succumbed on the fourth day after entry. Had the patient's marrow reserve been prepared for the sudden demand made upon it the outcome of the pneumonia might have been the opposite, but she had been carrying on for months ignorant of the disease which robbed her of what chance she might have had.

Case 3.

This case entered a local hospital under the care of the same physician attending the previous case cited, complaining of marked weakness, numbness and tingling of the lower extremities, and general debility, of several month's duration. The blood-picture on entry was as follows, and a diagnosis of Pernicious Anemia was made: R.B.C. 2,400,000. Hb. 45. Color Index 9

W.B.C. 5,000. Granulocytes 60%, Lymphocytes 40%. There was marked anisocytosis and poikilocytosis, with polychromatophilia and nucleated red cells present. The patient was found to have no free Hydrochloric Acid in her stomach during the test meal. She was placed on the Murphy-Minot diet, and received dilute HCl gtt. xv tidpc; Bone marrow, tablets one, tidac, and Blaud's pills, one tidac. A summary of her various blood-pictures from that given above, 5-19-27, until her dismissal, 6-15-27, will reflect the improvement in the clinical condition and the return to an
evident state of health.

5-23. R.B.C. 2,800,000 Hb.45. Color Index .9
      W.B.C.5,000. Granulocytes 56%. Lymphocytes 44%.
5-31. R.B.C.3,000,000 Hb.52. Color Index .8
      W.B.C.6,000. Granulocytes 62%. Lymphocytes 38%.
6-4. R.B.C.3,200,000 Hb.58. Color Index .9
      W.B.C.6,800. Granulocytes 70%. Lymphocytes 30%.
6-10. R.B.C.3,400,000 Hb.62. Color Index .9
      W.B.C.7,400. Granulocytes54%. Lymphocytes 46%.
6-14. R.B.C.3,900,000 Hb.64. Color Index .8
      W.B.C.8,200. Granulocytes 64%. Lymphocytes 36%.

Surely the marked improvement under the new dietary regime will speak for itself, in the light of its contrast with the cases previously cited.

Case 4.

The patient, a man aged 53, was brought to Dr._____ with a probable diagnosis of Carcinoma of the Stomach. He had no appetite; had been confined to his bed for one month; had lost 30 pounds in weight during the past 6 months; and was extremely weak. A clinical diagnosis was made of Pernicious Anemia. His red cell count at the time of the first examination was 1,800,000 and his hemoglobin stood at 40%. A transfusion was given, and the patient was placed on Ventriculin therapy, improvement soon being apparent. Within ten months his blood count was normal, he was able to do light work on the farm, had a good appetite, and had regained his weight, and was taking only three doses of Ventriculin in a week.

This case well illustrates how, with proper diagnosis and rational guidance of treatment, the patient may be given carte blanche and allowed to gauge the amount of medication to be taken by his general condition and wellbeing, when circumstances do not
permit him to be constantly under the observation of his physician.

Case 5.

This case gives an interesting side-light on the comparative values of Liver Extract and Ventriculin in the opinion of the physician who obligingly submitted this case history.

"The patient, the manager of a planing mill, aged 65, came into my office complaining of loss of appetite, nausea, marked weakness, and shortness of breath, of a duration of three months. More recently he had been bothered by numbness of the hands and feet.

On Feb. 20, the red blood count was 1,140,000, hemoglobin 30, color index 1.5; the white count was 2500. A smear showed marked poikilocytosis and anisocytosis. Blood platelets were very much diminished. He was unable to retain food or medication of any kind, as he vomited everything we gave him except water and orange juice. On the next day we gave him a blood transfusion of 500 cc. by the citrate method. On the following day he was able to retain his food and also Ventriculin. He took Ventriculin, 30 grams a day, from February 21 till March 5. His blood count then was 2,750,000, with a hemoglobin of 48, and a color index of 0.9. At this time he felt much better and had lost all gastric distress, but was still very weak.

I then stopped Ventriculin and gave him Liver Extract, one vial three times a day. This was taken until the 21st of March, when his red blood count showed 2,400,000, with hemoglobin
at 52, and color index of .1. At this time I stopped the Liver Extract and put him again on Ventriculin, one bottle three times a day. On April 6 his red count had risen to 4,400,000, with a hemoglobin of 70, and a color index of .7. The dosage of Ventriculin was decreased to two vials a day, and on April 21, his red cell count had risen to 5,400,000, with a hemoglobin of 90 and a color index of .8. He had gained about 20 pounds in weight; his cheeks, once pale, were rosy; appetite good, and able to eat anything he wished. From this time (April 21) until August 9, the dosage of Ventriculin was gradually diminished until the patient was taking only one vial a week. His red cell count stood at 5,400,000, with a hemoglobin of 100 and a color index of .9.

I have six other patients on Ventriculin, and I must say that I consider it by far the best treatment we have for Pernicious Anemia. While giving liver has given marked results, I find that my patient's red counts increase much faster under Ventriculin and that the dose can be reduced much sooner."

Whether or not all other physicians would agree with this one in his whole-hearted endorsement of Ventriculin, it is safe to say that the improvement of the patient in this case, when viewed through the gloomy light of therapy of former years, was little short of miraculous.
Case 6.

