

scribed the occurrence of fatty heart. Microscopical examination reveals the destruction of muscle striæ and their replacement by fat. The pericardial sac very often contains an excess of serum, rarely any blood. Ecchymoses, however, are quite common underneath this membrane as well as under the endocardium. The valves are normal, or superficial specks of atheroma may be seen on them. Similar changes are found in the intima of the aorta to a slight degree. The capillaries have been studied carefully, and Eichhorst says minute aneurisms may be seen; Mantz describes minute varicose dilatations in the retina, Charcot in the brain. Nykamp opposes these views, and attributes the hemorrhages to diapedesis. Rupture of the capillaries has been observed. Osler saw the small vessels and capillaries of the mesenteric glands studded with fat grains. The arrested development of the heart and aorta and the anomalous distribution of the blood-vessels, said by Virchow to be present in chlorosis, were seen in one of Müller's cases. The aorta at its origin was 1 cm. in diameter, and, in one of the writer's cases, admitted the little finger at the seat of origin of the cœliac axis. The heart, however, was not small.

RESPIRATORY ORGANS.—Secondarily to the failure of the heart an œdema or hypostasis of the lungs often occurs, and this is in a large number of cases the only morbid condition of these organs. Generally the lungs are extremely anæmic. Sometimes the remains of an old phthisis or an emphysema are seen; very rarely are the lungs the seat of a croupous pneumonia. Hemorrhages underneath the bronchial mucous membrane are found; sometimes there is a bronchitis; pallor of the membrane is noticeable. The pleura is healthy, or the seat of subserous ecchymoses; one cavity may contain serum in a large amount mingled sometimes with threads of fibrin, or both cavities may contain small amounts of serum. The effusion is sometimes sanguinolent.

ORGANS OF DIGESTION.—The mucous membrane of the gastro-intestinal tract is pale, often also œdematous. Very frequently, however, submucous hemorrhages and hemorrhagic erosions are seen. They have been noted in the mouth, œsophagus, stomach, intestines, and biliary passages. In the stomach, Fenwick, Ponfick, and Habershon have found a fatty degeneration of the tubular glands. An inflammation of the gastric mucous membrane has also been recorded. Hyperplasia of the connective tissue of the gastric mucosa, with atrophy of the tubules, is frequently met with. The presence of intestinal catarrh, of chronic follicular enteritis, and of enlargement of the follicles and agminated glands, has been recorded. Dysenteric inflammation of the intestines was observed by Quincke in one case, in the late stages of the disease.

The changes in the mesenteric glands have been previously recorded, as have also to a certain extent those in the liver. That organ is very often anæmic and generally fatty. This fatty degeneration of the liver was specially described early in the history of the disease by Wilks. Perroud thought the hepatic change was primary, the blood change secondary; the fatty degeneration interfering with the formation of blood. The degeneration is seen in the liver cells, large fat drops rendering the nuclei difficult of detection. Deposits of iron pigment have been described by Eichhorst and Quincke in the hepatic cells, the blood-vessels, and the interstitial tissue, in which parts they cause the iron-gray staining referred to previously. Minute extravasations of blood have been seen. Rarely the liver is congested. The size of the organ varies; while it is generally normal, it has been recorded as lessened and also as increased. The surface of the liver is usually smooth and normal; a perihepatitis has been recorded by Müller.

The liver tissue is smooth and compact on section, and the acini are well defined; a nutmeg appearance has been noted in a few instances. The biliary passages are normal or thin, and the mucous membrane is extremely pale. Suppuration of the gall bladder was present in

one of Pepper's cases. The gall bladder is generally full of bile.

On microchemical examination, in addition to the presence of iron, Lebert found leucin and tyrosin in abundance in the liver as well as in the pancreas, lungs, kidneys, and spleen.

The pancreas is usually normal. It is sometimes enlarged, and Eichhorst and Quincke found extravasated blood in the interacinous tissue. Huguenin observed fatty degeneration of the glandular epithelium. Iron pigment has been found in the cells in some cases.

