STENGEL (A.)

NATURE, DIAGNOSIS, AND TREATMENT

OF

PERNICIOUS ANÆMIA.

Read before the Philadelphia County Medical Society, May 9, 1894.

BY

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REPRINTED FROM THE THERAPEUTIC GAZETTE, JUNE 15, 1894.

DETROIT, MICH.:

GEORGE S. DAVIS, PUBLISHER.

1894.

Nature, Diagnosis, and Treatment of Pernicious Anæmia.

WE cannot approach the study of pernicious anæmia in an intelligent manner without first of all determining exactly what group of cases we are to consider under this head; and we shall find that the vagueness of the term has led to not a few misconceptions regarding the natural history, the prognosis, and even the treatment of the disease. The concise and, to this day, most accurate description of the principal features of what we regard as pernicious anæmia, published by Addison in 1843, and more particularly ten years later, is one of the striking evidences of the keenness of this great physician's power of observation. "For a long period," he says, "I had from time to time met with a very remarkable form of general anæmia occurring without any discoverable cause whatever,—cases in which there had been no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease." And further on, "It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to the earliest feeling of that languor which is shortly to become so extreme. The counte-

nance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted, the pulse perhaps large, but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement. There is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth, and waxy appearance; the lips, tongue, and gums seem bloodless, the flabbiness of the solids increases, the appetite fails, extreme languor and faintness supervene; breathlessness and palpitations are produced by the most trifling exertion or emotion; some slight œdema is probably perceived about the ankles; the debility becomes extreme, the patient can no longer rise from bed, the mind occasionally wanders, he falls into a prostrate and half-torpid state, and at length expires; nevertheless, to the very last, and after a sickness of several months' duration, the bulkiness of the general frame and the amount of obesity often present a most striking contrast to the failure and exhaustion observable in every other respect." This stands to-day as a faithful and accurate account of the disease; but we have learned that the disease is not always as obscure in its causal relations as Addison believed.

From the stand-point of our present knowledge four groups of cases are clearly distinguishable. Leber, Gusserow, and Channing pointed out the unquestionable relation of pregnancy and lactation to a first group of cases; while in a second the influence of in-

testinal parasites was clearly demonstrated by Sangalli and other observers in Italy, and by Bäumler, Schönbächler, and others in Germany. More recently a third group of cases has been reported, by the investigations of Fenwick, Nothnagel, Litten, Kussmaul, Henry and Osler, Kinnicutt, and others, in which degenerations of the gastric mucosa play an important part, probably causative, in the disease. Other causes of a less immediate nature, perhaps predisposing, have been assigned, but at least these three groups are definitely known and admitted. There is left a certain number of cases in which no etiological factors are discoverable, but in which the clinical manifestations are practically identical. Is the pathogenesis in these last cases similar or the same as in the first-named groups, and shall we include all four classes under the head of pernicious anæmia? The answer to these questions will, I think, require a little consideration of the nature of the disease as we now know it.

The study of the blood in pernicious anæmia shows as the most important feature the great reduction in the number of the red blood-corpuscles. In cases of moderate severity there may be 1,500,000 per cubic millimetre, in the most serious as few as 143,000, as Quincke observed the day before the death of one of his cases. This remarkable decrease in the number of red corpuscles must result either from decrease in the production of the red corpuscles, from increased destruction, or from a combination of the two. Now, I intend to show that in pernicious anæmia the important factor is hæmolysis, but that faulty hæmogenesis plays a part; that the gastro-intestinal tract is the

seat of the destruction, or at least the source, of the hæmolytic agents; and, finally, that since the four above-named groups are similar in the condition of the blood, in the pathogenesis, and in their pathological tendency, it is more accurate scientifically to place them together as comprising the condition pernicious anæmia. Many modern writers place the apparently causeless cases apart as true "Addisonian pernicious anæmia," regarding the other cases as severe secondary anæmias; but there is much and good reason to believe that all cases are secondary, and there is a manifest advantage in practical medicine in holding to this view and regarding every case as one of obscure anæmia whose nature may be discoverable on close scrutiny. A rooted belief in the idiopathic or essential character of pernicious anæmia cannot but lead to neglect of careful search for hidden causes.

