

the illness. A large number of them were under personal observation during the major part of the illness. There is one patient living, aged 11 years, who has been twelve months in the hospital with a continued fever during all of that time, and is now succumbing to heart failure. The records of reported cases indicate only a limited number of recoveries. Dr. Libman, in 300 cases, has seen only four recoveries. In a series of 189 cases reported by Sir Thomas Horder in 1922, there were four recoveries. Among our series we have one patient who has been bacteria-free and fever-free during the last three years. Another has been fever-free for six months. There are five patients in the series still living who have been ill for periods varying from twenty-two to fifty weeks, yet it does not seem likely that any of them will recover. The first patient in the series was a young man, seen during the primary rheumatic infection in 1911. He recovered from the acute rheumatism, but had an aortic insufficiency as the result. Six years later he passed through a ten weeks' course of fever, with a positive blood culture, and a diagnosis of subacute bacterial endocarditis was rendered. He recovered from this and was apparently well for about three years, when he developed the final attack of subacute bacterial endocarditis, being ill for a period of twenty-two weeks. At the necropsy there were definite healed areas on the mural endocardium, which were evidently connected with the period of infection sustained three years previously. It appears well established that such a healing process does occur in a limited number of cases, and these no doubt explain most of the so-called cures.

DR. JOHN H. MUSSER, New Orleans: Dr. Stone spoke about the importance of pneumonia as a cause of pericarditis. I might say that in 304 cases pneumonia was responsible for the greatest number of pericardial lesions.

TREATMENT OF PERNICIOUS ANEMIA BY A SPECIAL DIET*

GEORGE R. MINOT, M.D.
AND
WILLIAM P. MURPHY, M.D.
BOSTON

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, Habershon¹ 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 Biermer² 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."

* This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Disease.

* From the Medical Clinic of the Peter Bent Brigham Hospital, and the Medical Service of the Collis P. Huntington Memorial Hospital of Harvard University.

1. Habershon, S. O.: On Idiopathic Anemia, *Lancet* **1**: 518, 551 (May 9) 1863.

2. Biermer: Halt Zunächst einen Vortrag über eine von ihm öfters beobachtete eigenthümliche Form von progressiver perniciouser Anämie, welche mit Capillären Blutungen der Haut, Retina, des Gehirns &c., *Cor.-Bl. f. Schweiz. Aerzte* **2**: 15 (Jan. 15) 1872.

3. Pepper, W.: Progressive Pernicious Anaemia or Anhaematosi, *Am. J. M. Sc.* **70**: 313 (Oct.) 1875.

4. Osler, William: Pernicious Anemia: A System of Practical Medicine, edited by Pepper, W., assisted by Starr, L., Philadelphia, Lea Brothers Company **3**: 898, 1885.

During the last half century, many clinicians, following the suggestions of the pioneer writers on the subject of pernicious 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 an 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. Grawitz⁸ recommended a diet composed chiefly of fresh 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 Mosenthal⁹ 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 Menghini¹⁰ 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 Howard¹¹ 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 Smith¹² and of Barker and Sprunt¹³ 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

5. Fenwick, S.: On Atrophy of the Stomach in Relation to Pernicious Anemia, *Lancet* **2**: 77 (July 21) 1877.

6. Naegeli, O.: Blut Krankheiten und Blutdiagnostik, Leipzig, von Veit & Co., 1912.

7. Hunter, W.: Observations on Treatment of Pernicious Anemia Based on a Study of Its Causation, *Brit. M. J.* **2**: 1, 81, 1890.

8. Grawitz, E.: Zur Frage der entgegen en Entstehung schwerer Anämien, *Berl. klin. Wchnschr.* **1**: 641 (June 17) 1901.

9. Mosenthal, H.: The Effect of Forced Feeding on the Nitrogen Equilibrium and the Blood in Pernicious Anemia, *Bull. Johns Hopkins Hosp.* **29**: 129 (June) 1918.

10. Menghini, quoted by Christian, H. A.: A Sketch of the History of the Treatment of Chlorosis with Iron, *Medical Library and Historical Journal* **1**: 176 (July) 1903.

