M. Sc. Experimental Surgery

# THE SURGICAL TREATMENT OF EXPERIMENTAL ASCITES

by

Arthur N. Freedman, B.A.,M.D.,C.M.

Research Assistant in Experimental Surgery,
Demonstrator in Anatomy, McGill University.

Thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the Degree of Master of Science.

June, 1958. McGill University.

# PREFACE

The magnitude of the problem of ascites is not readily apparent to the clinician. A classification of conditions in which ascites occurs and a consideration of therapy occupy his thinking when confronted by a patient with the sign.

Those actively engaged in investigative work on ascites have attempted to proceed further than their clinical colleagues. The vast void that exists in our knowledge becomes apparent with review of the literature. Only relative success of surgery in ameliorating chronic ascites has prompted the efforts presented within this report.

The experiments reported in this manuscript were performed between July, 1957 and June, 1958, under the tenure of a Cancer Research Society Fellowship in the Department of Experimental Surgery, McGill University.

It is most pleasant to express personal gratitude to those whose assistance throughout this year have expedited and lightened the necessary labours.

To Dr. Donald R. Webster, whose guidance and introduction to scientific research have enhanced surgical training.

To Dr. Stanley C. Skoryna, whose experience and direction were freely offered during the entire year.

To. Dr. C. W. MacMillan, who guided the statistical analysis of experimental data.

To Dr. A. C. Ritchie, of the Department of Pathology, who kindly examined the histological material.

To Messrs. Albert Nagy, N. Vermes, J. Byers and S. Hardy who provided the animal care without which this project could not have been carried out.

To Messrs. Brian Thomlinson and Hans Torunski, who prepared the microscopic sections, and to Mr. Harold Coletta who took almost all the photographs.

To Mr. Bruce F. Smith of Dow Corning Silicones Limited for the silicone rubber, and Rediweld of Canada, Limited, for the polythene, both used to construct the prostheses.

To Mrs. Betty Rumball and Mrs. G. Jones who performed all biochemical determinations, and Mrs. Luba Trifonow who kept a large supply of glassware available.

The following companies provided drugs for use in this project: Ayerst, McKenna and Harrison (vitamins, antibiotics); Lederle (vitamins); Frank W. Horner (parenzymol); and Upjohn (neomycin).

It has been a pleasure to be associated with Drs. R. I. Constantine, A. R. C. Dobell, J. R. Gutelius, B. C. Mahanti and F. G. Murphy in this laboratory during the past year. Each has given of his time most willingly to assist and discuss any problems related to this project. Mr. Z. Makkay has helped with

certain technical procedures.

Mrs. B. M. Parker has been most conscientous in her task of ordering all supplies. She has done all clerical work associated with the Diploma Course in Surgery Lectures. Her typing of this manuscript is gratefully achnowledged.

My wife, Jacqueline, has been most patient throughout the course of this work. Her inspiration has led to the completion of this work throughout the ups and downsof research.

Arthur N. Freedman
Montreal,
June 30th, 1958.

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# CHAPTER I

## INTRODUCTION

Increasing interest in the problem of ascites has been apparent in the recent literature. Of late, with advances in biochemistry and metabolism, numerous papers have appeared attempting to explain the etiology and pathogenesis of this clinical condition.

Along with the above, investigators have tried to devise new surgical techniques for the amelioration of ascites. Medical measures will control about 50% of patients with chronic ascites. Something must be done for those whose fluid persists despite intensive non-operative treatment. These patients constitute the group with intractable wasting ascites, which has impaired their physiologic functions. Although their ultimate prognosis is poor due to the inherent nature of their underlying disease, nevertheless their lives may be prolonged and made more comfortable.

It is the surgeon's task to try to do something for these people who in most cases are doomed to die. If some surgical technique can be devised which will provide added comfort and a prolonged period of useful life for these individuals, then a valuable addition to medical armamentarium will exist. One stipulation exists, however, and this is a very important one indeed. The procedure must be accompanied by a reasonable success rate and morbidity and mortality must be low.

The work performed in the Department of Experimental Surgery consisted of the trial of several techniques reported in the surgical literature. The encouraging reports of certain operations, such as the recently innovated ileo-entectropy, prompted the author to evaluate these further. In addition, the author devised a prosthesis for the internal drainage of ascites. Although the results of the work do not indicate success of the venture in the case of dogs, nevertheless differences in human anatomy and ascites give optimism that the prosthesis may find usefulness in clinical application.

One cannot agree completely with the following statement, but it expresses a philosophy which should encourage the surgeon to continue his endeavors to develop some means of benefiting the chronic ascitic.

> "It is apparent that no single therapeutic procedure is uniformly successful in combatting ascites. Since ascites usually signifies serious disease, any rational therapy, even of heroic kind, seems quite justified."
>
> (114)

It is the futility of most surgical measures, as well as the confusion attendant on the actual mechanisms of ascites, that has led this investigator to conduct the research project which is reported in the following pages.

# CHAPTER II.

## THE MECHANISM OF ASCITES FORMATION

### Introduction

The term ascites is derived from the Greek word 'askites', meaning bag or belly. It is used clinically and pathologically to signify any collection of free fluid within the peritoneal cavity. This fluid is normally present within the peritoneal cavity in amounts of 150 to 200 cc., a quantity too small to elicit on physical examination. Usually clear and slightly yellow in color, modifications may occur, depending on the nature of the underlying disease which gives rise to its presence in detectable quantities; thus it may be chylous or chyliform, hemorrhagic or bloody, or pseudochylous.

The mechanism of origin of ascites is still largely theoretical. Hypotheses attempt also to explain the origin of the normally occurring peritoneal fluid. Filtration from the blood stream was used by Ludwig to explain its origin, while Heidenheim invoked secretion by the peritoneum as the mechanism. The most universally accepted thesis is Starling's, that the fluid is of intracellular origin and that formation and absorption depend upon capillary permeability and the osmotic pressure of the blood. Normally, the rate of formation is balanced by an equal rate of absorption and clinical ascites does not result. Therefore, ascites is either the result of excessive

formation or defective absorption of peritoneal fluid. A consideration of the pathogenesis of ascites is more complex than these two simple categories may suggest. Several causative factors must be used to explain either defect. There are, however, several exponents of a predominant single factor etiology and these shall be discussed in the ensuing pages.

Diseases Associated with Ascites

Ascites is thus a sign occurring in numerous diseases. Although the exact mechanism of origin is not known, nevertheless those states giving rise to ascites may be tabulated. Further experience with these disease entities themselves may one day elucidate exactly the factor or factors which result in the ascites. Bockus (22) has classified the diseases associated with ascites as follows:

1. Diseases of heart and blood vessels:

   Cardiac decompensation - regardless of cause
   Constrictive pericarditis
   Pericardial effusion
   Pulmonary arteriosclerosis
   Pulmonary embolism
   Aneurysm of abdominal vessels
   Thrombosis or obstruction of inferior vena cava

2. Diseases of liver and portal venous system

   Cirrhosis of the liver
   Syphilis of the liver
   Thrombosis of portal vein, splenic vein or hepatic artery
   Tumors or enlarged glands in porta hepatis with extrinsic pressure on the portal vein
   Cysts and tumors of the liver

3. Diseases of the peritoneum

Acute suppurative peritonitis
Simple chronic peritonitis
Hyperplastic peritonitis with perihepatitis
Tuberculous peritonitis
Peritoneal carcinomatosis
Cysts of the peritoneum

4. Diseases of the kidneys

As part of generalized anasarca in nephritis with associated oliguria and anuria
Secondary to heart failure induced by renal disease, lipoid nephrosis or the nephrotic stage of glomerulonephritis resulting in hypoproteinemia
Malignant lesions of the kidney invading inferior vena cava
Polycystic disease

5. Diseases of female reproductive organs

Hemoperitoneum due to ruptured ectopic pregnancy, ruptured graafian follicle cyst, etc.
Malignant tumors
Ruptured and unruptured cystadenomas
Meigs syndrome

6. Diseases of lungs and mediastinum

Pulmonary fibrosis
Pulmonary emphysema
Mediastinal adhesions and tumors
Primary and secondary tumors of lungs and pleura

7. Diseases of the blood

Anemia - primary or secondary
Blood dyscrasias: leukemia, aplastic anemia, etc.

8. Diseases of lymphatic system

Lesions of lymphatic vessels and nodes of peritoneum and mesentery
Injury, disease, or obstruction of receptaculum chyli or thoracic duct
Lymphomas

9. Rupture of hollow viscus (stomach, intestine, urinary bladder or gallbladder)

10. Nutritional deficiency states (hypoproteinemia, avitaminosis)

11. Generalized wasting diseases.

From perusal of the above list, certain points come to mind. Some of these are questions which may be answered readily while others still await clarification.

A. Although ascites of a chronic nature may occur in many disease processes, some are of relatively infrequent occurrence. This problem has been investigated on occasion, and Cabot (34) may be referred to for a discussion and compilation of the incidence of various diseases in a total series of 5,000 cases of ascites. He found that cardiac disease was the commonest cause, followed by nephritis, cirrhosis, tuberculous peritonitis, intestinal obstruction, diseases of the female genitalia, abdominal neoplasms and adherent pericardium. The order of occurrence of these in a numerical listing is different today, secondary to advances in therapy, but the same diseases would predominate - namely, cardiac, hepatic, renal and malignant disease. It is these patients with whom the surgeon is confronted when medical management has failed to alter appreciably the volume of ascites.

B. How often does ascites occur as a sign of various diseases? Cabot (34) in his series found it in 88% of cirrhotics, 82% with tuberculosis of the peritoneum, 76% with adherent pericardium, 46%

with abdominal neoplasms, 43% with intestinal obstruction, 29% with renal disease, 28% with heart disease and in 11% of patients with diseases of the female genitalia. Ratnoff and Patek (193) in an analysis of 386 cases of cirrhosis, found an incidence of ascites of 78%. This figure compares closely with others reported in the literature. No large series of cases has been reported wherein the incidence of ascites in other diseases has been presented.

C. What are the physical and chemical properties of ascitic fluid and are there sufficient differences between samples in various diseases to render a sample characteristic of that disease?

As stated above, ascitic fluid is of several types when its modifications are included - hemorrhagic, chylous, pseudochylous, chyliform, etc. The commonest types found are transudates and exudates.

The transudate is usually clear and yellowish-greenish in the absence of gross blood or staining by bile. Its specific gravity is 1005 to 1015, the range being related to the protein content; its total protein is usually less than 2.5 gms.%, and the fluid does not clot on standing unless large amounts of blood are present. The protein is especially albumium, with small amounts of globulin; fibrinogen is rarely found. The chloride level, due to the Donnan equilibrium, is usually higher than that of the blood plasma. The glucose, urea, uric acid, creatinine and bilirubin levels closely parallel those found in blood. Calcium is found in concentration of 4-5 mg.%, representing the level of the true ionizable blood calcium;

the higher the protein content, however, the higher will the level of calcium be because of its combination with protein. Few cells are found, endothelial cells predominate, with small numbers of lymphocytes, polymorphonuclear leucocytes and monocytes, and in the absence of malignancy of the peritoneum, rare red blood cells.

An exudate is turbid, with a specific gravity greater than 1015. It contains a high concentration of protein and cholesterol, tends to coagulate on standing and may be grossly bloody when neoplastic in origin. Cells are higher in number with lymphocytes predominating in tuberculosis, and large numbers of red blood cells and mitotic figures may be present in intraperitoneal malignancy.

True chylous ascites is a rare finding - it is milky white and contains a high fat content which may give rise to a creamy layer on standing. Pseudochylous or chyliform ascites is more common than the true chylous type, but it too is rare. Characteristically its opalescence varies from one paracentesis to another, a physical and chemical change between lecithin and protein perhaps accounting for this poorly understood feature. Much cellular debris and little fat with globulin as the predominant protein are features.

Foord, Youngberg and Wetmore (81) analysed a large number of ascitic fluid samples and found the following physical and chemical data:-

TABLE I.

PHYSICAL CHEMISTRY OF ASCITIC FLUID

| | | S.G. | Fibrin % | Albumin % | Globulin % | A/G Ratio | Total N | NPN | Urea N | Uric Acid | Creatinine | Chlorides | Sugar | Cholesterol | Lecithin | Inorg. P | Calcium |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cirrhosis | Max. | 1016 | + | 1.57 | 1.52 | 1.41 | 434 | 35.3 | 21.0 | 6.4 | 2.0 | 710 | 264 | 148 | 58.7 | 5.3 | 9.8 |
| 10 | Min. | 1008 | 0 | Tr. | Tr. | 0.73 | 73 | 20.1 | 11.9 | 1.8 | 1.0 | 593 | 86 | Tr. | Tr. | 2.5 | 6.8 |
| Samples | Av. | 1012 | 0 | 0.73 | 0.59 | 1.08 | 187 | 26.6 | 16.2 | 3.4 | 1.3 | 642 | 131 | 46.8 | 19.3 | 4.1 | 8.5 |
| Nephritis | Max. | 1010 | 0 | Tr. | Tr. | ? | 53 | 48.9 | 33.3 | 4.5 | 1.8 | 670 | 182 | Tr. | | 5.4 | 7.2 |
| 3 | Min. | 1009 | 0 | Tr. | Tr. | ? | 45 | 28.4 | 23.1 | 3.0 | 1.4 | 530 | 125 | Tr. | | 4.7 | 5.8 |
| Samples | Av. | 1010 | 0 | Tr. | Tr. | ? | 49 | 39.9 | 27.1 | 3.9 | 1.6 | 620 | 147 | Tr. | | 5.0 | 6.8 |
| Cardiac | Max. | 1018 | Tr. | 1.64 | 1.69 | 1.62 | 554 | 42.8 | 25.9 | 5.3 | 1.6 | 660 | 182 | 127 | 140 | 4.4 | 9.9 |
| 8 | Min. | 1008 | 0 | 0.32 | 0.21 | 0.91 | 129 | 21.5 | 13.3 | 3.5 | 1.1 | 600 | 121 | 5 | 22 | 3.1 | 7.5 |
| Samples | Av. | 1012 | 0 | 0.88 | 0.81 | 1.12 | 301 | 33.1 | 22.8 | 4.5 | 1.2 | 642 | 139 | 58 | 51 | 3.8 | 8.3 |
| Tuberculosis | Max. | 1023 | 3+ | 2.19 | 3.55 | 0.93 | 890 | 29.4 | 25.1 | 4.2 | 1.6 | 605 | 96 | 95 | 92 | | |
| 3 | Min. | 1020 | 2+ | 1.80 | 2.05 | 0.54 | 680 | 24.9 | 14.7 | 2.0 | 1.2 | 545 | 60 | 94 | Tr. | | |
| Samples | Av. | 1022 | 2+ | 1.96 | 2.65 | 0.78 | 775 | 27.3 | 21.6 | 3.1 | 1.3 | 577 | 78 | 94 | 34 | | |
| Carcinoma | Max. | 1019 | 2+ | 2.56 | 1.37 | 2.14 | 630 | 43.2 | 27.3 | 4.5 | 1.3 | 645 | 156 | 144 | 112 | 4.4 | 9.4 |
| 5 | Min. | 1010 | 0 | 0.49 | 0.34 | 1.44 | 160 | 26.7 | 13.3 | 3.5 | 1.0 | 545 | 60 | 19 | Tr. | 3.1 | 6.6 |
| Samples | Av. | 1014 | + | 1.28 | 0.86 | 1.67 | 406 | 34.5 | 20.0 | 4.0 | 1.1 | 613 | 114 | 94 | 45 | 3.7 | 7.7 |

The authors conclude rightly that examination of the ascitic fluid is not in itself diagnostic of the disease producing the ascites. The clinical features of the disease are of prime importance in establishing the differential diagnosis of an effusion's etiology. Recent advances in cytologic techniques, however, may aid differentiation.

