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to Pernicious Anemia*

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INFECTION OF THE GALL-BLADDER IN RELATION TO PERNICIOUS ANEMIA

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SIX years ago, one of us (N. W. J.) began the study of the case of Mrs. G. (Case I) who gave a history of weakness and anemia that had existed in a periodically relapsing manner for seven years and was punctuated by occasional attacks of rather severe pain in the right upper abdomen. She presented a lemon-tinted skin, a moderate degree of glossitis and a blood picture possessing the so-called persistent characteristics of a pernicious anemia during the period between relapses; namely, a plus color index, irregular and large red blood cells with irregular staining properties but without nucleated red cells. She was studied for a month in hospital as a borderline anemia, that is, a probable pernicious anemia which at the time does not show the presence of megaloblastic cells, and because of the continued pain and soreness in the upper abdomen she was operated for chronic gall-bladder disease. This condition was found and the gall-bladder was removed. A hemolytic streptococcus was obtained in pure culture from it. During convalescence the lemon tint of the skin disappeared and the blood assumed, in the course of a few weeks, the picture of a mild grade of secondary anemia. The patient is a true general asthenic in build and state of health; she has never been robust; is not strong now, but through two severe protracted illnesses during the past six years she has retained a general asthenic type of health and has not reverted to the picture of pernicious anemia.

The outcome of the treatment in this case suggested to the observer at the time as possibly of interest in throwing some light

upon the hidden cause of Addison's idiopathic anemia, and since then all similar cases have been studied with this in mind. But the diagnosis of chronic cholecystitis could not be made with sufficient positiveness in other patients to justify exploratory operation, so that for several years there was no opportunity to study the question further. With the development of the newer technic of George and Leonard for the roentgenological study of the gall-bladder, however, the problem was taken up again. During the past year and a half several cases of borderline anemia and of frank pernicious anemia have been intensively studied from this standpoint. To our associate in roentgenology, Dr. Dorwin Palmer, we owe very much for the clinical recognition of existing gall-bladder disease in these patients. Operation on 2 of the patients depended wholly upon the roentgen-ray evidence. The gall-bladder in 1 instance appeared macroscopically normal but was removed because of the positive shadows obtained on the films and because of the anemia. The results of this study are now detailed.

A cursory review of the prominent points in the history of pernicious anemia is sufficient to impress one with the probability that the anemia, which bears this name, is a symptom-complex rather than a disease entity and that various hemolyzing agents may produce the picture if they have the opportunity to work within the body in a slow manner over a long period of time. In fact, clinical observation of any series of cases suggests the same thought, for the downward course is a very variable one. It may be rapid, comparatively speaking, without remissions and lasting only a few months; it may present the ordinary frank pernicious anemia course which continues two or three years and is characterized by several remissions and relapses in the meantime; and then again it may present the borderline picture which may continue for years and is a pernicious anemia in all appearances save that of not having megaloblastic cells in the circulation. This variable clinical picture was noted by Addison¹ in 1855 and more in detail by Biermer² in 1872. William Hunter has maintained since 1890 that oral sepsis constitutes the source of the hemolyzing agent and that the tongue and the stomach and intestinal mucosa become infected secondarily. In a British Medical Association Lecture in 1921, Hunter³ makes the statement that the tongue in true pernicious anemia has become by reason of the oral sepsis the actual focal site for the infection which causes the disease and suggests the name of "glossitic anemia" for it. He does not offer evidence substantiating this belief.

The first important contribution to the etiology of a pernicious type of anemia was that of Schaumann and Tallqvist⁴ (1898) who found a hemolytic substance in the head and body of the fishworm, *Bothriocephalus latus*, and proved that it was the cause of the pernicious type of anemia in persons infected with this parasite.

Schaumann⁵ had already (1894) reported a study of 72 cases of fishworm anemia and had found the same clinical picture and the same megaloblastic metamorphosis of the bone-marrow as seen in true Addisonian anemia. The red blood cells averaged 131,100 per cm. in men and 1,272,000 per cm. in women. The bloods of all the patients showed megaloblasts in the circulation. Most of them had chronic achylia gastrica. The same changes were produced in dogs by feeding them extracts of the worms. Faust and Tallqvist⁶ determined that this hemolytic substance is oleic acid and that it owes its hemolyzing property to the fact that it is an unsaturated fatty acid.

The clinical picture and the morbid anatomy of uncinariasis anemia may be identical with that of true pernicious anemia (Ashford and King⁷). The hemoglobin content has been as low as 8 per cent (Dare and v. Fleischl) and the red blood cell count as low as 754,000 per cm. These extreme instances are associated with megaloblasts and the other characteristics of pernicious anemia. Eosinophila is variable. The more severe the intoxication the fewer the eosinophiles; they may be absent. These authors state that eosinophila shows a corresponding degree of resistance to the toxin. The bone-marrow may also show the same gray-red appearance and the same changes microscopically as in pernicious anemia, but usually also numerous eosinophilic myelocytes and myeloplaxes are present. Whipple⁸ quotes Preti as having found a hemolytic substance in Old World hookworms, which the latter believes to be related to the lipoids and to be similar to the hemolysin of *Bothriocephalus latus* found by Faust and Tallqvist. Whipple⁸ has found a weak non-specific hemolysin in New World hookworm which is soluble in salt solution, is destroyed by heat, and may be obtained in concentrated extracts from the bodies of the worms. The hemolysin acts on human blood and on that of laboratory animals. Whipple does not believe, however, that this weak hemolysin has much to do with the anemia of uncinariasis but that it is produced in the main by the direct extraction of blood from the bowel wall by the parasites, inasmuch as whole and partly disintegrated red blood cells floating in a bloody fluid are passed out from the intestinal tracts of the worms. From the work on experimental anemia of Bunting, who found that he was unable to produce a megaloblastic anemia by means of repeated hemorrhages alone, one would be inclined to believe that the hemolysin of the hookworm must play a role in the megaloblastic picture found at times in man.

Bunting's⁹ work (1905-1907) on experimental anemia is instructive. He produced what seemed like true pernicious anemia in rabbits and dogs by repeated small intravenous injections of ricin and of saponin. He was unable to produce such a type by repeated

small hemorrhages, which caused a secondary type with an occasional normoblast in the blood-stream, the bone-marrow never showing evidence of injury. In producing a pernicious type of anemia by means of hemolytic agents, it was necessary to place them into the circulation in sufficiently large quantities to saturate the red cells in the blood-stream and to exert a direct harmful influence on the erythrogenetic centers of the bone-marrow, which alone leads to a megaloblastic metamorphosis. He concludes (a) that a secondary anemia due to a toxin, as for instance, that of tuberculosis, is found when the toxin is taken up by the red cells and the bone-marrow is left free to regenerate; and (b) that a pernicious type of anemia is found when the toxin injures the erythrogenetic centers in varying degree and prevents a normal regeneration. An imperfect and often a short-cut regeneration leads to the formation of immature and megaloblastic cells, both of which may then be found in the marrow and in the blood-stream. It is produced only when the toxin is introduced in sufficiently large quantities. Thus a severe secondary anemia may assume a pernicious type. The red cell crises then are expressions of severe injury to the bone-marrow rather than of regeneration. Thus, Bunting believes that true pernicious anemia is due to some primary hemolyzing agent circulating in the blood and affecting the bone-marrow secondarily. The marrow change is not the primary lesion. He believes both *Bothriocephalus latus* anemia and experimentally produced anemias seem to prove this statement.

Madler¹⁰ (1913) produced crises of pernicious anemia in rabbits by feeding them large quantities of olive and cotton-seed oil. He believes that the toxicity depends on the amount of unsaturated fatty acids and that the anemia is produced in the peripheral circulation by its direct attack on the red cells. The effect on the bone-marrow he believes to be due to the excessive demand placed on it. One may easily believe, however, that, if the hemolyzing agent of *Bothriocephalus latus* is oleic acid, an unsaturated fatty acid, and if the toxic substance of olive or cotton-seed oil is the same, the action of the hemolysin on the bone-marrow centers may be direct, as Bunting maintains, if there is a sufficient quantity present in the circulation.

