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THE TREATMENT OF SOME CASES OF SO-CALLED "PERNICIOUS" ANEMIA

A REGIMEN THAT HAS BEEN FOUND HELPFUL *

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"Pernicious anemia," so called, formerly often overlooked, is now generally recognized, when encountered, by physicians who have been trained in the modern methods of examining the blood. Indeed, once the anemia is well developed, the appearance of the patient is so characteristic that its existence is likely to be suspected at first sight before any examination of the blood has been made. In the office of a consulting physician, where these patients are often entering, it is by no means uncommon to have an observant office secretary, who has grown familiar with the pallor, the lemon-yellow tint to the skin, the weakness and the dyspnea, remark that "the patient coming in looks as though he had pernicious anemia."

Though it is easy to place a patient of this sort in a great group designated "pernicious anemia," we know now that this group does not represent a unity. And, of late, we have learned to divide the general group into several subgroups, our classifications being based partly on the blood findings, partly on etiologic considerations. Formerly, it was common to speak of pernicious anemia as a primary or idiopathic anemia, to distinguish it from a secondary anemia due to disease of some organ, to hemorrhage, or to some other known etiologic factor. The terms "primary" and "secondary" anemia are still used, though we now realize that, in the last analysis, there can be no such thing as a strictly "primary" anemia. Again, Ehrlich's attempt to separate pernicious anemia from other anemias on the basis that the regenerative forms of red corpuscles found in the blood are of embryonal rather than of postembryonal type (megaloblasts rather than normoblasts) broke down when it was found that this criterion, though a helpful one, does not admit of strict application. Though no basis of classification of the severe anemias is as yet wholly satisfactory, a separation of those due to increased blood destruction (the hemolytic anemias) from those due to loss of blood by hemorrhage and from those due to defective or

decreased blood formation has been found helpful. The old group of so-called "pernicious anemias" contained subgroups belonging to at least two of these categories. Thus formerly the severe hemolytic anemias and the aplastic, or aregeneratory, anemias were lumped together in the pernicious group. By far the majority of cases that were designated pernicious anemia were, however, hemolytic anemias due to increased blood destruction; only a few of them were aplastic anemias due to decreased blood formation. And the matter was further complicated when it was discovered that a hemolytic anemia may sometimes, after exhaustion of the regenerative power of the bone marrow, enter into an aplastic stage. And, finally, an analysis of the severe hemolytic anemias themselves showed that they, in turn, are divisible into further subgroups depending on their etiology. Among these subgroups may be mentioned (1) the hemolytic anemia due to invasion of the intestine by *Dibothriocephalus latus*; (2) the hemolytic anemias due to syphilis, to carcinoma, and to intoxications in the puerperium; (3) the hemolytic anemias due to certain known chemical poisons, as potassium chlorate, nitrobenzene and phenylhydrazin, and (4) the hemolytic anemia that accompanies congenital hemolytic icterus. But after these subgroups had been recognized, it was found that the majority of severe chronic hemolytic anemias still remained unaccounted for, and it has been, and still is, customary to refer to these cases of unknown (or at least unsettled) etiology as "Addisonian anemia," or "Biermer's anemia," or as the "Addison-Biermer type of pernicious anemia."

Without further introduction, we may say that it is the last group of severe hemolytic anemias mentioned, and to it only, to which we shall refer in the present paper. We must agree with William Hunter and other writers who deprecate the use of the ill defined term pernicious anemia, unless, when it is made use of as a designation, the clinical description is such that the reader will have no doubt as to just what the writer means by it. Since the blood picture in the Addison-Biermer type of anemia is indistinguishable from the blood picture of the forms of hemolytic anemia of known etiology, some of which are curable, it is conceivable that still other groups will be separated out from the Addison-Biermer group as soon as their cause has been discovered. Or it may even be that the cases now remaining in the Addison-Biermer group will later be proved to have a single cause (focal infection? enterogenous intoxication?). The disease we are referring to has been so fully described in modern textbooks¹ that no extended account need

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* Owing to lack of space this article has been abbreviated in THE JOURNAL by omission of some of the case reports. The complete paper appears in the Transactions of the Section and in the author's reprints.

1. Cabot, Osler and McCrae: Modern Medicine, Ed. 2, 1915. Barker: Chronic Hemolytic Anemia of Unknown Etiology, Clinical Diagnosis of Internal Diseases, 1916.

here be given. It will suffice to recall that (1) it is commonest in people of middle age; (2) the well to do are affected almost as often as the poor; (3) men and women are affected in approximately equal numbers; (4) the onset is, as a rule, insidious, the patients complaining of weakness without apparent cause, of increasing pallor (with straw-colored tint to the skin), of dyspnea, of gastro-intestinal disturbances, and of nervous symptoms; (5) the urine is usually high colored and contains an increased amount of urobilin; (6) there is always gastric anacidity, and (7) the blood changes characteristic of a hemolytic anemia are demonstrable (reduced red count; anisocytosis; poikilocytosis; high color index; often regeneration signs, including nucleated red cells, polychromatic red cells and basophilic stippling; moderate leukopenia with relative lymphocytic increase, and a diminished number of platelets). There is often a little fever, but not always. Numbness and tingling in the hands or feet are not uncommon; in the later stages, the anesthetics, paralyses or ataxias due to the lesions in the spinal cord described by Frank Billings and others may be encountered. Pyorrhea alveolaris, peridental abscesses or other signs of oral sepsis may be present. Remissions in the course of the disease are common. They may occur spontaneously; more often, they follow, and seem to be produced by the application of one or another form of therapy. When a remission occurs, the patient may remain well for months, or even for years. Several exacerbations, separated by remissions, may be encountered in a single patient. Clinical experience teaches us to be very guarded regarding prognosis, for in the majority of cases, sooner or later, a relapse occurs that does not yield to treatment, but goes on to a fatal termination.

UNSATISFACTORY STATE OF PREVIOUS PLANS OF THERAPY

The bibliography of the subject contains great numbers of reports on the various methods that have been used in the treatment of pernicious anemia, and certain of these methods have been, and still are, warmly advocated by their adherents. Their very multiplicity is evidence that in none of them has, as yet, a really satisfactory plan of therapy been found. Indeed, until the etiology and the pathogenesis of the Addison-Biermer type of anemia are better understood, and until more is known of the mechanisms of pathologic hemolysis and of regenerative hemato-poiesis, an entirely satisfactory method, applicable in all cases, need scarcely be expected.