Taipale and Hokkanen (223) recently published their investigations concerning the mucoprotein levels of ascitic fluid in an endeavor to demonstrate a correlation between these values and the various conditions in which ascites occurs. Their results may be seen in Table II.

From this Table, one may state that the mucoprotein level of the ascitic fluid is of greater diagnostic significance than that of the serum; the values overlap, however, and so a differential diagnosis of the cause of the ascites may not be made with absolute certainty from this determination alone.

Recently Rovelstad and associates (202) examined the ascitic fluid and blood of patients by electrophoresis to determine if they could correlate lipid and protein fractions which were diagnostic. Of 116 patients with ascites, 57 had carcinoma, 37 had cirrhosis, and 22 had miscellaneous causes for their ascites. By selecting certain levels of protein fractions and lipids in serum and ascitic fluid, it was possible to separate out 100% of the patients

TABLE II.

MUCOPROTEIN LEVELS IN ASCITES

| | Mp Level of Ascitic Fluid mg/100ml. | | | Total Protein Ascites gms/100ml. | | | Serum Mp mg/100ml. | | |
|---|---|---|---|---|---|---|---|---|---|
| Malignant Tumor | 89-191 | Mean | 134.3 ± 10.10 | 2.4-4.9 | Mean | 3.9 ± 0.20 | 157-505 | Mean | 296.6 ± 35.26 |
| Congestive Heart Failure | 38-107 | with S.E. | 61.1 ± 4.75 | 2.0-4.4 | With S.E. | 3.0 ± 0.16 | 77-295 | With S.E. | 183.8 ± 15.67 |
| Cirrhosis | 7-37 | | 21.9 ± 2.70 | 0.5-2.9 | | 1.3 ± 0.21 | 30-198 | | 110.9 ± 15.77 |
| TB peritonitis | 187 | | | 6.7 | | | 400 | | |
| Disseminated Lupus | 49 | | | 4.9 | | | 231 | | |
| Polyserositis | 47 | | | 1.0 | | | 373 | | |
| Nephrosis | 26 | | | 0.3 | | | 232 | | |

with carcinoma, but no patients with cirrhotic ascites. Only cancerous fluids had fat levels of 0.35 gms./100 ml. or greater; no cirrhotic fluid had a specific gravity over 1018 or a total protein over 3.2 grams% while those in patients with carcinoma did. The carcinoma group had a higher gamma globulin level in their ascitic fluid, while this protein was higher in the serum of cirrhotics. But, 19 of 22 patients with miscellaneous causes for their ascites had fluid which met the criteria considered specific for carcinoma. History and physical examination continue to dominate the field of differential diagnosis.

The Causes of Ascites

Several mechanisms have been described in much detail to account for the pathogenesis of ascites. It would be useful at the beginning to classify the main groups of factors which appear to play a role in ascites formation. Volwiler (229) has done this very concisely as follows:

(1) Systemic factors which produce a generalized tendency to edema formation.

a) those factors which result in a decrease of plasma colloid osmotic pressure, i.e. which cause hypoproteinemia

b) those factors which result in an increase in the plasma antidiuretic substances.

(2) Intraperitoneal factors which result in the abdominal localization of the fluid collection.

a) Portal hypertension

b) Low tissue resistance

c) Intrahepatic congestion

d) An increase in small vessel permeability

(For the sake of completeness, one further localizing factor must be included, namely lymphatic obstruction),

Hypoproteinemia is primarily of importance in this discussion because of the action of albumin in maintaining plasma colloid osmotic pressure. The other components, globulin and fibrinogen, exert less oncotic pressure. A decrease in the plasma protein levels, and expecially of the albumin, may result from several factors (22, 51, 198, 229).

1) Insufficient dietary intake of total calories and protein in states of malnutrition.

2) Impaired gastrointestinal digestion and absorption of protein.

3) Liver disease which results in inadequate synthesis and utilization of protein.

4) External losses of protein by repeated paracenteses, massive haemorrhage, diarrhoea, urine loss, inflammatory exudates.

5) An increased destruction of protein in catabolic states such as long-continued fevers, extensive burns, etc.

6) Dilution of protein in expanded body fluid compartment, e.g. edema space, increased plasma volume.

The effects of hypoproteinemia are numerous (51). Edema, anemia and decreased blood volume occur; edema of the wall of the

gastrointestinal tract results in impaired motility; the liver is more susceptible to injury and less able to regenerate; the prerenal deviation of water into extravascular spaces as edema results in a decrease in urine volume; and there is defective and decreased fibroblastic proliferation in wounds with impaired healing.

Several authors have investigated the serum proteins in cirrhosis of the liver. Comparisons have been made between values in normal patients, patients with cirrhosis without ascites, and patients with cirrhosis and ascites. Ricketts (198) and Post and Patek (184) tabulated their results as follows:

TABLE III.

PLASMA PROTEINS IN NORMAL PERSONS, CIRRHOTICS WITHOUT ASCITES, AND CIRRHOTICS WITH ASCITES (198)

| | | PLASMA PROTEINS (gms%) | | | | | |
|---|---|---|---|---|---|---|---|
| | Number of Cases | Total Protein | | Albumin | | Globulin | |
| | | Mean | S.D. | Mean | S.D. | Mean | S. D. |
| Normals | 20 | 7.02 | 0.31 | 4.81 | 0.34 | 2.18 | 0.35 |
| Portal Cirrhosis without Ascites | 30 | 7.20 | 0.37 | 4.19 | 0.15 | 3.04 | 1.03 |
| Portal Cirrhosis with Ascites | 20 | 5.70 | 0.37 | 2.39 | 0.24 | 3.32 | 0.60 |

In the above series, the plasma albumin level in cirrhotics with ascites was consistently less than 3 gms%. The rise in globulin values were on the average higher in those patients who had ascites. An elevated globulin level may occasionally be of sufficient magnitude to raise the colloid osmotic pressure and perhaps lessen or even prevent the development of ascites and edema.

Post and Patek also expressed the opinion that a decreased plasma albumin level is essential to the formation of ascites. A decreased albumin level to a mean value of 2.3 gms% was present in 43 cases of cirrhosis with ascites; 28 cirrhotics without ascites showed an average albumin level of 3.7 gms%. Those with ascites had a mean globulin of 3.9 gms%, while those without had a globulin level averaging 3.7 gms%. Diuresis and loss of ascites in their patients was associated with an increase in the serum albumin, the mean value at diuresis being 3.1 gms% (S.D. $\pm$ 0.2 gms.), while ascites was rarely present when the serum albumin level was more than 3.5 gms%.

The fact that hypoalbuminemia plays a role in the formation of ascites has been stressed by others (23, 105, 109, 110, 120, 130, 140, 165). No absolute correlation exists, however, between the presence of ascites and a low-colloid osmotic pressure. The converse, however, is true, in that ascites is rarely found when

the plasma osmotic pressure is normal. Other evidence in support of the hypothesis that hypoproteinemia is associated with effusion formation is the presence of pleural collections of fluid with decreased serum protein levels and also of generalized edema in some cases. Thus, in chronic nephrosis with decreased serum protein levels, ascites is present commonly; generalized edema may also be evident.

The next problem of interest in relation to hypoproteinemia and ascites concerns the possible mechanism whereby decreased colloid osmotic pressure results in fluid accumulation. Kark (124) has attempted an explanation, which although it invokes a second mechanism, appears logical. In the presence of portal hypertension, protein depletion allows the depleted capillary endothelial lining cells to permit albumin under high pressure to pass through the mesenteric capillaries into the peritoneal cavity. High protein intake will restore the protein levels of the endothelial cells and albumin is prevented from passing through the capillary walls. Uniform agreement that ascitic fluid is simply a transudate from the splanchnic capillaries does not exist (117). Thus, although the proteins of ascitic fluid are electrophoretically similar to that of plasma, the elevation of portal pressure in cirrhosis may not be sufficient to account for the copious transudation that occurs; also, the amount of protein in most ascitic fluids is greater in concentration than that found in the superficial

edemas of congestion or hypoproteinemia. Nevertheless, Mankin and Lowell (149) express the belief that there is an approximate osmotic equilibrium between plasma and ascitic fluid during the unmodified formation and loss of ascites, and that a disturbance of this balance, in accord with Starling's hypothesis, results in a diffusion of plasma protein into ascitic fluid.

The problem of antidiuretic substances in the plasma resulting in ascites formation is a controversial one. Several substances have been claimed to be the antidiuretic factor whose elevation results in salt and water retention. Recent work in endocrinology, biochemistry and metabolism has shown older hypotheses to be incorrect.

Shorr and associates (210) have written that the hepatic vasodepressor ferritin (VDM) exerts an antidiuretic action. VDM, by acting on the posterior lobe of the pituitary gland, exerts its effect. They demonstrated large amounts of ferritin in the circulation of patients with cirrhosis, the nephrotic syndrome and congestive heart failure in association with edema, ascites and oliguria. Liver hypoxia may be the reason for the appearance of ferritin; the hepatic inactivation mechanism for VDM is impaired - this they feel explains ascites in cirrhosis and congestive heart failure. In the nephrotic, the underlying pathology is believed to be the fact that the kidney fails to form the VDM antagonist, VEM. Perusal of the literature fails to reveal any

evidence contradictory to this hypothesis.

The estrogens have also been implicated in an attempt to establish the mechanism of fluid and electrolyte retention leading to ascites. Preedy and Aitken (188, 189) investigated patients with hepatic, cardiac and renal disease with regard to the effects of estrogen on water and electrolyte metabolism. Nine patients with cirrhosis and ascites were given estrogens and a considerable sustained retention of sodium, chloride and water resulted. Estrogen administration to patients with cirrhosis without ascites or to patients with infectious hepatitis produced no difference in salt and water excretion to that in normal controls. Daily doses of estradiol benzoate produced marked sodium chloride and water retention in cases of constrictive pericarditis and in cardiac failure of other origin, but not in patients with peripheral venous obstruction, the nephrotic syndrome, nor patients with low plasma albumin and edema without renal disease. Because estrogens are inactivated in the liver chiefly, the authors postulated that the factor common to all those diseases which showed impaired salt and water excretion was a disturbance of hepatic circulation and not hepatocellular damage. This resulted in a decreased inactivation of estrogens by the liver, both the exogenously administered estradiol and that which occurs endogenously. In addition, mention is made of the fact that increased urinary titres of estrogens have been found in bioassay in acute and chronic liver disease. The fact that renal function tests revealed no abnormalities in the

above patients suggests that the kidney cannot be implicated primarily in the ascites accumulation, but that failure of hepatic inactivation of either normal or increased amounts of endogenous estrogens is of importance. Cameron (37), however, recently reported a study of patients with chronic liver damage in which no association could be found between increased urinary excretion of estrogens and the presence of ascites. But, one point should be noted with regard to his studies - only twelve patients were studied, and two of the four males who excreted increased amounts showed ascites. Perhaps in these patients estrogen metabolism was sufficiently and significantly altered to result in salt and water retention and ascites.

The posterior pituitary antidiuretic hormone, pitressin, has also been claimed to cause ascites accumulation. Physiologically, increased plasma sodium chloride appears to stimulate the osmoreceptors of the supraopticohypophyseal tract, which in turn stimulates the posterior pituitary to secrete ADH in increased amounts. Hydrated rats given urine extracts of patients with cirrhosis and ascites demonstrated antidiuretic effects similar to those produced by pitressin administration (63, 103, 105, 192). Liver extracts also possessed antidiuretic activity which confuses the situation. Also, the urine of rats with and without liver injury had antidiuretic activity, with no significant difference

between the two groups. Others have performed ADH assays on dogs using the urine of cirrhotics, concluding that antidiuretic substances apparently from the posterior pituitary can be detected in low concentration in 35 to 50 percent of patients with cirrhosis; some patients with ascites apparently excrete the hormone in higher concentration. But the role of ADH in the production of ascites is a minor one, (228); in fact, others express the belief that there is no evidence in their data for either decreased inactivation, persistent hypersecretion or increased renal tubular effects of endogenous ADH in edematous cirrhotics (20).

It was noted above that certain investigators have found the kidney function tests to be normal in patients with cirrhosis and ascites. (73). Controversy exists here too, however, for seventeen patients with liver cirrhosis were shown to have impaired renal function as evidenced by decreased glomerular filtration rate, decreased renal blood flow and decreased paraaminohippuric acid excretion (TmPAH) during the phase of ascites formation; these returned to normal with disappearance of ascites. The authors concluded that an important factor in diuresis is the re-establishment of normal kidney function which results in a physiological control of ascites (139).

The adrenal cortex and its hormones today exerts an important influence on our thinking regarding the mechanism of ascites. Several hormones have been isolated, and almost all possess varying ability to retain salt and water. The most potent of these are

desoxycorticosterone and aldosterone. The early literature dealing with the subject described antidiuretic substances, salt-retaining factors, etc. without mention of specific compounds. In recent years these compounds have been isolated in pure form and more complete investigations performed to determine their action. Patients with cirrhosis and ascites with congestive heart failure and with lipemic nephrosis have been shown to retain sodium and water to a greater degree than normal patients (144, 215, 217). This is part of a generalized phenomenon involving the colon, the kidney, the salivary and the sweat glands (15, 70, 76, 77); each shows a suppressed sodium excretion, demonstrating that some common factor is responsible for the impaired output. A hormonal mechanism has received attention, and today the balance of evidence weighs in favor of aldosterone.

The problem does not terminate with the isolation of the factor which results in sodium and water retention and potassium excretion in abnormal amounts. Increase of urinary corticoids having this action has been demonstrated by numerous investigators (31, 43). Further questions arise as to the reasons for this absolute or relative increase in salt-active hormones as well as their mode of action.

The liver is believed to metabolize many steroids, including estrogens, androgens and the adrenal cortical hormones. The

impaired liver of cirrhosis with ascites and of congestive heart failure probably is unable to perform the inactivation function adequately, and thus the sodium-retaining hormone accumulates with effects as described above (93, 138).

Blood estimations of aldosterone activity have also been carried out. These will be discussed further in the review of the problems associated with experimental ascites. Suffice it to state at this point that aldosterone levels fail to fall to low titres in response to an increase in the total body sodium in certain patients with hepatic cirrhosis and congestive heart failure as is the usual pattern in normal patients. This is probably an important factor in ascites and edema formation (65).

Papper and Saxon (175) have administered sodium chloride solutions of varying tonicity to patients with cirrhosis and ascites. Despite the presence of ascites and an increase in total body salt, these patients were able to excrete the excess. Hypotonic, isotonic and hypertonic saline infusions resulted in a similar response in patients with cirrhosis as in normal individuals. In fact, hypotonic infusions often resulted in an increased sodium excretion in edematous patients with cirrhosis. These results are obviously contradictory to what was discussed above.

Others have given 5% NaCl to cirrhotics with normal glomerular filtration rate and renal blood flow. Normal persons and cirrhotics without ascites excreted 12 to 54% of the administered

sodium and the rate of excretion increased markedly. Cirrhotics with ascites and/or edema, however, only excreted 0.2 to 10% of the infused sodium and their excretion rate showed minimal elevation only. This suggests some impairment of the renal mechanism for excretion of administered sodium in ascitic individuals; perhaps an increased tubular reabsorption occurs. (92). Merrill (160) suggested that in congestive heart failure, diminished cardiac output results in decreased NaCl and water excretion by the kidney as well as decreased RBF and GFR by contraction of the efferent arterioles. This may be due to the action of humoral substances elaborated by the adrenal cortex and pars intermedia of the posterior pituitary. Other stimuli may exist for the renal conservation of sodium during the accumulation of ascites and edema. These include the loss of large quantities of body sodium by repeated paracenteses, the reduction of plasma volume which occurs with paracentesis, and hyponatremia (86). In the final analysis, however, some common factor must be called upon to explain why these patients retain sodium and water in a generalized fashion - hormonal action seems the most logical, and aldosterone, by virtue of its physiological action, would appear to be the culprit. But, non-specific stress, as represented by any disease may determine the level of plasma antidiuretic activity. In one series studied, it was found that there was no relationship between the plasma antidiuretic level and the retention of water in patients with various diseases (219).