The hemolytic action of the spleen as a causative agent in pernicious anemia need be mentioned only in passing. Eppinger¹¹ and v. Decastello¹² brought forth this opinion independently in 1913. It led to splenectomy in a number of persons with pernicious anemia. One of us (N. W. J.) studied 7 such patients before and after operation without seeing any material change from the ordinary variable clinical course. The procedure has now been abandoned.

Association of pernicious anemia and chronic gall-bladder dis-

ease has been noted in medical literature from time to time. Probably Georgi¹³ (1887) was the first to mention it in a rather detailed report of a case presenting a frank pernicious anemia, gall stones being found at autopsy. This report called forth at once a retort from Ewald¹⁴ who cited the autopsy of another patient dead of pernicious anemia, in whom no macroscopical evidence of gall-bladder disease was found. Percy¹⁵ (1916) reported 37 cases of pernicious anemia operated upon for the removal of the spleen. The gall-bladder was removed twenty times for chronic cholecystitis and the appendix seventeen times because of chronic inflammation. In 9 cases the spleen, gall-bladder and appendix were studied bacteriologically. Hemolytic streptococcus was obtained seven times from some of these tissues, the *Streptococcus viridans* four times and the *Staphylococcus albus* once. The colon bacillus was also found in 5. Percy states that 58 per cent of 24 cases "were clinically in good condition" at varying intervals of time. One at the end of two years and eight months "is clinically perfectly well and carries no evidence of pernicious anemia in her blood, except that an occasional normoblast can be found." Later reports from this series of cases have not been obtained. Splenectomy was performed as the primary feature of the treatment, and removal of the gall-bladder and appendix was done as a part of the general process of ridding the body of septic foci, along with septic teeth and tonsils. Giffin and Bowler¹⁶ (1923) in a review of 628 cases state that 108 cases were associated with other diseases and that of this number 10 had had the clinical diagnosis of gall-bladder disease in addition to that of pernicious anemia. None of these patients came to operation. They state "On clinical examination no very convincing evidence of the condition (gall-bladder disease) is found."

This brief summary of the history of what is known regarding the etiology of pernicious anemia leads us now to recounting the following case records. Analysis of the important points in them will be discussed later. The pathological studies have been made by W. C. Hunter of the Department of Pathology with the counsel and aid of Dr. Benson, head of the department.

Case Reports. CASE I. Mrs. G., aged forty-five years, five para, three children living, was first seen June 6, 1917, complaining of general weakness, exhaustion, loss of weight and irregularly recurring attacks of pain and soreness in the upper abdomen, associated with constipation or, at times, bowel looseness. She had never been strong, but seven years ago she suffered a postpartum hemorrhage, since which time she has had a pale skin. At first it was a white paleness; some years later it became lemon tinted, a color noticed by herself and her family. There were periods when she had numb-

ness of the extremities. She had had measles, scarlet fever and sore throat earlier in life. At twenty all of her teeth were extracted, presumably for sepsis. Her family history was negative.

Examination. The patient is of a slight, asthenic build, moderately lemon-tinted skin, no jaundice. There is a moderate glossitis, a hemic heart murmur and some epigastric tenderness. The stomach acidity is 20 to 32; well chymefied food, and no blood. The stools show some blood from small hemorrhoids; no parasites. Five blood examinations, while in hospital from June 27 to July 17, gave practically the same findings; hemoglobin 80 to 85 per cent; red blood cells 3,680,000; white blood cells 7000; differential count: polymorphonuclears 65 per cent; small mononuclears 33 per cent; large mononuclears 4 per cent; transitionals 2 per cent; nucleated red blood cells negative; anisocytosis, poikilocytosis and polychromatophilia present; Wassermann negative.

Treatment. The patient was treated as a borderline anemia case, *i. e.*, a pernicious anemia which did not show nucleated red blood cells in the circulation. Receiving no relief from abdominal distress, she was operated upon July 20, on the assumption that she had a chronic gall-bladder disease. A large, distended, chronically infected gall-bladder was removed. The bile was greenish in color and contained much sediment. A hemolytic streptococcus was obtained from the gall-bladder wall. The appendix showed a moderate degree of obliterative inflammation.

Course. During the succeeding few weeks the patient improved slowly, as the general asthenic always does; her skin became clear and more or less pink in color. August 27, hemoglobin was 90 per cent; red blood cells 4,100,000; white blood cells 7100 with normal differential count. Irregular red blood cells and poikilocytes were present but polychromatophilic staining not. No nucleated red blood cells had been seen in six examinations. May 11, 1918, blood examination was recorded as follows: Hemoglobin 85 per cent; red blood cells 5,250,000; white blood cells 6300 of normal differential count. A few irregular red blood cells were seen but no irregular staining. In 1921, the patient suffered a supposed influenzal infection and some form of epidemic jaundice; at least, other members of the family and of the community had similar attacks of jaundice. As a result of this infection she was ill and weak for several months. May 3, 1921, blood examination showed hemoglobin 80 per cent; normal red cells 4,000,000; white blood cells, 9650. In 1922 the patient was ill, in and out of bed, with a sinus infection for nine months. On March 21, 1923, three blood examinations gave hemoglobin 80 per cent; red blood cells 4,500,000; white blood cells 6450 with normal differential count. There were some slightly irregular red blood cells but the general appearance of the blood was that of a mild secondary anemia. The patient, herself, felt

quite well, weighed 125 pounds, the skin was clear and the tongue showed no particular evidence of inflammation or atrophy.

Comment. The symptoms and physical findings in this case were those of a so-called chronic borderline anemia; an anemia characterized by the presence of the toxic or inflammatory symptoms of pernicious anemia and a blood picture possessing the permanent characters of pernicious anemia blood; namely, a plus color index and irregular shapes, sizes and staining properties of the red blood cells, but showing no nucleated red blood cells in the circulation. In addition to this, certain symptoms permitted the diagnosis of gall-bladder disease. The gall-bladder was removed and a hemolyzing streptococcus was obtained in pure culture from the wall. Six years have elapsed since the operation. The patient is fairly well. She has not progressed as a case of true pernicious anemia and the blood picture has regained fairly normal characteristics.

CASE II.—C., aged fifty years, was first seen February 7, 1916. For two years he had suffered spells of weakness, paleness, numbness and burning of the hands and feet, muscle soreness, constipation and distress in the abdomen and a mucous discharge from the nose. During the intermissions he has regained moderate health.

Examination. Heavy, gaunt type of build, pale, lemon-tinted skin and mucous membranes; no icterus; former dental sepsis; hyperplastic ethmoiditis with obstructing septal deflection. Stomach analysis shows complete achylia. The stools contain neither blood nor parasites. During February and March, 1916, while under treatment for pernicious anemia, the blood showed hemoglobin 73 to 90 per cent; erythrocytes, 2,420,000 to 3,480,000; leukocytes, 9000 to 4350; polymorphonuclears, 80 to 65 per cent; small mononuclears, 16 to 24 per cent; large mononuclears, 1.5 to 7 per cent; transitionals, 1 to 3 per cent; basophiles, 0.5 to 1 per cent; myelocytes, 1 to 1 per cent; normoblasts 2 cells found, megaloblasts negative; anisocytosis, poikilocytosis and polychromatophilia present. September 20, 1916, the hemoglobin was 100 per cent; erythrocytes, 5,280,000; leukocytes, 8600; 1 normoblast, fewer macrocytes and less irregular staining of the red cells was noted than formerly. In 1917, the patient spent four months in Johns Hopkins Hospital under treatment for pernicious anemia. September, 1921, four blood examinations showed hemoglobin 90 to 95 per cent; erythrocytes, 4,264,000 to 5,000,000; leukocytes, 6800; no nucleated red cells, moderate polychromatophilia and some macrocytes. July 19, 1922 to August 29, 1922, while under treatment, the hemoglobin was 60 to 82 per cent; erythrocytes, 1,240,000 to 3,370,000; leukocytes, 3200 to 6400. There were no nucleated red cells but marked variation in size and staining was present.