11. Gibson, R. B., and Howard, C. P.: Metabolic Studies in Pernicious Anemia, *Arch. Int. Med.* **32**: 1 (July) 1923.

12. Smith, quoted by Fitch, W. E.: Dietotherapy, ed. 2, New York, D. Appleton & Co. **3**: 257, 1922.

13. Barker, L. F., and Sprunt, T. P.: The Treatment of Some Cases of So-Called "Pernicious" Anemia, *J. A. M. A.* **69**: 1919 (Dec. 8) 1917.

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 Shakespeare¹⁵ 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 Jencks¹⁶ 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 Kühl¹⁸ on man, the favorable rôle 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.

14. McCarrison, Robert: Faulty Food in Relation to Gastro-Intestinal Disorder, *J. A. M. A.* **78**: 1 (Jan. 7) 1922. Benedict, F. G.; Miles, W. R.; Roth, P., and Smith, H. M.: Human Vitality and Efficiency Under Prolonged Restricted Diet, pub. 280, Carnegie Inst. of Washington, 1919, p. 364.

15. Shakespeare: Henry IV, act 2, scene 3.

16. Jencks, Z.: Studies in the Regeneration of Blood, *Am. J. Physiol.* **59**: 240 (Feb.) 1922.

17. Hammarsten, O.: A Text Book of Physiological Chemistry, trans. by Mandel, J. A., ed. 5, New York, J. J. Wiley and Sons, 1908, p. 244.

18. Morawitz, C., and Kühl, G.: Der Blutumsatz des Normalen unter verschiedenen Bedingungen (Eisen, Aisen, Fleisch), *Klin. Wchenschr.* **4**: 7, 1925.

19. Pearce, R. M.; Krumbhaar, E. B., and Frazier, C. H.: The Spleen and Anemia, Philadelphia, J. B. Lippincott Company, 1918.

20. Smith, A. H., and Moore, T. S.: Diet and Tissue Growth: The Regeneration of Liver Tissue During Nutrition or Inadequate Diets and Fasting, *J. Exper. Med.* **40**: 209 (Aug.) 1924.

21. Hirasawa, quoted by Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 334.

22. Whipple, G. H.; Hooper, C. W., and Robscheit, F. S.: Blood Regeneration Following Simple Anemia, *Am. J. Physiol.* **53**: 151, 167 (Sept.) 1920. Whipple, G. H.; Robscheit, F. S., and Hooper, C. W.: Blood Regeneration Following Anaemia, *ibid.* **53**: 236 (Sept.) 1920. Whipple, G. H., and Robscheit-Robbins, F. S.: Favorable Influence of Liver, Heart and Skeletal Muscle in Diet on Blood Regeneration in Anemia, *ibid.* **72**: 408 (May) 1925 (cf. p. 431); Iron Reaction Favorable, Arsenic and Germanium Dioxide Almost Inert, in Severe Anemia, *ibid.* **72**: 419 (May) 1925.

McCollum²³ 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 Rohdenburg²⁴ have shown that the products of nuclein hydrolysis can stimulate growth. Whipple²⁵ 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 Fraser²⁶ 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 rôle they may play in pernicious anemia. Stoeltzner²⁷ recently has reviewed the subject. Also, lipoids have been shown by Baker and Carrel²⁸ to be a factor in serum that can inhibit growth. Thus, founded on somewhat theoretical grounds, it seemed to us, as it did to Stoeltzner²⁷ 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

23. McCollum, E. V.: The Newer Knowledge of Nutrition, New York, the Macmillan Company, 1923.

24. Calkins, G. N., Bullock, F. D., and Rohdenburg, G.: The Effects of Chemicals on the Division Rate of Cells with Especial Reference to Possible Pre-Cancerous Conditions, *J. Infect. Dis.* **10**: 421 (May) 1912.

25. Whipple, G. H.: Pigment Metabolism and Regeneration of Hemoglobin in the Body, *Arch. Int. Med.* **29**: 711 (June) 1922.

26. Fraser, T. R.: Bone Marrow in the Treatment of Pernicious Anemia, *Brit. M. J.* **1**: 1172 (June 2) 1894.

27. Stoeltzner, W.: Ein Vorschlag zur Behandlung der Biermerschen Anämie, *München. med. Wchenschr.* **68**: 1558 (Dec. 2) 1921.

28. Baker, L. E., and Carrel, Alexis: Lipoids as the Growth-Inhibiting Factor in Serum, *J. Exper. Med.* **42**: 143 (July) 1925.