RENAL AND GENTAL ORGANS.—Ecchymoses have been observed under the capsule of the kidney, which is readily removed in most cases. The organs are pale and firm on section; often the appearance of fatty change is seen. Microscopical examination reveals the presence of fatty change in the epithelium of the tubules, and in some cases an infiltration with iron pigment is noticeable. The remaining portions of the urinary apparatus are normal, save the occasional presence of submucous hemorrhage.

The suprarenal capsules are normal. Broadbent recorded the occurrence of atrophy of the organ. The microscopical examination of these capsules in the writer's case revealed slight increase of the interstitial tissue, with infiltration of lymphoid elements. The vessels were engorged with blood and small capillary hemorrhages were seen. Pigmentation and slight fatty infiltration of the cells in the capsule were seen, but probably this was not greater than is normal. Granular masses, not unlike colonies of bacteria, were observed.

No changes are found in the sexual organs. Müller noted subinvolution of the uterus in a case of fatal anæmia following pregnancy.

NERVOUS SYSTEM.—The brain and spinal cord may be anæmic, and the seat of minute ecchymoses or even (with-in the brain) of large hemorrhages. The cerebral ventricles sometimes contain an excess of serum or blood. The hemorrhages are chiefly found in the region of the corona radiata or on the surface of the cerebrum. The pia mater or the inner surface of the dura is often the seat of ecchymoses. Eichhorst and Müller observed hemorrhagic pachymeningitis. These authors also have found œdema of the membranes. Microscopically, Eichhorst found no change, save increased pigmentation of the ganglion cells. Schumann ("Diss. Inaug.," Freiburg, 1875) found increase of the nuclei of the cerebral neuroglia. The changes in the vessels have been mentioned. Lichtheim in 1887 first observed sclerosis in the spinal cord. Numerous observations since then have confirmed his reports. The posterior columns are chiefly affected, together with less constant changes in the lateral tracts. The irregular distribution of the sclerosis indicates that it is not a systemic degeneration, but is due to the action of a toxic substance.

Since the earliest observations of pernicious anæmia, the appearances of the sympathetic system have been studied. Quickett found, in Addison's case, that the semilunar ganglia had undergone fatty degeneration. Brigid found (*Lo Sperimentali*, May, 1878; *London Medical Record*, vi., 430) proliferation of the nuclei, increase of interstitial tissue, and granular pigmentation of the ganglion corpuscles of the solar plexus. Wilks and Pye-Smith found no changes in the semilunar ganglia and surrounding plexuses. The writer found pigmentation of the nerve cells and along the nerve fibres, with a slightly granular appearance of the cells. Macroscopically, the ganglia and nerve filaments were unusually prominent. Sasaki (Virchow's *Archiv*, vol. xcvi., 1884) found in a case of pernicious anæmia, of the gastro-intestinal form, sclerosis of the ganglion cells, destruction of some of them, and homogeneous hyaline bodies in Auerbach's and Meissner's plexuses.

ORGANS OF SPECIAL SENSE.—*The Eye.*—The occurrence of retinal hemorrhages during life has suggested the necessity of making an examination of the fundus of the eye after death. The changes found are not different from those observed in other diseases, as at times in

chronic Bright's disease and in other severe anæmias. The changes in the vessels causing the hemorrhages have been previously referred to. Uhlhoff says the hemorrhages are chiefly limited to the nerve fibres and inter-nuclear layers, and are situated near the posterior pole, especially around the disc. Varicose hypertrophy of the nerve fibres, affecting the most internal layers and consisting of finely granular masses, spherical or spindle-shaped, was also present. Bettman found on microscopical examination (1) rupture of the membrana limitans interna; and (2) the presence of numerous clusters of varicose nerve fibres, due to transudation of lymph, producing swelling of these fibres. Optic neuritis has been seen; œdema of the disc and retina has also been observed.