Portal hypertension secondary to obstruction of some part of the portal venous system, either intra-hepatic or extra-hepatic, has been claimed by numerous investigators to be the predominant cause of ascites in cirrhosis and other diseases (23, 122). Thus, fibrous tissue obstruction of the portal vein results in an increased capillary blood pressure in tissues drained by the portal vein with the transudation of fluid from the vascular compartment into the extracellular spaces and peritoneal cavity. Further evidence of the relationship between portal hypertension and ascites has come from portacaval shunt procedure results. A series of five patients with portal hypertension, cirrhosis and ascites were subjected to the operation. With a diminuation of portal pressure, their ascites disappeared; although marked peripheral edema developed in several associated with hypoalbuminemia, nevertheless their ascites did not recur (71).

Much evidence exists contradicting the predominant role ascribed to portal hypertension in the genesis of ascites. It is a well documented fact that effusions often develop with extreme rapidity. This is not compatible with the view that ascites is solely due to increased venous pressure; if fibrosis produced the accumulation, then it should come on gradually, in harmony with the pathological progression. Rather than fibrosis of the portal vein resulting in portal hypertension, Herrick (108) attributed the ascites to the communication of the arterial pressure to the portal system through dilated capillaries in cirrhosis.

A large series of cases of uncomplicated portal venous occlusion was examined at the Mayo Clinic (6). In most cases, no ascites was found; only five cases in the whole postmortem series showed occlusion of the portal vein as the cause of ascites. But, ascites does occur in cases of chronic portal venous occlusion, and so portal hypertension must be an important contributing factor in the development of ascites. Furthermore, a well developed hepatopetal accessory portal collateral circulation appears to be a determining factor in the prevention of ascites.

In summary, portal hypertension is no doubt of great importance in determining the localization of edema fluid to the peritoneal cavity; but chronic elevations of portal pressure may exist without ascites. Portal hypertension may contribute to ascites formation in which a critical elevation of pressure is present, especially in those cases where hypoproteinemia exists with a lowered plasma colloid osmotic pressure.

Low tissue resistance is undoubtedly a contributory factor to the abdominal localization of ascites. Local tissue pressure against small venules, capillaries and lymphatics within the peritoneal cavity is practically negligible. Thus, when appropriate other circumstances exist, ascites develops.

Both clinical and experimental evidence confirms that intrahepatic congestion is of extreme importance to the development of

ascites. Increased pressure in the hepatic veins occurs secondary to large numbers of disease processes wherein ascites is present. Thus, patients with congestive heart failure due to many causes, constrictive pericarditis, tricuspid insufficiency, inferior vena caval obstruction, hepatic vein thrombosis (Budd-Chiari's Syndrome), and hepatic cirrhosis very commonly demonstrate ascites, even in the presence of normal portal pressure. Thus blockage of the outflow tract of the liver, the hepatic venous system, is associated with ascites, rather than inflow tract obstruction, represented by the portal veins (146).

Madden and associates (146) injected 22 human livers with colored neoprene latex and examined the blood vessel arrangement. Included were 14 cases of cirrhosis, 10 of which had irreversible ascites; 3 had extensive liver metastases; one patient had bronchogenic carcinoma with ascites; 2 had congestive splenomegaly secondary to congestive heart failure and one had anasarca. The normal liver showed a uniform pattern of blood vessel distribution, with free communications between the portal and hepatic veins. In cirrhotics with irreversible ascites, the hepatic venous outflow bed was decreased, while the inflowing portal venous and hepatic arterial systems were increased. Cirrhotics without ascites or with reversible ascites showed a symmetrical decrease in all intrahepatic vascular systems, most marked in the hepatic systemic and portal venous radicles. The three patients with metastases

did not show any characteristic disturbance of intrahepatic circulation. Those with congestive hepatomegaly characteristically manifested an increased diameter and surface area of the outflow tract, without changes in the inflow system.

From this and other evidence, one may postulate that the pathogenesis of ascites is obstruction of the outflow tract of the liver. This is common to all conditions listed above, and may bemanifested in the liver by dilated central veins and sinusoids (208). In irreversible ascites, the cause of the obstruction is obliterative fibrosis; in reversible ascites, diffuse parenchymal edema produces temporary obstruction of the hepatic venous outflow. Venous stasis with hypoxic edema of the hepatic tissue is the underlying defect in constrictive pericarditis and congestive heart failure, while ascites secondary to extensive liver metastases may be the result of functional hepatic venous outflow obstruction, related to protein and electrolyte changes.

How does hepatic venous congestion lead to ascites formation? An increased filtration pressure occurs in outflow obstruction and the flow of hepatic lymph may be increased to up to thirty times the normal (95). In patients with ascites, the subcapsular and portal lymphatics are dilated often with lymph dripping from

the surface of the liver; in addition enlarged glands are often present at the hilum (199, 226). Further evidence for the liver as the source of ascites comes from examination of liver lymph and ascitic fluid. Ascitic fluid is usually clear and faint yellow in color as is liver lymph, while intestinal lymph is opaque; furthermore, the chemical composition of liver lymph and ascitic fluid are remarkably similar (95).

The deep lymphatics of the liver in man follow the course of the portal veins and bile ducts and drain toward the hilus. In the presence of ascites due to many and varied causes, the hepatoduodenal ligament contains a larger number of lymphatics; these are of larger diameter and possess thicker walls due to an increase in muscular, fibrous and elastic elements. The increased number is probably due to the opening up of potential channels in response to the demands of increased flow; the changes in size are probably due to venous stasis, intrahepatic portal hypertension, tissue destruction and inflammation (5). Thus, when the escape of fluid due to increased flow cannot be handled by the above changes in the lymphatics, ascites forms.

An increase in the permeability of small blood vessels has been ascribed importance in the pathogenesis of ascites. Fiessinger (80) has written that the mesenteric capillaries are more permeable in cirrhosis permitting ascites to form. Others (110, 149) have expressed the same opinion. Much contradictory

evidence, however, has been presented to disprove this hypothesis. If capillary permeability was a highly significant factor in the pathogenesis of ascites, then certain phenomena should be associated. Marked congestion and edema of the gastrointestinal mucous membrane should occur; in addition, the protein content of the ascitic fluid would be higher than is actually found in cirrhosis and congestive heart failure. The establishment of an equilibrium between lymph and plasma may occur, however, whereby the protein content may adjust to balance hydrostatic and colloid osmotic pressures (229).

Increased capillary permeability is probably of significance, however, in ascites secondary to bacterial, chemical or mechanical inflammation. One would include here cases of ascites secondary to malignant deposits on the peritoneum. In the presence of inflammation-provoking agents, the vascular bed of the peritoneum is opened more widely and increased capillary permeability results. The elaboration of a fluid high in protein and cell content occurs; edema of the peritoneum is evident, decreasing the rate of blood flow. In addition, the high protein content of the exudate results in further fluid and electrolyte shifts, and the rate of absorption of the ascitic accumulation is diminished (22).

The pathogenesis of ascites in peritoneal carcinomatosis is still an unsolved problem. Despite this, little investigation has been reported in the literature. Most assume that the implanted

malignant cells irritate the serosal lining of the peritoneum, and that the ascites is the result of exudation from capillaries secondary to changes in permeability induced by inflammation. Thus, one invokes the mechanism of increased formation of fluid with accumulation; diminished absorption, however, must be considered of importance as well. The main route of fluid absorption from the peritoneal cavity is through the diaphragm. Tumor infiltration of diaphragmatic lymphatics and of lymph nodes just above the diaphragm has been shown to block the absorption of particulate matter injected into the peritoneal cavity (113). Thus, one may assume that further absorption of lymph through these channels is impossible, giving rise to ascitic accumulations. One point of argument against this hypothesis, however, is the fact that lymphatic obstruction gives rise to chylous ascites, while in carcinomatosis one most often finds serous fluid or haemorrhagic effusion.

The mechanism of ascites formation has been dealt with at length. Several concepts have been described to evaluate the ultimate factors. From a review of the subject one must agree that no one single mechanism explains all cases of ascites. A combination of factors, operating in various degrees in different situations is the most logical way of explaining the pathogenesis of ascites (67, 120, 130, 200). Each disease and each individual

case must be evaluated in order to attempt to establish those factors which exert most influence in the production of ascites. In summary, a decreased GFR with renal retention of sodium, excess ADH with water retention, excess estrogens and adrenal steroids with salt and water retention, an elevated portal venous pressure, decreased colloid osmotic pressure due to hypoproteinemia, hepatic venous outflow obstruction with stasis and increased liver lymph extravasation, lymphatic obstruction, increased capillary permeability and possible still unknown factors probably all operate in varying degrees to initiate and maintain ascites accumulations.

## CHAPTER III.

## THE MEDICAL TREATMENT OF ASCITES

It was shown above that ascites is a sign of many diseases within each of which several factors may be operative resulting in the fluid accumulation. Therefore, when considering the medical management of the patient with ascites, one must take into account the nature of the underlying disease process as well as the factors that are probably operative in producing the ascites in the particular individual. Furthermore, the therapy of chronic ascites from the medical viewpoint shows features common to all cases despite their origin, while certain specific measures may be added in other instances.

A. General Measures:

1. Bed Rest: Putting the patient to bed during active treatment for chronic ascites is probably of value for several reasons. By this means, the strain on the body's already disturbed physiology is diminished. Impaired respiratory and circulatory dynamics are improved with the patient undergoing minimal physical exertion. In addition, the processes of repair are aided by rest.

2. Diet: A high carbohydrate, low protein and low fat diet was in vogue before 1940. Since that time, however, with further understanding of protein metabolism, a high protein diet has been

used; today, therefore, one attempts to feed the patient with ascites about 120 to 150 gms. of protein per day (203, 221). Positive nitrogen balance may be achieved by means of high protein feeding, but there may not be any correlated increase in the serum albumin levels. Evidently in chronic ascites due to liver disease the cirrhotic patient absorbs and retains food protein, but the mechanism for synthesis of serum albumin is impaired (185). Impending coma must be watched for in the cirrhotic and should it occur, the protein intake must be decreased immediately to low levels. The high protein feedings may not be tolerated well, and if so, intravenous amino acids may be given in order to achieve normal nitrogen balance in patients unable to eat a full diet (183).

A high carbohydrate intake, of the order of 365 gms. per day, is recommended. (179). In many diseases which lead to ascites, liver glycogen is depleted, and the high intake may aid regeneration of the hepatic parenchyma. In addition, carbohydrate is useful for its protein - sparing effects, especially valuable in these patients who lose protein in their ascitic fluid.

Fat intake should be restricted, especially in patients with liver disease, but should be of such quantity that, in combination with the above recommended protein and carbohydrate ingestion, a

a total of about 3500 calories per day is achieved.

Vitamins should be added to the diet, especially those of the B complex group and vitamin C. The value of these in human nutrition need not be reiterated. The value of choline and methionine addition to the diet is still controversial; these supplements, as well as crude liver extract, may, however, be given.

3. Salt Restriction: Patients who form ascites tend to retain salt and water in abnormal amounts. On the average, the uncompensated cirrhotic excretes only about 200 mg. of sodium per day, and it has been recommended that this be the amount ingested (203, 221). A low sodium diet has been shown to decrease the rate of ascites formation, regardless of the level of the serum albumin (74).

Others have recommended different quantities of sodium in the diet; Sherlock (209) feels that 0.5 grams per day is the level of intake to be achieved in cirrhosis with ascites. Eisenmenger and associates (69) found that the average critical intake in 13 patients with cirrhosis and ascites was 1.2 grams of sodium chloride per day. On this regime, ascites formation ceased for three months in twelve of the thirteen cases; eight reformed their ascites when put back on a normal sodium intake at the end of this time.

In common with all clinical states where water excretion is diminished, patients with ascites should be on a restricted fluid

intake - 1500 to 2000 ccs. per day is usually recommended, with increased intake in hot weather or under other circumstances where fluid loss may be accelerated.

The value of a low salt intake in diminishing ascites formation may be due to its action in depressing ADH formation by the posterior pituitary. Thus a diet low in salt may result in an increase of salt-retaining hormone elaboration by the adrenal; furthermore, a decreased blood volume and GFR contribute to increased stimulation of volume receptors. The end result is a decreased production of ADH, with increased salt excretion without water retention and intoxication (67).

4. Diuretic Agents: The mercurials are extensively used in the management of ascites. They may be administered orally or parenterally and are very often effective in increasing salt and water excretion. Recently diamox has been used with good results, but acid-base balance disturbances may occur.

Potassium and ammonium chloride are also useful diuretic agents. Care must be exercised in using the latter, however, for increased blood ammonia levels may precipitate hepatic coma in cases of decompensated cirrhosis.

Recently the eation-exchange resins have been used. Good results have been reported in promoting diuresis (85, 94), but manifestations of portal-systemic encaphalopathy are frequent in patients given ammonium resins, while hydrogen resins may produce hypokalemia and acidosis.

Loss of body sodium through diuresis and diminished intake is, however, a double-edged sword. Hyponatremia with manifestations of the low-salt syndrome must be guarded against and treated when it arises. In addition, potassium deficiencies may occur with some diuretics due to increased urinary excretion of this electrolyte (196).

5. Osmotic Diuretics: Several agents have been tried in an attempt to promote salt and water excretion. Dextran, hypertonic dextrose, polyvinylpyrollidone and gelatin all produce a diuresis; however, they remain in the circulation for too short a time to exert continuing benefit, while PVP is undesirably deposited in reticulo-endothelial, liver and kidney cells (229).

Intravenous salt-poor human albumin has been used extensively in the management of cirrhotic ascites with good results (51, 75, 106). Prolonged administration is necessary, however, even before noticeable effects occur, and maintenance doses of albumin must be given for continuing benefits. Kunkel and associates (132) noted that patients with urines of high antidiuretic titre needed larger amounts for a longer period of time.

Many failures, perhaps equal to the number of successes, have been reported with intravenous albumin therapy. Armstrong (3) suggests that it probably will not work where there is severe mechanical obstruction to portal flow; here, the increased serum albumin levels would be balanced by an increased ascitic fluid albumin concentration and the effective colloid osmotic pressure

would therefore remain the same.

Intravenous albumin increases the plasma volume and this has been shown to have harmful effects in the presence of cardiovascular disease; rupture of esophageal varices with hematemesis may also occur. (106).

Increased transfer of albumin from the serum to the ascitic fluid also takes place, so that sustained diuresis and disappearance of ascites do not occur from single or multiple injections of albumin (178). It is effective in some patients, however, and this is perhaps due to elevation of serum albumin levels with increased colloid osmotic pressure and increased urine sodium excretion secondary to improved GFR and RPF.

Volwiler (229) has suggested that albumin therapy not be started for at least one month after other treatment has begun. In his experience, those patients who respond well to this form of management usually will improve on conservative dietary regimes. In those cases where rapid clearing of ascites is needed, however, serum albumin may be given from the outset.