America, in which areas the disease is relatively common. These different facts permit one to speculate on the possible partial rôle 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-Robbins³⁰ 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 rôle 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 Fenlon³¹ 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 diet³² used 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 grams or more of beef or mutton muscle meat.
3. Not less than 300 Gm. of vegetables containing from 1 to 10 per cent 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

29. Elders, C.: The Form, Course and Prognosis of the Anemia in Indian Sprue and the Etiology of Pernicious Anemia. *Nederlandsch Tijdschr. v. Geneesk.* 58: 2267, 1922.

30. Footnote 22, third reference.

31. Fenlon, R. L.: A Diet for Pernicious Anemia, *J. Iowa State M. Soc.* 11: 50 (Feb.) 1921.

32. Details concerning this diet with sample menus are given in a paper to be published soon in the *Boston Medical and Surgical Journal*.

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 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 usually within 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 per cent to usually about 8.0 and even to 15.5 per cent 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 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 synopsized 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

Average Red Blood Corpuscle Count*

Before Diet Started		After Diet Started					
Number of Cases	Average R. B. C. Count in Millions	About 1 Month		About 2 Months		4 to 6 Months	
		Number of Cases	Average R. B. C. Count in Millions	Number of Cases†	Average R. B. C. Count in Millions	Number 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.

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 per cent) 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 synopsizing 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

33. These changes in the blood and numerous others will be presented in a subsequent paper.

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 anemia 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 per cent. 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 per cent of all the patients had 2,000,000 or less red blood corpuscles per cubic millimeter, with their hemoglobin usually 55 per cent or less before beginning the diet. In contrast to this, approximately a month (from four to six weeks) later, 91 per cent had over 3,000,000 and 42 per cent over 3,500,000 red blood cells per cubic milli-

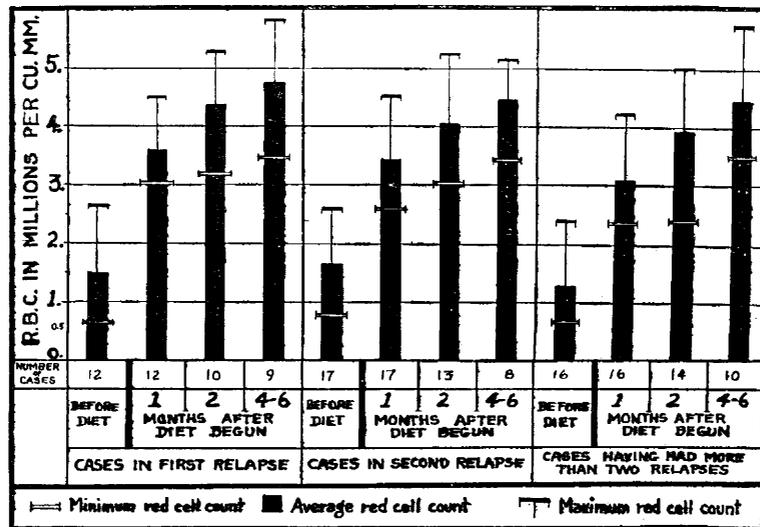
meter, with corresponding rises in the hemoglobin percentage. After taking the diet for about two months (from eight to eleven weeks), 89 per cent (of the thirty-seven that had taken the diet this length of time) had 3,500,000 or more red blood corpuscles per cubic millimeter, while 73 per cent had 4,000,000 or more. All had a hemoglobin of approximately 80 per cent 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 per cent had 4,000,000 or more, and the counts of 30 per cent were over 5,000,000 per cubic millimeter. The hemoglobin was 80 per cent or above in all, often 90 per cent, and in several cases reached more than 100 per cent. 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 per cent 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 per cent.

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 counts in forty-five cases of pernicious anemia before and after beginning special diet. Cases grouped according to the number of relapses the patients had 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.

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, relatively 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 rôle 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 per cent 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 per cent of the patients undergoing this operation, while about 15 per cent 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 Lee³⁶ noted in 1917 that about 35 per cent 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 per cent continued to have definitely improved health for at least many weeks than for some time before the procedure. Not more than 20 per cent 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 per cent 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 per cent 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.

