

## CLASSICS OF BIOLOGY AND MEDICINE

# Treatment of Pernicious Anemia by a Special Diet<sup>a</sup>

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This paper concerns the treatment in a series of forty-five cases of pernicious anemia in which the patients were given a special form of diet. While the problem of diet in the treatment of pernicious anemia is by no means new, in our opinion its possible importance has not heretofore been generally recognized. In 1863, seven years after the publication of Addison's second, but best known, description of the disease now called pernicious anemia, Habershon [1] wrote concerning this condition: "Many patients at an early stage completely recover under the influence of bracing air and a nutrient and stimulating diet." Other early investigators of the disease, as Biermer [2] in 1872, and Pepper [3], in 1875, appreciated the desirability of prescribing easily digested foods as a form of medication, but no greater emphasis was placed on the value of diet. Osler [4], however, in 1885, mentioned that "cases [of pernicious anemia] appear to have got well with change of air and a better diet after resisting all ordinary means."

During the last half century, many clinicians, following the suggestions of the pioneer writers on the subject of perni-

cious anemia, have advised various kinds of diet as an aid to induce a remission of the disease. More often than not, the recommendations have been of a general sort as might be given for many persons with an impaired condition of the gastrointestinal tract, which always is present in pernicious anemia. Thus, food for the pernicious anemia patient often has been selected because it appeared to be easily digested or because it seemed particularly nutritious and strength-giving. Rarely, diets have been chosen for some assumed direct effect on the blood.

The constant presence of achylia gastrica in pernicious anemia and the frequency of all abnormal bacterial activity within the intestines have been two main reasons for establishing certain forms of dietotherapy in the disease. On these accounts, Fenwick [5] in 1880, and Naegeli [6], among others, recommended diets relatively sparing in farinaceous foods and relatively rich in protein. For similar reasons, yet in contrast to the majority, Hunter [7], in 1890, and others have advised quite the opposite type of diet. Grawitz [8] recommended a diet composed chiefly of fresh

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vegetables, followed by one with generous amounts of protein. The idea that forced feeding with any sort of food, but especially meats, is valuable to make weak and feeble individuals healthy and strong has caused the frequent use of this form of therapy in pernicious anemia, and Mosenthal [9] has shown that it can restore in these cases a positive nitrogen balance.

Meats and green vegetables, partly because of their iron content, have for a long time been thought to be useful to improve "an anemic state of the blood." Meat apparently has been chosen at times simply because it contained blood, which was supposed to be beneficial as food for persons who had an insufficient blood supply. The scientific foundations of the value of iron-containing foods to affect the blood-forming organs were laid by Menghini [10] in 1746, when he showed that iron could be increased in the blood by feeding such foods to animals. About 200 years later, Gibson and Howard [11] made important observations on the effect of a high iron content of the diet in anemia, and showed that in pernicious anemia it can have a most favorable influence on iron metabolism. They also showed that, in cases constantly losing nitrogen, a positive nitrogen balance could be obtained without forced feeding.

One thus finds that the diet usually advised for the pernicious anemia patient is one containing a relatively high nitrogen-content and often a relatively large number of calories. The recommendations of Smith [12] and of Barker and Sprunt [13] are of this sort and, like some others, the latter wisely recommend that the food be selected with a view to giving an ordinary, well balanced diet to replace a quantitatively deficient and qualitatively ill balanced one, on which these patients are apt to have placed themselves during their illness.

In spite of attention to diet for the anemic patient, the influence of food on blood

formation and destruction has received comparatively little consideration, and special sorts of food, because of some particular effect, have seldom been chosen for patients with pernicious anemia.