6. Hormones and Hormone-Suppressing Agents: Cortisone has been used in the management of patients with portal cirrhosis. An improved plasma protein concentration may result, but no specific effects on other liver function tests nor improvement in hepatic architecture result (243).

Prednisone or delta-cortisone has also been used in the therapy of cirrhotic ascites (35, 82, 203). About fifty percent of patients were benefitted from this treatment as shown by disappearance of ascites, and edema, polyuria beginning about the third or fourth day after instituting treatment. Unimproved cases did not show a significant response to prednisone, while benefitted patients were put into negative sodium balance and liver function tests, especially plasma protein levels, improved. Complications of this steroid include hematemesis, which may prove fatal, while the drug must not be used in the presence of diabetes, gastro-duodenal ulcer, and pulmonary tuberculosis unless concomitant anti-microbial therapy is used. Exogenous corticoid may act through inhibition of endogenous aldosterone secretion.

Although good results have been reported, nevertheless others feel that ACTH and cortisone are contra-indicated in the management of cirrhosis. (183).

Amphenone, which suppresses thyroid and adrenal cortex function, has been used in patients with cirrhosis and ascites. The drug appears to inhibit synthesis of the adrenal cortical steroids, including aldosterone. Although sodium diuresis may occur, nevertheless toxic neurologic sedative effects are associated, and amphenone therefore has limited usefulness (240).

Paraaminosalicylic acid has also been tried in the treatment of non-tuberculous ascites. Twenty-five patients were given intraperitoneal PAS injections, with good results in 60%. The drug appears to act through antagonism of ACTH and thus adrenal inhibition. (181).

7. Blood Transfusions: Used cautiously in patients with already strained circulatory and respiratory systems, repeated transfusions of whole blood or of packed cells may be helpful in treating the anemia, hypoproteinemia and hemorrhagic tendencies often associated with ascites.

8. Abdominal Paracentesis: When other measures have been tried and have failed, or when distension impairs digestion, respiration and circulation, or for diagnostic purposes, paracentesis must be used. Some cures of ascites result from repeated abdominal tapping, probably related to the formation of omental adhesions and the gradual development of collateral circulation at the sites of puncture. (234).

Abdominal drainage certainly relieves the pressure effects exerted by the fluid, at least until reaccumulation occurs. Large amounts of protein and electrolytes are lost, however, with harmful results. After paracentesis, the serum protein concentration decreases due to loss of protein from the blood into the reforming ascites. Loss of fluid and electrolytes results in hemoconcentration, with a secondary increase in plasma protein values (38).

Plasma sodium depletion may result with hyponatremic manifestations such as cerebral and cardiovascular disturbances (167). In addition, hyperkalemia may be associated with harmful cardiac effects. Other hazards of paracentesis include puncture of collateral veins, peritoneal infection and shock due to rapid removal of ascites producing pooling of blood within the splanchnic bed.

B. Specific Measures

The program of therapy outlined above applies for the most part to ascites due to all causes. At this time, however, something additional must be said about specific regimes which may be used in medical treatment of abdominal effusions.

Digitalis and other cardiotonic agents are necessary often in the management of cardiac causes of ascites. The prevention of further hepatic injury due to toxins such as alcohol is strongly recommended in the management of cirrhosis.

Ascites due to carcinomatosis of the peritoneum may often be ameliorated by a variety of chemical agents. Radioactive colloidal gold, triethylene thiophosphoramide (Thio-TEPA) and 2-chloro-2'-hydroxydiethyl sulfide (hemisulfur mustard) have all been used in an attempt to treat neoplastic effusions.

Radioactive colloidal gold, given intraperitoneally in doses of 100 to 150 millicuries, results in decrease or disappearance of ascites in about 50% of cases treated with $Au^{198}$.

The beta particles emitted account for most of the radiation effects; penetration by this form of radiation is slight, and so the method of treatment cannot be expected to be very effective on large bulky metastates. Several theories attempt to explain the mechanism of action of gold. Superficial radiation damage with fibrosis of the tumor surface, production of an inflammatory reaction with resulting obliteration of the free peritoneal cavity, a selective tumoricidal effect on free cells in the ascites, and the carriage of radiogold to the regional nodes with control of the neoplasm there and relief of lymphatic obstruction, may all play a part in the beneficial effects which may occur (42, 119).

Thio-TEPA, given intraperitoneally, may act directly on the tumor nodules; once again, about 50% of patients benefit from this treatment (13).

Hemisulfur mustard is administered intravenously by which route it produces inflammation and thrombosis of the vein into which it is injected. Eight of thirteen patients treated with this drug were benefitted as was shown by a decreased accumulation of ascites for from two to ten months (207).

Common to all agents used in the chemotherapy of malignancy, these drugs produce toxic side effects. Nausea, vomiting, malaise and weakness often occur; dangerous manifestation of toxicity, such as depressed hematopoiesis and liver and kidney

impairment must be watched for and appropriate measures taken to combat them and prevent further damage.

C. Evaluation of Medical Therapy

From practical experience and statistical analysis, it is realized that although intensive medical treatment may be given, not all patients will show benefits therefrom in terms of decrease or disappearance of their ascites. Indeed, Sherlock writes that only about one-third of patients with cirrhotic ascites improve. (209); Patek and associates (179) found that in about 50% of their patients the ascites disappeared. At the end of one year, about 65% of medically treated patients are alive, with 50% at the end of 2 years, and about 30% at the end of 5 years. Spontaneous disappearance of ascites occurs in approximately 7% of patients (193).

Although intensive therapy should be given for at least two months before cirrhotic ascites is considered intractable (229), nevertheless the above statistics indicate that a very high percentage of patients need some other type of treatment. This is the point where the surgeon enters the picture, being called upon to treat the approximately 50% of all patients with chronic ascites. Not all of these can be exposed to surgical intervention, however, for their general condition related to the progress of their disease very often contra-indicates anesthesia and operation. The problems associated with the surgical treatment of ascites will be discussed in the next chapter.

CHAPTER IV.

## THE SURGICAL TREATMENT OF ASCITES

Surgeons have attempted to drain ascitic collections permanently since the late Nineteenth Century. Numerous reports have appeared in the literature, mainly of small series of cases, employing a wide variety of methods. None have, however, proven uniformly successful, and so, even today, attempts continue to try to find some technique whereby these patients may be benefitted permanently.

It would be useful at the outset to classify in general terms methods that have been used for drainage purposes. These include operations:

1) to provide external drainage

2) to improve collateral circulation

3) to provide internal drainage

4) to combine both improved collateral circulation and internal drainage

5) to interrupt hormonal mechanisms of production of ascites

6) to decrease the arterial inflow of the portal venous system

7) to remove pelvic tumors

### The External Drainage of Ascites

Drainage to the exterior from the peritoneal cavity has been established in two ways; first, directly from the peritoneum

through the abdominal wall to the exterior, and second, by use of the urinary tract.

Caille (36) established permanent drainage via a cannula to the external surface of the abdomen, placed in the midline suprapubically, and with a detachable cap allowing intermittent release of ascites; this procedure was, however, only used successfully in two reported cases.

Recently, Magrath (148) placed a tube of acrylic plastic into the anterior abdominal wall, anchored to the peritoneum suprapubically, in one case of hobnail cirrhosis. He also resected half of the omentum and sutured the rest to the roughened parietal peritoneum. By opening the screwed-on sealing head, he was able to release the ascites, with disappearance of the anasarca and improvement of kidney function in his patient.

Kirschner (125) recommended the establishment of a subcutaneous-dermic fistula for drainage of ascitic accumulations.

The establishment of a peritoneo-bladder fistula to drain ascites has been used by Rosenstein (1941) and Dziembowski (1924); the results of this procedure have been reviewed by Lotheissen (142).

Mulvany (164) also used the bladder for drainage purposes in both carcinomatosis peritonei and hepatic cirrhosis. By means of a plastic catheter anchored to the flank of the peritoneal cavity and introduced into the bladder, he has reported successful

drainage of ascites. Cases must be selected, however, for in those patients with more than little malignant growth, the catheter becomes blocked by tumor..

Ferguson (78, 79) has combined right nephrectomy with anastomosis of the ureteral stump. In a total series of 5 cases, one died of peritonitis, while the others were rendered free of ascites, although two of these died of hemorrhage from esophageal varices. No disturbance in blood proteins occurred in his patients due to constant loss of ascites.

Methods of Improving the Collateral Circulation

With both intrahepatic and extrahepatic portal venous obstruction, collateral circulation develops; in the former the collaterals are hepatofugal, while they are hepatopetal in the latter (204).

The hepatofugal collaterals include:

a) Veins in the gastrointestinal tract at the junction of absorbing and protective epithelium.

i) gastroesophageal - these shunt blood from the left gastric (coronary)vein via the inferior hemiazygos, the diaphragmatic and the azygos veins into the superior vena cava.

ii) hemorrhoidal - transfer blood from the inferior mesenteric (superior hemorrhoidal) vein via the middle and inferior rectal veins into the inferior vena cava.

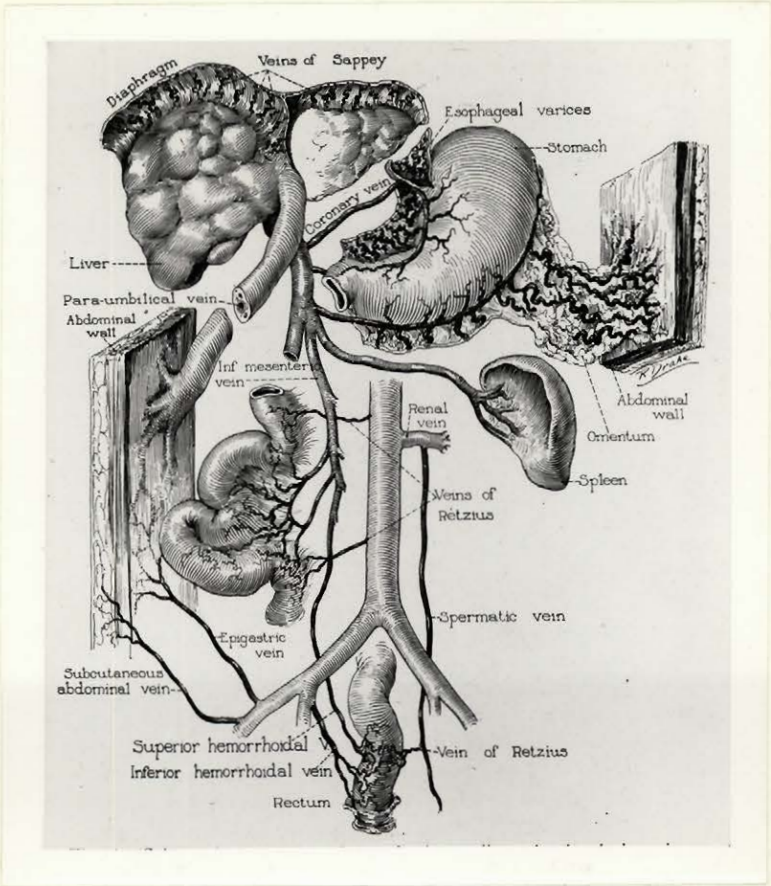


FIGURE 1.

Collateral Circulation in Portal Cirrhosis.

(Vascular Lesions of Portal Cirrhosis, A. H. McIndoe, Arch. Path. & Lab. Med. 5: 23-42, 1928).

b) Veins occurring at the site of obliterated fetal circulation, known as the accessory portal system of Sappey - these include the paraumbilical veins in the falciform and round ligaments which unite the epigastric and internal mammary veins with the azygos vein via the veins of the diaphragm; the venous channels of the

thoracoabdominal wall and the caput medusae are part of this group.

c) Veins in the abdomen at the sites where the gastrointestinal tract and glands derived therefrom become retroperitoneal in their development or adhere to the abdominal wall due to pathological processes (veins of Retzius.) These can arise from the duodenum, omentum, spleen, pancreas, small intestine or colon and establish communications between the portal circulation and the ascending lumbar, azygos and renal veins, and rarely via the adrenal vein.

Within the liver, collaterals may also develop through anastomoses between the smaller branches of the portal and hepatic veins.

The hepatopetal collaterals of extrahepatic portal obstruction are:

a) the deep cystic veins

b) the epiploic veins of the lesser omentum, hepatocolic and hepatorenal ligaments

c) The veins in the wall of the common bile duct

d) The diaphragmatic veins

e) The veins in the suspensory ligament of the liver

f) the paraumbilical veins

Because of the prominent interest in portal-systemic anastomosis in the treatment of portal hypertension, much work has been done in recent years to investigate further the possible routes of collateral circulation. Anastomoses have been found between the portal vein and the vertebral plexus, the coronary and left renal

veins, the veins of the gastric fundus and lower esophagus with the pulmonary and pericardial veins, the splenic and left renal veins, the splenic and hemorrhoidal plexus of veins and between the superior mesenteric and right renal veins (62).

Various procedures have been used to establish additional collateral circulation. These include omentopexy, visceropexy, ligation of vessels, anastomosis of vessels, and other non-specific procedures, such as laparotomy or some non-related surgical procedure.

Omentopexy, whereby the omentum is fixed to a portion of the abdominal parietes, has been used by several surgeons in an attempt to establish improved collateral circulation and thus prevent ascites. Talma was the first to use the procedure in 1889 (224), but Drummond and Morison first reported anastomosis of the peritoneum and omentum inorder to establish vascular channels to prevent the development of ascites in cirrhosis (64). From that time on, various modifications of the procedure were developed, some of which are shown in Figure 2.

Reports of results of omentopexy have appeared in the surgical literature through the years. Eliot and Colp, in 1919 (72), described fifteen cases they had operated on, seven of which showed definite benefit from the procedure for periods from three months to three years. They also note the work of

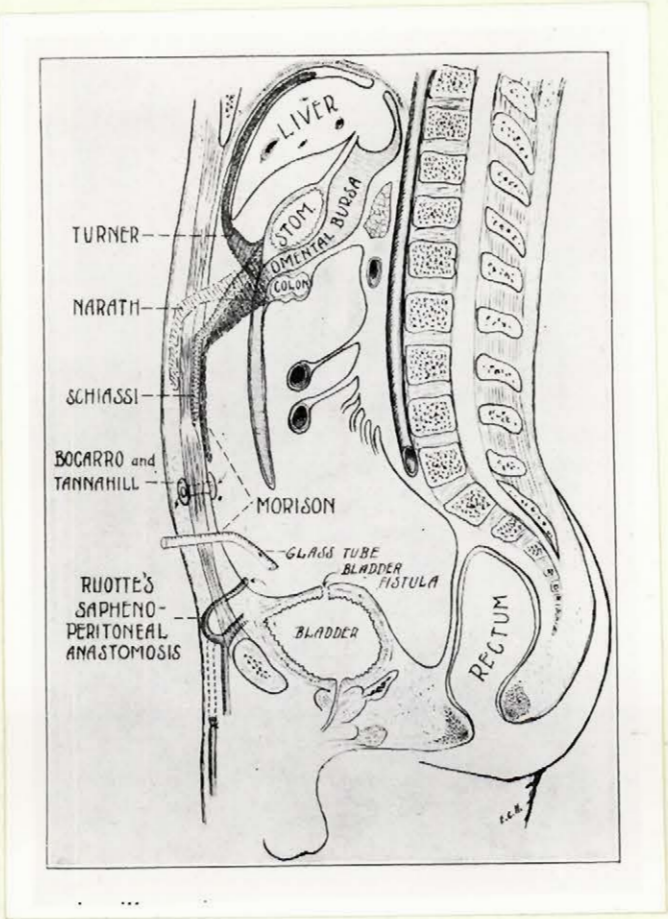


FIGURE 2.