34. Cabot, R. C.: Pernicious Anemia, in Osler and McCrae's Modern Medicine, ed. 2, Philadelphia, Lea and Febiger 4, 1915.

35. Krumbhaar, E. B.: Late Results of Splenectomy in Pernicious Anemia, J. A. M. A. 67:723 (Sept. 2) 1916.

36. Minot, G. R., and Lee, R. I.: Treatment of Pernicious Anemia Especially by Transfusion and Splenectomy, Boston M. & S. J. 177:761 (Nov. 29) 1917.

Following the diet, all the patients showed a prompt, rapid and distinct remission of their anemia, coincident 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 the diet 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 the same number two months later, although symptomatically he seemed better. The tenth patient could not obtain the proper diet between the second and fourth month, and had at the latter time 3,000,000 per cubic millimeter.

The patients 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 on page 474 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.

Resistance to Flow of Bile.—The reaction of the gastric contents may conceivably influence the resistance to the flow of bile into the intestine. For there is an immediate lessening in the resistance on the taking of food, and a gradual increase in the half hour or hour following, during which the reaction of the gastric contents is presumably becoming more acid. Since food may at this time be passing through the pylorus, a possible mechanical effect of peristalsis may in addition be invoked to explain the findings.—Elman, Robert; and McMaster, P.D.: *J. Exper. Med.*, Aug. 1, 1926.

THE RELATION OF ANEMIA, PRIMARY AND SECONDARY, TO VITAMIN A DEFICIENCY *

KARL K. KOESSLER, Ph.D., M.D.
SIEGFRIED MAURER, M.D.
AND
ROSEMARY LOUGHLIN, M.S.
CHICAGO

The opinion that the toxemia responsible for the production of the symptoms of pernicious anemia (hematopoietic, gastro-intestinal and nervous) is of intestinal origin is chiefly based on the prominence of the gastro-intestinal symptoms of the disease. The atrophic degeneration of the tongue, the Hunterian glossitis, the achylia gastrica which frequently precedes the anemia by many years, the atrophy of the gastric and intestinal mucosa found occasionally post mortem as the anatomic substratum of the achylia, direct the attention to the gastro-intestinal tract. To this may be added the association of severest anemia with intestinal parasites and occasionally with incomplete obstruction. Though the anemia found in intestinal malignancy can usually be distinguished from the pernicious anemia of unknown etiology, it is noteworthy that a relatively small carcinoma of the ileum or first part of the cecum is frequently associated with a profound anemia.

It may be assumed that the involvement of the three organ systems (hematopoietic, gastro-intestinal and nervous) has a common cause and is therefore dependent on the same toxic factor, or that the phenomena are dependent on one another. The latter view would concede to the achylia gastrica and the atrophic changes in the fundus glands and intestinal mucosa a dominant rôle, which leads secondarily to the involvement of the other systems by the absorption of a hemotoxic and neurotoxic substance.

It seems true that the stomach, and especially the upper small intestinal tract, are invaded by a flora in pernicious anemia which is absent or scanty in normal conditions. Certain investigations, following the earlier work of Christian Herter, have directed attention again to the presence of large numbers of *B. aerogenes-capsulatus (welchii)* in the duodenum, and Kahn and Torrey¹ were able to produce by intravenous injection of the toxin of this organism a disease picture in monkeys that is very suggestive. In the opinion of these investigators it is a "specific toxin" which produces the profound anemia with its characteristic features, the achylia and the combined sclerosis of the spinal cord.

Other investigators observed that the common colon bacillus is found in much greater frequency and number in the upper intestinal tract in pernicious anemia patients than in normal persons. Both *B. welchii* and *B. coli* being normal inhabitants of the human intestinal tract, their etiologic relation to pernicious anemia must depend either on an abnormally large number present in a part of the small intestine, where they are normally exceedingly scarce and uncommon, or on certain specific strains that have the faculty of forming a specific poison not formed by other strains of the same bac-

* From the Otho S. A. Sprague Memorial Institute and the Department of Pathology, University of Chicago.

1. Kahn, M. C., and Torrey, J. C.: A Pernicious Anemia-Like Blood Condition Produced in Monkeys with *B. Welchii* Toxin, *Proc. Soc. Exper. Biol. & Med.* 22: 8-13, 1925.