The later and, at the present day, most popular view of the origin of pernicious anæmia is that hæmolysis, or blood destruction, becomes increased beyond the powers of normal hæmogenesis to restore the blood. This view has been advocated by many writers, but none has done so much to bring it to the point of positive proof as Dr. William Hunter. The evidences of hæmolysis are found, in the first place, in the blood itself, in the numerous small, apparently fragmented, red corpuscles, in the decolorized corpuscles, showing merely the framework of the corpuscle, and, I believe, in the poikilocytes themselves. It is difficult to imagine these bodies as resulting from anything but destructive causes; but in them-

selves they would not constitute positive evidence. There are, however, resulting conditions which indicate the ultimate fate of the coloring-matter and other constituents of the blood-corpuscles after their disintegration. The most important of these, and one which, so far as we now know, is peculiar to pernicious anæmia, is the deposit of iron-containing pigment in the outer zones of the hepatic lobules. This increase of iron in the liver was first observed by Quincke, and later by Rosenstein, Peters, Hunter, Burr and Griffith, Scott, and others, and in some of its features is perhaps characteristic of pernicious anæmia. It results, as Hunter has recently shown, not from the hæmolytic action of the liver itself, but from the storing up of the pigment matter after its liberation in other parts of the portal circulation. The yellow pigmentation of the skin and eyes is doubtless of similar nature. Not only is iron deposited in the liver in excessive quantity, but the amount discharged in the bile is generally increased, and the color of the urine has been found to be deepened by the presence of an altered form of urobilin. The fact that some cases do not show this increased color of the urine does not by any means diminish the importance of the observation when made. Destruction of white corpuscles, which their decreased number might lead us to suspect, is further evidenced, though not absolutely, by the excess of uric acid generally present in the urine; and it may well be that the fever of the disease is due to the same cause. Mott says that his experience warrants him in asserting "a constant relation between the pyrexia, the diminution in the red corpus-

cles, and the color of the urine." Finally, there is experimental evidence that pernicious anæmia may be the result of active hæmolysis, the anæmia resulting from injection of certain hæmolytic poisons, such as pyrogallol (Silbermann), into animals being strikingly like the natural disease as observed in man. These evidences I believe are sufficient to warrant the belief that hæmolysis plays a most important *rôle* in the pathogenesis of the condition under discussion.

The indications of faulty hæmogenesis are less numerous, though their existence cannot be doubted. In the first place, as Henry has pointed out, the large, flabby, ill-formed macrocytes of pernicious anæmia cannot but convey the impression that they result from some error in blood formation, and surely cannot be regarded as products of hæmolysis.* With these must be ranked the nucleated red corpuscles, whose presence in the blood after hemorrhage, or after rapid blood destruction, is doubtless an indication of partially unsuccessful efforts at restoration of the normal number of corpuscles. Finally, the lymphoid character of the bone marrow in pernicious anæmia is probably a consequence of the intense blood destruction, and results from the effort to supply corpuscles, as is the case, though to a less degree, in other forms of anæmia. Rindfleisch has studied this subject with particular care, and

* Ehrlich has sought to show by their peculiar reaction to stains that they are degenerative in nature, but the studies of frog's blood by Gabritschewski indicate that the younger corpuscles present this peculiarity rather than the older and therefore more likely to be degenerated.

concludes that there is some obstacle in the way of the extrusion of red corpuscles from the hæmatoblasts of the marrow, which in consequence become greatly increased in number.

We have then, I believe, sufficient evidence to indicate that pernicious anæmia is both hæmolytic and hæmogenetic, but that the former process is the more important of the two.

As to the seat of the hæmolytic changes, we derive most information from those cases in which a distinct causal relation has been determined, and especially from the cases in which the gastro-intestinal tract is the seat of morbid lesions. Of the latter a great number has been recorded, though in some of the earlier cases the diagnosis of pernicious anæmia was not determined with the accuracy we could wish. Fenwick first pointed out a remarkable atrophy of the gastric mucosa and glands; Nothnagel observed cirrhotic contraction with disappearance of the glands; Nolen described a form of interstitial gastritis with atrophy of the glands; ulcers of the duodenum and stomach were found by Zahn and Litten; Homolle found simple duodenitis; while Banti, Sasaki, and others described changes in the sympathetic nerves and in the ganglia of the stomach walls. In the case of some of these lesions it may properly be urged, as has been done, that the anæmia was the cause of the gastric changes rather than the reverse; but in such instances as those of cirrhotic thickening of the stomach, with destruction of the mucosa, this explanation does not suffice. In a recent case under my own observation there was a history of marked gastric trouble for fifteen years,

during which the patient remained in a fair state of health. Finally, the patient began to grow more anæmic, her blood and general appearance assumed the characters seen in pernicious anæmia ; and on subseqent examination of the stomach a marked degree of cirrhosis, with partial destruction of the tubules, was discovered. Surely in a case of this kind the gastric lesions could not be regarded as secondary to the pernicious anæmia. The morbid conditions of the intestines with which pernicious anæmia has been found to be associated are similar to those in the stomach ; but attention has been directed more particularly to the influence exerted by intestinal parasites, particularly the *Bothriocephalus latus* and the *Anchylostomum duodenale*. In a few isolated cases other parasites were found,—*Ascaris lumbricoides* (Demme) and *Tænia saginata* (Eisenlohr),—but in these the diagnosis of pernicious anæmia is open to some doubt.