Complete starvation in man is not considered to cause anemia, but may do so in animals. However, it is known that improper food can cause, and suitable food alleviate, anemia; for example, the "iron starvation anemia" arising in infants who have partaken too long of only a milk diet, and who can be cured by food particularly containing complete proteins and iron. Incomplete diets, particularly those low in protein and relatively rich in concentrated carbohydrate food, can lead to anemia [14], and even Shakespeare [15] recognized that improper food might impair the state of the blood. Likewise, patients with conditions due to, or associated with, vitamin deficiency experience anemia, and Jencks [16] has noticed that an abundance of vitamins favors blood regeneration. Certain foods, including liver, may benefit patients with sprue. This disease is considered by some partly dependent on a faulty diet, and resembles in numerous ways pernicious anemia, including the fact that the blood picture in the two diseases may be quite similar. Carnivorous animals and thin persons tend to have a greater percentage of hemoglobin in their blood than herbivorous animals and fat persons [17]. This further suggests, as do the observations of Morawitz and Köhl [18] on man, the favorable role that animal protein food may play in blood formation, although dehydration may account for the differences observed.

Some of the earlier experimental work concerning the effect of food on blood regeneration is reviewed by Pearce, Krumbhaar, and Frazier [19]. Adequate proteins as well as iron are necessary for the formation of hemoglobin. Certain proteins will not suffice, such as gliadin [20].

However, the amino-acid tryptophane may have a special ability to enhance blood formation [21]. The most important recent work concerning the effect of food on blood regeneration has been done by Whipple and Robscheit-Robbins and their associates [22]. Their carefully controlled work on dogs has demonstrated clearly the value of certain foods, especially liver, on accelerating blood regeneration following acute hemorrhage and the value of iron added to the diet to decrease the anemia due to chronic blood loss.

McCollum [23] has pointed out that liver and kidneys give an exceptionally high quality protein for a low protein intake and can enhance remarkably the growth of animals. These foods are rich in nucleins, and Calkins, Bullock, and Rohdenburg [24] have shown that the products of nuclein hydrolysis can stimulate growth. Whipple [25] has suggested that in pernicious anemia there may be a scarcity of the material from which the stroma of the red blood cells are formed, or that a disease of the stroma-forming cells of the marrow exists. Thus, theoretically perhaps liver and other foods rich in complete proteins may enhance the formation of red blood cells in this disease, especially by supplying material to build their stroma.

Fresh red marrow was first used as a means of treatment for pernicious anemia by Fraser [26] in 1894. He reported beneficial results when a patient ate for some time about 100 gm a day. It was then and has since been given apparently on the supposition of some hormone effect. Thus, numerous reports have appeared concerning the use of preparations of small amounts of concentrated bone marrow, but without definite evidence of advantage to the pernicious anemia patient. Reports regarding the effect of eating generously of fresh marrow are few and brief, but suggest that it may be beneficial. The nutritional composition of red bone marrow is

similar to that of liver and kidneys. If generous amounts of red marrow and liver can improve the state of the blood in pernicious anemia, may their influence not be due to the same, but unknown, cause?

Various investigators have commented on the blood-destroying properties of certain substances derived from fats, and the role they may play in pernicious anemia. Stoeltzner [27] recently has reviewed the subject. Also, lipoids have been shown by Baker and Carrel [28] to be a factor in serum that can inhibit growth. Thus, founded on somewhat theoretical grounds, it seemed to us, as it did to Stoeltzner [27] and to Gibson and Howard [11], that decreasing the amount of fat in the diet of the pernicious anemia patient might have a favorable effect on the state of his blood. Excess of fat in a diet is considered by some to favor putrefaction within the intestine, a condition frequent in pernicious anemia. Hence one might attribute any benefit derived from a low fat content of the diet to alterations in the bacterial flora rather than to some more direct effect on blood formation or destruction.

A further hypothetical reason for decreasing the fat in the diet is that we have noted it is not uncommon for these patients to have consumed throughout life unusually large amounts of food rich in fats. Patients with pernicious anemia also may give a history of partaking for years of some other type of one-sided diet. It is common for them to do so after the definite onset of their illness, when it is not unusual to find that they have a disgust for meat. Pernicious anemia is rare in certain parts of the world where diets are quite different (containing fewer dairy products, less free sugar, and muscle meat) from those of the northern parts of Europe and America, in which areas the disease is relatively common. These different facts permit one to speculate on the possible partial role that some nutritional excess or deficiency may play in the etiology of the dis-

ease. These different facts permit one to speculate the possible partial role that some nutritional excess or deficiency may play in the etiology of the disease. Similar thoughts have occurred to others, including the idea that a vitamin deficiency might be a causative factor, as has been mentioned, for example, by Elders [29].