Some Surgical Methods of Treating Ascites.

("Cirrhosis of the Liver," E. C. Henrikson, Arch. Surg. 32: 434, 1936.)

Bunge and White; the former reported 273 cases, of which 45.4% were either improved or cured of ascites due to cirrhosis; the latter reported 227 cases, 50.3% of which showed improvement or

cure. W. J. Mayo reported improvement in 24 of 28 cases of cirrhotic ascites treated with omentopexy (151). Strode (222) implanted the omentum into the anterior abdominal wall to establish epigastric-gastroepiploic collaterals; only two of eight cases no longer required paracentesis. Grinnell also reported a small series of cases in 1935; of twenty-three operated cases, and with an operative mortality of 27%, a total of 41% of patients were either improved or completely freed of symptoms (99). Cates was more sceptical of omentopexy in that of 38 cases operated on for cure of ascites, 42% died within two weeks of operation, and 68% were dead within six months; indeed, he believed that the prognosis after operation for patients with cirrhosis and ascites was no better than if medical treatment alone had been used. (39).

The most recent modification of omentopexy is that devised by Kopf (128). From anatomical studies he found that the rich venous and lymphatic plexus of the pelvis around the rectum and genitourinary tract could be used to establish improved collateral circulation. (Figs. 3 and 4). Accordingly, he anchored the omentum in the prevesical space extraperitoneally as far down as the bladder neck. Two cases of cardiac ascites were improved by this procedure. One end of the rectus muscle with its blood vessels and nerves intact has been sutured to the peritoneum with relief of ascites in two cases (50).

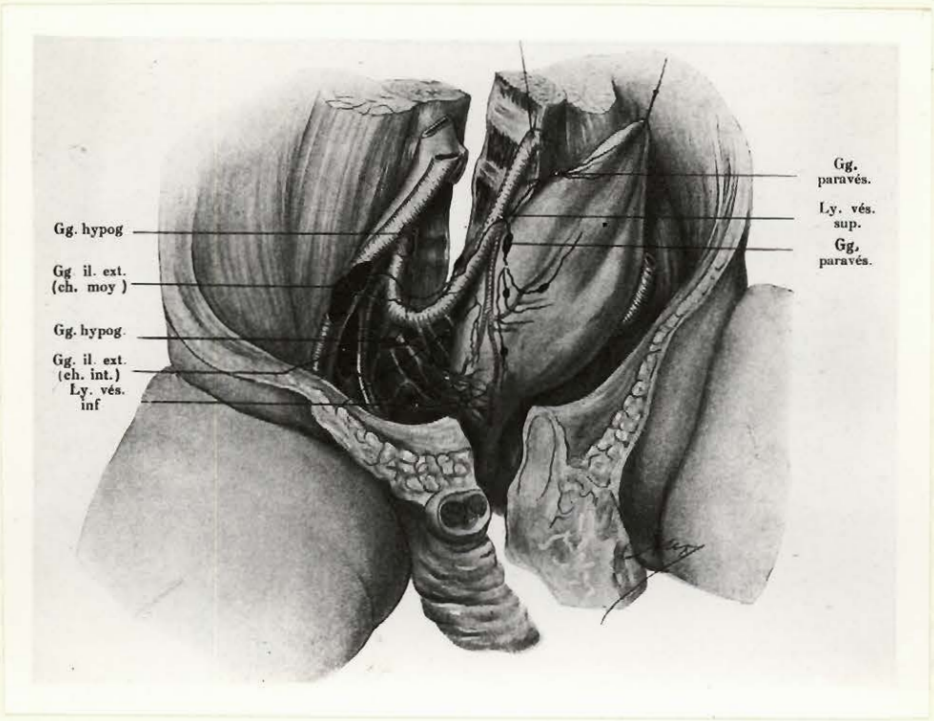


FIGURE 3.

Lymph Trunks in Region of Anterior Wall of Urinary Bladder.

(Anatomie des Lymphatiques de L'Homme. H. Rouviere, Masson et Cie, Editeurs, 1932, p. 380).

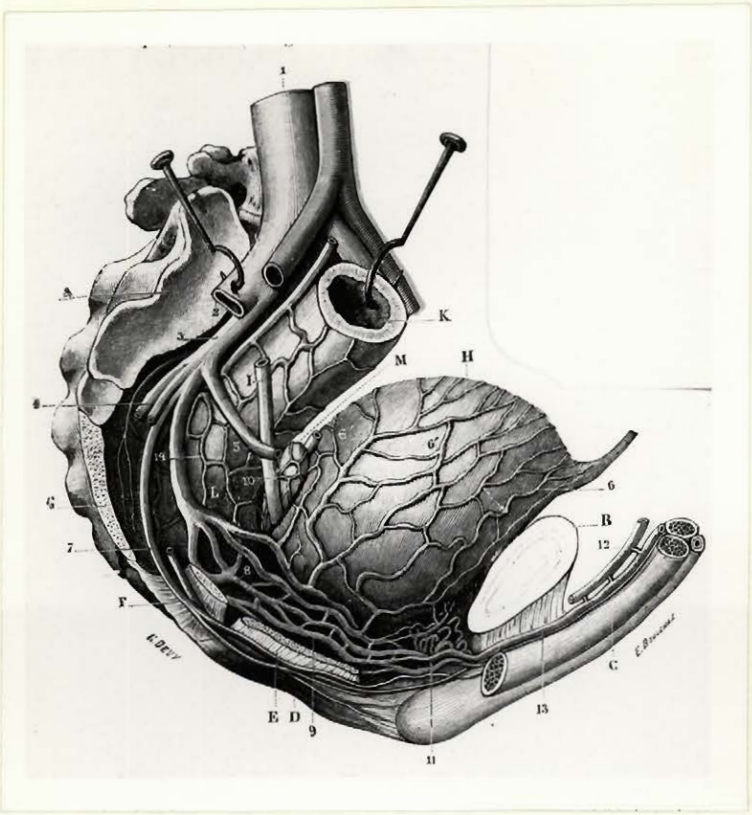


FIGURE 4.

Veins of Pelvis in Man

(Traite D'Anatomie Humaine, L. Testut, 7th Ed. Vol. 4. Librarie Octave Doin, 1923, p. 486)

Visceropexy has also been used to establish additional collaterals. Otto (174) reported three cases of hepatic cirrhosis whose ascites did not recur following hepatopexy. Splenopexy, testicular transplant and excision of patches of peritoneum have also been used, as shown in Figure 5.

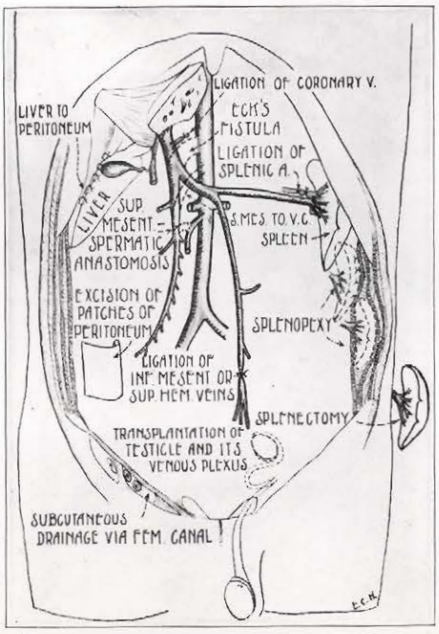


FIGURE 5.

Further Surgical Procedures in the Treatment of Ascites.

(Cirrhosis of the Liver, E. C. Henrikson, Arch. Surg. 32: 433, 1936).

Ligation of vessels to hasten the formation of collateral venous pathways has also been tried; Moynihan ligated the inferior mesenteric vein, while Mayo combined inferior mesenteric or superior rectal vein ligation with epiplopexy in the treatment of ascites (107).

Anastomosis of the vessels of the portal to the systemic venous circulation has been used to alleviate ascites. Borgoraz (32) and Ody (73) both anastomosed the superior mesenteric vein to the inferior vena cava; Ball cured the ascites in one patient for eight months by saphenous - sigmoidal veno-venostomy (8).

Portacaval and splenorenal shunt operations have been used in an attempt to relieve the intractable ascites of hepatic cirrhosis. Blakemore (21) was successful in alleviating ascites in some cases; he believed that ascites was an indication for the shunt operation only when it was so severe as to lead to wasting of the patient. Eisenmenger and Nickel (71) reported a series of five patients treated by end to side portacaval shunt whose portal hypertension and ascites disappeared after operation, although some developed marked peripheral edema associated with hypoproteinemia. They noted that ascites may occur temporarily after operation and attributed this to interruption of the lymphatics of the portahepatis with flow of lymph directly into the peritoneal cavity or else to lymphatic blockage with lymph

exudation from the hepatic surface; with reestablishment of continuity, the ascites no longer forms. In another series, four of seven operated cases showed no recurrence of their ascites for a period of two to six years; all of these patients excreted an increased urinary sodium and had an increased serum sodium in the postoperative period. Perhaps the disappearance of ascites was related to improved liver function with further metabolism of aldosterone, thus leading to improved salt and water excretion (197). The negative sodium balance associated with disappearance of ascites after shunt procedures has also been noted by others; although sodium excretion is increased, nevertheless a low salt intake must be maintained until the patient demonstrates the ability to excrete sufficient urinary sodium to be in normal balance (100).

By means of a side to side portacaval shunt the portal vein is left in continuity with the low pressure vena caval system at both the splanchnic and the hepatic ends. Thus, part of the hepatic artery blood drains via the natural intrahepatic arterioportal (formed in cirrhosis) and artificial portacaval anastomoses. This technique would help to overcome the hepatic venous outflow block so important in the etiology of ascites. Welch and coworkers (235) have performed the operation in six patients with intractable ascites. The fluid accumulation has been checked for short follow-up periods of 8 months to 2 months; liver

function tests have shown improvement, and the patients are on a normal salt intake.

Whipple (239) has also reported portacaval and splenorenal shunts in cirrhotics with ascites; some did lose their ascites, but the shunts were done primarily for bleeding varices rather than for chronic ascites. This agrees with Linton, who feels that chronic ascites without varices is not a satisfactory indication for the operation. (204). This agrees well with Macpherson who, on the basis of his results with porta-systemic venous anastomosis in cirrhosis where ascites was the main presenting symptom, concluded that surgery had no place in the treatment of ascites (145). Hughson pointed this out over thiry years ago when he found that surgical treatment for the purpose of establishing collateral circulation was perhaps not even of slightest benefit in portal cirrhosis with ascites. On the basis of 26 cases treated by simple laparotomy, scrubbing of the peritoneum and liver, omentopexy, cholecystostomy, splenectomy and painting of the liver with iodine, he arrived at his conclusions. Furthermore, he pointed out that in chronic ascites, the peritoneum is markedly thickened and non-absorbing (116).

One other point must be made before concluding this discussion of improving collateral circulation as a means of relieving ascites. In principle, although heroic measures are sometimes indicated in surgical practice, the poor prognosis of

patients with cirrhotic or cardiac ascites, their limited ability to withstand extensive operative trauma, and the high morbidity and mortality associated with portal-systemic venous anastomosis, would all appear to contra-indicate such a procedure. If methods of improving collateral circulation which are less traumatic may be used with a moderate hope of success, then these should be considered initially. Therefore, omentopexy, which apparently will benefit about 50% of patients with cirrhosis and ascites, and which is a relatively innocuous operation, should be used first; shunt procedures should be used as life-saving measures, that is, primarily in patients with bleeding esophageal varices.

Operations to Provide Internal Drainage of Ascites

Numerous techniques have been devised to provide internal drainage of ascitic accumulations. Each attempts to transfer fluid from the peritoneal cavity back into the circulation so that the body may use to its own benefit the protein and electrolyte components which otherwise are lost for the most part through sequestration in the ascitic collection.

Peritoneosaphenous anastomosis was first used by Routte in 1907 (Fig. 2); it was again used by Bernheim in one patient who died eight days later of morphine poisoning (19). Button reported venous-peritoneal anastomosis in a child with post-traumatic chylous ascites in whom success was obtained (33).

Rather than direct anastomosis, Schnee has interposed a vitallium button anchored to the peritoneum and with a side-arm implanted into the saphenous vein, with "varying degrees of success.....and a number of failures." (206).

The disadvantages and reasons for failure of drainage with this procedure are numerous. The anastomotic site may be covered over by peritoneum, or the omentum or bowel itself may block the drainage orifice; thrombosis of the vein often occurs, or it may be occluded by surrounding fibrous fascial sheaths. Nevertheless, from 1909 to 1936, forty-two cases of saphenoperitoneal anastomosis were reported in the literature, twenty of which were improved (107).

Button-like prostheses have been tried in an attempt to drain ascites from the peritoneal cavity to other areas where lymphatic absorption might return it to the general circulation. The work of Boccaro and Tannahill is shown in Figure 2. The review of some of the materials used, the types of cases treated and the results of such implantation may be seen in Table IV.

Examination of these results would indicate that about 50% of all patients treated by means of plastic or glass button drainage into either the subcutaneous tissues of the abdominal wall or into the space of Retzius are benefitted. Although the underlying disease is unaltered, which in effect determines the

TABLE IV.

"BUTTON" PROCEDURES FOR INTERNAL DRAINAGE OF ASCITES

| Author | Materials Used | Patient Disease | Results |
|---|---|---|---|
| Chalmers et al (41) | Leucite or glass button | 12 chronic alcoholism with cirrhosis<br>2 postnecrotic cirrhosis<br>1 unclassified cirrhosis<br>1 congestive heart failure with probable cirrhosis<br>1 Chiari syndrome (hypernephroma) | 6 postoperative deaths. 11 survivors - recurrent ascites within 2 weeks to 14 months; 5 benefitted by operation. No functioning buttons in 10 autopsied patients - plugged by fibrin, omentum, subcutaneous pseudoperitoneal cavities in 6 cases |
| Crosby & Cooney (48) | Glass button | 5 cirrhosis<br>1 chronic constrictive pericarditis | 1 postoperative death. 4 benefitted - no ascites, but edema lower abdomen and thighs. 1 (?) benefit - perhaps medical treatment cured patient |
| Kolb and Lorbek (126, 127) | Palladon button into space of Retzius | 13 cirrhosis<br>5 carcinomatosis | 5 excellent results - 3 cirrhosis, 2 carcinoma. 13 died within 6 weeks postoperatively. |
| Lane (133) | Glass spool | 7 cirrhosis | 2 failures. 3 fair to moderate improvement. 2 excellent benefit |
| Parker & Breckler (176) | 6 perforated polyethylene tubes from peritoneum to subcutaneous tissues | 2 cirrhosis | Drained ascites until death from hepatic failure. |
| Paterson (180) | Glass button | Several cases malignant ascites and cirrhotic ascites | Marked decrease in distension and relief to patients |
| Steinhardt & Saexinger (220) | Plastic button into space of Retzius | 1 posthepatitic cirrhosis<br>1 carcinomatosis | Needed paracentesis 10 days postoperatively only |
| Welch (236) | Glass button | 2 cirrhosis | Failure |

prognosis of the patients with chronic ascites, nevertheless relief from the harmful effect of distension, without loss to the exterior of important electrolytes and proteins, may be achieved in a significant proportion of cases. Causes of failure are numerous, only some of which may be eliminated; thus, plugging of the perforations with omentum may be prevented by omentectomy, but fibrin or malignant obstruction may result in unavoidable failure. In addition, the formation of a thick fibrous-walled subcutaneous space or of a pseudoperitoneal cavity at the site of the button's attachment will preclude further ascitic fluid drainage and absorption. Complications of the procedure are rare however, including such things as wound disruption or infection, ascitic fluid fistula and the more common occurrence of subcutaneous edema extending down from the lower abdomen to the thighs. As the mortality ratesfrom such procedures are low as well, and as probably 50% of patients are helped by the operation, it has much to recommend its use.