The manner in which these gastric and intestinal lesions bring about the anæmic condition of the blood must still be regarded as an open question, though we have undoubtedly reached a point where some measure of positiveness is justified. In the first place, it is, I believe, definitely ascertained that pernicious anæmia is a hæmolytic disease to a great degree, and that we cannot, therefore, regard the operation of the lesions described as being merely that of causes which interfere with proper nutrition. This may be a factor, but it is surely not the important one. Clinical observations and latterly experimental evidence, on the contrary, point to the development and action of poisonous substances within the in-

testinal tract, which by their hæmolytic action outrun the blood-making powers. A remarkable case of Sandoz may be cited in this connection. This observer records an instance of marked and progressive anæmia, in which there were prominent gastric symptoms and great fetor of the breath, and which showed decided improvement in the gastric conditions, the breath, and the anæmia after repeated lavage of the stomach. A similar case has recently been reported by Meyer. Jürgensen observed a similarly pertinent case, in which marked anæmia rapidly disappeared after administration of purges and the discharge of immense numbers of the Bacterium termo. The question of the relation of the animal parasites of the intestines to the anæmic condition is less easily determined than that of such organisms as bacteria, but there is much in favor of the view that it is by the generation of hæmolytic poisons, either in their natural growth or, as Schapiro claimed, from their death and decomposition. The belief that the anchylostomum causes anæmia by the abstraction of blood was attractive at first sight, but there are recorded cases of marked pernicious anæmia in which the worms were far too few to account for more than a trifling loss of blood. In addition, the discharge of the parasites is often followed by such rapid improvement in the symptoms that the conclusion that some source of intoxication has been removed seems well-nigh irresistible.

Finally, the important experiments of Hunter furnish additional evidence, in showing the active part the gastro-intestinal tracts may play in blood destruction when hæmolytic agents are

administered. The poison employed by him was toluylendiamin. After injection of small doses the blood of the splenic vein alone showed hæmolytic changes; after large doses that of the mesenteric veins was also affected; and when the spleen had been removed, the chief hæmolysis was exercised in the intestinal circulation. Whether or not the spleen would play the secondary *rôle* in case of administration of poisons through the stomach must for the present remain conjectural. Enough is shown, however, to prove the importance of gastro-intestinal intoxication in its relation to hæmolytic anæmia.

Thus far we have considered only two of the groups of pernicious anæmia. The study of the puerperal cases is less satisfactory. No definite organic lesions have as yet been determined in these, and as a discussion of their nature could only be theoretic, they may be left out of consideration for the present. Suffice it to say that in this group, as well as in those cases in which no etiological factors of any kind are discoverable, there are the same indications of active hæmolysis in the blood, the secretions, and the organs as in the gastro-intestinal forms, and the clinical features are identical.

The *rôle* of hæmogenesis in pernicious anæmia, though of secondary importance and sequential, is doubtless an essential one. There must be some reason for the different effect of the same lesion in different individuals. Some persons may harbor the bothriocephalus or anchylostomum for years without the development of any unusual anæmia, just as certain persons manifest only gastric symptoms as a result of marked gastric atrophy. This differ-

ence in the state of the blood, I believe, depends more upon acquired or native deficiency in the hæmogenetic powers than in any obscure differences in the lesions themselves. This theory would furnish a ready explanation, as has been claimed by D'Espine and Picot, for the rarity of pernicious anæmia in children, in whom hæmogenesis, in common with other reparative processes, is more active than in older persons. It would harmonize with the clinical observations such as those I have cited before in the case in which pernicious anæmia was developed only after many years of gastric disorder and disease, and then ran a rapid course. Another interesting observation pointing to a natural deficiency in hæmogenesis was reported some years since by Luzet. A girl who had been under the care of Jaccoud for chlorosis recovered entirely, but four years later, after her second confinement, came under the notice of Luzet with 781,200 red corpuscles to the cubic millimetre, and with a relative hæmoglobin value of 1.091. Doubtless, as Luzet claims, the disease was now pernicious anæmia. The previous chlorosis with subsequent pernicious anæmia are strong indications to my mind that there was here some original defect in the blood-making powers. Dr. Henry, in commenting on the above case, remarks that he had observed exactly the same conditions in one of his cases.