Leafy vegetables and fruits usually are considered desirable for anemic patients, especially because of their iron content, and strawberries rich in iron appear beneficial for patients with sprue, a disease, as noted, resembling pernicious anemia. We prefer to add these foods to the pernicious anemia patient's diet not only because they are healthful ones for any person to eat, but also because, as Whipple and Robscheit-Robbins [30] have shown, certain ones have an especially favorable influence on hemoglobin production. It is quite probable, however, that their chief effect is not because of their iron content. It seems that such a factor as the character of the proteins or amino-acids in the diet is of much more importance than the iron content for pernicious anemia patients.

Numerous authorities hold the view that an intestinal bacterial toxemia plays an important etiologic role in this disease. One may choose to believe that any benefit these patients derive soon after beginning to take certain foods is to be attributed to changing rapidly the intestinal flora, thus decreasing a bacterial toxemia, rather than considering that the foods influence in some unknown, but more direct, manner the formation or destruction of red blood cells.

Gibson and Howard [11], taking cognizance of Whipple and Robscheit-Robbins' work and the fact that certain lipid substances could enhance hemolysis, fed pernicious anemia patients a relatively low caloric diet (from 1,500 to 1,900) "rich in iron [liver (daily), fruits, green vegetables, egg yolk] and low in fat" and adequate in vitamins. A somewhat

similar diet but containing a less amount of food rich in purines was recommended by Fenlon [31] in 1921. Gibson and Howard [11], besides demonstrating the favorable influence of their diet on nitrogen and iron metabolism in pernicious anemia and some other anemias, suggested that it enhanced a remission in pernicious anemia and urged its use.

## MATERIAL STUDIED AND OBSERVATIONS

Following the work of Whipple and Robscheit-Robbins, we made a few observations on patients concerning the influence of a diet containing an abundance of liver and muscle meat on blood regeneration. The effect appeared to be quite similar to that which they obtained in dogs. These observations, together with the information given above, led us to investigate the value of a diet with an abundance of food rich in complete proteins and iron — particularly liver — and relatively low in fat, as a means of treatment for pernicious anemia.

Observations set forth below have been made on forty-five patients with typical pernicious anemia first partaking of such a diet when in a relapse and continuing it to date (except temporarily omitted by three), or, from six weeks to two and a half years.

The special diet [32] was made as palatable as possible and for each day was practically as follows:

1. From 120 to 240 gm and even sometimes more, of cooked calf's or beef liver. An equal quantity of lamb's kidneys was substituted occasionally.
2. One hundred and twenty gm or more of beef or mutton muscle meat.
3. Not less than 300 gm of vegetables containing from 1 to 10 percent of carbohydrate, especially lettuce and spinach.

4. From 250 to 500 gm of fruit, especially peaches, apricots, strawberries, pineapple, oranges and grapefruit.
5. About 40 gm of fat derived from butter and cream, allowed in order to make the food attractive. However, animal fats and oils were excluded so far as possible.
6. If desired, an egg and 240 gm of milk.
7. In addition to the above mentioned foods, breads especially dry and crusty, potato, and cereals, in order to allow a total intake of between 2,000 and 3,000 calories composed usually of about 340 gm of carbohydrate, 135 gm of protein, and not more than 70 gm of fat. Grossly sweet foods were not given, but sugar was allowed very sparingly.

This diet is rich in iron and purine derivatives, containing about 0.03 gm, of the former and about 1 gm of the latter.

At the time the diet was advised for many of the patients, they were able to take only a small amount of food of any sort. Under these circumstances they were encouraged to take as much as possible of liver and fruits, and at least some vegetables, while other sorts of food were not forced. During the first week of the diet, the intake was often less than a thousand calories. After about this period of time, the patients usually felt distinctly better, and their appetite began to improve. Then the food was increased gradually until the complete diet was taken. The patients as a rule did so within two weeks after the diet was begun. In fact, frequently they soon became "ravenously hungry" and often anxious to eat more than the customary allowance of liver and meat.