Positive roentgen-ray shadows of the gall-bladder were obtained July 19, and August 31.

Treatment. The patient was treated four times in hospital for pernicious anemia during these six years. Cholecystectomy and appendectomy were made September 7, 1922 (by T. M. J.).

Pathological Report. The wall of the gall-bladder is slightly atrophied. The mucosa is bile-stained and appears atrophic. Sections disclose a thinning and scarring of the wall and atrophy of the mucosa. Sections stained for bacteria reveal the presence of a few groups of organisms looking like staphylococci. A few diplococci are also present.

Pathological Diagnosis. Chronic atrophic cholecystitis.

Course. Convalescence from the operation was prompt. The lemon-tinted color of the skin cleared quite rapidly, the nail beds and mucous membranes showing pink. Fourteen blood examinations during the month in hospital showed a fairly graduated transition from the pernicious picture to a moderate secondary anemia. The last one, October 11, 1922, showed hemoglobin, 90 per cent; erythrocytes, 4,300,000; leukocytes, 8100; polymorphonuclears, 61 per cent; small mononuclears, 32 per cent; large mononuclears, 4 per cent; transitionals, 1 per cent; eosinophiles, 2 per cent; nucleated red cells, negative; very slight changes in the character of the red cells.

A month after operation the numbness and hurting of the legs and arms and at times over the entire body became worse. Since Christmas these symptoms have slowly abated and do not bother the patient as much now. He has returned to his work as a timber bruiser but is not yet strong enough to stand hard work. He feels, however, that he is gaining in strength progressively. Examination on May 5, 1923, revealed a physical state quite different from that seen at any time during the past seven years. The patient's color is good; the skin is red from his out-of-door life, and there is no evidence of sallowness or lemon tinting. The tongue shows a moderate glossitis but is not sore. The knee kicks are absent. There is slight swaying of the body with the eyes closed but no distinct incoördination. The patient states that a certain unsteadiness at night is less now than it formerly was. Four blood counts show hemoglobin, 88 per cent; erythrocytes, 4,570,000; leukocytes, 5200; with normal differential count. The red blood cells are well stained. There are a few macrocytes, and in the four examinations 1 normoblast is found. Undoubtedly the blood still possesses slight evidence of its former pernicious type but it approaches more nearly the picture of normal blood than it has done since the patient was first seen in 1916. His general health and strength is also better.

Comment. This patient had suffered for about eight years with the symptoms of a slowly progressing frank pernicious anemia

before the diseased gall-bladder was recognized and removed. A certain degree of change had taken place in the spinal cord as evidenced by the severe paresthesiæ, the loss of deep reflexes and a slight Rombergism. Since the operation the patient has regained much of his former health and the cord symptoms seem to be lessening. How much permanent damage has been suffered by the spinal cord and the erythrocytic centers of the bone-marrow only time will tell. Cultures from the gall-bladder were not obtained. Microorganisms possessing the morphological characters of a staphylococcus and a diplococcus were found, however, in stained sections of the gall-bladder wall. Nine months have elapsed since the patient was operated upon and he seems to be progressively moving away from the picture of pernicious anemia rather than downward as seemed to be the one prospect in the summer of 1922.

CASE III.—Mrs. K., aged twenty-nine years, 4 para, was received January 29, 1923. She had suffered from recurring periods of weakness, paleness, nausea and constipation since scarlet fever at twenty years of age. Her skin had been of a sallow type of paleness since this time, but following a miscarriage in June, 1922, it has become a more pronounced lemon tint and the weakness and distress more severe. She has suffered slight paresthesiæ. Her history revealed typhoid fever at eighteen, measles in childhood, scarlet fever at twenty, influenza at twenty-six, two miscarriages and a phlebitis of the right leg.

Examination. Extreme asthenic type of build, weight 116 pounds, skin lemon tint and pale, severe dental sepsis; the tongue shows a blotchy glossitis; the stomach complete achylia; the gall-bladder gives faintly positive shadows on the films, and there is no indirect roentgen-ray evidence of gall-bladder disease. The stools are negative for blood and parasites. Nine blood examinations during a month in hospital showed, on an average, hemoglobin, 80 per cent; erythrocytes, 3,990,000; leukocytes, 12,000 to 6800; no nucleated red cells, anisocytosis, poikilocytosis and polychromatophilia present. The extraction of all teeth did not change the blood picture. Blood Wassermann was negative.

Treatment. After one month in hospital with bed rest, arsenic, hydrochloric acid, and so on, the patient was operated upon March 5, 1923 (by T. M. J.). The gall-bladder did not reveal any gross appearance of disease. The lymph nodes along the common bile duct were not enlarged. The common bile duct, itself, seemed to be somewhat dilated. In spite of the normal appearance and because of (a) the positive roentgenological evidence and (b) the type of the patient's anemia, the gall-bladder was removed. The appendix showed more evidence of disease and was also removed.

Pathological Report. The gall-bladder wall is slightly thickened and fibrous. The mucosa is bile-stained and atrophic. Sections

disclose a desquamation of the epithelium of the mucosa; slight diffuse fibrous increase in the muscular coats and the rest of the wall. In the sections stained for presence of bacteria a few microorganisms resembling staphylococci are found. Cultures of the wall of the gall-bladder yield a slightly hemolytic *Staphylococcus albus*. Cultures of the bile are negative.

Pathological Diagnosis. Slight catarrhal cholecystitis.

Course. The patient convalesced quite rapidly from the operation; within one week the lemon tint of the skin was fading rapidly. On March 27, 1923, the blood showed hemoglobin, 89 per cent; erythrocytes, 4,700,000; leukocytes, 6000; polymorphonuclears, 69 per cent; small mononuclears, 24 per cent; large mononuclears, 4 per cent; eosinophiles, 1 per cent; basophiles, 1 per cent; transitionals, 1 per cent; nucleated red cells, negative; poikilocytes few, macrocytes negative, polychromatophilia absent.

May 5, 1923, the patient was again examined. She states that she feels stronger and has a desire to work for the first time since she became ill. Numbness in both hands lasted for a week after she went home but has not returned. The skin is now pale pink in color; it has lost its lemon tint. The septic tonsils still remain; they are to be removed later. The blood shows in four counts—hemoglobin, 75 per cent; erythrocytes, 4,540,000; leukocytes, 7000; of normal differential count. The red cells stain uniformly with pale centers. There are no macrocytes and no nucleated red blood cells are seen. The picture is that of a moderate grade of secondary anemia.

Comment. The transformation of this patient's blood picture after cholecystectomy from a pernicious type to that of a secondary anemia was quite rapid. A gain in general health has been quite as rapid also. From the gall-bladder wall *Staphylococcus albus* was obtained in pure culture and cocci resembling staphylococci were found also in stained sections. Although this patient is a general asthenic of marked degree, her progress toward recovery has seemingly been more rapid than that seen in Case II. It is possible that the pernicious anemia in this case has existed for only one year.

CASE IV.—H., aged sixty years, farmer, was received April 13, 1923. Paleness, weakness, shortness of breath and pains in the shoulders began one and a half years ago together with numbness in the ankles and knees, wrists and hands, and tingling of the toes and fingers. The patient has not lost much weight.