Among the forms of therapy that are most in vogue may be mentioned (1) dietetic-hygienic measures; (2) pharmacotherapy (iron, arsenic, quinin, hypophosphites, cholesterin, glycerin, oxygen inhalations, hydrochloric acid, intestinal antiseptics, salt infusions), radium, thorium and the roentgen ray; (3) subcutaneous or intravenous injections of whole or of defibrinated blood; (4) the combating of oral, gastric and intestinal sepsis, and (5) splenectomy.

William Hunter did a great service in emphasizing the importance of not being content with the application of single measures in the treatment of addisonian anemia, urging a "general management of the case, with close observation of all its features, especially of its gastric and intestinal symptoms, of its fever, and of its hemolytic symptoms, extending not merely over the period of acute illness, but also over many months and years subsequent to the first remission."

In this paper we wish to make no extravagant claims for the methods we have employed, but desire simply to set forth a general regimen that, during the past few years, has, when it has been systematically applied, yielded favorable results in at least one group of cases of anemia of the Addison-Biermer type. We say "one group of cases," for we have had other cases that have not responded favorably to the regimen. Why the one set of cases responded whereas another set did not, we do not know. Thus far, we have been unable satisfactorily to differentiate between the two classes of cases before the therapy has been applied.

REGIMEN USED BY THE AUTHORS

1. *The Diagnostic Study.*—When an anemia of the Addison-Biermer type is suspected, the patient is sent at once into a *private room in the hospital*, where the physical examinations and laboratory tests are made with the least possible discomfort to the patient and with avoidance of exertion on his part. If the anemia is severe, we ask the patient to give himself over to us entirely for a time, gaining his *consent to forego both letters and visits*, even from members of his family, for a time. He is required to remain in bed, undressed, constantly, the *rest in bed* being made as nearly absolute as possible, aside from the interruptions necessitated during the first week by the application of diagnostic methods. An experienced *special nurse* is secured whose sole duties consist in administering to the care and comfort of the patient, tactfully securing observance of all directions issuing from the physicians.

After the anamnesis has been recorded, and the general physical examination of the different systems made, the blood, gastric juice, feces and urine are carefully studied and a thorough *search for focal infections* is undertaken. In this search, the special domains of the body known to be prone to focal infection are closely examined, whenever possible by men who devote their whole attention to particular fields. Thus the teeth and gums are inspected by a consulting dentist, expert in oral diagnosis; the extent of any pyorrhea present is reported; roentgenograms of dead teeth are made and the films closely examined for periapical areas of resorption and for paradental infection. Glossitis, or stomatitis, if present, is carefully noted. A nose and throat specialist is asked to report on the condition of the nose, throat, ears and paranasal sinuses as revealed by direct inspection and by transillumination. In addition, roentgenograms of the paranasal sinuses by the method of Waters and Waldron are made in every case as a supplement to, and control of, the rhinologist's examination. The digestive tract, already studied by physical and chemical methods, is further examined by roentgenoscopy (after barium intake), and if there is any suspicion of ulcer, of appendicitis, of cholecystitis, of ileal or cecal stasis, or of diverticulitis, serial roentgenograms are also made. The urogenital tract is subjected to special examinations also, urethritis, cystitis and pyelitis being sought for in both sexes, in addition to a search for prostatitis and seminal vesiculitis in the male, and for vaginitis, cervicitis, endometritis and pelvic inflammatory disease in the female.

2. *Surgical Treatment.*—In case focal infection is found, even though it appears to be trivial, we usually attempt to eradicate it, for in our experience it pays in the severe anemias, just as in the arthritides, to be radical rather than conservative in the treatment of any infection found.

In the mouth, stomatitis and glossitis receive appropriate local applications; infected teeth are extracted and the sockets are curetted and treated for a few days with iodine solution; gingivitis and pyorrhea alveolaris are treated by a pyorrhea specialist. Any teeth loosened by pyorrhea are extracted. Pyorrheal pockets are carefully curetted and locally treated. After the mouth has been put in good condition, the patient is instructed in the details of a proper mouth toilet, the nurse seeing to it that the technic is acquired and regularly applied.

In the nose, throat and ear, any active infection found is treated at once. For example, a suppurating sinus (antrum, ethmoid, etc.) will be drained; infected adenoids or badly infected tonsils will be removed, though great care should be taken not to subject the patient to an operation on the tonsils merely because they are adherent, or because tonsillitis has previously existed. Here the common sense of the physician in charge may often be required to check the *cacoethes secundi* of an overzealous specialist. Similarly, the best judgment of the physician will be called on in deciding for or against operation for suspected infection elsewhere (gallbladder, appendix, renal pelvis, endometrium, etc.).

In our experience, infections of the teeth and gums have more often than any other infection required immediate attention in pernicious anemia. Rapid improvement has so frequently followed the treatment of such oral sepsis that we cannot help but feel, with William Hunter, that this side of the treatment is, in many cases, very important, and that poisoning from oral sepsis may, in some cases at least, play an etiologic rôle.

It is surprising how well patients with severe hemolytic anemia bear the operations necessary for the removal of foci of infection. At first we were loath to permit even minor surgical operations on these patients, but after a few trials we became convinced that our reluctance had been unfounded. Even with a red corpuscle count as low as 1,500,000 and a hemoglobin of 30 per cent., the patients stand, without harm, a short general anesthesia for extraction of teeth, or for such a procedure as the puncture and cleaning of an infected antrum. It has been rare, too, to see any unusual bleeding follow these minor surgical measures. Should any major operation be indicated, it is best deferred, unless very urgent, until a decided improvement in the condition of the blood has been obtained. Thus one of our patients, who suffered from a cystitis, due to leading a catheter life because of prostatic hypertrophy, came in with a hemoglobin percentage of 38 and a red corpuscle count of 1,400,000. He had several infected teeth, which were removed at once. The blood rapidly improved, and when the hemoglobin had reached 80 per cent., we asked Dr. Young to remove the prostate. The patient bore the operation perfectly well, the cystitis soon cleared up, and he has remained well since.