Twenty-four of the forty-five patients carried out the regimen by weighing portions of liver and meat and estimating the amounts of the rest of their food for at least three weeks, and often for the first six after commencing the diet. The other

patients, like those after leaving the hospital, have taken their diet at home, following out written directions but not weighing any of their food. Our data strongly suggest that the patients who commenced treatment in the hospital and those few able to have a trained nurse at home have improved on the average rather faster and to an even better degree than the others. When the patients had remained much better for many weeks, their diet was sometimes modified particularly by decreasing the amount of liver and fruit.

The therapeutic regimen for these forty-five patients, besides the special diet, included rest, usually at first in bed for twenty-four hours a day. All but three also took each day about 15 cc of diluted hydrochloric acid (U.S.P.). These three, however, improved at least as much as the majority of the others. None of the patients received any especial treatment shortly before or after the diet was begun except as follows: a man, aged 69, with pronounced spinal cord lesions and advanced arteriosclerosis, was given five transfusions of blood within about six weeks while attempts were made to get him to eat. Now, three months later, he remains the least well of all forty-five, except for one woman who recently has omitted her diet. Blood was transfused to three others at about the time they first took the special diet. The red blood cell count of none was over 1,400,000 per cubic millimeter four days after transfusion.

The forty-five patients represent an essentially consecutive series seen in a relapse, and are all that have taken the special diet except one noted below. The series is not entirely consecutive, because during the time the forty-five cases were seen the following additional ones came under observation:

1. Four patients who had had their disease a long time were exceedingly sick, able to take little or no food, and died within a few weeks after

they were seen. They ate no liver or kidneys.

2. Five patients consulting us but once and not taking the special diet. Letters indicate that three improved somewhat and two did not.
3. One patient that was in much better condition soon after taking the diet. This patient is not included in the series of forty-five because of several unusual complications.

Many of the forty-five patients had definite symptoms due to pernicious anemia for more than two years, and two of them experienced such symptoms ten years before taking the special diet. A number of the cases were observed during a year or more before the diet was begun, others for several weeks, and some for only a few days. Many of the patients had remained in distinctly poor health and were unable to do their usual work for from a few months to more than a year before eating the food especially prescribed. During this time, many received various forms of therapy without distinct benefit, including transfusions of blood.

When the special diet was started, the forty-five patients that have continued to eat this kind of food fell naturally into the three following groups (1) twelve in their first distinct relapse; (2) seventeen in their second relapse; (3) sixteen having had two or more relapses. It is thus evident that all sorts of variations of the disease occurred among the patients, and that the series was not composed chiefly of those in their first relapse, following which considerable "spontaneous" improvement is the rule.

The condition of all forty-five patients became much better rather rapidly soon after commencing the diet. All except one, who has recently omitted her diet, are now at the least in a very fair state of health, and if it were not for disorders in some due to spinal cord lesions, would have an appearance to a layman of being essentially well. However, there are only eleven

patients who began the diet a year or more ago, two of whom have taken it for more than two years. Eighteen began taking the diet less than five months ago.

One of the earliest signs of improvement has been a change in the frequency of bowel movements believed to be due particularly to the diet and probably not to diluted hydrochloric acid. Within a few days, those who had had a tendency to diarrhea often began to have one formed stool a day, while, interestingly enough, those who had had normal movements or had been constipated frequently had for several days a few loose stools in each twenty-four hours. The latter patients, then, had a more natural regularity of their bowel movements and a more normal stool than they had had for some time before the diet was taken. The laxative effect of the diet has been observed also to occur in some normal persons.