The drainage of ascitic fluid through lymphatics at a distance from the peritoneum and not directly draining the abdominal cavity under normal conditions has also been developed. Handley was the first to place silk sutures from the abdominal cavity into the subcutaneous tissues through the femoral canal for drainage purposes (107). Behan also used this technique success-

fully in two cases; he also paraffined the excised internal saphenous vein and sutured pieces of it to the peritoneum, with the other end being anchored to the subcutaneous tissues of the abdominal wall, the perirenal tissues and the retroperitoneal pelvic tissues. He did not observe sufficient cases over a long enough period of time to allow evaluation of his technique (14). It would appear, however, that the principle of establishing and using auxiliary lymphatics should be successful in draining ascitic accumulations, that is, until these lymphatics become blocked either by fibrin or tumor cells or else by thrombosis.

Methods which Combine Improved Collateral Circulation and Internal Drainage.

Tannahill (225) sutured the omentum to the upper part of the posterior rectus sheath for purposes of improving collateral circulation; he also implanted two Paterson buttons to create a peritoneal-subcutaneous fistula. Only one case report is published; this patient required only one paracentesis ten days postoperatively.

Lord (141) has combined excision of a six-by-six inch layer of fascia exposing the abdominal muscles as well as excision of Scarpa's fascia to expose the superficial fat with the insertion of a Crosby-Cooney button in an attempt to get lymphatics of the muscle to absorb ascites; if the omentum is found to be long

enough to perhaps plug the button, it is also removed at the time of operation.

The most recent operative procedure to attract attention is that devised by Neumann and associates (168), and called ileo-entectropy. After three revisions, the method they currently employ is omentectomy, gastrostomy, exclusion of the terminal 15-18 inches of ileum, with entectropy of this segment. Maintaining the blood supply of the excluded portion of ileum, they open it near the attachment of the mesentery and attach it, serosa to peritoneum, to the posterior abdominal wall. The caecum and proximal ascending colon are resected, with closure by end-to-end ileo-ascending colostomy. Of a total of ten patients with cirrhosis and ascites, five died within three weeks postoperatively of acute hepatic necrosis and massive esophageal bleeding; one patient was lost to follow-up. The four survivors have not required paracenteses, although two had recurrence of a small amount of ascites for periods of follow-up of five weeks, six months, six months and one year. Both absorption through the ileal mucosa and systemic-portal collateral circulation appear to be important in drainage of ascites by this technique. Several criticisms may be levelled at the authors, however, in their use of this operation. Firstly, although it is granted that the prognosis of their patients was not good in view of their underlying disease, nevertheless 50% of cirrhotics with ascites should not die of their disease within such a short time after surgery. Obviously, the severity of the

operative trauma must have played a large part in their deaths, and therefore, the operation is not sufficiently innocuous to be used in all cases. Secondly, ignoring the fact of protein absorption for the present, electrolyte and water absorption must be considered. A dynamic equilibrium exists between extravascular sodium and chloride and that which is intravascular (191). It would appear that resorption through the isolated everted loop may be limited by this factor, and that perhaps complete absorption of ascites cannot occur. Furthermore, in cases of ileal diversion of the urinary stream, there is only little if any tendency to electrolyte disturbances; although the urine may remain in the loop for long periods of time, very little is absorbed (2, 66). This would tend to negate the value of the absorptive action exerted by the ileal mucosa. The phenomenon of protein absorption is more complicated. Proteins are usually absorbed as amino acids, but some investigators have demonstrated naturally occurring proteins in portal blood and lymph, and some protein complexes must pass through the bowel wall as evidencedby thyroid extraction absorption. In addition, amino acids are absorbed by an active and selective mechanism, there being a limiting concentration above which the absorptive rate is constant (129). This causes doubt about absorption through the bowel wall as the effective mechanism of action of the operation, and that

perhaps they have merely added to the long list of procedures designed to improve collateral circulation. In addition, the mortality of the procedure, as well as the possible complications of necrosis of this separated loop of bowel through impairment of its precarious blood supply or intestinal obstruction due to twisting or kinking of other loops of bowel by the excluded ileum's mesentery, all must be considered before using the operation to surgically treat ascites.

In theory, if patients who have either operative procedure performed improve in a significant number of cases, then operations which combine both improved collateral circulation and internal drainage should lead to still better results. Practical experience has failed to corroborate this, however; perhaps a better understanding of the mechanisms which lead to ascites formation will ultimately show why such is the case.

Operations to Interrupt Hormonal Mechanisms of Ascites Formation

A better knowledge of the adrenal cortex and its steroids has led to removal of the adrenals in an attempt to ameliorate ascites. As discussed above, many believe that the retention of salt and water which occurs in ascites is related to excessive production or diminished destruction of aldosterone; removing the source of endogenous aldosterone should therefore improve ascites.

Marson was the first to report a case of hepatic cirrhosis with ascites treated by bilateral adrenalectomy. Although the report was published while it was still too early to assess the ultimate value, nevertheless complete disappearance of ascites did occur. Postoperatively, the patient's sodium excretion increased significantly, even to the point where weakness, nausea, hypotension and hyponatremia occurred in association with complete absence of ascites; therefore, a small amount of ascites was maintained, with the patient receiving cortisone, 0.5 grams of sodium per day in his diet, resins and mercurial diuretic therapy (150).

One more patient has been reported who underwent bilateral adrenalectomy for massive ascites due to postnecrotic cirrhosis (90, 237). This individual demonstrated a rapid weight gain in the postoperative period in association with a liberal dietary sodium intake. The authors suggest that perhaps extra-adrenal factors are involved in the genesis of fluid retention in cirrhosis and that a residual defect persists in salt and water metabolism after adrenalectomy; an increased sensitivity to glucocorticoids either due to impaired hepatic metabolism or increased tubular reabsorption may be responsible for the observed salt retention. From these two cases, no significant conclusions may be drawn. It does, however, appear that the whole answer to salt and water retention does not lie entirely within the adrenals; furthermore, all patients

with ascites will probably not benefit from adrenalectomy.

Decreasing the Arterial Inflow of the Portal System

Herrick (108) first showed that arterial pressure was transmitted to the portal system to a greater degree in cirrhosis than under normal conditions. This led to the development of operative procedures to decrease the blood flow in the portal system in an attempt to relieve ascites. Some of the literature is reviewed in Table V.

The only real support for these operative procedures comes from those who believe that portal hypertension is responsible for ascites formation. By decreasing the arterial inflow to the portal system, that blood which does reach the liver is either handled better from the point of view of metabolism of salt-retaining steroids, or else the smaller volume of blood may be handled more rapidly. Those who believe that outflow block is responsible for ascites due to lymph exudation resulting therefrom would probably be reluctant to treat outflow block by decreasing inflow to an already damaged liver. In addition, ligation is probably only of temporary value, for collaterals develop thereafter and so the net portal blood flow is ultimately the same. But, results speak for themselves, and the fact that some

TABLE V.

MEASURES USED TO DECREASE THE PORTAL VENOUS LOAD

| Author | Procedure Used | Patient Disease | Results |
|---|---|---|---|
| Berman & Hull (17) | Hepatic, splenic and left gastric arterial ligation | 12 cirrhosis | 25% immediate mortality (first week). Ascites decreased greatly; 3 survivors needed paracentesis |
| Fuller et al (84) | Resection 6'8" small intestine | 1 cirrhosis | Rate of accumulation of ascites decreased by half and ceased 9 months postoperatively. Free of ascites for 29 months. |
| Henrikson (107) | Reviews Splenectomy 1909-1936 | 55 cirrhosis | 45 improved |
| Mayo (151) | Splenectomy | 34 cirrhosis | 27 improved |
| Moore et al (163) | Splenic artery ligation | 6 cirrhosis | 3 showed 12-17 month remissions; 2 showed moderate improvement; 1 died at home |
| Rienhoff & Woods (199) | Hepatic and splenic artery ligation | 11 cirrhosis<br>2 carcinomatosis | 2 dead<br>11 improved |
| Smith et al (216) | Hepatic artery ligation | 2 cirrhosis | No longer needed paracentesis |
| Theron and Allan (226) | Ligation hepatic, splenic and left gastric arteries. | 7 cirrhosis | 2 died; 5 no longer needed paracentesis |

patients are benefitted thereby makes one want to use the procedure when other techniques with less morbidity and mortality have failed. Once again, before completely condemning the operation, more insight into the mechanisms of ascites must be gained.

The Removal of Pelvic Tumors

One of the most readily treated causes of chronic ascites lies within the realm of the gynecologist. Very commonly, in association with benign ovarian or uterine neoplasms, peritoneal effusions are present. Ashby (4) pleaded for laparotomy in cases of ascites as far back as 1889 in order that these growths might be removed and the ascites thereby cured. Meigs also noted the occurrence of ovarian fibromas with ascites and hydrothorax. Several have speculated concerning the mechanism of ascites in these conditions, but no theory appears very plausible.

The place of surgery in the treatment of chronic ascites has been considered; the results using various procedures have been reviewed. Although some have written that no type of surgery is indicated in the treatment of ascites (40), nonetheless until medical management is able to deal successfully with all cases of intractable ascites, surgery will continue to be necessary for relief of some patients. Unfortunately, much criticism has been

directed to the surgeon for attempts to treat ascites which have often failed; he must continue to try to alleviate patients who have been sent to him, often in a very poor preoperative general condition. Older less traumatic procedures should continue to be used until some completely effective technique is evolved. This is the problem of the investigator, both to determine how various causative factors operate to produce ascites, how each factor may be measured exactly, and ultimately to find some means of relieving the ascites based on sound physiopathological principles.

# CHAPTER V.

## EXPERIMENTAL ASCITES

Review of the literature reveals the extensive amount of work that has been done by numerous investigators. Much of the research has a bearing on the problems of human chronic ascites, and so it would be most useful to examine some of the problems with which animal investigators have interested themselves.

### The Production of Ascites in Animals

Lower was the first to produce ascites in dogs in 1669 (143). Since that time, his method, namely by ligation of the thoracic inferior vena cava, has been modified by numerous investigators (Table VI).

Thoracic inferior vena cava constriction is the most widely used means of producing experimental ascites. The ascites formed does not persist; it is self-limited, lasting for only about three to six months in dogs. The reason for this is probably the development of collateral circulation, shown most prominently in the abdominal wall, but also manifested in the dilated azygos system of veins, and dilated esophageal veins draining in the azygos, but never do submucosal varices appear. Tricuspid avulsion followed later by the production of pulmonary stenosis results in the production of permanent ascites (47).

TABLE VI.

THORACIC INFERIOR VENA CAVA CONSTRICTION

| Author | Animal Used | Material Used | Amount Constricted | Results |
|---|---|---|---|---|
| Berman & Hull (16) | Dogs | 1/4" polythene band tied with 2 silk sutures | 50% | Ascites in 4 - 7 weeks. |
| Bollman (24) | Dogs | Broad cellophane band | Progressive fibrosis to 1/4 original diameter | Ascites in few weeks. |
| Bolton (29) | Cats | Rubber catheter 1/4" long closed by silk sutures | to 60% original | Ascites in few weeks. |
| Jacobson et al (121) | Dogs | Pneumatic rubber cuff with catheter to exterior | Not sufficient to cause collapse | Reversible ascites by releasing cuff; disappearance within 20 days. |
| Jefferson & Necheles (123) | Dogs | Polyethylene strip 1" wide tied around IVC | 70-75% | No ascites with constriction $<$ 70-75%; Constriction $>$ 80%. All died of shock and blood pooling in liver |
| Laufman et al (135) | Dogs | Aluminum band | 50% | Ascites within 2-3 weeks |
| Nayak et al (160) | Albino Rats | Silk ligatures | to 1/3 original | 20-41 died within 48 hours. Ascites in 3/5 at 24 hrs, 5/5 after 2 days, 4/5 after 7 days, 1/6 after 28 days. |
| Parsons and Holman (177) | Dogs | Umbilical tape | 50% | Ascites in 7 days, decreasing by 20th day, absent by 140th day. |

Pressure changes in the portal vein have been measured. The normal portal pressure in the dog is about 6-11 cms. of water; after caval constriction, portal pressure may rise to 16-30 cms. of water, while with portal vein constriction alone, the portal pressure is increased to 9-14 cms. of water, without the formation of ascites (111). This, and other work, whereby two-stage portal vein ligation was performed in rabbits without ascites resulting (162), would tend to demonstrate that there is no causal relationship between portal pressure and the presence of ascites. Furthermore, with inferior vena cava constriction either before or after portal ligation, the latter procedure does not appear to markedly affect ascites formation, additional evidence against portal hypertension being a direct causal factor in fluid accumulation. Species differences may exist, however, for Kunkel and Eisenmenger found that partial ligation of the portal vein produced a small amount of ascites in 69% of 110 rats; all showed increased portal pressure, but the degree of increase did not correlate well with the amount of ascites (131). Furthermore, Volwiler and coworkers found that simultaneous implantation of cellophane bands around the main portal vein and inferior vena cava below the liver did not result in ascites spontaneously; plasmapheresis was necessary in addition to the operative procedure, resulting then in a different type of fluid than that produced by supradiaphragmatic constriction. The ascitic fluid was thin

and watery with a protein content only 8% that of the plasma, a transudate probably the result of increased capillary permeability, secondary to hypoproteinemia and localized to the peritoneal cavity due to extrahepatic portal vein obstruction (231).

The effects of diet in altering ascites formation in dogs with thoracic inferior vena cava obstruction has been studied. Even when completely deprived of sodium intake, 60% of dogs will form ascites (10, 11). Furthermore, when fed a diet containing excessive sodium chloride, the volume of ascites may be increased, and the fluid contains sodium in amounts approximately equal to the excess administered. This increased intake accentuates the abnormality already produced by caval constriction, namely sodium and chloride retention, with augmented potassium excretion (203). On the other hand, altering the quantity of water ingested has little role in affecting the volume of ascites formation (16). A high-protein low-salt diet will result in minimal ascites under experimental conditions, but the protein concentration of the ascitic fluid increases, as do the plasma proteins. Adding excessive salt to the high protein intake increases the volume of ascites, while the plasma and ascitic fluid protein concentrations decrease. Without salt, a low protein diet does not allow plasma proteins to increase, while only a small volume of ascites results; a high sodium low protein diet, however, produces a large volume

of ascites, with decreased ascitic fluid and plasma protein levels. Therefore, ascites constitutes an internal plasmapheresis, whereby protein is removed from circulating plasma and tissue protein stores; this ascitic fluid protein, however, remains in dynamic equilibrium with the remainder of the body protein (154, 156). Further reference to these factors will be made later when the possible mechanisms involved in experimental ascites formation are discussed.

Other methods of producing ascites are outlined in Table VII.

Mechanisms of Experimental Ascites Formation

One of the most popular explanations to account for ascites formation is that hepatic venous congestion is essential to its development, especially ascites with a high protein concentration (54). This fluid comes largely from the liver or extrahepatic liver lymphatics in association with which the rate of flow of hepatic lymph is augmented (98). In addition, distended and dilated lymphatic vessels have been observed in dogs with thoracic inferior vena cava constriction and ascites. These lymphatics are found in the hilum, capsular and subcapsular regions (Fig. 6). (95, 231). Furthermore, a large volume of fluid may be seen escaping from the surface of the congested liver. The physical

TABLE VII.