Examination. The skin is pale and lemon tinted. The mucous membranes are pale. The tongue is pale and glossy. The lower teeth and tonsils show infection. An upper plate is worn. The upper teeth were removed for sepsis. A hemic murmur is heard over the precordium. The stomach shows complete achylia. The

stools are negative. The antrum of the stomach is spastic. The bulb of the duodenum is drawn slightly to the right, and the lesser curvature margin is hazy. Films of the gall-bladder show positive shadows without stones. The blood Wassermann is negative.

Treatment. Ten blood examinations were made during four weeks in hospital under treatment. The first one showed: Hemoglobin, 40 per cent; erythrocytes, 1,780,000; leukocytes, 8850; polymorphonuclears, 35 per cent; large mononuclears, 6 per cent; transitionals, 1 per cent; eosinophiles, 1 per cent; normoblasts, 2; megaloblasts, 1. Many macrocytes and marked polychromatophilic staining was present. The last examination before operation showed: Hemoglobin, 71 per cent; erythrocytes, 2,450,000; leukocytes, 3600; 1 normoblast; polychromatophilia and anisocytosis were less marked than on entrance.

Cholecystectomy May 14, 1923 (by T. M. J.). Recovery from the operation was uneventful. The gall-bladder showed macroscopically little change from the normal. A small section of the liver was removed for examination. The change in the appearance of the patient during the first week was marked. The lemon tint of the skin disappeared quite completely and was replaced by a pink color. The blood showed: Hemoglobin, 76 per cent; erythrocytes, 3,080,000; leukocytes, 7200; polymorphonuclears, 72 per cent; small mononuclears, 14 per cent; large mononuclears, 9 per cent; eosinophiles, 4 per cent; transitionals, 1 per cent. The red cells stained fairly evenly and there were but few macrocytes.

Pathological Report. The gall-bladder is of average size, wall slightly thickened and scarred, mucosa intact, no concretions, contains about 15 cc of light brownish viscid bile.

The clipping from the liver measures 0.5 by 1 cm. and appears normal.

Microscopically there is a slight increase in the fibrous tissue throughout the wall of the gall-bladder. Scattered through the scar tissue are moderate numbers of small round cells. The mucosa is partially desquamated but the greater portion is intact and shows no noteworthy changes. Sections stained for bacteria disclose the presence of small numbers of organisms occurring in pairs and short chains.

Diagnosis. Slight chronic diffuse cholecystitis.

Bacteriological Findings. Cultures from the gall-bladder in meat infusion broth enriched with blood disclose the presence of non-hemolytic *Staphylococcus albus*. Whether this is a contamination from the skin of the patient or not is difficult to determine. No other microorganisms are found.

Bile. Sterile.

From the bit of liver tissue, alpha-hemolytic streptococcus, producing definite greenish zones about the colonies and occurring in both short and long chains, is isolated in pure culture.

Comment. The clinical appearance and the megaloblastic blood picture of this patient is typical of a true progressive pernicious anemia. The change in the general appearance of the patient, the rapid clearing of the skin and the equally rapid change in the condition of the red blood cells is seemingly more marked than that noted in the former three patients. The finding, however, of non-hemolytic organisms in the liver tissue and morphologically similar organisms in the wall of the gall-bladder brings up the question whether the anemia may be produced by the effect of some chemical substance entering the circulation from the infected gall-bladder rather than from the direct lytic action of the bacteria and their products on the red blood cells and the erythrocytic centers of the bone-marrow. A similar organism was obtained at autopsy in Case VIII. A portion of liver tissue was cultured for the first time in this case. The organism obtained in pure culture bears resemblance to the morphological characteristics of that found in the stained sections from the gall-bladder wall.

CASE V.—Mrs. J., aged thirty-seven years, 2 para (1 miscarriage at three months, seven years ago) was received December 7, 1922. Patient complained of periodic weakness and paleness which began after a miscarriage seven years ago. For the last three years the spells have been especially severe, but during the summers she has partially regained health. She suffered from loss of weight and strength, shortness of breath, swelling of the feet, nausea, vomiting and constipation and numbness of the hands and feet.

Examination. There was found pale, lemon-tinted skin, dental plates (history of previous sepsis), moderate glossitis, hemic murmur over the precordium, edema of the legs, complete achylia and stools negative to blood and parasites. The urine, blood chemistry and blood Wassermann are negative. Positive shadows of the gall-bladder are obtained December 18.

Eight blood examinations from the 8th to the 29th, inclusive: December 8, the blood showed hemoglobin, 20 per cent; erythrocytes, 1,550,000; leukocytes, 5200; polymorphonuclears, 67 per cent; small mononuclears, 29 per cent; large mononuclears, 2 per cent; transitionals, 1 per cent; eosinophiles, 1 per cent; occasional normoblasts, no megaloblasts; anisocytosis, poikilocytosis and polychromatophilia was present. December 29, the blood count was hemoglobin, 10 per cent; erythrocytes, 440,000; leukocytes, 6600; polymorphonuclears, 59 per cent; small mononuclears, 40 per cent; large mononuclears, 1 per cent; normoblasts were present; megaloblasts 1, the changes in the red cells more pronounced than before.

The first megaloblast was found on December 22, 3 were found on the 26th, and 1 on the 29th. Death occurred December 29, 1922.

Autopsy. The body of a white female, aged thirty-seven years. There is a general pallor of the skin, teeth absent, gums smooth,

subcutaneous fat is light yellowish and finely lobulated. Lymph nodes in root of mesentery are hyperplastic. Mucosa of stomach pale and atrophied. Small hemorrhages are numerous beneath capsule of liver. Liver parenchyma is pale and friable and the blood which exudes is pale.

The gall-bladder is free from adhesions; its wall is slightly thickened and opaque. The bloodvessels beneath the serosa are unusually prominent. Bile is dark greenish-black and viscid. The mucosa is bile-stained but apparently intact. The biliary lymph nodes are slightly hyperplastic. Petechial hemorrhages are found in the serosa of the pancreas. Spleen is about one-third larger than normal, cut surfaces reddish, moderately firm and somewhat fibrous. Kidneys are pale and anemic. Heart is yellowish-brown and flabby, no valvular lesions. Lungs are unchanged. There is marked hyperplasia of the bone-marrow.

Microscopically. The muscle fibers of the heart are rather shrunken. A yellow pigment appears in most of the cells lying between the fibrils and especially around the nuclei. Some of the cells are vacuolated and appear to have contained fat droplets. There are no red blood cells in the vessels.

Gall-bladder. Sections disclose the mucosa to be bile-stained, denuded and roughened. There is a slight thickening in the submucosa. A lymphoid follicle is seen in one part of the serosa. In sections stained for bacteria a few cocci in short chains and a few diplococci are found.

Liver. The cord of liver cells stain palely and are quite shrunken so that the capillary spaces are relatively wide. Nearly all the cells but mostly those around the central veins contain fat droplets. There is much yellow pigment both intra- and extracellular. No bacteria are found in the sections.

Spleen. The Malpighian bodies are prominent. The pulp is packed with red blood cells and yellowish pigment, evidently from broken down red cells. The pulp is relatively free from lymphoid cells. The blood sinuses are definitely outlined but contain few red blood cells and many white cells.

Bone-marrow Sections from a rib and the femur show marked cellular activity. The fatty reticulum present in the normal adult femur is replaced by active marrow elements so that the sections from the two bones are indistinguishable. The large number of megalocytes, megaloblasts and normoblasts seen among the marrow cells is striking. A differential count made of several areas to get an idea of the percentage of the different types shows approximately in each area, respectively: (a) 8 myelocytes, 10 myeloblasts, 5 normoblasts, 4 non-nucleated red blood cells; (b) 4 myeloblasts, 5 normoblasts, 4 non-nucleated red blood cells, and (c) 4 myeloblasts and myelocytes, 1 polymorphonuclear leukocyte and 4 lymphocytes.