Clinical improvement has been obvious within two weeks. This has been heralded in the peripheral blood before the end of the first week by the beginning of a most definite rise of the reticulocytes (young red blood corpuscles) of from about 1.0 percent to usually about 8.0 and even to 15.5 percent of all the red blood cells. This rise occurred in all fifteen patients that have had such counts made every day or so for from one to three weeks before and some weeks after beginning the diet. By the end of the second week, these cells usually had returned close to their normal percentage. Later, when the red blood cell counts were distinctly high, it was frequent to find, as we have noted formerly, an abnormally small number of reticulocytes. Before they began to increase, the icterus index of the blood serum in these fifteen patients started to fall, and soon the yellow tint of the patient's skin disappeared. This index reached normal in about from two to four weeks, and often has fallen to below normal even when the red blood cell count

had increased to only 2,500,000 per cubic millimeter [33].

The accompanying chart and table give in a synopsis manner the trends of the state of the blood in the forty-five patients, taking into consideration, on the one hand, the character of the case, and, on the other, the level of the red blood cells when the diet was begun. The data are given for all forty-five patients before and about one month (from four to six weeks) after the diet was started. Although all the patients have been observed repeatedly, data can be given for only thirty-seven at the end of about two months (from eight to eleven weeks) of treatment, and for twenty-seven between four and six months after treatment began, because eight have taken the diet for less than two months, and eighteen for less than four months. As a measure of the patient's condition, we have chosen to give in the table and chart the red blood cell count rather than the hemoglobin percentage, partly because the latter in pernicious anemia may be at about

the same high level (80 percent) with red blood cell counts of from 2.5 to 4 million per cubic millimeter. It is recognized that figures for both may vary considerably within a few hours. The figure used in synopsisizing the data often represents in each instance an average of several counts made within a few days of each other.

Inspection of the chart and table shows the rapidity with which the red blood corpuscles increased, the high level they attained at the end of about one month, two months and from four to six months after the diet was begun, and the rather slight differences that occurred in the bloods in the cases falling into the three groups based on the number of relapses that had occurred. The percentage increase of cells (and the same is true of the hemoglobin) at the end of a month was usually very much greater in patients starting the diet when their red blood cell count was less than 1,200,000 per cubic millimeter than in those in whom it was distinctly higher. This occurs in other pernicious

**Table 1. Average red blood corpuscle count.\***

Before diet Started		After diet started					
		About 1 month		About 2 months		4 to 6 months	
No. of cases	Average R.B.C. count in millions	No. of cases	Average R.B.C. count in millions	No. of cases**	Average R.B.C. count in millions	No. of cases**	Average R.B.C. count in millions
19	0.90	19	3.28	15	4.08	12	4.50
15	1.60	15	3.25	13	4.09	10	4.54
11	2.30	11	3.83	9	4.41	5	4.47
45	1.47	45	3.40	37	4.16	27	4.50

\* The figures represent the count per cubic millimeter before and after starting special diet in three groups of cases of pernicious anemia: (1) with less than 1.2 million; (2) having from 1.2 to 2 million; and (3) having from 2 to 2.75 million before diet was begun. Also, averages for all forty-five cases are shown.

\*\* The differences in the number of cases after about one month is because some have not taken the diet for as long as two, and others as long as four months.