3. Dietetic Treatment.—We believe that attention to the diet of the patient is especially important. Gastrointestinal disturbances are so common in the disease that they have come to be looked on as more or less characteristic of the symptomatology. Owing to the gastric anacidity there is hypermotility of the stomach, too rapid emptying of that viscus, and frequently diarrhea. The disinfectant properties of the gastric juice are lost, owing to the absence of hydrochloric acid, and abnormal fermentative processes doubtless occur.

Eructations, meteorism and general abdominal discomfort are common, and there are sometimes critical exacerbations of these abdominal disturbances. Anorexia is a prominent symptom, and nausea and vomiting are frequently present. It is but little wonder that, as a result of all these conditions, the patients, either on their own initiative, or at the advice of physicians, make attempts to modify their diet so as to secure relief from symptoms. As is well known, these symptoms tend to persist for a time, no matter what kind or quantity of food is ingested. We find that most of the patients that have come to us have reduced their food intake quantitatively far below their needs, and that nearly all are on a qualitatively ill-balanced diet. Moreover, though they may be perfectly willing to rest, their aversion for food and their fear of what may follow eating often make them quite unwilling, and at first even unable, to eat. For this reason, it is our custom to begin, in the severer cases, with the milk diet of Dubois; on the first day we give $2\frac{1}{2}$ ounces of milk every two hours from 7 a. m. to 9 p. m., the two hourly quantity being increased each day until by the sixth day the patient is receiving some 3 liters (quarts).

On the seventh day, we permit a small piece of bread and a little jam at breakfast time, and at mid-day we send in a full tray of easily digestible foods. From the beginning, the patient is encouraged to drink all the milk brought to him, regardless of any disinclination he may feel, or of any consequences that may follow it, and the special nurse tactfully but firmly sees that he takes it. Even if there is some vomiting, the milk is given again at the regular times. The same system is followed after the milk diet has been succeeded on the seventh day by a full and varied diet. The patient is encouraged to eat regardless of choice or of inclination, and to empty each dish on the tray. At first the portions sent are not too large, but during the next few days they are rapidly increased in size until the patient is on an abundant roborant diet, rich in protein, and, if he is thin, in carbohydrate and fat also. At this time, too, the patient is asked to swallow a raw egg (with a little orange juice) immediately after each of the three meals. A little later on, two raw eggs after each meal may be given. In our experience, most patients find it easier, when taking three large meals, to swallow the raw eggs immediately after the meals rather than to take them as "intermediate nourishment." Extra milk, too, is given, as far as possible, with meals, rather than between them. Many patients may, within two or three weeks, be induced to take six raw eggs, a quart and a half of milk and a pint of cream, each day, in addition to three full meals. In this way, the daily dietary of the thin patient may easily reach an intake of 4,000 or 5,000 calories. After the first period is over and some gain in strength has been made, an intelligent patient may often be helped, if eating is still hard for him, by giving him a book like Locke's "Food Values," and asking him to figure out, with the aid of the nurse, the number of calories in the diet ingested and to keep a food chart recording the intake of protein, carbohydrate and fat. Interest is soon aroused in securing a gain in weight, as well as in the rising red corpuscle curve and hemoglobin curve after these begin to show improvement. Not a few anemic patients are overweight, and when such obesity exists, we make sure of a large intake of proteins (meat, eggs), green vegetables in purée form, and stewed fruits, keeping the intake of carbohydrates and

fats low, in such instances, so that the total caloric intake does not exceed 1,000 or 1,500 calories per day.

The dietetic treatment can be materially aided, also, by measures taken to improve the appetite and to overcome the oral, gastric and intestinal disturbances (see pharmacotherapy).

4. *Fresh Air*.—The windows of the patient's room are kept constantly wide open, though care is taken to insure his warmth in bed. After the diagnostic study has been completed and any preliminary surgical therapy has been got through with, the patient's bed is wheeled out on a porch, where he spends a large part of each day (preferably in the sunshine); in some cases, the patient is encouraged to spend the whole night in the open air, carefully protected from cold.

5. *Pharmacotherapy*.—This plays a subordinate but, in our opinion, a very helpful part in the treatment of a severe anemia. Above all, pharmacotherapy can be a great aid to digestion in patients who suffer from pernicious anemia. On account of the gastric anacidify, we give from 20 to 30 drops of dilute hydrochloric acid (with or without pepsin) with each meal, and the same dose is repeated about half an hour after the meal. Croftan has used even larger doses and, he believes, with good results. In addition, it is our custom to give 45 grains of pancreatin with 45 grains of calcium carbonate three hours after each meal. In view of the fact that hydrochloric acid is absent from the stomach juice and that the pancreatin is further protected by the alkaline calcium carbonate that is given with it, it seems reasonable to assume that much of the pancreatin may pass through the stomach uninjured and reach the intestine in a form capable of aiding in intestinal digestion. Certain it is that many of our patients on this regimen quickly become able to eat large amounts of food, making but few complaints of abdominal discomfort. We regard the hydrochloric acid treatment, however, as much more important than the treatment with pancreatin and calcium carbonate; and when patients, as some will, complain of finding the swallowing of the pancreatin disagreeable, we omit this part of the treatment.

A bitter tonic—say 10 minims of tincture of nuxvomica in 1 dram of compound tincture of gentian—given ten or fifteen minutes before each meal may do something toward improving the appetite, though the hydrochloric acid treatment alone, along with the encouraging psychotherapy, is usually followed by a sufficient food intake. The digestive disturbances often clear up in a remarkable way after the measures described have been applied. If they do not, one must keep a close watch for the development of signs of an underlying malignant disease, for, as is well known, a carcinoma of the stomach may for a time masquerade as a pernicious anemia.

Medical tradition as regards the beneficial effects of arsenic in the treatment of these patients we believe to be well founded, and we have used it in every case. Formerly, we used either liquor potassii arsenitis (Fowler's solution) or pills of arsenous oxid and pepper (Asiatic pills²), but of late we have given the arsenic in the form of sodium cacodylate, by intramuscular injection. It has seemed to us best to use rather small doses. We give only 50 mg. per dose, once daily for eight days; after an interval of two weeks, a second course of eight injections is given.