SYMPTOMS.—The first indication of the patient's illness is the occurrence of debility, pronounced on exertion, with the coincidence of breathlessness and possibly cardiac palpitation. These increase in severity; the complexion is seen to be changed, the bloodlessness of the external parts is made manifest, the appetite is lost, digestion is impaired, hemorrhages occur, the sight fails, subjective noises in the head are complained of. As the disease progresses, languor becomes more and more decided, dyspnoea is extreme, fainting grows common; while indifference to physical or mental acts, as well as incapacity to perform them, is most noticeable. The "air hunger" which the patient has renders the ebb of life intolerable, and its close is marked by agonizing efforts to carry on respiration. Or the end is marked by a low delirium, passing into somnolence and then fatal coma. At times death takes place suddenly from cardiac failure or from hemorrhage in the brain. The following brief outline indicates the special symptoms more fully:

External Appearances.—The color of the face is striking—an earthy yellow, yellowish-white, or waxy hue, or a faded-leaf appearance; this color is also seen on the hands. It contrasts strongly with the extreme pallor of the lips, the gums, the tongue, the conjunctivæ. Slight jaundice has been observed, but, as Mackenzie points out, care must be used in making the observation, as it may be due to the unusual yellow coloring of the subconjunctival fat. Very early the expression is lost, the eyes lose their lustre, the face becomes vacant and ghastly. In the later stages the face is a little puffy, the eyelids œdematous. This œdema may be seen on the hands and around the ankles. It is due to the hydræmic state of the blood and to degeneration of the blood-vessels. It rarely amounts to an anasarca. The hair is soft, turns gray, or has a peculiar lustre as if it had been dyed and is losing the artificial color. Eichhorst notes a loss of hair. The nails are fragile and pale and grow very slowly.

Although there is a flabbiness of the tissues, yet there is generally no wasting of the adipose tissue. This has been well preserved in all but a few of the recorded instances of the disease. Pain and tenderness over the bones have been noted. Eichhorst observed, in a few instances, a peculiar cadaveric odor arising from the body a few days before death, and from Hutchinson's patient a peculiar musty odor arose.

Hemorrhages have been cited as peculiar to pernicious anæmia. They occur subcutaneously, as small purpuric spots, chiefly about the extremities. They are also seen in other forms of anæmia, and in all the forms they are observed particularly in the retina.

Temperature.—The presence of increased temperature of the body was thought to be pathognomonic by Immermann and others. Some even insisted on its presence, but there are many authentic cases of its absence during the entire disease, while its presence is noted in other forms of anæmia. Generally it occurs at certain periods of the disease, either in what may be termed the middle period or at the end. Thus, a case is without fever at first, then there is a rise of temperature for a while, but toward the close the temperature returns to normal, or may be subnormal. The fever is characterized by frequent remissions, by a moderately low range, by irregu-

lar intermittency, and by fluctuations under slight influences. Those who hold that the disease is due to hæmolysis, the result of toxæmia, cite this fever as an argument in favor of their view.

Gastro-intestinal Symptoms.—The mucous membrane of the mouth is pale. The tongue is furred, or it may be clean and smooth; sometimes it is red and raw. Hemorrhages occur from the gums, and toward the close sordes collect on the teeth, gums, and lips. Salivation has been observed. Gastric symptoms may mark the onset of the disease, and are always present in its course. Loss of appetite is generally present, and nausea very frequently occurs, while pain, flatulency, weight and fulness after eating, are prominent. Thirst is not marked. Hydrochloric acid is diminished or absent, and the motor power of the stomach is deficient. The vomiting, especially toward the end of the disease, is so persistent as to lead one to think ulcer or cancer of the stomach may be present. In addition to the food taken, a clear or greenish-yellow acid fluid, mucus, and rarely blood, black in color, are ejected. The vomiting occurs after eating, and is often more like regurgitation of food, and is always attended with nausea. The occurrence of diarrhœa with thin light-colored stools, has often been observed. The diarrhœa is painless. Wilks has seen blood in the stools. On the other hand, the bowels may be regular or confined. Huguenin found leucin and tyrosin in the passages on chemical examination.