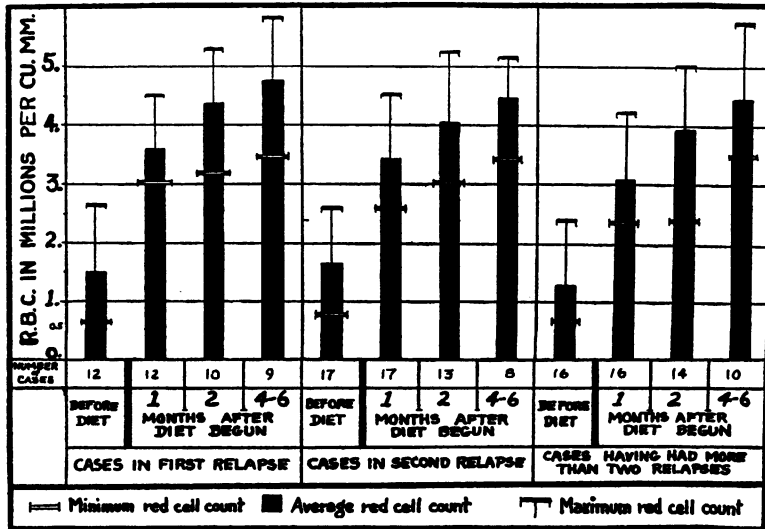


Figure 1. Red blood cell count in forty-five cases of pernicious anemia before and after beginning special diet. Cases grouped according to the number of relapses the patients had. One and two months after diet began indicates an approximate amount of time and for any given case is not less and often somewhat more than four or eight weeks. The differences in the total number of cases after about one month are caused by the fact that some patients have had the diet for less than two, and others for less than four months.

anemic patients, rapidly restoring their blood. The blood of patients with rather high counts of their red blood corpuscles and prominent signs of injury to the spinal cord responded more slowly perhaps and less well than others, and, as is to be expected, no striking change occurred in very marked symptoms or signs due to spinal cord degeneration.

In pernicious anemia, remissions after two relapses are frequently less marked than previous ones, so that the red blood cell count is apt to be lower in a third or subsequent relapse than in a former one. In spite of the excellent remissions our patients had soon after beginning the diet, the data in the chart show what might be expected; namely, that not only did the third group of patients (those having had more than two relapses) have on the average a slightly lower red blood cell count

before the diet was started, but also that afterward their counts were apt to increase more slowly and not become quite so high as in the other two groups. Only four of the patients had red blood cell counts as low as between 3 and 2.5 million per cubic millimeter after taking the diet for about a month. The cases of three belong to this third group. Even so, two had 4,000,000 or more red blood cells per cubic millimeter at the end of four months. The other, the patient transfused several times, has now, after three months of dieting, only 2,600,000 per cubic millimeter. However, his hemoglobin has risen from 25 to 70 percent. The fourth case with a red blood cell count of less than 3,000,000 per cubic millimeter at the end of a month belongs to the second group, and now, two and a half months after the diet was started, shows a



red blood cell count of 3,300,000 per cubic millimeter.

The data from which the table and chart were prepared have been analyzed in various ways, and the following statements indicate in a different manner than they do what satisfactory improvement was shown in the patients' blood. Seventy-six percent of all the patients had 2,000,000 or less red blood corpuscles per cubic millimeter, with their hemoglobin usually 55 percent less before beginning the diet. In contrast to this, approximately a month (from four to six weeks) later, 91 percent had over 3,000,000 and 42 percent over 3,500,000 red blood cells per cubic millimeter, with corresponding rises in the hemoglobin percentage. After taking the diet for about two months (from eight to eleven weeks), 89 percent (of the thirty-seven that had taken the diet this length of time) had 3,500,000 or more red blood corpuscles per cubic millimeter, while 73 percent had 4,000,000 or more. All had a hemoglobin of approximately 80 percent or over. None of the patients studied after they had eaten the food selected for them for between four and six months had less than 3,500,000 red blood cells per cubic millimeter; 81 percent had 4,000,000 or more, and the counts of 30 percent were over 5,000,000 per cubic millimeter. The hemoglobin was 80 percent or above in all, often 90 percent, and in several cases reached more than 100 percent. However, it is to be noted that none of these cases observed between four and six months after the diet was started had appeared as advanced as several of those in patients that improved the least, but which have not yet had the diet for four months. The observations on the eighteen patients who have been on the diet for more than six months show that their count may fluctuate, though it has remained above 3,200,000 per cubic millimeter, and usually has been over 4,000,000, with the hemoglobin remaining at 80 percent or

more. There are three exceptions to this statement, for three patients had a relapse about eight weeks after changing their diet. One did so a year and another seven months after the special diet was begun. There was a count slightly below 3,000,000 per cubic millimeter in both for two or three weeks. Their red blood cells and hemoglobin then very rapidly increased under rest and on eating an increased amount of liver and fruit. The third patient's red cell count was 4,200,000 per cubic millimeter a month before she changed her diet. She has just resumed the special diet, and her red cell count is 1,900,000 per cubic millimeter and hemoglobin 50 percent.