The patient, a woman aged 63, entered a local hospital complaining of extreme weakness, loss of weight, jaundice, anorexia and nausea, numbness and tingling of the extremities, and difficulty in walking, of a duration of three months. Two and a half years previously she had been under treatment for pernicious anemia, had been relieved of the minor complaints of that date, and had ceased the prescribed diet. On entry, there was mental confusion, at times almost amounting to a delirium.

Physical examination revealed nearly every cardinal diagnostic feature of pernicious anemia. The sclerae were icteric, the skin exhibited a waxy, lemon-yellow tint, and all the mucous membranes were quite pale. The tongue was bald and glistening, and the patient recalled recent soreness of this member. There was no palpable evidence of enlargement of either liver or spleen. A soft systolic blow was heard clearly over the mitral and systolic areas. The abdominal reflexes were missing, and patellar reflexes were also gone. There was a positive Babinski sign on the right.

The urinalysis was negative save for a marked trace of albumen. The blood-picture was as follows:

R.B.C. 1,050,000 Hb. 20 Color Index I. There was extreme anisocytosis and poikilocytosis, and many megalocytes were present, as well as a fair number of normoblasts.

W.B.C. 3,800. Granulocytes 46%, Myelocytes 2%, Lymphocytes 44%. 
She was put on a diet including Liver, 100 grams, twice daily; she also received beef kidney, heart, and sweetbreads at various meals. Twice daily, at breakfast and lunch, she received one of the following fruits—- apricots, peaches, prunes, or apples. In addition to this diet she was given 4 vials of Lilly's Liver Extract daily, and 2 cc. dilute Hydrochloric acid three times daily.

Due to her extreme condition, it was decided to push the Liver Extract harder, and on the next day she received 6 vials, 2 in the morning and 2 in the evening, with 1 at noon and at dinner. However, marked nausea supervened on the evening of this same day, and the patient became semi-comatose, with complete loss of sphincter control. On the following day, the third day after admission, the diet with Liver Extract as specified, was continued, but, since the patient was unable to retain but a fraction of this diet because of emesis, she was given 1 vial of Liver Extract by milk retention enema every four hours, and also received 1 ampoule of intramuscular Liver Extract (Lederle) intraglutelally. During this day her general condition was such that both adrenalin and caffeine-sodic-benzoate had to be used as stimulants.

On the following day there was still considerable of the nausea, but the general condition was not quite so precarious. Treatment was much the same as on the previous day, and patient was able to retain a reasonable amount of fluid in the form of fruit juice and broths. During the next five days there was but little clinical improvement, and so the patient was given 250 cc. of whole blood by transfusion. On the following day (the fifth
after her admission) her blood picture was as follows:

R.B.C. 2,300,000 Hb. 30 Color Index .7 The appearance of the red cells was much the same as before, and there had been only a slight reticulocyte response.

The same diet schedule, with Liver Extract, vials 4 daily was kept in force, and, in addition, the patient received 2 intra-gluteal injections daily of 2 cc. intra-muscular Liver Extract. Muriatogen, tablets 2, was given with each meal, and Liver extract was continued by retention enema every four hours.

On the seventh day after admission the general condition had improved moderately, the patient being able to talk rationally with her family and to take her meals and retain them. On this date her blood-picture was as follows:

R.B.C. 2,400,000 Hb. 31 Color Index .6. At this time the reticulocyte response was evident, the percentage of the reticular cells being 16.

W.B.C. 4,360. Granulocytes 46%, Lymphocytes 52%.

During the next four days there was steady improvement in the patient's general condition, and the diet and medication already outlined were continued in force. At the end of two weeks in the hospital, although the red cell count had not increased materially, the patient's condition seemed so good to her family that they took her home. However, at this time the reticulocyte response had reached a good peak, and the attending physician, appreciating the economic factor, consented to her removal and continued treatment in the home. At the end of two months, during which time the
patient was on a modified Murphy-Minot diet and was taking 3 vials of Liver Extract daily, the red cell count had increased to over 5,000,000, the hemoglobin had risen to slightly less degree, and the patient was relieved of all her complaints save for occasional paresthesias in the extremities. At present, she is taking only one vial daily, and is able to be up and about, eat freely, and enjoy her former routine of existence.

This case, more than any other which I have ever seen, illustrates how radical Liver therapy, given by mouth, by rectum, and intra-muscularly, can change an almost moribund person to a person of normal health and vigor within an amazingly short time. Six years previous to this writing, this patient would have been dead within a week after entry into the hospital.
SUMMARY

The Treatment of Pernicious Anemia has been traced from the time when the disease was first recognized as an entity, with a hopeless prognosis, to its present status of a deficiency disease, readily amenable to treatment with the recently discovered vital anti-anemic principle contained in the Liver and in the Stomach wall.

Cases have been presented to illustrate the end results obtained by the various means of therapy in the different periods of the evolution of the present treatments at our disposal.

Pernicious Anemia has joined the ranks of the other diseases which modern medical science has brought back from the limbo of the hopeless to the light of successful treatment.
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