Liver and Spleen.—The liver is not generally affected. Rarely it has been recorded as enlarged. The spleen, while it may be slightly enlarged, shows no other alterations. This enlargement is scarcely great enough to be demonstrated during life.

Cardio-vascular Symptoms.—The patient complains at first of palpitation on exertion; later, palpitation occurs even at rest. The action of the heart is extremely feeble and at times rapid. The least excitement increases the palpitation and tendency to fainting. Cardiac pain is sometimes present. On physical examination the apex beat is found lower than normal, the impulse feeble and diffused. Sometimes the area of dulness is increased, this increase being due, in the later stage of the disease, to dilatation of the heart or to retraction of the lungs (Quincke). The first sound is extremely feeble, the second clear and bell-like, but not accentuated. Systolic murmurs, chiefly pulmonary and aortic, but also mitral and tricuspid, are almost always heard, loud and distinct. The occurrence of a diastolic murmur has been noted in a few instances. These murmurs are due to the fluid state of the blood, and possibly to a regurgitation of the blood through incompetent valves. The papillary muscles are so highly degenerated as certainly to interfere with normal valve closure.

A loud hum is heard in the jugular vein. In the carotid arteries a systolic bruit is heard. Such a murmur may be heard in more distant vessels also. The carotids pulsate at times; the veins are large and full, and have been seen to pulsate. The pulse is feeble and compressible, dicrotic, at times irregular and quite rapid. The cardiac symptoms and physical signs of this form are similar to the same symptoms of the other forms of anæmia, while the mechanism of the production of murmurs is the same. The latter, however are much more intense than in simple anæmia.

Respiratory Symptoms.—The occurrence of dyspnoea is noted early in the disease, at first on exertion only; later, it becomes constant, and toward the close of life the sufferings from it are extreme. The dyspnoea occurs independently of any organic disease, and is due to the destruction of red corpuscles and the lessened supply of hæmoglobin. Rarely is a hydrothorax found during life, and the same may be said of any organic disease of the lungs or pleura. Pneumonia occurs in a few instances as a complication. Hemorrhages from the nose are frequent; often the source of bleeding is in the lungs. A Cheyne-Stokes respiration is sometimes present, probably due to the fatty heart or to cerebral complications.

Late in the disease œdema of the lungs or even hypostatic congestion is liable to occur.

Genito-urinary Symptoms.—These are few; it may be said, in fact, that no complaints are made by the patient of renal symptoms. There are no lumbar pains, and there is no painful or increased frequency of micturition. The urine is clear or dark in color, acid in reaction, varies in specific gravity from 1.010 to 1.020, being usually below 1.015, and is normal in amount. The amount depends on the occurrence of vomiting or diarrhœa, being lessened when these conditions are present. Although the daily amount is about the normal average, cases have been reported in which the amount was increased from 2,000 to 3,500 c.c. daily (Immermann); in some instances the amount was reduced to 800 c.c. (Müller). The excretion of urea is variable and not characteristic, while that of uric acid is increased.

Apart from the changes mentioned in the normal constituents of the urine, few if any pathological products are found. In the later stages of the disease albumin is sometimes observed. It is present in small amount, and its occurrence corresponds with that of some general depression or temporary cardiac embarrassment. Quincke observed a large amount of albumin, in one instance, as did also Müller. The kidneys were highly fatty in the latter observer's case. With the albuminuria that precedes death, there are found hyaline casts (Müller, *op. cit.*, obs. xlvi., p. 239).

Sugar does not occur in the urine of patients with pernicious anæmia. Müller found leucin and tyrosin. Indican is increased in quantity, a fact that favors the theory of the toxic origin of the disease. Blood has been observed at times in the urine; it comes from hemorrhages into the pelvis of the kidney or from the walls of the bladder. Reynolds, in a careful analysis of the urine of one of Dr. Finney's patients, found an increase in the percentage of iron, both when the patient was taking the drug and when it had been discontinued for some time. In the first instance he found 0.7845 grain of iron, and in the second 0.308 grain in 72 ounces of urine. Hunter found in one case 32.5 mgm. of iron in the day's urine (3 to 5 mgm. normal). He has also found quite constantly pathological urobilin.