Diagnosis.—Before proceeding with the diagnosis it is important once more to set clearly before the mind the conception of pernicious anæmia which we have arrived at,—viz., that it is a form of intense oligocythæmia with a tendency to progressive deterioration, and cer-

tain definite symptoms, altogether irrespective of our ability or inability to find a distinct cause. The diagnosis, then, turns upon the character of the blood and the general symptoms, and not at all upon the absence or presence of etiological factors.

In an historical review of the study of the blood in pernicious anæmia we find a succession of observations each of which was in turn regarded as pathognomonic of the disease. One of the striking features on examination of the blood is the great irregularity in the shape of the red corpuscles,—the condition to which the terms poikilocytosis (Quincke) and schistocytosis (Ehrlich) have been applied. This was first found by Damon ("Leucocythæmia," Boston, 1864) in leukæmia, but was subsequently claimed by Quincke to be characteristic of pernicious anæmia. That this is not the case has been abundantly proved by the detection of marked poikilocytosis in cases of advanced carcinoma of the stomach, chlorosis, and other diseases. No more characteristic is the great difference in size of the red corpuscles, the existence of macrocytes and microcytes, and in particular of the small red cells of bright color and high refraction to which Eichhorst called attention in his work on pernicious anæmia, and which for a time were regarded as characteristic. All of these conditions are found in other intense anæmias, though, like poikilocytosis, less frequently and less distinctly than in pernicious anæmia. Another feature which has been falsely interpreted as pathognomonic is the mobile or amœboid character sometimes seen in the red corpuscles, but which has also been found in other diseases. The nearest ap-

proach to a characteristic condition is the relative excess of hæmoglobin, to which Hayem and Laache called particular attention. According to these authors and others after them, the blood of pernicious anæmia shows great reduction in the number of the red corpuscles without an equal decrease of hæmoglobin; so that the individual corpuscle is too rich in coloring-matter, though, of course, the actual decrease of hæmoglobin is very considerable. The presence of these conditions is doubtless practically diagnostic, but unfortunately we do not always find a relative richness in hæmoglobin. In four out of five cases of undoubted pernicious anæmia in which I have recently examined the blood, the reverse was the case, though the reduction of hæmoglobin was never much in excess of that of the number of corpuscles. The same observation was made in cases reported by Brakenridge, Dehio, Demme, and others. In all cases of genuine pernicious anæmia, however, the reduction in number of the red corpuscles is very considerable,—usually below 1,500,000. In two cases which I have recently examined, the examination of the blood showed 900,000 (eighteen per cent.) red corpuscles with ten per cent. of hæmoglobin, and 800,000 (sixteen per cent.) with thirty-five per cent. of hæmoglobin respectively. As a contrast to these figures I may cite the average result of the blood-examination in one hundred consecutive cases of gastric, intestinal, cardiac, nervous, pulmonary, and intestinal diseases, in which a certain degree of pallor led to examination of the blood. The average number of red corpuscles was 4,430,000 (88.6 per cent.), the average worth of hæmoglobin seventy-four per

cent. The average of the five most anæmic of these cases was 3,820,000 (76.4 per cent.) red blood-corpuscles with 49.4 per cent. of hæmoglobin. In cases of gastric cancer the degree of anæmia, judging by the pallor of the skin, is often quite as marked as in bad cases of pernicious anæmia, but in three advanced cases I found the average result 2,890,000 (57.8 per cent.) red blood-corpuscles and thirty-one per cent. of hæmoglobin. In the four most decided cases of anæmia due to cardiac and arterial disease I have examined, the average was 4,210,000 (84.2 per cent.) of red corpuscles and forty-seven per cent. of hæmoglobin. In no case of the whole series were the red corpuscles reduced below 2,300,000, or forty-six per cent., and in none was there relative excess of hæmoglobin. The contrast between these figures and those given for pernicious anæmia is so striking as to need no further comment. Finally, Ehrlich has insisted upon the diagnostic significance of large red corpuscles containing nuclei, structures for which he proposes the name megaloblasts. These corpuscles, however, are not invariably present in pernicious anæmia, and they have been observed in other diseases attended with severe anæmia. I have seen them well marked in a case of purpura with large hemorrhages.

It is clear, therefore, that no one of the characters cited is pathognomonic standing by itself. On the other hand, a combination of all of them would make the diagnosis practically certain. In particular, I would urge that too much importance has been attached by physicians to poikilocytosis, one of the least important of the abnormalities named. What characters,

then, can we regard as significant? My own observation leads me to regard as pernicious anæmia any case presenting suspicious clinical features in which the red corpuscles number less than 1,500,000 per cubic millimetre, and in which the hæmoglobin shows about the same proportionate reduction. The diagnosis becomes certain in cases in which the hæmoglobin is relatively in excess, and in which great alteration in the size and shape of the red corpuscles and the presence of large nucleated red corpuscles are observed. In addition to these characters of the blood, pernicious anæmia presents a train of clinical manifestations scarcely to be mistaken when present in their typical form. These symptoms have been so well described in the paragraph quoted from Addison that nothing further need be said on this head.