Bacteriological. Cultures of the bile were negative for all organisms. *B. coli* was obtained from the gall-bladder wall, but this is thought to be a contamination.

Anatomical Diagnosis. Hyperplasia of the bone-marrow; generalized pallor of the skin; atrophy of gastric mucosa; multiple hemorrhages of serous membranes; chronic atrophic cholecystitis; pernicious anemia; hyperplasia of mesenteric and biliary lymph nodes; yellow atrophy and slight interstitial fibrosis and slight fatty changes of the myocardium.

CASE VI.—(Multnomah Hospital Service). W. H., aged twenty-three years, was received December 1, 1922. Patient had suffered for four years with relapsing weakness and paleness, swelling of feet, numbness of hands and feet, and periodic pain and swelling in left hypochondrium for two years. During the past summer the patient was in bed for seven months with such an attack to which a chronic dysentery was added. The present attack of pain began one week before entrance to the hospital. It was associated with chills, fever and profuse sweating. He had developed an acute gonorrhoeal iritis from an old urethritis, smears showing Gram-negative intracellular diplococci. He presented a general septic appearance with a profound lemon-tinted type of anemia.

The history revealed measles and jaundice in childhood, left-sided pleurisy, many attacks of sore throat and a Neisserian infection three years ago.

Examination. A pale, asthenic male, profoundly weak, severe dental infection; first heart tone, left, possesses a rumbling murmur at times—absent at other times. There is diffuse abdominal tenderness, more marked in the left hypochondrium, together with a mass felt beneath the left costal arch. The feet are edematous. The stomach chemistry is not investigated. The urine shows albumin and pus with Gram-negative diplococci and Gram-positive chained streptococci. Gall-bladder not examined. The blood Wassermann is negative and one blood culture is also negative. Six blood examinations showed hemoglobin, 68 to 58 per cent; erythrocytes, 2,944,000 to 1,896,000; leukocytes, 3000 to 4600; polymorphonuclears, 40 to 64 per cent; small mononuclears, 26 to 36 per cent; large mononuclears, 8.5 to 20 per cent; eosinophiles, 0 to 1.5 per cent; transitionals, 0 to 2.5 per cent; myelocytes, 2 to 4 per cent; nucleated red cells negative; marked changes in the size and staining of the red cells. Death, February 9, 1923.

Autopsy. This is the body of a moderately emaciated white man, aged twenty-three years, skin pale; skin about the ankles pits on pressure. Pelvis and abdominal cavities contain about 2 liters of straw-colored fluid. Liver is large. The lower pole of spleen is seen just below the costal margin in the left midclavicular line. Four septic anemic infarcts are present in the spleen. The upper

pole is adherent to the diaphragm by fibrous bands; when dissected away a well walled-off subdiaphragmatic abscess 2 x 3 x 5 cm. is found. The capsule of the spleen is tense. The cut surfaces disclose a moderate hyperplasia of the pulp and engorgement with blood. The spleen weighs 1500 gm. The gall-bladder is greatly swollen due to edema of the wall. Beneath the serosa there are numerous small hemorrhages. The sac contains viscid brownish bile. The biliary lymph nodes are hyperplastic. The main bile ducts are patent.

Each pleural cavity contains a liter of straw-colored fluid in which the lungs float. Petechial hemorrhages are abundant in the visceral pleural of each lung. The lung is densely adherent to the diaphragm. The pericardial sac is distended with straw-colored fluid. The heart is dilated and flabby; its musculature is pale. At the junctions of the leaflets of the mitral valve there is a ragged ulceration with destruction of a few of the chordæ tendineæ. The cut surfaces of the lungs reveal a passive hyperemia and atelectasis at the bases. The cut surfaces of the kidneys are dark, glomeruli red. In the liver the lobules are well outlined, parenchyma friable, and the blood which exudes is pale reddish and thin.

Microscopically the heart shows areas of focal necrosis, hyaline degeneration, and scar tissue, which has the appearance of having been recently formed, scattered throughout the myocardium.

Liver. Sections disclose a moderate atrophy of the cells, especially about the central veins, where also fatty changes and intra- and extracellular pigment is found. No bacteria in the liver. The abundance of pigment obscures the picture.

Gall-bladder. Sections reveal small hemorrhages in the serosa, marked edema of subserosa, moderate increase in fibrous connective tissue, and partial desquamation of epithelium of mucosa. A few round cells are present. Sections stained by Unna's alkaline methylene-blue method for bacteria disclose many organisms in chains that look like streptococci.

Spleen. The sinuses are filled with red blood cells and pigment containing phagocytes. There is a slight hyperplasia of the lymphoid cells. Other sections disclose septic anemic infarcts covered with fibrinous exudate.

Kidneys. There is hemorrhage, recent and old, into the subcapsular spaces of Bowman and into the convoluted and straight tubules.

Lungs. Chronic passive congestion and atelectasis.

Bone-marrow. Not examined.

Bacteriological. A pure culture of long-chained hemolytic streptococcus was obtained from the bile and the wall of the gall-bladder. Cultures from an infarct in the spleen gave the same organisms and *B. coli*. Cultures of the spleen pulp were negative. Intravenous injection of the organisms in a rabbit produced purulent arthritis

and bacteriemia in two days. The organisms were recovered from the joints and the heart blood. Cultures of the bile and gall-bladder of the animal were sterile.

Anatomical Diagnosis. Subacute ulcerative endocarditis—mitral valve; multiple septic infarcts in the spleen; small subdiaphragmatic abscess involving upper pole of spleen; focal necrosis and scarring of the myocardium; moderate atrophy; chronic and acute dilatation of all chambers of the heart; moderate ascites, bilateral hydrothorax, hydropericardium and edema of the ankles; chronic passive congestion of the liver; atrophy, fatty and pigment changes; chronic passive congestion of the lungs, atelectasis of lower lobe; subacute and chronic cholecystitis with hyperplasia of biliary lymph nodes; marked chronic anemia; moderate emaciation; chronic hyperplasia and hypertrophy of the spleen; petechial hemorrhages in visceral pleuræ and serosa of gall-bladder; hemorrhage in kidneys; fibrous pleuritis, base of left lung. Examination of bone-marrow was overlooked.

CASE VII.—(Medical Division U. S. Veterans' Bureau). F. M., male, aged forty years, was not studied during life by us but came to autopsy by Dr. Hunter, March 9, 1923. The history from the Veterans' Bureau is that of a frank pernicious anemia beginning some time previous to January, 1918, and characterized by several relapses and remissions until death occurred March 8, 1923.

Examination. The patient is emaciated; weight 114 pounds; very anemic; of sallow, brownish hue; some dental and tonsil sepsis; hemic heart murmur. The blood on several occasions showed hemoglobin, 50 to 25 per cent; erythrocytes, 1,500,000; leukocytes, 3000. The red blood cells are irregular in shape, size and staining properties. There are no nucleated red blood cells found. A blood culture is negative.

Autopsy. This is the body of a poorly nourished white man, aged forty years. There is a general brownish pigmentation of the skin.

The gall-bladder is small, thick walled and contains a single large soft bile-pigment stone. The mucosa is desquamated and denuded. The cystic, hepatic and common bile ducts are patent. The surface of the liver is finely pebbled; the parenchyma cuts with increased resistance; the blood which exudes is pale and watery.

The lungs are emphysematous. On section, small discrete consolidations are seen. In the visceral pericardium are numerous petechial hemorrhages. The heart is large, flabby and pale. The musculature, especially at the bases of the papillary muscles, is pale and fatty. The endocardium presents the mottled appearance described as "tigering;" no valvular lesions. A number of calcified lymph nodes found at the bifurcation of the trachea. The spleen is slightly enlarged; cut surfaces reddish and moderately fibrous. The marrow of the long bones is markedly hyperplastic.