The genital organs in the male or female are not especially influenced in the course of the disease. In the female the menstruation may be more profuse than normal or it may recur too frequently, and even menorrhagia may develop. The pregnant female will abort, or premature labor will take place.

Nervous System and Special Senses.—Headache and giddiness, with subjective noises in the head and ears and subjective flashes of light, develop in proportion as the anæmia grows profound. There are but few cases in which these symptoms are absent. They are due to the hydræmic condition of the blood. As the disease progresses loss of memory is seen; an apathy and sluggishness of action of the cerebral faculties is quite remarkable, and low wandering delirium gradually advancing to stupor and coma often mark the close of the disease. Rarely convulsions occur, while in some instances paralyses, chiefly limited to monoplegias, have taken place some time before death. These cerebral symptoms are due to hemorrhages within the brain substance and in the membranes, and to œdema of the brain. Symptoms of involvement of the spinal cord occur. They usually conform more or less closely to the symptom complex of tabes dorsalis, or occasionally to that of combined posterior and lateral sclerosis.

One of the symptoms on which Biermer had laid much stress was the ophthalmoscopic appearance of the fundus of the eye. By him, and for a time by others, actual hemorrhages were thought to be constant attendants of this disease. It has been shown, however, that they are present in other cachexiæ and may be absent in this. In two of the writer's cases they were present, but in a third they were absent. Their presence does not imply a fatal termination, nor their absence a favorable one (Coup-land). In some instances they were so large as to impair

vision and even to cause blindness; generally they are small. They are many in number generally, and are situated around the optic nerve entrance, or they follow the course of the blood-vessels in the nerve-fibre layer. They are most frequently in the lower and outer quadrants. They are seen as black, reddish- or yellow-brown spots, round or oval, sometimes linear-striated or "flame-shaped." The retina is very often clouded or hazy, the vessels are pale, the arteries reduced in size, and the veins enlarged. In some instances an œdema of the disc or a neuro-retinitis has been observed, and Mackenzie noted white patches and yellow spots in the effused blood, due to "leucocytic infiltration, and to degeneration in the disturbed retinal tissues."

COMPLICATIONS, DURATION, PROGNOSIS.—The complications of pernicious anæmia are rare—in fact, pneumonia, erysipelas, dysentery (Quincke, one case), nephritis, and local suppurations are the only ones that have been observed. Sequelæ are absent in those cases which get well, but the progress to full health is slow and fitful, and may be marked by serious relapses. The duration is variable. The average appears to be about five months. In some few instances the disease has terminated as early as six and eight weeks after its inception. The writer's fatal case was of three years' duration, dating from the first evidences of failure in health. Coup-land found that 12 out of 110 cases were ill for periods extending beyond two years.

The prognosis is generally grave. A small proportion of cases get well. Pye-Smith analyzed 122 cases; of this number, 20 recovered. Two only of the 27 cases of primary essential anæmia collected by Eichhorst recovered. The elements that influence the prognosis are hard to establish. It had been thought that a diminution of corpuscles to 500,000 or under would render a prognosis unfavorable, yet one of Quincke's cases recovered, although there were but 143,000 red corpuscles per cubic millimetre. Quinquand determined that 26.5 gm. per 1,000 c.c., about one-fifth of the normal quantity, was as small an amount of hæmoglobin as was compatible with life. Yet here again Quincke's observations are at variance. He found in four cases the reduction to be one-eighth, one-tenth, one-fifteenth, and one thirty-fifth of the normal; the last was a case in which recovery took place. The prognosis is more grave under the following circumstances: first, when the disease occurs in a pregnant woman; second, when there are numerous syncopal attacks; third, when fever is marked and hemorrhages are profuse; and lastly, when cerebral symptoms, apoplexy, paralysis, etc., ensue. Labor pains in a pregnant woman affected with anæmia are the forerunner of death. Ehrlich considers the occurrence of numerous megaloblasts of bad prognostic omen.

