EDITORIAL

PERNICIOUS ANEMIA FOLLOWING GASTRECTOMY

Disappointment in the ultimate results of cancer treatment is frequent enough to discourage even the most optimistic. But the final straw is to see a patient, cured, we may say, of carcinoma of the breast, come back after ten years of freedom from the disease with an inoperable carcinoma of the rectum, or a patient with a ten-year cure of carcinoma of the cervix with radium suddenly develop extensive pelvic recurrences. Recently it may be noted that another burden is placed upon the surgeon who attempts to cure cancer of the stomach, for there are now appearing in the literature only too frequent examples of pernicious anemia following gastrectomy. Attention has been drawn to this situation by our better understanding of the etiology of pernicious anemia as a disease in some way dependent upon a hormone present in the mucous membrane of the stomach and the substance of the liver. That achylia is a feature of pernicious anemia has been known for a long time, and generations of clinicians have regarded the atrophy of the mucous membrane of the tongue and of the stomach as features of the disease. It has been repeatedly noted, also, that patients complain of sore tongues after extensive gastric operations.

The demonstration by Minot and Murphy 1 of the response of pernicious anemia to small quantities of liver extract led Castle 2 to suspect that it was a deficiency disease. The fact that, although the blood of the patients treated with liver extract returned to normal, the achylia did not disappear further suggested that the deficiency was due to the failure of some digestive process in the stomach. Proceeding on this hypothesis Castle carried out remarkable experiments. He administered to patients with pernicious anemia material recovered from the normal human stomach in which the early stages of protein digestion had been allowed to take place. With this treatment he produced remissions comparable to those obtained with liver therapy. He then showed that

normal fasting gastric juice alone was incapable of producing re-
mission of the anemia, but that when the gastric juice was incu-
bated with beef muscle a decided response was obtained. These
experiments proved conclusively that the failure of blood formation
in pernicious anemia is due to the lack of a substance produced by
the interaction of protein and normal gastric juice in the stomach.
The treatment of pernicious anemia by desiccated animal stomach
was a logical conclusion from these experiments.

The surgeon who resects the stomach for carcinoma should be
interested in these findings, for on their basis he should expect the
development of pernicious anemia when all or a large portion of
the stomach is removed. Indeed, in 1929 when Castle published
his striking experiments, there were already on record a few iso-
lated case reports of pernicious anemia following gastrectomy.
Moynihan in 1911 had reported the first case. In 1907 he did a
complete gastrectomy for carcinoma involving the whole stomach.
The patient developed symptoms of pernicious anemia two and
one-half years later and died after a year's illness. Autopsy
showed no carcinoma, but changes characteristic of pernicious
anemia. Hartman described a second case in 1921. His patient
had a complete gastrectomy for carcinoma in 1917. A year and
a half later he developed typical signs of pernicious anemia and
went steadily down hill. In 1925 Ellis reported the case of a
man who had had a partial gastrectomy for carcinoma in 1909.
Fourteen years later he had signs of subacute combined degenera-
tion of the spinal cord, a sore tongue, and a blood picture of per-
nicious anemia. Hurst was impressed by the importance of
achylia in pernicious anemia and in 1923 stated that he knew of
five cases in which Addison's anemia followed the artificial achylia
produced by total gastrectomy performed for cancer. He did not
present the details of these cases, however.

Castle's decisive demonstration of the part which the stomach
plays in controlling blood formation furnished a logical explana-
tion of these cases of pernicious anemia following gastrectomy.
Surgeons all over the world began to look for such cases and a consid-