Microscopically the gall-bladder shows a greatly thickened and fibrous wall. The mucosa is desquamated and denuded except in the deeper portions of the crypts. Ulceration extending to the muscularis occurs, and in these areas polymorphonuclear leukocytes and small round cells loaded with bile pigment are numerous. Foreign body giant cells containing bile pigment are also present. Bacteria are numerous; morphologically they resemble staphylococci.

Liver. There is considerable atrophy of the hepatic cells especially about the central veins, so that the capillary spaces are widened. Intracellular pigment is abundant. In certain areas the bile capillaries are hyperplastic and newly formed capillaries are numerous. In other areas there are small focal necroses and distinct patches of scar tissue, which in some instances entirely surround islands of liver cells. In sections stained for bacteria the large amount of pigment obscures the field and no organisms are found.

Bone-marrow. Stained smears disclose well-marked poikilocytosis, anisocytosis, moderate numbers of nucleated red cells, 1 megaloblast, and polychromatophilia.

Bacteriological Findings. Cultures not made on account of embalming.

Anatomical Diagnosis. Subacute and chronic ulcerative and endurative cholecystitis with cholelithiasis; numerous fibrous adhesions between gall-bladder and other organs; hyperplasia of bone-marrow; pernicious anemia; focal biliary cirrhosis of the liver with atrophy; fatty and pigment changes; fatty change in the myocardium—"Tiger heart;" petechial hemorrhages in pericardium; moderate emaciation; generalized brownish pigmentation of the skin; moderate atrophy of suprarenal cortex; slight fatty and myxomatous changes in the aorta; calcified tuberculous lymphadenitis; rudimentary right kidney, weight 40 gm.

CASE VIII.—(Multnomah Hospital Service). C., aged forty-seven years, was received April 8, 1923. The patient has suffered from a progressing weakness and paleness for more than eight months. Six months ago his hands became numb and soon afterward failing strength in his legs prevented his walking. On entrance he was unable to stand. For two months he has been awakened at night with indefinite pains in the region of the stomach. He thinks he was jaundiced when the pains began but he considers himself jaundiced now. He has had repeated nose bleeding and possibly two chancroid infections. He has lost much in weight.

Examination. The patient is profoundly weak and undernourished though not emaciated. The skin is pale and lemon tinted. The teeth are foul with sepsis and neglect. The tonsils are septic. The tongue is inflamed. There is some generalized lymphadenopathy. There is a discharge from the left ear. A hemic murmur is

heard over the precordium. The patient is considered too weak to make stomach analyses or to study the gall-bladder. There is some increased muscle resistance in the right upper abdominal quadrant; the reflexes are present but weak. The blood Wassermann is negative. Several blood counts show on an average: Hemoglobin, 40 per cent; erythrocytes, 1,640,000; leukocytes, 4800; polymorphonuclears, 62 per cent; small mononuclears, 22 per cent; large mononuclears, 11 per cent; eosinophiles, 1 per cent, transitionals, 1 per cent; questionable myelocytes, 3 per cent; irregular red cells and irregular staining at present. No nucleated red blood cells are found.

Death May 12, 1923.

Autopsy. This is the body of a somewhat poorly nourished white man, aged fifty-one years. The skin, particularly of the face, had a lemon-yellow tinge. The subcutaneous fat is firm and lemon-yellow. There are petechial hemorrhages in root of the mesentery and in the mucosa of sigmoid. The blood is darker red than normal. The gall-bladder is empty and collapsed; it is free from adhesions but its wall is whitish and slightly thickened. The bloodvessels are unusually prominent. It contains a very small amount of stringy brownish bile. The mucosa is intact and there are no concretions. The biliary lymph nodes are small. The larger bile ducts are unchanged. The central veins in the liver are prominent. The spleen weighs 250 gm. The cut surfaces are reddish and firm; Malpighian bodies are visible.

The rugæ of the stomach are lacking; the mucosa is atrophic. The marrow of a portion of the middle third of the tibia discloses a patchy hyperplasia of the blood-forming tissue. The marrow of the ribs is soft and hyperplastic. There are no gross lesions in the brain or spinal cord.

Microscopally the sections of the yellow marrow disclose a moderate hyperplasia of erythrocytic islands which partially replace the fat. In these islands there are seen megaloblasts, normoblasts, poikilocytes and microcytes and also an increased number of myeloblasts and myelocytes. Phagocytes containing pigment are present. Sections of the red marrow disclose a marked hyperplasia of the blood-forming tissue.

Gall-bladder. The mucosa is intact and normal in appearance. There is a slight diffuse increase in fibrous tissue throughout the wall with scattered round cells in moderate numbers between the fibers. Sections stained for bacteria disclose bacteria for the most part in the form of diplococci.

Spleen. The Malpighian bodies are prominent. The sinuses are engorged with red blood cells in all stages of disintegration. Phagocytes containing broken red cells and pigment are numerous. All types of abnormal red cells are found.

Liver. About the central veins there is almost complete atrophy of the hepatic cells with some fatty degeneration. Phagocytes containing brownish pigment and shadows of red cells are seen in these regions. The bile capillaries are unchanged.

Stomach. The mucosa shows well marked atrophy with replacement of fibrous tissue and an infiltration of small round cells and plasma cells.

Heart blood	Pneumococcus in pure culture.
Lung	Pneumococcus in pure culture.
Gallbladder	Pneumococcus and alpha-hemolytic streptococcus.
Bile	Pneumococcus and alpha-hemolytic streptococcus.
Liver	Pneumococcus and Bacilli coli.
Bone-marrow	Pneumococcus in pure culture.

Anatomical Diagnosis. Well marked hyperplasia of the red bone-marrow, slight hyperplasia of the yellow bone-marrow; yellowish pigmentation of the skin; petechial hemorrhages in root of mesentery and mucosa of sigmoid; atrophy of gastric mucosa; pernicious anemia; slight chronic diffuse cholecystitis, isolated streptococcus and pneumococcus; syphilitic arteriosclerosis of the aorta; old fibrocaseous tuberculosis of upper right lobe; atrophy and pigment changes in the liver; slight atrophy and fatty changes in the myocardium; moderate hypertrophy of the spleen; lobar pneumonia, lower right lobe; pneumococcus septicemia; sero-fibrino-purulent, right; purulent bronchitis; slight parenchymatous degeneration of the kidneys; interstitial orchitis and atrophy of interstitial cells.

After reviewing the data presented, Dr. Everett O. Jones (Seattle, Wash.) operated on a patient suffering from a frank pernicious anemia, who was under the care of Dr. Edward P. Fick. We are indebted to him for the records of the case, a résumé of which follows:

CASE IX.—(The Swedish Hospital, Seattle, Wash., Service of Drs. Jones and Fick). W. J. B., aged fifty-two years, ship captain, had been sick at irregular intervals for three years with weakness, paleness, anorexia, diarrhea and numbness above the left knee. One year ago the attack lasted two months. October, 1922, he was delirious for a week during an attack, after which he slowly recovered until January, 1923, when the present relapse began. The patient has used alcoholics to excess. He has spent seventeen years in the Orient and had cholera in 1893.

Examination. The patient is well nourished; the skin pale and lemon tinted; the mucous membranes pale; dental sepsis is severe. The tongue shows no atrophy or inflammation. There is a murmur over the precordium. The stomach shows complete achylia. The reflexes are normal except the knee kicks, which are sluggish. Eight blood examinations were made; one of them is herewith recorded: Hemoglobin, 15 per cent; erythrocytes, 1,200,000; leukocytes,

6000; small mononuclears, 60 per cent; large mononuclears, 40 per cent; 1 normoblast was found in the eight examinations, and the red blood cells show marked anisocytosis and polychromatophilia. The blood Wassermann was negative.