Differential Diagnosis.—Pernicious anæmia must be distinguished from cases of secondary anæmia, so called, especially from gastric cancer, and from chlorosis. In certain cases the striking symptoms from first to last refer to the heart or the nervous system, and may draw the attention away from the real disease.

The anæmia following hemorrhage is often intense, and the patient's face may have a deathly pallor; rarely, however, or never, in my experience, does it show the lemon color so frequently seen in pernicious anæmia. There is absence of the marked gastric symptoms and generally of the fever. It must be confessed that this last symptom is sometimes present in the anæmia of large hemorrhage, but it is exceptional. The history of the case leaves little doubt, pernicious anæmia rarely coming on ab-

ruptly. In any case, however, whether the anæmia had an acute onset after a large hemorrhage or a gradual development from repeated small hemorrhages, as in ulcer of the stomach, uterine or rectal hemorrhages, the character of the blood is sufficiently different to make a positive diagnosis. In acute post-hemorrhagic anæmia the blood rarely shows less than 2,500,000 corpuscles and the hæmoglobin is rarely below forty per cent., death resulting in cases where greater loss of blood has been sustained. In cases of repeated bleeding the blood-count may be lower, but the hæmoglobin in these cases is nearly always disproportionately diminished. Blood-counts below 1,000,000 are exceedingly rare in such cases, as they are very common in pernicious anæmia.

The similarity in their clinical manifestations of some cases of gastric cancer to pernicious anæmia has often been remarked. The differential diagnosis is especially difficult in cases where the cancer is small and occupies the posterior wall of the stomach. In these the absence of a palpable tumor and of rapid emaciation makes the diagnosis often uncertain, as in the following case.

Case I.—Mr. X., aged about sixty-three, had been ill for some time, complaining of gastric distress after eating, great weakness, and progressively increasing pallor. He never vomited, except occasionally after some distinct dietary indiscretion, and at such times the vomited matter presented no characteristic features. The patient came under my observation some months after his illness grew severe enough to prevent his continuing at his

usual occupations. He was then decidedly pallid, the color being waxy,—neither the sallow hue of cancerous cachexia nor the lemon yellow of pernicious anæmia. He was somewhat, but not greatly, emaciated. The symptoms had grown decided, but no new ones developed. There were occasional elevations of the temperature to 99.5° or 100.5° F. in the evening. Physical examination revealed no thickening or induration in the region of the stomach. The stomach was not at all dilated. There was no pain at the stomach,—at most, discomfort after food. The examination of the blood showed 3,200,000 red blood-corpuscles and forty per cent. of hæmoglobin. The disease continued without much change of symptoms, but after four months a decided induration could be detected in the epigastrium, and after death, which soon followed, a small tabular, scirrhous carcinoma was found in the posterior wall of the stomach, near the pylorus, but not obstructing it. The stomach was not dilated.

The diagnosis in cases of this description is manifestly very difficult, and it will be seen how great a service was rendered by the blood-examination. The presence of a certain degree of emaciation was really the only point of service in the diagnosis, and this cannot be regarded as of great significance, as will be seen in the next case; neither was the absence of the lemon hue of the skin a certain indication. It may be fairly urged that the examination of the blood alone could be relied upon in instances of this kind.

A second case may be cited in which the symptoms of pernicious anæmia resembled

those of cancer of the stomach. This case occurred in the practice of Dr. John Boger, with whom I saw it.

CASE II.—Mrs. X. Y., aged forty-seven years, ceased to menstruate three years previously. Her illness began apparently a year and ten months previous to her death and continued, with a single break of three months, progressively until her death. From the first she complained of marked gastric disturbances, especially vomiting. The matters ejected were reported to have been dark-colored, sometimes like coffee-grounds and at other times greenish, but there was never distinct blood. Dr. Boger never saw it otherwise than as yellowish or greenish liquid containing much mucus. The amount of vomiting was remarkable, often being repeated fifteen times during the day, and the average number being five times daily. The patient grew very weak, complained that she felt as if her heart was not beating, but did not have much actual dyspnœa or palpitation. She was habitually constipated. She is reported to have lost a great deal in weight (sixty pounds), but when I saw her a few weeks before her death she was not apparently emaciated; on the contrary, I noted the persistence of considerable subcutaneous fat, and the face was distinctly fleshy. The color of the skin and conjunctivæ was lemon yellow, the patient was weakened to the last degree, and the heart was extremely feeble, the sounds being muffled and toneless; a systolic murmur could be detected at the base and in the cervical vessels. The urine which was shown me was light in specific gravity, but darker than normal. The examination of the blood showed 800,000 red

blood-corpuscles and thirty-five per cent. of hæmoglobin. Physical examination of the abdomen discovered a degree of resistance in the epigastrium, with some tenderness, but no definite tumor. The stomach was not at all dilated. She died soon after, but autopsy was not obtained.