MISCELLANEOUS TECHNIQUES OF PRODUCING EXPERIMENTAL ASCITES.

| Author | Animals Used | Technique | Results |
|---|---|---|---|
| Bollman (25,26) | Dogs | Ligation common bile duct | 3 mos. after ligation, addition of meat to diet produced ascites within 24 hrs. Reversal in most cases by resumption carbohydrate diet. |
| Bolton (28) | Cats | Constriction pericardium by sutures | Ascites and edema of mediastinum and pleural effusion |
| Craig et al (47) | Dogs | Tricuspid avulsion followed later by pulmonary stenosis | Ascites without later spontaneous remission. |
| Cross et al (49) | Dogs | Complete occlusion hepatic veins with associated porta-caval shunt | Ascites in 8 out of 15 dogs (53%). Portal hypertension in 10 out of 15 |
| Davis et al (58) | Dogs | Ligature constriction of main trunk of pulmonary artery by 65-75% | Congestive heart failure with ascites. Sodium retention always associated with high atrial venous pressure |
| Davis et al (59) | Dogs | Cellophane implanted into pericardium & wrapped around heart | Scarring parietal pericardium and superficial myocardium. Elevated venous pressure and ascites. |
| Hahn et al (102) | Dogs | Intravenous radioactive colloid gold - 3 injections 2 wks. apart | 2 of 3 dogs developed ascites associated with hepatic vein obliteration and central fibrosis of lobules |
| Hamilton et al (104) | Dogs | Controlled progressive constriction mitral ring | Ascites does not result - denies previous reports where actually due to IVC constriction |
| Mehrotra et al (159) | Albino Rats | Biweekly subcutaneous $CCl_4$ injections | 6/17 developed ascites with added salt and DOCA; 5/18 developed ascites without added salt or DOCA; DOCA produced larger fluid volume with low protein content. Ascites in both groups related to degree of hepatic fibrosis. |

TABLE VII. (CONTINUED)

MISCELLANEOUS TECHNIQUES OF PRODUCING EXPERIMENTAL ASCITES

| Author | Animals Used | Technique | Results |
|---|---|---|---|
| Nuland et al (172) | Dogs | IVC - right pulmonary artery anastomosis | Ascites in 11 of 12 long-term survivors, with average appearance of fluid at 3 months, associated with hypoproteinemia; high protein diet without effect on volume of ascites nor on serum protein; low salt high protein diet decreased ascites and increased serum protein |
| Parsons & Holman (177) | Dogs | 1) Constriction right side of heart by excision pericardium and suture edge to heart, SVC and IVC with injection sodium morrhuate into sac 4 wks. later<br>2) Constriction right auricle<br>3) Constriction pulmonary veins | 1) Ascites at 20th postoperative week<br>2) No ascites resulted<br>3) |
| Sprafka et al (218) | Dogs | Transventricular severance chordae tendineae of tricuspid valve; 2 wks. later produced pulmonary infundibular stenosis | 16 of 21 dogs developed ascites, 56% within 3 weeks. Rapidity of ascites onset related roughly to degree of right atrial pressure elevation. Ascites permanent. |

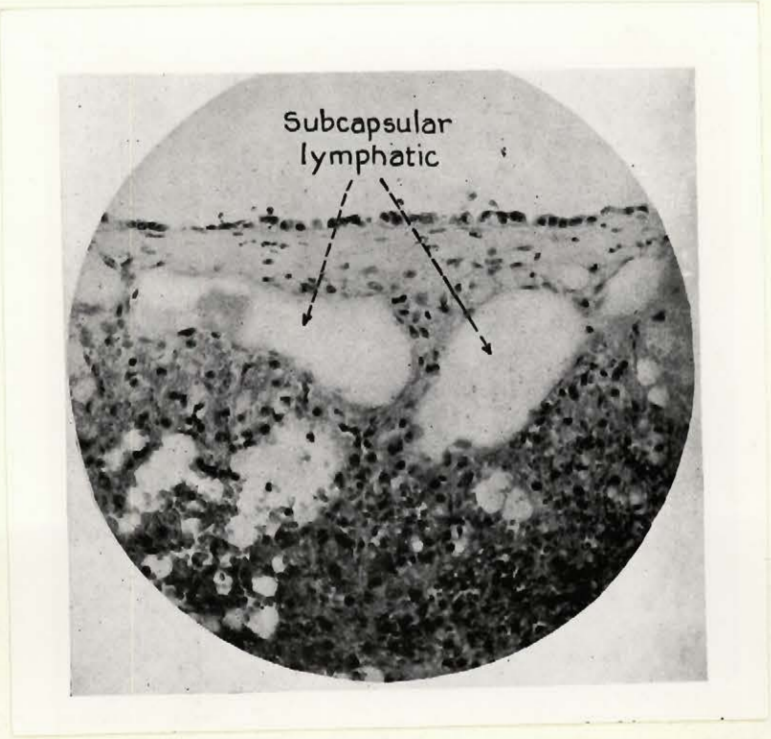


FIGURE 6.

Subcapsular Lymphatics of Liver Engorged After Experimentally Produced Venous Congestion of the Organ.

(The Relation of Certain Mechanical Factors to the Production of Ascites. W. Volwiler in A Ciba Foundation Symposium - Liver Disease. J&A Churchill Ltd. 1951, facing p. 128).

chemistry of liver fluid, plasma, hepatic lymph and ascites would also confirm that the liver is the source of the ascites; the lower protein content of the latter is probably related to dilution of the fluid by peritoneal transudation of water and electrolytes (98, 118). Another interesting confirmatory observation stems from the work of Devic and associates (61). They found that after hepatic venous ligation, transposition of the liver into the thorax resulted only in pleural effusion, with no fluid collecting in the abdomen.

Experimental investigations have shown that portal hypertension is not essential to the formation of ascites. Dogs, when subjected to portal vein constriction or two-stage ligation, develop increased portal venous pressure, but not ascites. The same level of portal pressure may be achieved by inferior vena cava constriction with resulting ascites; here, however, outflow block and hepatic exudation are present. In portal vein obstruction, only inflow interference is present, and plasmapheresis is essential for the formation of ascites. (112, 232).

The adrenal cortex has been the subject of much attention in an attempt to elucidate the mechanism of ascites. All of the known steroids have been studied, the most recent being aldosterone. A definite and significantly increased plasma and urinary titre of this steroid has been demonstrated in dogs with ascites due to

thoracic inferior vena cava constriction or right-sided congestive heart failure (12, 53, 60). Increased aldosterone secretion is dependent upon hepatic venous congestion, however, rather than on increased adrenal venous pressure; constriction of the inferior vena cava just above the adrenolumbar veins does not result in elevated aldosterone levels, sodium retention or ascites (9). Even when food and water, including sodium, are witheld, dogs will still form ascites. A sequence of factors resulting in ascites is suggested beginning with increased hepatic venous pressure; this leads to extravasation of plasma fluids and electrolytes to initiate ascites. The adrenal cortex is then stimulated to secrete aldosterone; the steroid compels the kidney to retain salt and water, and thereby the initial volume of ascites is increased (10, 11). Although the exact stimulus to aldosterone secretion is unknown as yet, nevertheless, hypophysectomy in dogs with experimental ascites has shown that it is not solely dependent on pituitary hormone function (52).

For purposes of completeness, older work on the adrenal cortex in relation to ascites must be mentioned. Excessive adrenal cortical salt-retaining hormone was believed to be an essential factor in the production of ascites in experimental preparations in dogs; thus desoxycorticosterone acetate was implicated, rather

than cortisone (55, 57, 91). More recent advances in endocrinological research have shown that aldosterone is more potent with regard to salt and water retention.

The role of the pituitary in ascites formation is the next subject to be discussed. Hypophysectomy in dogs rendered ascitic by either inferior vena cava constriction or tricuspid avulsion followed by pulmonary stenosis results in a return to about 75% of normal salt and water output; restriction of water intake produces a negative fluid balance with diuresis and loss of ascites. Once the ascites has disappeared, replacement therapy with ACTH, cortisone, DCA or pitressin does not result in reaccumulation of the fluid. The possibility of growth or thyroid-stimulating hormone producing salt and water retention is still under investigation (46, 47, 56).

After removal of the ascites by hypophysectomy, an interesting phenomenon occurs. Further constriction of the vena cava will result in ascites once again. With the return of femoral venous pressures to prehypophysectomy levels (the level drops after hypophysectomy) there is again marked sodium retention, although only the zona glomerulosa of the adrenal cortex remains normal or only slightly atrophic. From this it would appear that a pituitary factor is essential to the maintenance of high venous

pressure levels adequate to result in ascites. (114). In addition, although pituitary hormones appear necessary for the low urinary-fecal ratio of potassium excretion that occurs, sodium retention is not dependent on pituitary function (115).

In defence of the argument that posterior pituitary antidiuretic factor is important in the pathogenesis of ascites, much work has been carried out. Intravenous assay of ADH in dogs has revealed no significant difference in salt and water retention between dogs with and those without ascites. Furthermore in dogs with diabetes insipidus secondary to neurohypophyseal tract destruction, ascites formation is no different to that in non-diabetic dogs. These points of evidence would tend to deny the importance of the pituitary antidiuretic factor in the pathogenesis of ascites. (134).

The possibility that the kidney itself plays a primary role in the production of ascites has also been investigated. Inferior vena cava constriction produces an increased renal venous pressure and in dogs with ascites there is a decrease in renal blood flow and glomerular filtration rate; urine flow and sodium excretion are markedly decreased. Removal of the ascites, however, produces a sudden 100% increase in sodium excretion, and a lesser increase in urine flow, although renal clearances are unchanged. A pure mechanical release of pressure from the kidney has been refuted; a sudden inhibition of secretion or an increased destruction of sodium - retaining hormone may be the causative factor (89, 227).

An interesting experiment was set up by Whelan and his associates (228). They transplanted one kidney of a small series of dogs to the neck and performed a contralateral nephrectomy. These dogs did not develop ascites as readily as those with abdominal kidneys and inferior vena cava constriction, and they also showed an elevated sodium excretion in response to salt-loading. Whether this is due to removal of the kidney from the obstructed circulation or to transplantation per se was not established, but the fact that the kidney appears to play some role in ascites formation is strongly suggested.

What conclusions may we derive from experimental investigations to help explain the pathogenesis of ascites formation? Firstly, it is apparent that no one single factor is responsible for its development. Secondly, experimentally produced hepatic venous congestion is probably very similar to that seen in the outflow block of cirrhosis, constrictive pericarditis, the Budd-Chiari Syndrome and congestive heart failure. Thirdly, lymphatic dilatation and exudation secondary to these causes or to intrinsic obstruction by carcinoma, etc., probably initiates the development of ascites. Localization to the peritoneal cavity probably results from pressure relationships in this area, in that once adrenal cortical production of excessive aldosterone is stimulated (by some still unknown mechanism), further ascites accumulates, while other parts of the body may be unaffected. The regulation of

endocrine secretions has not yet been established conclusively, nor have all the possible factors contributing to ascites formation been reproduced successfully in the laboratory. When this has been achieved then perhaps some investigator will evaluate all these phenomena in their proper perspective and devise some surgical technique which will cure all cases of ascites. The likelihood of one operation curing all is unlikely, however, for with multiple factors producing the condition, probably one form of treatment will not be all-embracing.

## The Treatment of Experimental Ascites

Most of the standard methods of therapy employed in the management of chronic ascites were first used in the laboratory. In addition, because of the small series available to most surgeons, many investigators have tried to evaluate various techniques in animals where a larger group of subjects could be obtained. Many of the procedures to be discussed were dealt with in the chapters dealing with the treatment of ascites in human patients. In this chapter, only those which have been used in animals will be reviewed.

McKee and his group (157) have investigated the effects of plasma, amino acid mixtures, and ascitic fluid given parenterally, and of ascitic fluid orally to the ascitic dog. Whole dog plasma

infused intravenously caused an elevation of the plasma protein to normal levels, but concomitantly the outpouring of ascitic fluid resulting therefrom caused a protein loss equivalent to about 65% of that injected.

When given amino acid growth mixtures intravenously in distilled water, dogs lost weight; the circulating plasma proteins increased, and even with a slightly negative nitrogen balance, there was no ascites formed. By substituting normal saline for the distilled water, plasma protein levels diminished and significant ascites production resulted, accompanied by a negative nitrogen balance.

Ascitic fluid administration, either by the intravenous or oral route, resulted in a decreased level of circulating plasma proteins and an increased volume of ascites production, containing most of the protein given.

From this work, it would appear that whole plasma or ascitic fluid administration is valueless in ameliorating ascites. Amino acids when free of salt do exert a beneficial effect. This would suggest that the ascitic animal handles proteins adequately, but that a generalized defect of salt and therefore of water metabolism is the primary problem in the genesis and management of ascites. This is borne out by the ease with which some human ascitics are managed by vigorous salt restriction and diuretics, as well as by the finding of elevated aldosterone levels in these patients.

McDill in 1913 (152) wrote that ascites may be managed by lymphangioplasty through a trocar wound under local anesthesia. In an experimental study performed on rabbits, he suggested the implantation of silk into the subcutaneous tissues with one inch projecting into the lower peritoneal cavity, thus establishing a silk-connective tissue peg for internal drainage. He reported no results, but other work in human beings has relegated this type of procedure to a minor position.

Laufman and associates (137) were able to decrease the portal pressure in experimental animals by sympathectomy in proportion to the drop in systolic blood pressure produced thereby; this, however, was without any effect on the ascites, and therefore, the procedure is valueless. Furthermore, this helps to demonstrate that the control of portal hypertension alone is not adequate to relieve ascites.

Massive intestinal resection in ascitic dogs has been advocated for the control of ascites (18). Resection of 80% of the mid-portion of the small intestine prevented the accumulation or reaccumulation of ascites in dogs with thoracic inferior vena cava constriction, while resection of 50% resulted in a decrease of 50% in fluid volume; the addition of splenectomy was without further benefit. Mere exclusion of 50% of the small intestine leaving the mesentery in place resulted in the return of 85-90%

of the ascites. The beneficial effects appear related to the diminution of the portal pressure secondary to removal of part of the portal vascular bed. The physiological disturbances resulting from removal of such a large segment of the small bowel would, however, contra-indicate such a procedure in such poor operative risks as are patients with chronic ascites; in addition, outflow block and defective salt handling are not corrected.

Vascular ligations with or without splenectomy have been used in dogs to ameliorate experimental ascites. Bollman, however, has shown that hepatic artery ligation does not materially alter the blood flow through the liver of cirrhotic animals; complete occlusion of the portal vein decreases the liver blood flow to about one-half that of the normal dog (27).

The results of various procedures which attempt to decrease the volume of blood entering the portal system are demonstrated in Table VIII.

None of the series in this table is large enough to derive any statistically significant conclusions from them. Taken collectively, however, certain trends are demonstrated from which certain ideas may be derived. Ligation of branches of the coeliac axis results in a decreased portal pressure and a decreased volume of blood entering the liver (contrary to Bollman's

TABLE VIII.

