A Method for Experimental Production of Gradual Occlusion of the Portal Vein.* (17398)

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A sudden complete occlusion of the portal vein is invariably fatal. However, a gradual occlusion of the portal vein in the dog and other laboratory animals is compatible with life, as was demonstrated first by Oré[1] and later by Bernard,[2] Tilmann,[3] Ito and Omi,[4] Neuhof,[5] Boyce *et al.*,[6] Dragstedt,[7] and Brunschwig *et al.*[8] Survival is dependent upon the development of collateral venous channels in the gastrohepatic mesentery, and anastomoses with the esophageal, caval, renal, and rectal veins.

Gradual occlusion of the portal vein has been used by Dragstedt[7] as a substitute for Eck fistula in physiologic studies of the liver and the abdominal organs draining into the portal system. It has also been studied experimentally by Brunschwig *et al.*[8] with a more clinical application in mind. The proximity of the portal vein to the pancreas, and its occasional invasion by pancreatic carcinoma in man, led Brunschwig and his co-workers to investigate methods for the production of adequate collateral channels, thereby enabling excision of this vessel. Menon[9] and Kershner *et al.*[10] attempted to produce portal hypertension in the laboratory animal by gradual occlusion of the portal vein. Consistent increases in portal venous pressure with ascites, esophageal varices, and splenomegaly were not obtained.

All of the methods reported for gradual occlusion of the portal vein were ligature technics with various modifications. Each of the technics required at least a 2-stage operative procedure, with the exception of that described by Brunschwig *et al.*[8] These workers were able to occlude the portal vein successfully by means of a linen thread looped around the vein, the ends of which were brought out through the operative wound and tied over the back of the animal. These ends were pulled upon slightly each postoperative day until the intact loop was pulled out, denoting that the loop had passed through the portal vein. Although gradual occlusion of the portal vein was accomplished successfully by this method, the incidence of fatal peritonitis was high.

The present study is a report of the use of irritative cellophane (Polythene‡) and tantalum to produce gradual portal vein occlusion. It is believed that this method possesses certain advantages over the ligature technics formerly used. It eliminates the repeated operative procedures necessitated by ligation in stages, and also obviates the substantial incidence of peritonitis associated with ligature transection of the portal vein.

Method. Healthy adult mongrel dogs were used. Following intravenous sodium pento-

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1 Oré, *Compt. rend. Acad. Royal d. sc.*, 1856, **43**, 463 (cited by Brunschwig *et al.*[8]).

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3 Tilmann, H., *Deutsche med. Wchnschr.*, 1899, **25**, 284.

4 Ito, H., and Omi, K., *Deutsche Z. f. Chir.*, 1902, **62**, 141 (cited by Brunschwig *et al.*[8]).

5 Neuhof, H., *Surg., Gynec. and Obst.*, 1913, **16**, 481.

6 Boyce, F. F., Lampert, R., and McFetridge, E. M., *J. Lab. and Clin. Med.*, 1935, **20**, 935.

7 Dragstedt, L. R., *Science*, 1931, **73**, 315.

8 Brunschwig, A., Bigelow, R., and Nichols, S., *Surgery*, 1945, **17**, 781.

9 Menon, T. B., *J. Path. and Bact.*, 1938, **46**, 357.

10 Kershner, D., Hooton, T. C., and Shearer, E. M., *Arch. Surg.*, 1946, **53**, 425.

‡ Polythene (DuPont), type NV-7-14 with dicetyl phosphate, 1.5 mils in thickness, furnished by The Cellophane Division, E. I. DuPont de Nemours and Company, Wilmington, Del.

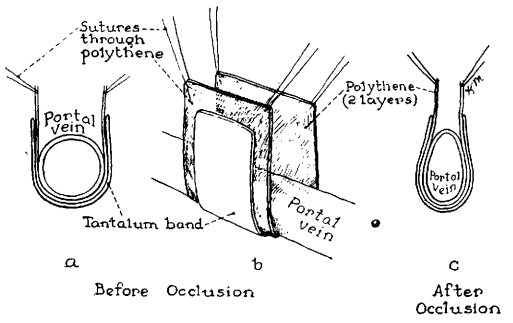

FIG. 1.
Schematic drawing illustrating application of Polythene and tantalum band to the portal vein.

barbital anesthesia, the abdomen was opened through a high right upper rectus muscle-splitting incision. The portal vein was mobilized and a double thickness cuff of Polythene, 1 to 2 cm in length, was wrapped about the vein at the porta hepatis. The Polythene casing was anchored by 2 interrupted No. 00000 arterial silk or cotton sutures. A narrow tantalum band was then placed about the Polythene and tightened so as to decrease the transverse diameter of the portal vein to approximately one-half to two-thirds of the original size (Fig. 1). A cuff of Polythene protruded from beneath the band at either end, and the tantalum did not contact the vein at any point.