In this case the onset of the disease, the persistence of marked gastric symptoms, and the rather characteristic vomiting warranted the suspicion of cancer of the stomach, and yet in the later stages the appearance of the patient was enough to dispose of this diagnosis. The flabby fat with the lemon hue of the patient in themselves were strong points, for never, in an experience embracing quite a large number of cases of gastric cancer, have I seen the fat anything near so well preserved, and the yellowness of the skin in this case was very unlike the color we see in cancer, even when the liver is involved. With the examination of the blood the diagnosis was certainly unquestionable. Examination of the stomach contents could have given no reliable information, for free hydrochloric acid is frequently absent in pernicious anæmia, and the constant presence of this sign, even in cancer of the stomach, may be doubted. The slight induration in the epigastrium may have been due to a variety of causes, such as thickening of the walls of the stomach by interstitial gastritis, old gastric ulcer, and the like. It was not sufficient to constitute any evidence at all in favor of cancer, and probably was similar in nature to that found in a case of Dr. William Pepper's, which I had the opportunity to examine recently during life and post mortem. In this in-

stance the symptoms were almost identical with those in the case detailed, excepting that the vomiting was less pronounced and the vomita never brown in color. The blood-examination showed 900,000 red corpuscles and ten per cent. of hæmoglobin. There was the same induration in the epigastrium, and this was found, post mortem, to be due to thickening of the walls of the stomach near the pylorus, probably in some measure the result of an old healed ulcer, but largely to a diffuse cirrhosis.

The history of these cases illustrates rather well the points by which the two conditions—cancer of the stomach and pernicious anæmia—are to be distinguished, but one or two have not been alluded to. Not infrequently in the latter affection patients complain of discomfort or even considerable distress at the stomach, but rarely of the severe pain of carcinoma; and a tumor cannot, of course, be detected. In cases, however, where these distinct signs are absent, I should place most reliance on the presence of marked emaciation, of an ashy or sallow hue of the skin in place of a yellow tinge, and on the evidence of dilatation of the stomach. The character of the vomited matters and the presence or absence of free hydrochloric acid give us little assistance. Evening rises of temperature are more common in pernicious anæmia, but may occur in either. Finally, the examination of the blood is of signal importance. Rarely in carcinoma do the corpuscles fall below 2,000,000, and the hæmoglobin is disproportionately reduced.

Chlorosis and pernicious anæmia would, at first sight, appear easily distinguishable, as, indeed, they are in most cases. There are some

instances, however, of inveterate chlorosis in which the blood becomes progressively poorer and which eventually resemble pernicious anæmia very closely. This difficulty would be most marked in cases of *chlorosis tarda* or chlorosis in later life. Ordinarily, the great reduction in hæmoglobin with little diminution in the number of red corpuscles, together with the absence of marked poikilocytosis and of macrocytes, microcytes, and nucleated red corpuscles, render chlorosis easily recognizable. It is a mistake, however, to believe that the number of red corpuscles is never much reduced, as two recent cases of my own would prove. In one the examination showed 2,700,000 red blood-corpuscles with thirty per cent. of hæmoglobin; in the other, 2,270,000 red corpuscles and twenty-two per cent. of hæmoglobin. Even lower counts than this have been recorded. The age of the patient, the sex, the prominence of menstrual disturbances in many cases, and the absence, as a rule, of fever, usually give material aid in the diagnosis. In any case, however, in which the blood-count falls below our standard for pernicious anæmia (1,500,000 red corpuscles per cubic milimetre), and in which the reduction of hæmoglobin ceases to exceed that of the corpuscles, a transformation into pernicious anæmia might properly be suspected.

Reference has been made to the prominence of nervous symptoms in certain cases. This has been suggested prominently by the observation by Lichtheim, and after him by Minnich, Burr, and others, of organic changes in the spinal cord in this disease. The changes noted have been, in the earlier stages, small areas of

hemorrhage or extravasation of blood, similar to those seen in the retina and in the serous surfaces, and in the later stages of system degenerations, especially in the posterior columns. The latter changes are probably in no way connected with the small hemorrhages. Unfortunately for diagnosis, these changes occur other anæmic diseases, and the resulting symptoms are, therefore, of no value in diagnosis. In three cases I have examined, there was complete absence of the knee-jerk, and in two of them other symptoms which drew attention prominently to the nervous system.