Occasional remissions occur during the course of the disease, preceded by gastric crises and an increase of the erythroblasts. The number of red blood cells increases and may reach almost to the normal. The general symptoms improve simultaneously, but this is only temporary.

DIAGNOSIS.—The recognition of this condition would be easy if there were some pathognomonic alteration in the blood. But most observers believe that there are no specific changes. Ehrlich, however, asserts with great positiveness that the presence of megaloblasts and numerous megalocytes is quite diagnostic. While this question is in doubt, the recognition of the disease must depend on a careful consideration of every available sign—the clinical picture, the blood picture, and the possible etiological factors.

Chlorosis is distinguished from pernicious anæmia with ease in most cases. The former disease occurs in girls near the age of puberty. The general condition is never so grave: retinal and cutaneous hemorrhages, and hemorrhages from mucous membranes almost never occur. The "color index" of the blood is always less than normal, while in pernicious anæmia it is increased. Chlorosis is promptly relieved or cured by iron; this is an unailing test.

Leukæmia is not likely to be confounded with pernicious

cious anæmia if an examination of the blood is made. In leukæmia the white blood cells are enormously increased in numbers, while the leucocytosis of pernicious anæmia is never very great, the highest we are aware of being 30,000 per cubic millimetre. The spleen or the lymphatic glands are enlarged in leukæmia—conditions which do not obtain in pernicious anæmia.

Simple secondary anæmias, not pernicious in type, may sometimes reach an extreme degree. Their differentiation from pernicious anæmia is more difficult, but can usually be made on the basis of slighter degrees of blood changes and the more ready response to treatment. If megaloblasts are not present, the case is certainly not one of pernicious anæmia. Simple secondary anæmias are never more severe than the primary condition would seem to warrant, while a disproportionately severe anæmia is characteristic of the pernicious secondary type.

PATHOGENESIS.—This still remains obscure, although recent investigations have begun to shed some light on it. The etiological factors already spoken of are probably all in the nature of predisposing causes. The exciting cause is certainly something more profound. This is evident when we consider how commonly these predisposing factors are present, and yet how seldom pernicious anæmia occurs.

Three theories have been advanced to explain the development of the anæmia. They will be presented in the order of their plausibility.

The theory that is best supported by evidence is that which attributes the anæmia to excessive blood destruction (hæmolysis) caused by toxins absorbed from the gastro-intestinal tract. The anatomical and experimental evidence in favor of this view seems almost conclusive. Deposits of iron pigment in the liver, spleen, and other tissues were observed many years ago, but in 1889 Sir William Hunter made the observations significant by demonstrating experimentally that hæmolysis occurring in the general circulation gave rise to hæmoglobinuria, but that if it were produced in the portal circulation, excretion of urobilin and other iron pigments occurred, while many tissue cells, particularly of the liver, became infiltrated with iron pigment. The occurrence of urobilin in the urine and of iron pigment in the liver cells strongly suggests that in pernicious anæmia the hæmolysis occurs in some part of the portal circulation. The most likely cause of such hæmolysis is, of course, toxic products from the gastro-intestinal tract. The fever that occurs is an additional indication of toxæmia.

The other two theories advanced to explain this disease have less to support them. Stockman in 1895 suggested that minute capillary hemorrhages brought about by a simple anæmia so impoverish the blood that further fatty degeneration of small vessels occurs, causing additional hemorrhage. Thus a *circulus vitiosus* is established that leads from bad to worse until a fatal issue supervenes. The theory is one well worthy of consideration, but it is defective in not accounting for the influences that start the blood on its downward course in certain cases, while the majority of grave simple anæmias do not become pernicious.