This does not upset digestion, whereas Fowler's solution sometimes irritates the digestive tract. In a few cases, we have used small intravenous injections of salvarsan (0.3 gm.), and with Byron Bramwell and with T. R. Boggs have felt that it had a good effect; as a routine mode of giving arsenic to these patients, however, we adhere to the intramuscular injection of sodium cacodylate.

6. *Massage; Exercise*.—As we have said, we keep the patients at the beginning of treatment at as nearly absolute rest as possible. This is especially important, if the hemoglobin percentage is very low. A little gentle massage may, however, be started early in the treatment, its amount and force being increased gradually as the patient's condition improves. We usually order it, as a routine measure, to be given three times a week, taking the precaution to engage the services of operators who have been well trained and who have shown, earlier, good judgment in estimating the quantity and quality of massage beneficial at different stages of severe illnesses. The massage is continued as long as the patient is confined to bed.

The patient is not permitted to exercise, even in bed, until the hemoglobin is above 60 per cent.; after that, however, he is instructed in gentle resisting exercises to be taken in bed. The exercises described in S. Bennett's "Old Age: Its Causes and Prevention," are excellent for this purpose. It is a pity that Bennett's book, aside from the description of the exercises, contains much arrant nonsense and misleading advice; if placed in the hands of patients, they should be warned to pay attention in it to nothing but the exercises.

Rest in bed is maintained until the hemoglobin percentage is above 80 and the red corpuscle count above 4,000,000. Toward the end of this period, the patient is allowed to sit up in bed with a back-rest and to occupy himself with reading and with other mild diversions. He is then permitted to sit up in a chair, for one hour on the first day, for two hours on the second and for three hours on the third day. On the fourth or fifth day he is allowed to walk for five minutes. The exercise is then gradually increased until one or two hours of gentle exercise are taken in the open air daily. When the patient leaves the hospital, he is warned of the danger of relapse, is cautioned against excess in mental or physical exertion, and is advised to have his family physician keep a close eye on him even after apparently complete recovery. He is urged to keep up the hydrochloric acid treatment continuously, for the gastric anacidity probably always persists, and he is warned especially against deviating from the well-balanced dietary, arranged in caloric intake according to his needs.

7. *Other Measures, Including Blood Transfusion and Splenectomy*.—In the one group of cases to which we refer, we have usually had a favorable response with no therapy other than the measures outlined above. Some of the patients showed immediate and rapid improvement. A larger number began to show improvement in the blood findings only after two or three weeks of treatment. In many cases, the red count rose to 4,000,000 and the hemoglobin to 80 per cent. within eight or ten weeks. In some cases improvement began only after patient persistence with the regimen for a much longer period. In the group of patients that did not respond at all to this treatment, the blood picture remained unaltered, or grew worse.

2. Asiatic (Tanjore) pills are compounded of arsenous oxid, 5 grains; powdered black pepper, 10 grains; powdered acacia, 3 grains; water, enough to make a mass, divided into twelve pills.

Only after the regimen outlined had been given a thorough trial without benefit did we think it worth while to resort to other measures (transfusions, splenectomy). One exception to this rule has been made: when the red corpuscle count is below 1 million and the hemoglobin percentage below 20 when

Chart 1.—The blood in Case 1: A, reported by home physician. In this and the accompanying charts, the solid line with solid dots denotes red blood corpuscles; the dotted line with hollow dots, hemoglobin, and the solid line with stars, white blood corpuscles.

the patient is first seen, we have found transfusions very useful in raising the blood to a higher level before starting on our usual regimen. When blood transfusions are used, we take especial care to find a suitable donor (negative Wassermann reaction; same group as regards agglutinins and hemolysins).

ILLUSTRATIVE CASES

As examples of favorable response to the method of treatment employed, a few case summaries with blood charts are given. These patients, except in Case 7, are now very well. They all know of the danger of relapse; they are living carefully regulated lives and are having occasional blood examinations made. Patient 7 made a good start, but had a marked setback with fever. Unfortunately, he could not remain at the hospital, but is now trying to gain a remission at his home in a distant state.

CASE 1.—History.—C. L. M., business man, aged 45, married, admitted, Oct. 24, 1912, discharged, Dec. 23, 1912, complained of indigestion, constipation and "liver trouble." The diagnosis was pernicious anemia, gastric anacidity and oral sepsis. The family history was good. Seven brothers were all well except one, who had had a similar trouble.³ The patient had had measles, whooping cough and mumps in childhood; pneumonia at 17; tonsillitis at 43; chronic catarrh

3. This brother, J. H. M., aged 53, came into the hospital the following spring, March 17. He had had bad teeth for eighteen years, typical symptoms of pernicious anemia for nine months, gastric anacidity, blood count of 1,000,000 red blood corpuscles, fever and tachycardia. His course was progressively downward and he died, April 30, in spite of salvarsan, of whole blood subcutaneously, and of a transfusion of 500 c.c. of defibrinated blood.

for twenty years, and otitis media at 30. He was accustomed to three or four colds each year. He had had abdominal pain, coming on occasionally at night, during the past five years; it was relieved by a drink of water. Constipation had been present for three or four years, and hemorrhoids for two years. The patient's habits were good. The onset occurred in November, 1911, one year before admission, with asthenia. The patient stopped work in April, 1912. Other symptoms were loss of weight, anorexia, constipation, and numbness of fingers. Three months before, vomiting spells occurred, with nausea but without pain. His physician said that in August, there was an acute attack with fever, jaundice, choluria, acholic stools, nausea and vomiting, very suggestive of cholangitis. He had had reverses in business, and was depressed and introspective.

Physical Examination.—The patient was undernourished. There was bronze pigmentation of the skin, and pallor of the mucous membranes; the tongue was flabby and of a brownish color. There were some infected dental roots and a few palpable cervical lymph nodes. The heart and lungs were negative. The liver edge was palpable, two fingers breadths below the costal margin. Slight resistance was encountered in the gallbladder region. There was slight edema of the ankles; a few external hemorrhoids were noted.

The blood picture was that of a severe anemia (Chart 1). There was gastric anacidity. The stools were normal. The Wassermann test was negative. The Calmette reactions were negative.