Case III.—Mr. O. B., a shoemaker aged fifty-five years, came under observation complaining of progressive weakness and pallor and of gastric disturbances. His illness commenced three months or more previous to my first visit, and made steady progress. The patient's habits were good, he had never contracted syphilis, and had never been seriously ill. He complained of pain in the region of the stomach, especially after eating, and occasionally he vomited. I was at once struck by the man's general appearance and by his gait. He walked rather slowly, with the legs far apart, and brought his foot down upon the ground flatly, as in locomotor ataxia. Sensation was somewhat slow in certain areas about the soles and the dorsum of the foot. The knee-jerks were entirely wanting and station was uncertain. There was no pain excepting in the stomach after food. The pupils responded normally in accommodation and to light. His face wore an habitual heavy, melancholy expression very like that in paralysis agitans, and, indeed, there was frequently a tremor in either thumb and

forefinger, as in that disease. His mind was sluggish, and he could be aroused to interest in matters about him only with great difficulty. He was rather fleshy, the tissues being soft and flabby. His color was dead white, though for short periods it would assume a somewhat yellow appearance. The earlier examinations of the blood were unfortunately lost, but after some improvement in color and decided improvement in his general symptoms had taken place, the examination showed 2,000,000 red corpuscles and thirty per cent. of hæmoglobin. The patient first came under observation in May. In August he had retention of urine and had to be catheterized; subsequently cystitis developed. In spite of this, however, he improved slowly and presented a quite healthy appearance, and was free of the gastric symptoms the following winter. In the spring of the following year he again became anæmic, and afterwards passed from my observation.

In the second case there was loss of knee-jerks, somewhat ataxic gait, impaired station, and areas of diminished sensation in the skin of the feet and legs.

There may thus be marked nervous symptoms, due, no doubt, to changes in the spinal cord, but these symptoms never dominate the disease, and would not, therefore, obscure the diagnosis. In like manner, cardiac weakness, palpitations, or dyspnœa may be prominent symptoms, but their connection with the anæmic state is rarely doubtful.

Treatment.—The tendency of pernicious anæmia to a fatal issue must not lead to any laxity in treatment, for it is well known that temporary improvement may often be brought

about, lasting a few months or even years, and permanent cure seems to have been attained in some cases.

Byron Bramwell rendered a great service to medicine in calling attention to the value of arsenic in this disease. Sometimes the rapidity of the improvement following the use of this drug stamps it as almost a specific ; in other cases, however, it seems entirely powerless. It is best given in the form of Fowler's solution, beginning with 2-drop doses and rapidly increasing to 10 drops, then more slowly to 15 or more. The remedy should always be given after meals. Frequently I have hesitated to administer it on account of gastric disturbances ; but I have more often found in these instances that the gastric symptoms subsided after the drug was given than the reverse, and this has been the experience of others. It is true, however, that the stomach sometimes will not tolerate Fowler's solution or pills of arsenous acid. In urgent cases it may then be used hypodermically, but generally proves somewhat irritating. Under no circumstances should arsenic he pushed so far as to produce diarrhœa or other gastro-intestinal symptoms, as the loss of ground from an attack of diarrhœa may more than counterbalance the gain secured by weeks of judicious treatment. The tolerance of the drug is sometimes remarkable, but there is little need of increasing the dose beyond 15 drops, even when it is well borne. The value of arsenic in pernicious anæmia has been a little too well recognized, for it has at times led to a neglect of other measures almost as essential.

The patient should always at first be confined to bed, and should be required to use the

bed-pan and urinal. The diet should be nutritious and easily assimilable. Meats should not be given too freely, on account of the diminished secretion of hydrochloric acid; nor, on the other hand, should sugars or starchy food be allowed in large quantity, from their tendency to fermentation. Symptomatic treatment is generally required to aid digestion and to allay gastric irritation. For the former purpose hydrochloric acid is often essential, and should always be tried where gastric fulness and fermentation are complained of. Where vomiting is severe I have found that small doses of bismuth subnitrate (5 grains) with cocaine ($\frac{1}{30}$ to $\frac{1}{12}$ grain) act more happily than any other remedies; and it has seemed to me that arsenic could be administered more freely and continuously with than without these adjuvants. They are best administered some time before the meal.

Our knowledge of the pathology of the disease would indicate that measures should be taken to prevent putrefactive changes in the stomach and intestines and to minimize the absorption of poisons from this source. In the remarkable case of Sandoz the good effects of lavage of the stomach were most apparent, and Kaufmann and others report similar results.