After a period of 5 to 10 minutes the small bowel was examined for evidence of dangerously increased venous congestion. If marked venous congestion with cyanosis of the bowel was present, the tantalum band was loosened slightly. The abdominal wall was closed in layers only after the bowel was seen to be normal. A slight distention of the intestinal veins, with approximately a doubling of venous pressure, was usually present. Venous pressures in the portal bed were measured before and after placing of the tantalum band by means of the Burch phlebomanometer or by a spinal fluid manometer.

The animals were either re-explored or sacrificed 3 to 60 days later and the portal vein removed for gross and microscopic examination.

Results. The portal vein in 28 dogs was wrapped with Polythene and partially occluded with tantalum. One dog died within 3 hours of the time of operation, and 3 dogs expired within 12 hours. Postmortem examination revealed the characteristic findings of sudden acute portal occlusion. The mesenteric vessels were engorged, the spleen congested, and there were hemorrhagic areas in the mesentery and intestinal wall.

The remaining 24 dogs showed no immediate ill effects from the procedure. The portal vein was excised from 16 of these dogs without a fatality, at intervals ranging from 5 to 60 days (Fig. 2). At the time of the second operation, extensive collateral venous channels were present in the gastrohepatic mesentery. In addition, an increased tendency for the animal to go into shock was noted at the second operation, and was combatted by the use of intravenous fluids and cardiac stimulants. This was an important finding and deserves further study. Two dogs expired following portal vein excision on the fifth postoperative day. The remaining 6 dogs were sacrificed at varying intervals, with the collateral circulation being extensively studied.

Upon gross examination, the wall of the portal vein was thickened, the extent of thickening being dependent upon the length

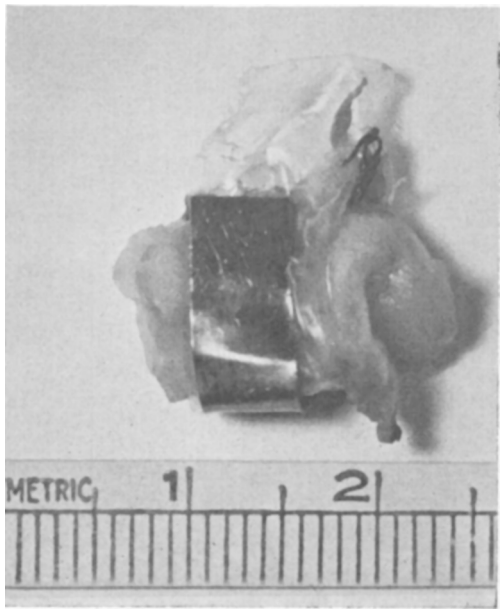

FIG. 2.
Photograph of excised portal vein with the Polythene and tantalum band in place.

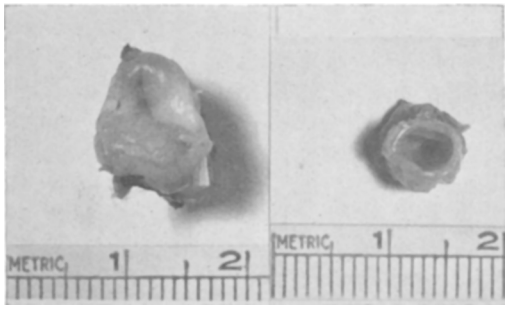

FIG. 3.
a. Photograph of excised portal vein segment showing the reaction caused by the application of Polythene 60 days before. Note the absence of lumen and the marked thickening of the vessel walls.
b. Normal portal vein segment.

of time during which the vessel had been in contact with the Polythene. The lumen was reduced in all animals and by 30 days after wrapping only a small aperture remained. The lumen was completely obliterated in 4 dogs at 40 to 60 days. Surrounding the vein there was a moderately thick, brown gelatinous pseudomembrane (Fig. 3).