The theory of defective hæmogenesis was based on the condition of the bone marrow. The marrow of the long bones reverts to the embryonal type and is undoubtedly engaged in active hæmogenesis. This is also indicated by the occurrence of nucleated red blood cells in the circulating blood. It was supposed that the red cells produced were turned out into the circulating blood in an immature and more vulnerable condition, and that on this account increased hæmolysis occurred. But the occurrence of identical changes in severe simple anæmias, not pernicious in type, and the absence of the change in certain cases of pernicious anæmia make it almost certain that the medullary changes are secondary to the changes in the blood, and not their cause.

A number of observers have described protozoan and bacterial parasites in the blood in pernicious anæmia, but their relationship is so doubtful that it does not seem worth while to give place to their discussion here.

TREATMENT.—Rest, massage, a liberal, nutritious, and easily digested dietary, the moderate use of stimulants, cheerful surroundings, and probably a change of scene are the chief non-medical means used for the restoration of health. Yet no definite results can be given of the beneficial effects of the above means, either singly or combined, unless it be of the last measure. One of Fre-rieh's cases appeared to be cured by removal to a mountainous territory, while, on the other hand, one of the writer's cases improved at a city hospital, suffered relapse in his mountain home, and was completely cured on his second visit to the hospital.

The remedies commonly used in anæmia have been disappointing in this affection. Iron, phosphorus, cod-liver oil, quinine, and strychnine have failed as blood restorers or general tonics. Arsenic, however, has been found of inestimable service. Its value was first discovered by Bramwell, who used it first from a knowledge of its good effects in fatty degeneration of the heart.

Padley carefully considers the use of arsenic, and shows the results of treatment by this drug in 70 cases collected from various sources. Of the 70, 48 were treated without arsenic; 42 proved fatal, 2 were still under treatment, in 3 the result was unknown, and 1 recovered (authorities, Hobson, Coupland, Mackenzie, Bramwell, Barclay). Comparing this with the remarkable results derived from the use of arsenic, the most skeptical person will be convinced of its utility. Twenty-two cases were treated by arsenic; 16 recovered, 2 improved, and 4 were fatal (Coupland, Hobson, Bramwell, Finney, Broadbent, Withers, Moore, Lockie, and Padley). The drug should be given in small doses, gradually increasing until its physiological effects are produced. If gastric irritation is produced, hypodermic injections of arsenic in the form of Fowler's solution in five- to ten-drop doses may be employed. Transfusion has been employed with temporary relief in some instances; rarely has it been actually curative; four undoubted cases only are recorded by Pye-Smith as being cured. Quincke prefers arterial transfusion, others the venous. The transfusion may be done by the direct or by the indirect method. In addition to blood, milk has been used (Thomas, Pepper). It appears that a simple saline solution, used either subcutaneously or intravenously, as the urgency of the case demands, meets all the requirements, and is not by any means as dangerous as the use of the other liquids. Bone marrow has recently been introduced on the supposition that it would supply either red blood cells or an internal secretion supposed to be found in the bone marrow. The results obtained from its use are far from convincing, yet sufficiently good results have been reported to justify continued trials of the method, though it finds little support on theoretical grounds. Stengel recommends the use of "marrow jam," made by mixing in a mortar equal parts of red marrow from a calf and glycerin. From two to four drachms of this may be given three times a day.

Excellent results, and even cures, have been reported from the use of gastric lavage and colonic irrigation, together with intestinal antiseptic measures. Believing as we do, tentatively at least, that auto-intoxication from the gastro-intestinal tract is the cause of the disease, we judge these measures to be most rational.

Da Costa has benefited some cases by inhalation of oxygen. J. K. Mitchell, in experiments on the normal individual, showed that massage increased the number of corpuscles in the circulating peripheral blood. The effect was due, no doubt, to the dislodgment of corpuscles accumulated in small vessels and capillaries. Massage is therefore to be recommended in pernicious anæmia as a means of mobilizing the small army of stagnated corpuscles, in order to wage more effective war against the hæmolytic agent.

The symptomatic indications for treatment are generally met by the adoption of suitable measures. These indications are gastro-intestinal symptoms, the dyspnoea, the cardiac palpitation, and hemorrhages. The writer has seen very much benefit result from the use of cal-