Aside from the question of its influence on the disease itself, lavage may prove of great advantage in controlling obstinate vomiting and in improving the digestive power. There will generally be some difficulty at first, but after the patient has grown somewhat accustomed to the tube the stomach may be flushed every few days with little disturbance. In cases where gastric atony seems prominent and

the patient's appetite is poor, bitters may be given with advantage before meals.

Intestinal lavage has been less frequently practised, and has not as yet yielded definite results. If, as has been claimed, the small intestines may be flushed out by high injections, there is reason to hope for some advantage from this method of treatment, and in the later stages of the disease it would be of additional service in supplying a certain amount of fluid to the empty vessels. The use of intestinal antiseptics, such as salol, naphthol, and carbolic acid, has been highly lauded, but the results are thus far uncertain. Free use of purgatives is distinctly less advisable than in chlorosis, excepting in the cases of parasitic pernicious anæmia. There is always the danger of deranging the stomach and of adding to the weakness of the patient. Enemata or suppositories will generally be sufficient for the purpose of securing action of the bowels, and beyond this we should not attempt to go.

Sooner or later in pernicious anæmia there comes a time when the deterioration of the blood, for which the excellent term *cachæmia* has been suggested, reaches such a grade that remedies seem altogether powerless. In this stage I have felt that the patient suffers quite as much, if not more, from the decreased quantity of the blood in circulation or from its inability to circulate freely. At this stage measures directed to assist the circulation are even more essential than arsenic. Of these measures not the least powerful is systematic massage. The interesting investigations of John K. Mitchell have shown very pointedly the effect of massage in putting larger masses of blood into circulation,

and in pernicious anæmia less than in any other condition can the system spare any portion of the blood to rest idly in the tissues. A still more advanced case would call for injections of water or of blood. The safest and perhaps the best method would be the hypodermic injection of normal salt solution in large quantities (two pints to two quarts). The intestinal flushings of which I spoke before might be of assistance here, but they could hardly prove as satisfactory as hypodermoclysis. The transfusion of blood itself has been practised by a number of investigators, and some, as Brakenridge, report remarkable improvement following the operations. It is doubtful, however, if blood-serum or blood has any great advantage over salt water, and certainly the danger of fibrin-ferment intoxication and other accidents would deter us. The administration of dried blood by the rectum possesses no special advantages.

In cases of pernicious anæmia in which improvement is seen to be taking place the treatment should be continued with great care. Under no circumstances should the hygienic and dietary regulations be relaxed or the use of arsenic discontinued. As in chlorosis relapses are frequently due to the neglect of the use of iron as soon as the patient's color is normal, so in pernicious anæmia I believe the intervals between recurrences could be materially lengthened, and perhaps permanent cure more frequently attained, by the unbroken administration of arsenic. During convalescence also I have found iron to be a valuable adjunct to arsenic. In the earlier stages of the disease,

however, it is not only of no value, but often disagrees decidedly.

One word in conclusion. It seems to me that the best classification of the anæmias should assign to pernicious anæmia all cases in which the deterioration of the blood has reached the point I have indicated, whether a cause be found or not. This seems reasonable, because we have in all forms of severe anæmia presenting the features of pernicious anæmia the same evidences of great hæmolysis and defective hæmogenesis, and clinically the same tendency to further deterioration of the blood, whether the anæmia is secondary to gastro-intestinal disease, to pregnancy and parturition, or apparently quite causeless. In the last group of cases no doubt similar causes will some day be found. According to this view, we look upon pernicious anæmia as a symptomatic condition, a high degree of *cachæmia*, which experience shows is a condition of great gravity, and which tends to grow worse. We are thus constrained to consider the diagnosis incomplete until the cause of this cachæmia is discovered, and the treatment requires attention to the underlying causes as much as to the blood itself.

JANUARY 16, 1893.

WHOLE SERIES, VOL. XVII. No. 1. THIRD SERIES, VOL. IX.

—THE—

Therapeutic Gazette

A MONTHLY JOURNAL

—OF—

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EDITORIAL OFFICE, 222 South Fifteenth St., Philadelphia, U.S.A.

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GEORGE S. DAVIS, DETROIT, MICH., U.S.A.,
OR
714 Filbert Street, Philadelphia, Pa.

Published on the Fifteenth Day of Every Month.

SUBSCRIPTION PRICE, TWO DOLLARS A YEAR.

Agent for Great Britain: Mr. H K. LEWIS, Medical Publisher and Bookseller, 136 Gower Street, London, W. C.

Entered at the Post-Office at Philadelphia, Pa., as second class mail matter.

PRINTED BY J. B. LIPPINCOTT COMPANY, PHILADELPHIA.