## COMMENT

Cases of pernicious anemia undergoing distinct remissions often show rapid and striking improvement, such as occurred in almost all our patients. A considerable number of them have made such remarks as, "I feel better than for several years," "better than for two years," and "stronger than after the two times my blood went low before." Such statements, to be sure, are made by pernicious anemia patients having remissions that have not taken this diet, and there is no case in this series of forty-five that cannot be paralleled by a similar one having a so-called spontaneous remission. However, the records of eleven cases show that the red blood cell count in the remission following the "liver diet" has remained distinctly higher, not only than in a former remission, but also in three cases higher, for at least two months, than in their three previous remissions. It is, thus, again pointed out here that it is rather unusual to find the red blood corpuscle count in a late remission distinctly above the level obtained in several earlier ones. A few of the patients observed for many months before they took the special diet ate, by our advice, rel-

atively small amounts of liver two or three times a week, together with other food of the sort contained in the special diet. Under such a regimen a moderate degree of improvement occurred in some, to be followed later by a relapse of their case. It was rather striking that when the same patients were placed on a diet rich in liver they improved markedly. This suggests, as do similar observations we made some time ago in other cases, that if liver and food like it play a role in improving the blood of pernicious anemia, it is desirable for the patients to take such food daily and in large amounts.

The spontaneous remissions of pernicious anemia and the bizarre course it often runs make it notoriously difficult to determine accurately the effect of any procedure on the disease. All sorts of therapeutic procedures have been advised; many because a few cases improved promptly after their trial. Waves of enthusiasm for certain methods have vanished soon when it was shown that the earlier reports of benefit could be attributed readily to the natural course of the disease. There is, however, no doubt, as shown by some of the early and more recent investigators, that a well balanced, nutritious diet sometimes aids to enhance a remission. The patient may be helped by numerous other forms of treatment, such as those to change the intestinal flora, the injection of protein substances, the taking of arsenic, the transfusion of blood, and splenectomy.

At least one remission, as has been noted by Cabot [34], takes place at some time, but at no regular time, in about 80 percent of pernicious anemia cases. Precise data are sparse concerning the frequency, degree and rate of remissions in similar groups of cases treated in different ways. Splenectomy has caused quick and marked improvement in 64 percent of the patients undergoing this operation, while about 15 percent more have shown some benefit from the procedure [35]. However,

the remissions that followed have been of no longer duration than those heretofore reported as of a spontaneous nature. Excluding desperately ill patients, Minot and Lee [38] noted in 1917 that about 35 percent of forty patients treated in no especial manner had a moderate or better remission soon after they were seen. Following the transfusion of blood into forty-six similar patients, about 50 percent continued to have definitely improved health for at least many weeks than for some time before the procedure. Not more than 20 percent of the ninety-six patients of these two groups soon had rapid and marked increase in their red blood cells. An analysis of fifty other cases observed between 1916 and 1923 in sequence, except for several in a terminal condition, indicates that 45 percent developed a definite remission soon after we saw them. These patients were treated in various ways by numerous physicians, but did not eat large amounts of liver or similar food. The remissions were seldom of marked degree, with the red blood corpuscles reaching 4,000,000 or more per cubic millimeter.

No entirely satisfactory data have been found concerning the frequency of remissions following the use of a nutritious high caloric diet and such a regimen as that prescribed by Barker and Sprunt. We have treated in this manner twenty-five partially selected cases, from which it appears that distinct remissions may follow such therapy in about 65 percent of the instances. Even so, apparently the red blood cell counts of patients on such a diet and who were improved distinctly at the end of one or two months averaged less than for all forty-five who have eaten generously of liver for the same amount of time.