Treatment. It seemed evident that the patient would not survive this relapse, so an exploratory operation was advised and accepted. The gall-bladder was normal in appearance. It was removed and from the gall-bladder wall a pure culture of a hemolyzing *Staphylococcus albus* was obtained. The bile was sterile.

Death occurred on the day following operation.

Abstract of Autopsy Record. The autopsy was made the same day by Dr. D. H. Nickson. The general appearance of one dead of pernicious anemia is present. Multiple pin-point submucous hemorrhages in the fundus of the stomach exist. The mucosa of the pylorus and first part of the duodenum is markedly thickened and edematous, measuring $\frac{3}{8}$ cm. in thickness. The liver appears normal. The site of the operation is normal; there has been no hemorrhage. The spleen weighs 320 gm. Smears from the spleen pulp show many megalocytes and some nucleated red blood cells. The bone-marrow of the tibia is dark red, hyperemic, and sections show hyperplasia of the elements.

Comment. (N. W. J.) This patient presented during life the course of a frank pernicious anemia. Never had there been any suggestion of gall-bladder disease either before or during his final illness. At operation the gall-bladder appeared to be normal but it was removed and a hemolyzing *Staphylococcus albus* was obtained in pure culture from its wall. The patient, already approaching his end, was unable to withstand the shock of operation.

CASE X.—Mrs. D., aged sixty years, 4 para, was received March 23, 1923. Patient first noticed an oncoming anemia, weakness and loss of weight following the extraction of the teeth for dental sepsis one year ago. These symptoms together with nausea, vomiting, dyspnea, pains in the chest and arms and a recurring soreness of the tongue have been more marked during the last four months. Her past history has been negative.

Examination. The skin is pale and lemon tinted; the mucous membranes are pale; the tongue shows a bright red inflammation about the tip and the dorsum is glossy and fissured. The tonsils are septic. A hemic murmur is heard over the precordium. The stomach shows complete achylia. The stools are negative. The blood Wassermann is negative. Thirteen blood counts were made during the five weeks the patient was in hospital under treatment. The first blood count showed: Hemoglobin, 50 per cent; erythrocytes, 1,990,000; leukocytes, 4200; polymorphonuclears, 57 per cent; small mononuclears, 38 per cent; large mononuclears, 2 per cent;

eosinophiles, 1 per cent; normoblasts, 1; megaloblasts, 2; marked anisocytosis and polychromatophilia. The last blood count showed: Hemoglobin, 75 per cent; erythrocytes, 3,470,000; leukocytes, 3400; polymorphonuclears, 70 per cent; small mononuclears, 28 per cent; large mononuclears, 2 per cent; basophiles, 1 per cent; eosinophiles, 1 per cent; no nucleated red blood cells, and less marked changes in the size and staining of the erythrocytes.

Faint but positive shadows of the gall-bladder were obtained April 30, 1923. There was no distortion or spasm of the duodenum. Operation was performed May 28, 1923. A chronically infected gall-bladder and appendix were removed (by T. M. J.). A small bit of liver was removed for examination.

Pathological Report. The gall-bladder wall is moderately thickened. There is a small amount of viscid bile in the sac. The gall-bladder is partially necrotic (due to delayed examination). Necrosis is too marked for accurate histological study. The wall appears thickened and fibrous. The mucosa is desquamated and the cellular outline is indistinct. Sections stained for bacteria are negative, probably due to autolysis. Sections of the liver show slight necrosis of the cells. Some contain granular brownish pigment. The walls of the capillaries are thickened, due to increase in fibrous tissue in which a few small round cells are present. The epithelium is intact. Sections stained for bacteria show no organisms. Cultures of the bile and gall-bladder are negative. Cultures of the liver show a prolific growth of green producing alpha-hemolytic streptococcus.

Pathological Diagnosis. Chronic cholecystitis and chronic cholangitis.

Course. Convalescence from operation was prompt. The rapid change in symptoms and general appearance noted in the other patients operated upon was observed again. The skin lost its lemon color and became pink. The patient's general sense of feeling became different. (This change has been noted and commented upon by the other patients operated upon.) A very sore glossitic tongue became symptomless within three days. The soreness of the tongue returned, however, after three weeks and still bothers somewhat. The blood before operation showed: Hemoglobin, 75 per cent; erythrocytes, 3,440,000; leukocytes, 5700; moderate changes in size and staining properties of the red cells. On leaving the hospital it showed: Hemoglobin, 85 per cent; erythrocytes, 3,390,000; leukocytes, 5600, and less marked changes in the red cells. And the last examination, August 4, 1923, was: Hemoglobin, 78 per cent; erythrocytes, 2,580,000; leukocytes, 4650, and more marked changes in the red cells.

Comment. This patient represents the type of pernicious anemia characterized by a rapid downward course, with few or no remissions and with many megaloblastic cells in the blood stream.

The same clinical betterment has been noted as in the other patients operated upon and this improvement seems out of proportion to the changes which have taken place thus far in the blood cells. Nevertheless, it is so noticeable to the patient herself that she believes she is going to become well. She bases this upon her increased strength, the fact that she is able to walk up short hills and stairs without shortness of breath and undue fatigue, and that her general sense of well-being has been markedly changed. Although only two months have elapsed since operation and one is not justified to form any conclusions regarding the outcome, still we recognize in this instance, as in the others, a more profound change than we have ever noted in any other form of treatment employed, including splenectomy. Whether the cause of the anemia has been removed or not, nevertheless, the effect thus far seen justifies the hope that some definite modification of the disease has taken place. The streptococcus obtained from the liver tissue undoubtedly existed in the wall of the gall-bladder also.

The brief records of the following 3 patients are also included for the reason that all of them have shown roentgenological evidence of gall-bladder disease. No thought of the existence of such disease would have been seriously considered in 3 of them. In 1 patient recurring attacks of pain and a possible attack of jaundice might have caused the association of gall stones and the anemia to be considered.

CASE XI.—Mrs. L., aged fifty-one years, 6 para, was received for the first time October 17, 1914. She had suffered all her life from gastro-intestinal disturbances, vomiting, periods of bowel looseness, fever lasting at times for months, and in later years relapsing periods of paleness and weakness. She had had jaundice in childhood, and tonsil, sinus and dental sepsis for many years. At one time pain in the lower right abdomen led to the diagnosis of chronic appendicitis but she was not operated upon. Later she suffered pain attacks in the left chest. The heart was normal in all examinations except for hemic murmurs heard during relapses. For some years she suffered from numbness, burning and tingling of the hands and feet and of the tongue. Between October, 1914, and June, 1922, the patient was in our care eight times for longer or shorter periods of observation. She suffered from a complete achylia and a severe secondary bowel disturbance. Twenty-three complete counts were made. The persistent characters of pernicious anemia were always present. Nucleated red blood cells were never found. Positive shadows of a diseased gall-bladder with the presence of stones were obtained June 5, 1922. Cholecystectomy was urged at that time as a possible relief for the anemia but was not accepted.

Death occurred during a relapse at her home in an adjoining state, in March, 1923.

CASE XII.—Mrs. McP., aged forty years, 1 para, was seen June 20, 1922. Patient had complained for a year of exhaustion. Constipation had existed for fifteen years and the skin had been sallow for a long time. Once for a short time, one year ago, and lately for six weeks, patient has had some dull distress in right upper abdomen. She has had a dental sepsis. The tongue is negative; the stomach shows complete achylia. There are no paresthesiæ. Two blood examinations show: Hemoglobin, 90 per cent; red blood cells, 3,400,000; white blood cells, 5000. The red blood cells show a moderate number of megaloblasts and some polychromatophilic staining. There are no nucleated red blood cells. The blood Wassermann is negative. Positive gall-bladder shadows, without evidence of stones, are obtained on the films. Operation is not accepted.