The only untoward event in his otherwise favorable course was an acute febrile period of four or five hours' duration, with temperature of 102 F., chilly sensations, and nasal discharge. About a month after his discharge from the hospital, his physician, Dr. James A. Work, Jr., wrote that his hemoglobin was 94 per cent. (Gowers). The patient was then feeling well, and was at work. While in the hospital, his systolic blood pressure was about 100; his temperature rose occasionally to 99.5, but usually was not over 99, with a tachycardia of from 90 to 100. Weight increased in the hospital from 120 to 140 pounds.

Treatment.—This consisted of rest, full diet, dilute hydrochloric acid (twentieth normal) before and after meals; arsenic in the form of sodium cacodylate; neosalvarsan (one dose); and, for a time, liquor potassii arsenitis. Bland's

Chart 2.—The blood in Case 2.

pills were given after meals. A solution of potassium chlorate was used as a mouth wash. The teeth and gums were put in good condition.

This patient, who lives in Indiana, has returned from time to time for observation. He is well and carries on an active business. His hemoglobin has, at times, been as high as 107 per cent.

CASE 2.—History.—W. C., business man, aged 38, admitted, May 17, 1913, discharged, July 10, 1913, for about eight years, had had a low fever at times accompanied by chilly sensa-

tions; the disease had been supposed to be malaria, though the symptoms were much like those manifested on admission. He had been troubled with bad teeth for many years. The present illness had grown worse for four months, with loss of weight, marked asthenia, fever, and tachycardia. On admission to the hospital, several teeth were found to be loose, with pus about their roots. The physical findings and

F. There was no fever during the last three weeks. He gained only a few pounds in weight while in the hospital. Later, at a nursing home, he made a good gain in weight. On leaving there, he went to the country to live. His blood is now normal and he is taking up his work again in Alabama.

CASE 4.—History.—A. E. H., man, aged 43, white, married, admitted, May 18, 1916, and discharged, July 30, 1916, complained of sensitiveness of the plantar surfaces of the feet, and of weakness. The family history was good. He has three children, living and well, and no children have died. The patient has worked hard at confining office work, but his health has been, in general, good. He has had the usual children's diseases. He had influenza four years ago, but has had no sore throat. He has had alveolar abscesses recently. His habits have been good. Patient said his illness began about nine months previously with numbness in hands and, later, in feet and knees. The numbness had disappeared, but he said the toes and the bottoms of his feet were very sensitive. There had been some loss of weight. Blood examined at home had disclosed marked anemia. Three small transfusions of whole blood had been given, each containing from 30 to 50 c.c.

Physical Examination.—The patient was fairly well nourished, though pale and with slightly pigmented skin. The scleras were slightly icteroid. The heart was negative except for a soft systolic murmur. The lungs, the spine and the abdomen were negative. There was definite hyperesthesia on the plantar surfaces of the feet. There were no other evidences of lesion of the nervous system.

The blood revealed the usual picture of a moderately severe pernicious anemia as seen in Chart 4. The Wassermann reaction was negative. The roentgenoscopic examination of the gastro-intestinal tract was negative. After an Ewald test meal nothing was recovered through the tube after thirty-five minutes. There was no fever and no tachycardia. The urine was of low specific gravity, and otherwise normal. Dental consultation and examination revealed periapical areas about three teeth, and these teeth were extracted and

Chart 3.—The blood in Case 3.

blood picture were typical of pernicious anemia of severe grade. The red corpuscle count was below a million cells; hemoglobin 20 per cent. (Chart 2).

Treatment.—This consisted of rest, food, hydrochloric acid, Bland's pills, and arsenic in the form of sodium cacodylate; neosalvarsan, two doses; and for a time, liquor potassii arsenitis. The teeth and gums were put in good condition by dental specialists.

Note on Discharge.—The symptoms have all cleared up; the patient has gained 12 pounds in weight; the pallor is gone; the blood is rapidly improving.

CASE 3.—History.—J. C. L., business man, aged 37, admitted, March 21, 1913, discharged, April 25, 1913, complained of a "general tired feeling," nervousness and sleeplessness. The family history was unimportant. The patient's general health had been good. He had had measles and mumps as a child, and gonorrhea, twenty years before admission, followed by stricture of the urethra, which was completely cured. He had a tendency to worry about business affairs, became very irritable at times, and suffered from insomnia. He had meals at irregular times, ate rapidly and, formerly, smoked excessively. The onset began about thirteen months before, following an attack of grip. He did not go to bed, but kept at work, with progressive increase in the asthenia, irritability, insomnia and anorexia.

Physical Examination.—The patient was a well-nourished, muscular man. His face showed marked pallor. The liver edge was palpable 1 cm. below the costal margin. The firm, round edge of the spleen was felt just beneath the costal margin. The blood examination disclosed a moderately severe anemia, with high color-index and leukopenia, as shown in Chart 3. There was gastric acidity. The Wassermann test was negative. The diagnosis was pernicious anemia and gastric acidity.

Treatment.—This consisted of rest, full diet, hydrochloric acid, calcium carbonate and pancreatin, 3 drams of each, three hours after each meal, and sodium cacodylate.

At time of discharge, April 25, the spleen was not palpable. At first, there was an occasional rise of temperature to 99.6

Chart 4.—The blood in Case 4: A, three teeth extracted; B, diarrhea and abdominal pain; C, diarrhea checked.

their sockets curetted. The diagnosis was pernicious anemia and oral sepsis.

Our usual regimen for the treatment of pernicious anemia was begun. Improvement began at once, but, after eight weeks, was interrupted by an attack including diarrhea and abdominal pain. After a few days, however, the counts again started upward. Recent reports from his home in Texas state that the patient is very well.

CASE 6.—*History*.—S. B. F., aged 73, business man, married, was admitted, April 27, 1917, and on examination pernicious anemia and peridental abscesses were revealed. The patient complained of weakness, loss of energy, pallor, dyspnea, and anorexia. He had had one attack of diarrhea. The family history was negative. The patient had had measles, mumps, chickenpox and malaria. He has had a great deal of trouble with his teeth (pain, abscesses). He had an attack of influenza three years ago with bronchitis. He has some frequency of urination, and is unable to empty his bladder. His habits are good. For three years, he had felt loss of his usual energy, and had had vague abdominal discomfort, constipation and anorexia. The weakness had increased steadily and, for one year, had been quite marked. The other symptoms noticed include dizziness, loss of weight, and dyspnea on exertion.