Microscopic examination of the portal vein from animals dying within 12 hours showed a fibrinous reaction with occasional lymphocytic infiltration in the tissues immediately adjacent to the portal vein. At 5 days, changes consisted of edema of the media and adventitia, round cell infiltration, and beginning fibroplasia; in addition, a fibrinous deposition in the tissues adjacent to the vein was noted. Localized hemorrhage into the wall of the vein was occasionally seen. At 10 to 15 days the acute reaction was less evident and the significant finding was medial, adventitial, and periportal fibrosis. At 18 to 20 days there was increased fibrosis and chronic inflammatory response in the outer half of the vein wall and periportal tissues. After a period of 30 to 60 days, intimal thickening with marked fibrosis of the media and adventitia was present (Fig. 4). Apparently the degree of fibroplasia was dependent upon the duration of Polythene application. It was also noted that the chronic inflammatory response was significantly decreased after 30 days.

One of the original objectives of the study was to attempt to produce portal hypertension by this method. However, at the time of re-exploration there was no elevation of venous pressure in the intestinal veins. Extensive collateral channels joined the renal, rectal, and caval veins, and were present in the gastrohepatic omentum. In some instances gastrohepatic collateral vessels were larger than the portal vein prior to Polythene and tantalum wrapping. The number and size of the collateral vessels was in direct proportion to the duration of portal occlusion. Injection studies of the venous collaterals, using liquid latex and Hill's media, revealed no instance of a collateral vessel passing directly into the liver. Significant anastomoses with esophageal veins were not demonstrated. This is of interest when compared with the usual collateral channels found in man following blockage of the portal vein.

Discussion. Irritative cellophane has been used in the treatment of aneurysms,[11,12,13] the experimental production of aortic stenosis and obliteration,[14,15] and in attempts to obliterate a patent ductus arteriosus.[16] The dicetyl phosphate present in the Polythene is responsible for the irritative properties of the material,[17] and differentiates this cellophane from the non-irritating type which does not induce fibroplasia and which has been used in certain orthopedic procedures.[18,19] We have not encountered any reports in the literature regarding the use of irritative cellophane in occlusion of major veins. It has

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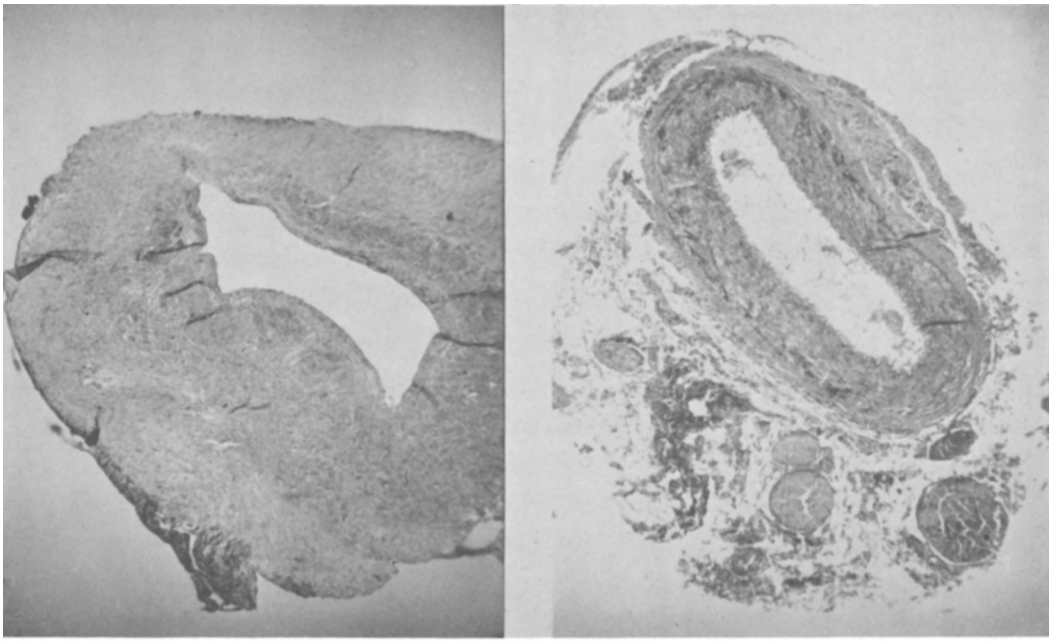

a. b.