\footnotesize{Castle, W. B.: Loc. cit.}
\footnotesize{Moynihan, G. B. A.: A case of complete gastrectomy, Lancet 2: 430, 1911.}
\footnotesize{Hartman, H. R.: Blood changes in a gastrectomized patient simulating those of
pernicious anemia, Am. J. M. Sc. 162: 201, 1921.}
\footnotesize{Hurst, A. F.: Achlorhydria. Its relation to pernicious anemia and other diseases,
Lancet 1: 111, 1923.}
\footnotesize{Castle, W. B.: Loc. cit.}
erable number were reported within a short time. Dennig described a case of typical pernicious anemia developing eight years after total gastrectomy for ulcer. Liver therapy produced marked improvement. Breitenbach reported a similar case in which the anemia began six and one-half years after the gastrectomy. Hochrein described two cases. In the first case resection of the stomach for colloid carcinoma was followed in eight years by pernicious anemia with symptoms of spinal cord involvement. The second patient had most of his stomach resected for ulcer in 1920. Nine years later a severe anemia developed. Although on the basis of the blood picture it was secondary in type, it responded remarkably to liver therapy. Because of this response, Hochrein classed the anemia as pernicious. Hangarter reported a case in which resection of one half of the stomach and a Billroth I anastomosis was done for ulcer in 1928. Two years later the blood picture was characteristic of pernicious anemia. Liver therapy produced marked improvement. In a case reported by Scheidel gastric resection for an ulcer on the lesser curvature near the cardia was done in 1922. Six years later pernicious anemia with a smooth tongue, lemon yellow color, and the typical blood picture developed. The response to liver therapy was prompt. Berger described a case in which resection of two thirds of the stomach with an anastomosis of the Hofmeister-Finsterer type was done for carcinoma in 1921. Pernicious anemia was observed six years later. The most recent report is that of Poole and Foster Their patient had a complete gastrectomy for probable syphilis of the stomach in 1926. Four years later the characteristic picture of pernicious anemia developed. Desiccated stomach therapy had a prompt effect.

This makes a total of eleven definite cases and five probable cases of pernicious anemia following gastrectomy. At first glance this number seems small, but it must be remembered that the

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number of patients surviving total gastrectomy for any appreciable length of time is also small. Finney and Rienhoff in 1929 found reports of only sixty-two cases of total gastrectomy, adding five of their own. The operative mortality was 53.8 per cent. Only two patients survived longer than two and a half years. These two patients lived four years and eight months and four years, respectively. The great majority succumbed to an early recurrence of the carcinoma. In the cases of pernicious anemia following gastrectomy noted above, the average interval between the operation and the development of the anemia was six and one tenth years, the shortest interval being one and a half years and the longest fourteen years. It is apparent that the great majority of gastrectomized patients do not live long enough to develop pernicious anemia. As time goes on, and earlier diagnosis and improvements in operative technic enable more patients to survive gastrectomy for a significant length of time, pernicious anemia will probably be encountered more frequently. Indeed, it may be found that every patient whose stomach has been completely removed will develop pernicious anemia.

Partial resection of the stomach may also be a sufficient cause for pernicious anemia. Five of the cases of pernicious anemia described above followed partial gastrectomy. It is not apparent from the descriptions of these cases just which portions of the stomach were resected. The present knowledge of the factor in the stomach controlling blood formation has not localized this function to any particular portion of the stomach. It is, therefore, impossible to predict how much, and what part of the stomach may be resected without engendering pernicious anemia. The surgeon doing partial gastric resections should keep in mind the possibility of the development of pernicious anemia.

The question may be raised as to whether carcinoma of the stomach itself, by destroying a large portion of the gastric mucosa, may cause pernicious anemia. This sequence would be most probable in diffuse fibrocarcinoma (limitis plastica) of the stomach. It is well known that this type of carcinoma often grows slowly—survival for as long as five years after simple gastro-enterostomy has been reported. It is no doubt true that the great majority of anemias occurring in gastric carcinoma are secondary in type, but occasional cases have been reported in which the anemia conformed

in every respect to what has been regarded as pernicious anemia. Brandes\textsuperscript{17} collected the reports of ten such cases and added four which he had observed. His four cases all showed the typical clinical picture of pernicious anemia. At autopsy, however, in only one case was the entire stomach found to be involved by a scirrhus carcinoma. In the other three cases the gastric carcinoma was small. The question of whether pernicious anemia may be caused by gastric carcinoma can be solved only by a reliable criterion for distinguishing pernicious from secondary anemia. If, as now seems possible, a favorable reticulocyte response to liver or stomach therapy is an accurate distinguishing feature of pernicious anemia of the Addison-Biermer type, the answer may soon be available.