Physical Examination.—The patient showed moderate obesity; had a typical lemon-yellow color of skin and scleras; marked pallor and spade-like hands with abundant soft parts, almost like myxedema. There was severe oral sepsis and tachycardia. A slight pitting of ankles and a slight arterial hypertension were noted. The blood pressure was 150/80.

Blood examination revealed a marked anemia as seen in Chart 6. Gastric analysis shows anachlorhydria; total acidity 7 acidity per cent. Stools were small, soft and light yellow, but contained no parasites, ova, or blood. The Wassermann reaction was negative. Dental consultation and examination revealed large periapical areas with pus-sacs about many of the teeth, some ten of which were accordingly extracted.

Roentgenographic examination of the stomach and the intestines disclosed a spastic pylorus and a duodenal cap rotated and flattened out, suggesting a lesion in the neighborhood of the gallbladder. The laryngologic examination was negative. The urologic examination revealed phimosis, chronic prostatitis, and seminal vesiculitis. Further cystoscopic examination will be made when the patient's strength permits. The urine is of normal amount. The specific gravity is 1.015, and there is a faint trace of albumin, hyaline and granular casts, and abnormal amounts of urobilin.

The patient was at first extremely asthenic, and dyspneic on the slightest exertion. These symptoms improved markedly along with improvement in the blood condition. The usual regimen was followed. The chart shows the beginning of an improvement that has continued steadily since. The patient returned to his home in Delaware.⁴

ABSTRACT OF DISCUSSION

DR. H. A. CHRISTIAN, Boston: Forced feeding is evidently important, but in our own experience often we have found it exceedingly difficult to carry out because so many patients have nausea or a distinct aversion to food. In overcoming that aversion to food we have sometimes found transfusion valuable. I would suggest transfusion as an appetizer in some of these cases of pernicious anemia. In regard to the treatment with hydrochloric acid, pancreatin and calcium carbonate, we have found great difficulty in getting our patients to take this treatment (on account of the bad taste, especially

of pancreatin). We have carried it out as Dr. Barker has suggested, and some patients have taken it very well; other patients have refused. There may be something wrong with our pancreatin, or we lack that persuasive power that Dr. Barker has.

Clearing up foci of infection of course is important. The prolonged rest, with the patient going frequently out into the fresh air or spending the whole day in the open, adds a great deal to the results because the patients take their food so much better, and their general condition is greatly improved. Frankly, however, I do not think we have succeeded in accomplishing much in the attempt, possibly a poor attempt, to carry out the regimen that Dr. Barker has indicated. In some cases we have had good results and in others we have had no results at all.

I should like to emphasize the importance of gastric acidity in these cases. The point is that sometimes the condition exists for several years before the development of the symptoms of anemia. I have seen a case in which it existed for five years and in one of our cases, which was studied very thoroughly, with a complete blood examination and nothing abnormal made out except gastric acidity, the patient returned in two years with typical primary anemia. I should like to emphasize the presence of fever as a symptom. As we see it in the hospital, we find fever present with almost no exceptions; if the patient is sick enough to come to the hospital, he almost invariably has fever. These cases have been sent in as typhoid fever and tuberculosis because the general practitioner did not recognize the fever as a symptom of anemia. In these cases transfusion, when it increases the blood, relieves the fever.

DR. N. E. BRILL, New York: I know of no subject in the domain of the pathology of the blood which is surrounded by as much darkness as is the subject of anemia, whether primary or secondary. This is perhaps due to the fact that we as clinicians have not paid much attention to the biologic, physiologic and pathologic conditions associated with anemia. We speak of anemias in a general way as reduction in the number of the red cells of the blood. When we take into consideration the fact that the spleen is constantly destroying blood cells, that the life of a red blood cell, as estimated by Quincke is only thirty days, that therefore of all our blood we are losing one-thirtieth every day, it must strike us that there must be a nice balance between this daily loss and the new red cells formed to keep a constant of 5,000,000 red blood cells to each cubic millimeter of blood. What is the factor that regulates this wonderful balance? For over ten years I have been teaching my students that the regulating cause of this production resided in the red blood cell itself, particularly in its hemoglobin, and was particularly dependent on the oxygen-carrying capacity of the blood. When there is a diminution of oxygen in the blood, whether it be due to deficiency in the number of red cells or in the available oxygen, that deficiency of oxygen is the instigator or the hormone to the marrow for the production of new red cells. Clinically that theory is borne out by many factors. We know that in deficient aeration of the blood such as occurs in emphysema or in cardiac disease, the bone marrow responds to that diminution of oxygen by producing new cells, and polycythemia is a not uncommon accompaniment. Take carbon monoxid poisoning: there is no poison that will dissipate or force aside the oxygen from the hemoglobin as intensely and completely as will carbon monoxid gas, and in every case of this poisoning reported you will find that the bone marrow was distinctly red and that the circulating blood was full of nucleated cells, which means bone marrow activation. Take the blood of people living up on the mountain tops and you will find that the average number of red cells is 6,000,000 instead of 4,000,000 or 5,000,000, which is the number present at sea level, owing to the diminution of oxygen, the result of variation in barometric pressure. Take pernicious anemia, or even Minkowski's disease, in each of which the hemolysis which accompanies them results in the splitting up of the hemoglobin and, therefore, in the oxygen content, as a result of which bone marrow stimulation obtains. Haldane has shown that the blood in pernicious anemia contains the lowest amount of hemoglobin, hence the

Chart 6.—The blood in Case 6: A, extraction of ten teeth, May 4, 1917.

4. In the summer (1917) he wrote that he was well—better than he had been in years.

amount of bone marrow activation is most marked in that disease.

DR. GEORGE R. MINOT, Boston: Dr. George I. Lee and I have studied the anemias at the Massachusetts General Hospital for the past three years, and there is one point about the activity of the bone marrow which was not brought out, yet which seems to us important.

It has been pointed out that the skeined cells (reticulated cells) and polynuclears give us information about bone marrow activity. The blood platelets are formed from the giant cells of the bone marrow and are also important elements to observe when studying bone marrow activity. We feel that if we were given, in a case of pernicious anemia, but one of the three chief marrow elements to judge the activity of the marrow from, we would rather know the number of the platelets than any other single factor.