CASE XIII.—Mrs. E., aged sixty-three years, 6 para, was received March 22, 1923. Since an acute illness two years ago the patient has been developing an increasing weakness and paleness; constipation exists but no bowel looseness. Soreness and burning of the tongue have been present for the last two weeks. Parasthesiæ have been absent. There is an old history of dental sepsis. The patient has a marked lemon-tinted paleness of the skin, glossitis, complete achylia and a megaloblastic blood picture. Positive gall-bladder shadows with stones are obtained. On entrance to hospital the blood examination showed: Hemoglobin, 42 per cent; erythrocytes, 1,680,000; leukocytes, 3200 and numerous normoblasts and megaloblasts. She remained one month under treatment in preparation for a cholecystectomy but finally refused operation. On leaving her blood showed: Hemoglobin, 70 per cent; erythrocytes, 2,500,000; leukocytes, 3400; 1 normoblast, fewer macrocytes and no megaloblasts.

Discussion. In the accounts of the 13 cases there is presented certain clinical, operative and postmortem evidence pointing to the fact that idiopathic pernicious anemia is related to and possibly caused by the action of hemolytic or other microorganisms which have invaded the wall of the gall-bladder and from this organ as a focal site are producing their effect upon the red blood cells and erythrogenetic centers of the bone-marrow. In the 10 operated or autopsied cases the wall of the gall-bladder afforded organisms by culture or by staining the tissues, or by both methods. In the 7 instances in which cultures were obtained hemolyzing organisms were found in 4, alpha-hemolytic streptococcus in 2 and non-hemolytic *Staphylococcus albus* in 1. In Cases III and IX hemo-

lytic *Staphylococcus albus* was obtained and in each instance it was believed to be a pathogenic organism and not one of contamination. Case IX is of special note for the pathological and bacteriological examination was made by other observers and in-so-far as one case may decide it serves as confirmation of our own observations. Case VIII is also of special interest because in the presence of a terminal pneumococcic septicemia; an alpha-hemolytic streptococcus was obtained locally from the gall-bladder wall. The organisms lie most abundantly in the areas of scar tissue within the muscularis where possibly a lowered oxygen tension permits of a better growth. In this respect it reminds one of the localization of *Streptococcus viridans* in the leaflets of the heart valves in subacute infectious endocarditis. It raises the query whether or not the organisms may be able to seal themselves up within a suitable medium that permits growth over a long period of time and thus allows an organism of low virulence to produce death of the host after many months or years, even as the *Streptococcus viridans* does in the heart. In Cases IV and X a bit of liver tissue gave a pure culture of alpha-hemolytic streptococcus. In none of the autopsied cases have organisms been thus obtained. They also have not been found in sections of the liver stained for bacteria, but the presence of pigment obscures the picture. Whether these organisms will be universally found in the liver substance, as Graham¹⁷ has shown in ordinary cholecystitis, remains to be determined.

The macroscopical appearance of the gall-bladder is important. In Cases III and IX it was considered normal by the surgeon. In Cases II, IV, V, VIII and X the macroscopical evidence of disease was slight. In Case VI an unsuspected gall stone was found at autopsy. In all cases studied roentgenologically by Dr. Palmer for the presence of chronic gall-bladder disease sufficient proof was found to justify the removal of the organ. This emphasizes again the contention that positive gall-bladder shadows are more conclusive of disease than the macroscopical appearance of the gall-bladder at operation. In only 1 case of the series (Case I) was there sufficient clinical evidence to justify the thought that chronic gall-bladder disease might be present.

From the therapeutic standpoint there is much to be learned that only the experience which comes with time will teach. If these observations are proven to be true in a reasonable percentage of cases, it would seem justifiable to perform cholecystectomy in those instances, at least, in which roentgen-ray evidence of gall-bladder disease is obtained. Indeed, if suitable roentgen-ray studies are not available, it might still be proper to remove the gall-bladder inasmuch as we are dealing with an incurable disease. With a record of only 5 operated patients but little may be said. One patient has lived for six years after operation with apparent abeyance of those

symptoms of pernicious anemia from which she suffered at the time of operation. The second patient was suffering from a severe and frank although slowly progressing pernicious anemia. The result of operation in his case after eleven months' time is certainly all that could be hoped for. One must not wait for the appearance of megaloblastic cells in the blood stream or the presence of cord changes before thinking of pernicious anemia. If the disease is caused by various organisms of special characters and of different degrees of virulence the variations in its clinical course are easily understood, and the earlier treatment is instituted the more perfect may be the end-result obtained. A case in point is the following: A strongly built woman, aged fifty-seven years, began in November, 1922, to have nausea and vomiting. Two months ago an annoying flowing of saliva and a distressing soreness of the mouth began, which were laid to the door of septic teeth and tonsils. These were removed. About the same time one hand became numb. A recent examination of the patient did not reveal any local cause of the salivary disturbance within the head. The chemistry of the stomach was normal. The blood examination showed hemoglobin 100 per cent and red blood cells 4,900,000. There were some macrocytes present. Positive proof of a gall-bladder disease was obtained. With this combination of subjective symptoms and gall-bladder disease a beginning pernicious anemia may well be considered *

One more point in regard to the treatment of these cases may be mentioned. For over twenty years large doses of arsenic, especially of sodium cacodylate, have been empirically used with benefit in the treatment of streptococcic infections. For a much longer time arsenic has been the most efficient means employed in prolonging the life and alleviating the suffering of the patient with pernicious anemia. The underlying reason may be the same because of the inhibiting power which arsenic has on these organisms. We have safeguarded our operative results by treating the patient in bed with arsenic to the point of physiological tolerance, forced feeding and hydrochloric acid. With each patient we have aimed to raise the hemoglobin content above 70 per cent, the red cell count to 3,000,000 and to add several pounds to the weight before operating, and then to operate before the beginning of another relapse. The 1

* Cholecystectomy and appendectomy was performed on this patient June 14 (by E. W. St. P.). The pathological report is as follows: The gall-bladder wall is slightly thinned, the mucosa atrophic sections show thinning of the wall, slight fibrosis of the muscularis, atrophy and desquamation of the epithelium of the mucosa. In the wall are some large lymphocytes and small round cells. Sections stained for bacteria show the presence of a few diplococci and intracellular cocci. The bit of liver tissue is not sectioned. Cultures of the bile, the gallbladder and the liver are negative.

Pathological Diagnosis. Chronic atrophic cholecystitis. *Course.* Convalescence from the operation was normal. The drooling and the numbness of the hand practically disappeared before the patient left the hospital.

death recorded occurred in the wake of a relapse. It is not unlikely that an exaggerated risk may be present at this time, although the experience of splenectomizing such patients does not wholly bear out this view.

Experimental work has been started in the pathological laboratory in an effort to determine whether some of the organisms isolated from the gall-bladders of pernicious anemia patients are pathogenic for animals. It is the purpose also to determine if possible whether pernicious anemia is caused directly by the lytic action of bacteria and their products on erythrocytes, or whether the anemia may be the effect of some chemical substance entering the circulation from the infected gall-bladder. The fact that the lytic substances causing the pernicious anemias of *Bothriocephalus latus* and of hookworm infections are lipoid in character, and that a megaloblastic anemia may be produced experimentally in rabbits by using a similar agent, suggests the possible changes in the cholesterol content of the bile, especially within the gall-bladder, by means of organisms possessing special properties as being the cause of another group. These studies will be reported later.

Conclusions. 1. Evidence is brought forth pointing to the presence of hemolyzing and other microorganisms in the wall of the gall-bladder as being the possible cause of idiopathic progressive pernicious anemia.

2. In a series of 13 cases the presence of chronic gall-bladder disease was found by special study in each one.

3. Cholecystectomy on 5 patients of this series seemingly has removed some or all of the symptoms of the disease.

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