FIG. 4.

a. Photomicrograph of a segment of portal vein 30 days after the application of Polythene and tantalum (× 25). Note the marked fibrosis and chronic inflammatory response in the media and adventitia.

b. Photomicrograph of a normal portal vein segment (× 25).

been stated that the aorta of the dog may be occluded with Polythene and tantalum in 12 weeks.[15] The interval required for total occlusion of the portal vein was approximately 6 to 8 weeks and the tissue response of the vein was similar to that described for the aorta.

The 4 dogs which died within 12 hours of operation illustrate the difficulty in securing maximal immediate constriction without occluding the vein to a point incompatible with life.

The shortest time interval compatible with survival between partial ligature occlusion of the portal vein and excision or complete ligation of this vessel has been reported as 10 days.[6,8] Four of 6 dogs in this series which were subjected to excision 5 days after partial occlusion survived. This suggests the development of a more extensive collateral venous network with the present method of occlusion, and clinically may be important in preparing for elective ligation of the portal vein.

It is believed that the gradual fibroplastic obliteration of the portal vein produced by the irritating cellophane (Polythene) more closely approximates the gradual reduction of portal blood flow as seen in certain disease states, *e.g.* the cirrhotic diseases, and will facilitate the study of these diseases.

Conclusions. 1. The fibroplastic response in the outer half of the vein wall and in the periportal tissues is similar to the reaction seen in the aorta following application of Polythene and tantalum.

2. At least 6 to 8 weeks are required for complete occlusion of the portal vein by Polythene-induced fibroplasia.

3. The gradual occlusion of the portal vein produced by irritative Polythene may be valuable in preparing for elective ligation of the portal vein and in the experimental study of decreased portal blood flow.

Summary. A one stage procedure for gradual occlusion of the portal vein using an irritative type of cellophane (Polythene) and tantalum is described.

The portal vein in 28 dogs was wrapped with Polythene and partially occluded with a tantalum band. The veins were removed for gross and microscopic examination 3 to 60 days later. Extensive venous collateral channels developed in the gastrohepatic mesentery and along the posterior peritoneum, passing into the renal, rectal, and caval veins. In 4 of 6 dogs venous anastomoses were adequate to sustain life following excision of the portal vein 5 days after partial portal occlusion.

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Neutralization of Three Immunological Types of Poliomyelitis Virus by Human Gamma Globulin.* (17399)

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Recent studies of antigenic groups of poliomyelitis virus have shown the existence of at least 3 distinct types.[1,2] Two of these are widespread in their distribution, but the third is represented thus far by only one strain (Leon) isolated in Los Angeles, California in 1937.[3] In an attempt to determine whether this strain is perhaps unusual in its occurrence, or is sufficiently widespread to be considered of importance in the epidemiology of this disease, neutralization tests with human gamma globulin were caried out using this strain as well as representatives of the other two antigenic types, Lansing and Brunhilde.[1]

Methods. The viruses used have been described in detail before,[1] and the pools used are designated as Brunhilde III, Lansing VIII, and Leon I. These virus pools are of high titer, and consist of 10 or more cords of rhesus monkeys killed on the first day of paralysis. Only lumbar and cervical enlargements were used. Aqueous suspensions were prepared with a Waring blendor, and aliquots sealed in glass ampules and stored on dry ice. Titrations of these pools are shown in Table I.

The globulin solution used was a sample supplied by the courtesy of the American National Red Cross who distribute it for measles prophylaxis. The sample used was prepared by E. R. Squibb and Sons, and information regarding it was kindly supplied by Dr. J. W. Palmer of the Squibb Company. The human plasma pool used in the preparation of the globulin pool from which this sample was derived totalled 3,000 liters and consisted of the surplus plasma returned to the American Red Cross by the armed forces after the war. The plasma is therefore representative of about 20,000 to 50,000 individuals who contributed blood to the Red Cross during the war. These individuals lived predominantly on the East Coast and in the Great Lakes Area. A small fraction of the plasma was also collected in the Far West. The plasma was originally dried and subsequently reconstituted. The primary fractionation was made following method 6 of Cohn, *et al.*;[4] the subfractionation was made according to method 9 of Oncley, *et al.*[5] The preparation of the globulin fraction from plasma does not appear to result in deterioration of antibody.[6] The effect of prolonged storage of the plasma in the dried state might conceivably have had a detrimental effect on antibody levels, although this seems doubtful in view of the

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