We have treated approximately 100 patients with pernicious anemia; about 40 of these patients received only fresh air, suitable diet and arsenic; about 40 more have received transfusions, and 19 (chiefly unselected cases) were splenectomized. Splenectomy should, however, be reserved for selected cases, and is to be looked on as only the best means of inducing a remission. It usually gives the most satisfactory results in young patients with large spleens and considerable hemolysis. About 85 per cent. of the splenectomized patients showed some definite improvement following the operation, and 45 per cent. showed marked rapid gains; 50 per cent. of the transfused patients showed definite improvement beyond a simple filling up with blood, and 18 per cent. showed marked rapid gains; while in a similar period of time but 35 to 40 per cent. of the nonsplenectomized and nontransfused patients showed any improvement at all, and 7 per cent. showed marked rapid gains. There was a greater degree of improvement in the transfused and splenectomized than in the other patients.

DR. FRANK SMITHIES, Chicago: I am glad that Dr. Barker emphasized the important causal relationship of bacteria to the severe anemias. I personally believe that in the majority of these cases of addisonian or "pernicious" anemia we have to deal with a peculiar type of bacterium of the hemolytic group. It is probable that the ailment represents end-results of long continued, intermittently active, low-grade sepsis.

In regard to the treatment, I believe in the early and frequently repeated transfusion of undoubted blood. I think that if we knew how to use transfusion, splenectomy would not be necessary in the majority of cases. Does transfusion do anything? Dr. Christian said that it is an appetizer; it certainly is, in the majority of cases. It will aid Dr. Barker in giving these large masses of pancreatin, which of course physiologically have no action within the alimentary tract. Transfusion will enable the patient to fight infection and its products, and probably stimulate blood formation. It will do in a week what Dr. Barker's rest treatment in bed for a month or more will do. This is an important service when one is treating anemic patients whose time and money are both limited. The individual who is energetically treated from the start has a fighting chance. I think that we ought not to go from this room and say, respecting our addisonian anemias, that the treatment is only "lots of fresh air, good food and sunshine, and Heaven help them." If we let the patient consider that he has a hopeless disease, then he will not do well; but if we get into the patient's mind that there is a cause for this disease and that we are treating that cause as far as possible, we are going to have a fighting group of patients with anemias. Many will get well and be useful citizens.

DR. EDWARD LINDEMAN, New York: The most typical feature of pernicious anemia to me is its atypical and capricious course. One must be constantly guarded lest one attribute to any form of therapy that which rightly belongs to the natural course of the disease.

As to the value of the different measures of treatment as advocated in Dr. Barker's paper, I never give hydrochloric acid, cacodylate of soda or other medicinal remedies mentioned. I do not crowd the food, for the simple reason that after transfusions patients crowd the food without advising it. I do not advise rest in bed after transfusions. Patients are given blood transfusions in quantities from 1,200 c.c. to

2,300 c.c. These transfusions are given by the syringe cannula system and no reactions follow transfusions. Under no circumstances is sodium citrate or other anticoagulant used. I do not find it necessary to transfuse more than once in two months, one and two years, or even longer intervals, depending on the type of case.

When one sees a patient in a semiconscious state with dyspnea, generalized edema, persistent nausea and vomiting, rapid pulse and fever, and four hours after receiving 1,600 c.c. of blood, finds a disappearance of all nausea and vomiting, with the return of full consciousness, with absence, at the end of twenty-four hours, of all signs and symptoms enumerated, and the patient remains well for a period of two years, one cannot help but respect that form of therapy.

In regard to splenectomy, every patient I have had has returned with a blood crisis. What splenectomy has done for some is that it has prolonged the remissions of the disease and only carefully selected cases have proved favorable for this procedure.

In all cases of pernicious anemia coming under my observation in which the patients were in the first year of their disease, and who have remained where I could treat them at opportune times, there has been no death in the last two years. Treatment consisted almost entirely of blood transfusions in large amounts.

DR. E. L. TUOHY, Duluth, Minn.: I wish to emphasize the value of Schneider's method of estimating pigment output in the duodenal contents. The original investigations of Eppinger and Hess were made on the stools. Splenectomy, as advised by Eppinger, was the outgrowth of this work. Whatever may prove ultimately to be the merits or demerits of this operation, it can be said that certainly splenectomy is not logical in those patients not showing pleiochromia in the duodenal contents. I have studied about thirty cases of severe anemia, using this method in addition to the usual methods of investigation. Interestingly, two cases of *Bothriocephalus latus*, with very severe anemia, did not show any excess of pigment in the duodenal contents. In many severe anemias where I live the patients have shown positive Wassermanns; all of these have shown the same sort of duodenal contents as are seen in the usual severe secondary anemia. All have improved under specific treatment. The true pathology of pernicious anemia still seems obscure. The spleen cannot be looked on as the only destructive agent. These severe syphilitic anemias point to the possibility of striking injury done the bone marrow by syphilitic toxin.

DR. ALFONSO CASTELLI, New York: In the treatment of secondary anemia, exercise, diet, rest, fresh air and transfusion, of course, give relief, but in my experience in the treatment of secondary anemia the best results have been accomplished by the intramuscular injection of arsenate of iron. Iron, we know, is the time honored drug in the treatment of anemia, and we can trace its use to those early, empiric times when it was obtained for medicinal purposes, from having a red hot piece of iron immersed in water so as to produce aqua ferrata or chalybeate. We also know that iron, which enters into the constitution of the human body, 2.1 gm. being present in the average 65 kg. body, makes hematoblasts become adult erythrocytes, thus entering into the formation of hemoglobin, which is the important functional element in the red cells and the most important medium in the exchange of oxygen (oxyhemoglobin) from the air to all the tissues.