The evidence at hand suggests that the dietetic treatment of pernicious anemia is of considerable importance. It has been possible to demonstrate in forty-five cases

seen essentially in sequence that following a diet rich in liver and low in fat a distinct remission of the anemia occurred rather promptly. The promptness and rapidity with which the red blood corpuscles and hemoglobin increased, coincident with at least rather marked subjective improvement in the sense of well being and clinical appearance of all the patients and the strikingly better health of many, is at least unusual in pernicious anemia. It is also not customary for the red blood cell counts during remissions of pernicious anemia to be so frequently of the height that occurred in these patients. We are inclined to believe that something contained in the foods rich in complete proteins is particularly responsible for the improvement in the state of the blood. The low fat content of the diet is assumed to have a less important effect than the character and amount of protein, although probably excess of nitrogen per se is unimportant. If liver and similar food is of value, every means must be taken, including the skill of the nurse and cook, 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.

There are no data to indicate whether the remissions in these forty-five cases will last longer than those of others.

It is possible that this series of cases eventually may be proved to be unusual in that there happened to be treated a group that would have taken a turn for the better under other circumstances. Also, time may show that the special diet used, or liver and similar food, is no more advantageous in the treatment of pernicious anemia than any ordinary nutritious diet. Let this be as it may, at the present time it seems to us as it has to Gibson and Howard, that it is wise to urge pernicious anemia patients to take a diet of the sort described.

## SUMMARY

The dietetic treatment of pernicious anemia is of more importance than hitherto generally recognized. Forty-five patients with pernicious anemia observed essentially in sequence are continuing to take a special diet that they have now been living on for from about six weeks to two years but which was temporarily omitted by three. This diet is composed especially of foods rich in complete proteins and iron — particularly liver — and containing an abundance of fruits and fresh vegetables and relatively low in fat.

Following the diet, all the patients showed a prompt, rapid and distinct remission of their anemia with at least rather marked symptomatic improvement except for pronounced disorders due to spinal cord degeneration. Improvement was often striking, so that where the red blood cell count averaged for all before starting the diet 1,470,000 per cubic millimeter, one month afterward it averaged 3,400,000; and for the twenty-seven cases observed from four to six months after the diet was begun, the average count was 4,500,000 per cubic millimeter.

Patients having had two or more relapses showed on the average slightly lower red blood corpuscle counts about one and two months after commencing than did those who had started it in their first or second relapse.

Change in the frequency of bowel movements, temporary increase of reticulocytes in the peripheral blood, and decrease of the icterus index of the blood serum were among the earliest signs that heralded the patient's better health.

All the patients have remained to date in a good state of health except three, who discontinued the diet, two rapidly improved on resuming it, and the other has just commenced it again. As the diet was advised for most of the patients less than eight months ago, enough time has not yet elapsed to determine whether or not the

remissions will last any longer than in other cases

### SUBSEQUENT OBSERVATIONS

Since the data presented in this paper were compiled, the following additional information has been obtained: The eight patients who had taken the diet for only about one month had red blood cell counts at the end of about two months of between 3,500,000 and 6,000,000, with an average of 4,400,000 per cubic millimeter. One of these had but 2,500,000 at the end of one month and now at the end of three and a half months has 4,500,000 per cubic millimeter.

The ten patients recorded as having taken the diet for only about two months showed in four to six months after starting it as follows: seven had an average red blood cell count of 5,100,000 per cubic millimeter. One who had had about 5,000,000 had but 3,500,000 per cubic millimeter. Another who had 2,500,000 per cubic millimeter at the end of the second month had at the latter time 3,000,000 per cubic millimeter.

The patient who had the diet from four to six months, or longer, when the data were compiled, continued in the next two and a half months to have on the average as satisfactory counts, except as noted below. The majority of these have shown higher counts than formerly. Two of the cases have had at three different times red blood cell counts of 6,000,000 or more per cubic millimeter. Two patients who have had the diet for more than six months have recently eaten very little liver, and their counts have fallen in two months from about 4,000,000 to about 3,000,000 per cubic millimeter. The red blood corpuscles of the patient referred to previously as in a relapse increased 3,000,000 per cubic millimeter during the first eight weeks after the diet was resumed.

Information at hand suggests that some cases in which transfusion is done many times before the diet is started may respond but little to it.

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