Arsenic, the well known tonic and alterative, on the other side, seems directly to stimulate bone marrow and the other hematoplastic organs in their blood-cell producing function, and therefore in the combination of the two elements, iron and arsenic, we have an ideal product with which to treat anemia. Of course, we know that iron must not be given by mouth, because patients will get either diarrhea or constipation, and we know that the intestines do not absorb heavy metals like iron, to say nothing of its teeth-blackening property. Likewise, arsenic tends to show untoward effects—nausea, dyspepsia, gastralgia, etc.—when administered by mouth, while the administration by the transcutaneous route of the two elements in solution avoids all that trouble and gives, beside, a fair estimation of the dose of the compound

which is deemed advisable to inject, according to age, size, etc., of the patient. We may start with 0.1 gm. of iron arsenate in 1 c.c. of solution, to be administered every day or every other day, children and undersized patients accordingly, and the dose may be increased up to 0.7 gm. After a number of injections of this arsenated iron the blood picture has become normal, not only in relation to the number of cells, but even to the index of hemoglobin, and the patient who was low spirited, pale, emaciated and underweight when he started the treatment, has regained his normal condition, is feeling well and looking rosy when he has taken the necessary series of intramuscular injections of iron arsenate. This holds good in cases of obscure anemias, as well as in those cases which accompany or follow such diseases as tuberculosis, syphilis, malaria, etc., and in the disorders of metabolism in general.

DR. ALFRED STENGEL, Philadelphia: Hemolysis alone cannot be the basis for our judgment as to methods of treatment. Hemolysis is one factor in true pernicious anemia, and only one. There is the question of marrow activity after hemolysis has been reached, to a certain extent. Observations have been made pointing to specific infection of the bone marrow in some cases. These observations have not been published, but are under way at present. The question of syphilitic anemia, I think, is a proper one. I recall a case of syphilitic anemia of a grade which we see in the most severe pernicious anemia; this patient recovered quickly under antisyphilitic treatment. There are also infectious cases with speedy recovery after removal of the infection.

There are conditions closely resembling pernicious anemia that get well with either Dr. Barker's treatment or Dr. Smithies' treatment; but I am unable to give any positive opinion as to what plan of treatment is going to be effective. I think we are getting nearer to proper treatment in removing subsidiary causes or in coaxing back the bone marrow into its previous activity.

DR. L. F. BARKER, Baltimore: Two points have come out in this discussion: first, the great difficulty in differential diagnosis in some of the cases, and second, the clear advantage in therapy of the removal of foci of infection, and in some instances, of transfusion. As to aversion to food, I believe that we can often do much by urging patients to take food in spite of absence of appetite. Dr. Christian has observed that transfusion increases appetite. In many cases it is necessary to tell a patient that his appetite is not a sufficient guide and that he should eat what the nurse brings him, despite anorexia. An abundant, mixed, roborant diet should be given; the patients should be encouraged to take it and to bear any slight discomfort that follows its ingestion. I agree that pancreatin and calcium carbonate in the amounts mentioned are somewhat unpalatable. We have given them on the theory that, in the absence of hydrochloric acid and of proper secretin-production, some aid to intestinal digestion might be beneficial. Many of us will overlook foci of infection even when we think our search has been thorough.

This brings me to the question of fever. I think it may be due sometimes to the anemia itself, but I think we should first assume that it is due to some focus of infection that we have not yet discovered and we should continue the search for an overlooked focus. If, in a severe anemia, a focus of infection be found, say in the teeth, one might be inclined to say "wait," but I think we should go ahead, give an anesthetic, even to a man with a hemoglobin of 30 per cent., and perform the operation to get rid of the focus of infection. I have done this in several instances with gratifying results. What has been said about transfusion has interested me very much, and I certainly think that patients that do not respond to other methods of treatment should be transfused. I do not want to be understood as being pessimistic about the outlook in even very severe cases, because we now feel that at least many of these anemic patients can be speedily returned to health and to work, and to the enjoyment of life.

Suckers.—We believe that the person who coined the statement, "A sucker is born every minute," sold patent medicines. Cumberland (Md.) *Health Bulletin*.

WOUND INFECTION AMONG LATHE WORKERS

AN INVESTIGATION INTO SOME OF THE FACTORS CAUSING WOUND INFECTION IN INDUSTRIAL SURGERY AND METHODS OF OBVIATING THEM *

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While serving in the emergency hospital of a large manufacturing plant last summer, I was impressed by the great number of infections and cases of furunculosis with which we had to deal. On some men a pinprick, if left unattended, developed into a severe lymphangitis; a slight scratch in twelve hours into a linear mass of pus; a slight abrasion into a suppurating ulcer, and a laceration into a mass of necrotic tissue and pus. There were dozens of cases of multiple furunculosis, some patients developing as many as fifty boils at once on their arms and legs and faces. It is probable that ours was not the only manufacturing plant troubled with experience of this sort, since out of the total amount paid for deaths by the Industrial Commission of Ohio last year, 22 per cent. was for those resulting from infections, and of the total amount paid for disabilities and loss of time, 10 per cent. was for the same cause.

In our plant there are employed about 2,000 men, representatives of many nations—Americans, Canadians, Irish, English, Scotch, Welsh, Swedes, Russians, Poles, Germans, Austrians, Lithuanians, Hungarians, Italians, Armenians, Slavs, Bulgarians, Serbians, etc. Their standards of living vary as much as their nationalities, some of them living in places as crowded, filthy and unkempt as are found in our city slums, others in clean, tidy cottages with little gardens. In age, they vary from 16 to 60. Their general health is good, seeming not to be affected in the least by personal filth or cleanliness. The tenure of employment is exceedingly variable, some men working only a few hours, while others have been with the company for twenty years. The majority of laborers, however, are transient.

Situated on a hill, the plant gets its electric power and water from Cleveland. The plant includes a carpenter shop, old machine shop, new machine shop, structural shop, forge shop, bond room, packing room, pumping station, power house, yard where the structural work is assembled, hospital and offices. Each department has its own toilet rooms, wash rooms and shower baths.

All these departments were represented by patients who came to the hospital. From fifty to sixty patients were seen daily, and of these from 8 to 10 per cent. had furunculosis, and about 5 per cent. had wound infections of various sorts (these percentages are mutually inclusive). It was soon noted, however, that these cases all came from the two machine shops. When this was investigated further, it was discovered that of all the 1,200 or more men in the machine shops, none had multiple furunculosis save those who worked on lathes, and furthermore that 90 per cent. of the infections occurred in men working on lathes. The new machine shop is given over to the manufacture of

* From the Laboratories of the Department of Hygiene and Bacteriology, Western Reserve University School of Medicine.

* Awarded \$100 prize offered by the American Association of Industrial Physicians and Surgeons for the best paper on industrial medicine or surgery by any undergraduate medical student in America.