VASCULAR LIGATIONS (AND SPLENECTOMY) IN EXPERIMENTAL ASCITES

| AUTHOR | OPERATIVE PROCEDURE | RESULTS |
|---|---|---|
| Berman & Hull (16) | 1. Reverse Eck fistula (side-to side portacaval shunt) | 1. Increased ascites |
| | 2. Hepaticartery ligation | 2. Decreased formation of ascites to 500-600 cc every 2 weeks |
| | 3. Hepatic & splenic artery ligation | 3. Ascites formation decreased to 500 cc per month |
| | 4. Ligation of coeliac axis | 4. No improvement from (3) |
| Jefferson & Necheles (123) | 1. Occlusion IVC below renal veins | 1. No effect in 4 dogs |
| | 2. Occlusion IVC above renal veins | 2. Reversal of ascites in 4 out of 11 dogs |
| | 3. Ligation splenic artery | 3. Disappearance of ascites in 2 out of 3 dogs. |
| | 4. Partial or complete hepatic artery ligation | 4. No effect on ascites in 9 dogs. |
| Laufman et al (135,136) | 1. Partial portal vein occlusion. a) above gastroduodenal vein. b) below gastroduodenal vein | 1. a) Complete to almost complete absence of ascites for 3-12 weeks b) Ascites reformed in 2 weeks |
| | 2. Simultaneous partial occlusion of IVC and portal vein above and below liver | 2. 10 out of 20 surviving animals had no ascites or temporary accumulations of small amounts during 4 months follow-up |
| | 3. Ligation portal vein weeks after IVC constriction | 3. Less success with larger volume and longer duration of ascites |
| Milnes (161) | 1. Ligation hepatic and splenic arteries | 1. Diminished ascites |
| | 2. Splenectomy plus arterial ligations | 2. No further benefit |
| | 3. Hepatic artery-portal vein anastomosis | 3. No appreciable effect on ascites |
| Nuland et al (172) | 1. Splenectomy, nephrectomy and caval ligation below right renal vein | 1. Early decrease in ascites and increase in plasma proteins; 1 sustained for over 6 months; 2 dogs reverted to pre-operative state within 1-2 months; although with less ascites. |
| | 2. Hepatic artery ligation & splenectomy in 2 dogs | 2. One dog lost ascites for over 6 months with return ofproteins to normal. Other dog showed some diminuation of ascites. |

observations). Lateral pressure is increased, however, and collaterals are formed, creating a new capillary bed which may improve hepatic parenchymal cell nourishment. In this way, some beneficial effects on ascites may be derived. Splenectomy, on the other hand, probably removes a source of collateral circulation and thus impedes improvement. Not all animals, however, derive benefit from arterial ligations; those which do are probably without the realm of chance and so one must conclude that true value is obtained. On the other hand, not all factors which possibly play a role in the genesis of ascites are eliminated by vascular ligations, and so failures are numerous, both early and late in the postoperative period.

Ravdin (194) has reported another operative procedure for the amelioration of experimental ascites. His method of treatment appears to rest on sound footing, in that it takes account of outflow block. By anastomosing the spleen to the liver, increased outflow tract collaterals have resulted with an increased splenohepatic flow and a diminished intrahepatic pressure. Added benefit is probably derived from collaterals formed as a result of the operative trauma with adhesions between the liver and diaphragm. He has reported that in a few dogs, splenohepatic anastomosis has prevented fluid accumulation.

Another method of treatment which takes account of hepatic venous outflow obstruction is that derived by Gage and his group (87). In dogs with thoracic vena cava constriction and thus ascites secondary to subcapsular lymphatic dilatation and exudation, they observed marked benefit after hepatopexy. Adhesions were created by mechanical abrasion of the free surface of the liver and the adjacent diaphragm, together with the instillation of 6-12 grams of talcum powder into the raw areas. In 6 out of 10 dogs, ascites did not recur after the operation; 2 of the remaining 4 were ascites - free after a second procedure wherein remaining free liver was abraded. The other two showed a markedly diminished amount of ascites, 500 and 900 cc. at the time of sacrifice, as compared with an average of about 5000 cc. in untreated animals.

Both procedures are quite reasonable in that they attempt to overcome one mechanism of ascites formation. Criticism must be levelled at them, however, for not all cases of chronic ascites are secondary to hepatic venous outflow obstruction. In these patients, such an operation would probably not be effective.

The most recent technique for relief of experimental ascites is the operation of ileo-entectropy. By excluding a loop of ileum and attaching its serosa to the parietal peritoneum, thus exposing its mucosa to the peritoneal cavity, Neumann and associates (169, 170, 171) have improved the ascites of dogs. In 8 animals on whom

ileo-entectropy was performed, the fluid either did not recur or did so in greatly reduced quantities; only one required paracentesis and after a second similar operation, tapping was no longer necessary.

In order to try to elucidate the mechanism of improvement, two other series of dogs were subjected to the operation in modified form. One group had serosa to serosa suture of excluded ileum to an adjacent loop of ileum; in the second group, the mucosa was removed from the isolated segment. The former collected fluid at almost the same rate as the control series of animals, while the latter showed some improvement which increased with the passage of time. It would therefore appear that the operation's benefits are derived from two sources - first, from anastomoses between the portal and systemic circulations which both decreases portal pressure and provides a secondary route of escape for fluid absorbed by the mucosa, and second, absorption of fluid by the mucosa.

Before accepting ileo-entectropy as the panacea for ascites , pitfalls of the operation must be pointed out. The procedure is an extensive one especially when debilitated subjects are exposed to it and morbidity and mortality will be high. It is also not clear as to how the protein content of the ascites is absorbed. It would appear that most of the fluid and electrolytes are absorbed

through the mucosa, while the protein passes through the usual diaphragmatic and other lymphatic pathways. Some protein probably does pass through the intestinal mucosa unchanged, however, and enters the lymphatics and not the blood capillaries directly. (241). Further comments relating to causes for failure of the operation will be discussed in a later chapter.

## CHAPTER VI.

## THE CIRCULATION OF ASCITES

The ascitic fluid is in dynamic equilibrium with the other fluids of the body. Using tritium-labelled water, it has been demonstrated that about 40-80% of the total ascitic fluid volume enters and leaves the peritoneal cavity each hour. This represents a total rate of transfer of 2.47 to 7.45 litres per hour in 6 patients studies by Prentice and associates (190).

Protein, represented especially by albumin and globulin, also are readily exchanged. It has been found that the rate of transfer of albumin across the peritoneal membrane is at least three times faster than that of globulin in terms of weight. Using labelled protein, it has also been shown that 200-400 cc of ascites is formed per day by dogs. When tagged plasma is injected into the blood stream or into the peritoneal cavity, the rates of portein transfer in opposite directions tend to become equal as the concentration of labelled proteins in the two compartments approach equilibrium; in the early stages, the movement is approximately undirectional. In one dog after the injection of $C^{14}$ - labelled plasma into the peritoneal cavity 0.09 grams of albumin and 0.03 grams of globulin, each per hundred cubic centimeters per hour, were transferred to the plasma during the first eight hours (153, 155, 158).

The Absorption of Ascites.

Certain aspects of the problem of ascitic fluid absorption have been well established, but others remain unclarified. Thus, the routes of lymphatic absorption have been determined, but the mechanism of this absorption is controversial.

The lymph vessels of the diaphragm constitute the most important pathway for drainage of fluid and particulate matter from the peritoneal cavity (214). These vessels form an anastomosing network in subpleural, intermuscular, perivascular and subperitoneal locations, the last being separated from the peritoneal cavity by a single layer of mesothelial cells, a few connective tissue fibres, and the endothelial cells of the lymphatics. In the dog these vessels issue in the parasternal lymph trunks along the internal mammary artery, and then drain in turn into the cephalic group of anterior mediastinal lymph nodes and blood stream via the right lymph duct. Some drainage is through the crural vessels into the lumbar lymph glands.

The role of the omentum in absorption has been studied extensively. Poynter (187) was able to demonstrate omental absorption, but did not feel that lymphatics were present. Simer studied both animals and man. In the dog and cat, he was able to show lymphatics along the blood vessels of the omentum draining into the duodenal and splenic nodes and then into the cisterna chyhi.

He did not believe, however, that these channels were of much importance in the cat (211, 212). The distribution of the omental lymphatics is similar in man; vessels accompany the blood vessels, with a dense plexus surrounding the arteries. The lymph passes from this perivascular plexus to the longitudinal collecting vessels located near the margin of the fat strips and especially to the gastroepiploic nodes; the splenic nodes are of secondary importance. From the gastroepiploic nodes, the lymph passes to the coeliac nodes and then to the cisterna chyli (213).

Although most absorption from the peritoneal cavity is undoubtedly through the diaphragm, the role of other lymphatics is of importance too. The remainder of absorption occurs through lymphatics of the mesentery, omentum, visceral and parietal peritoneum, lymphatics of the gallbladder, and the lymph glands of the ileocecal region. Most of this drainage goes into the thoracic duct, and this route is slower than via the diaphragmatic lymphatics (45, 101).

Several factors affect the rate of absorption of fluid and particles from the peritoneal cavity. Indeed, the same dog will show different rates of absorption at separate times. It is also not surprising that various dogs show differing rates of absorption.

The effects of anesthesia in relation to peritoneal absorption constitute an interesting study. Nembutal anesthesia increases the circulating plasma volume and parenchymal tissue plasma volume in mice (83). In dogs, ether increases the lymph flow by about 50%, while barbiturates decrease it a similar amount, the fluid in the latter case shifting from the tissues to the blood. This also affects the protein concentration of lymph, in that it is higher under barbiturate anesthesia (182).

Nembutal anesthesia decreases the rate of absorption of labelled protein from the pleural and pericardial cavity in rabbits and cats (44). This is probably due to a decrease in the activity of the diaphragm and by diminished intra-abdominal pressure due to flaccidity of the abdominal muscles (241). The stimulation of respiration by breathing 5% $CO_2$ increases the absorption from the peritoneal cavity of the cat to a level approximating that by the unanesthetized animal (45). In addition, the lymph flow in the dog and cat increases with oxygen want and expiratory resistance (233). All these factors must be taken into account in attempting to establish an absolute value for the rate of absorption of ascites in the experimental animal.

The mechanism of lymphatic absorption of peritoneal fluid continues to trouble investigators. It would appear that there are three stages in absorption (44).

1) The movement of material to the absorbing surface - this is influenced by respiration, posture and intestinal movement.
2) The passage of material through the mesothelial lining, subserous tissues and lymphatic wall.
3) The propulsion within the lymphatics - this appears related to respiratory movements, active lymphatic contraction, and compression of lymphatics by adjacent tissues.

It is in relation to passage of the material into the lymphatics that most controversy exists. Allen and Vogt (1) have expressed the opinion that relaxation of the subserous tissues increases the volume of the lymphatic terminals. This produces a difference in pressure on either side of the sero-endothelial membrane which separates the lymphatic lumen from the peritoneal cavity, and particles and solutions are sucked into the lymphatic lumen. In addition to this "stomata" theory, Webb has written that particles appear to force their way between the contiguous borders of the diaphragmatic mesothelial cells and the endothelial cells of the lymphatic vessels (233). On the other hand, others believe that absorption occurs through the cells, and that with the protein go the fluid and electrolytes (44).

The fact that most absorption from the peritoneal cavity takes place through the lymphatics has several implications when planning the surgery of chronic ascites. It would be logical

that two approaches to therapy should guide techniques. One is to decrease the volume of fluid that the existing lymphatics are required to handle, while the other is to increase the number of lymphatics that may absorb the ascites. Taking cognizance of hepatic venous outflow obstruction with sinusoidal dilatation and increased lymph flow and exudation will give rise to procedures to decrease ascites production. A knowledge of the fact that diaphragmatic absorption is the chief route for peritoneal loss of fluid should force investigators away from other sources within the peritoneal cavity for improving drainage. Extraperitoneal sources, if attempts to increase the number of lymphatics are made, should be used and techniques to drain the ascites to these areas, whence their lymphatics will drain the fluid, must be devised.

## CHAPTER VII.

## MATERIALS AND METHODS

This experiment was designed to evaluate the relative efficacy of various surgical techniques in the amelioration of experimental ascites. For purposes of comparison, procedures previously described in the literature were compared with that using a prosthesis devised in this laboratory.

All experiments were carried out on dogs. This animal was selected because of the ease with which ascites can be produced in dogs, as well as the similarity of the peritoneal cavity and its contents between the dog and man.

Mongrel dogs, without selection and both male and female, weighing from twenty to fifty pounds, were obtained from local sources. An attempt was made to exclude all animals which showed any evidence of distemper. In addition, most dogs were given anti-distemper vaccine (Lederle) in an attempt to prevent the occurrence of the disease. Standard kennel diets were given to all animals, consisting of beef heart, proprietary dog food, milk and water. Where necessary, animals were given intravenous fluid therapy with added vitamins. Most animals were given penicillin or penicillin and streptomycin the first few days postoperatively, while bowel cases were also given neomycin preoperatively.

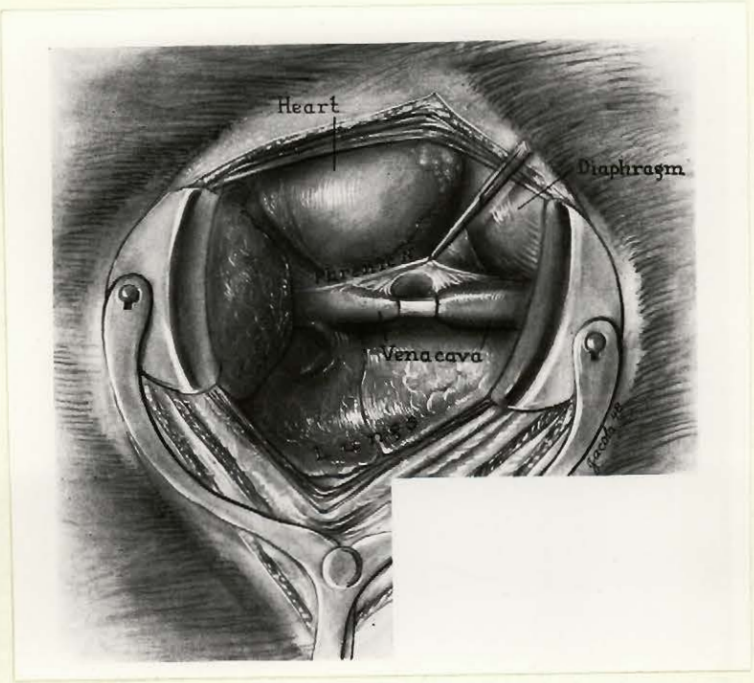


FIGURE 7.

Anatomical relations of inferior vena cava in the chest showing site of constricting band.

(Experimental Ascites: Effects of Sodium Chloride and Protein Intake on Protein Metabolism of Dogs with Constricted IVC. F. W. McKee et al, S.G.O. 89: 531, 1949).

## I. Production of Ascites

A total of seventy dogs were used in this study. The animals were anesthetized using veterinary nembutal (Abbott), one grain per cubic centimeter, given to effect. An endotracheal tube was passed, and the tubing was connected to a mechanical respirator.

The animals were postured on the left side, and the chest incision was made through the right fifth or sixth intercostal space. All bleeding points were secured either by ligatures or with the electric cautery. Using the cutting current, the pleural cavity was entered, following which a Balfour retractor was used to separate the ribs. The lung was retracted exposing the inferior vena cava with the right phrenic nerve lying against it. This was gently dissected away from the vessel, as was the loose areolar tissue attaching the middle portion of the thoracic inferior vena cava to the posterior mediastinum. The inferior vena cava was measured in all cases, and the diameter varied between ten and nineteen millimeters. Those vessels less than fifteen millimeters were constricted using a stainless steel ring as shown in Fig. 8, while larger vessels were constricted using a larger ring containing the water-absorbing casein plastic, ameroid, (Fig. 9). Using heavy forceps the former type of ring was closed an appropriate amount, while the latter's opening was encircled by two heavy cotton ligatures. In each case the inferior vena cava was constricted by fifty to sixty percent of its original diameter. The chest wall was then closed in layers with cotton sutures for all deeper tissues and stainless steel wire for skin. All air was expelled from the chest cavity by inflation of the lungs and underwater catheter which was removed after skin closure.

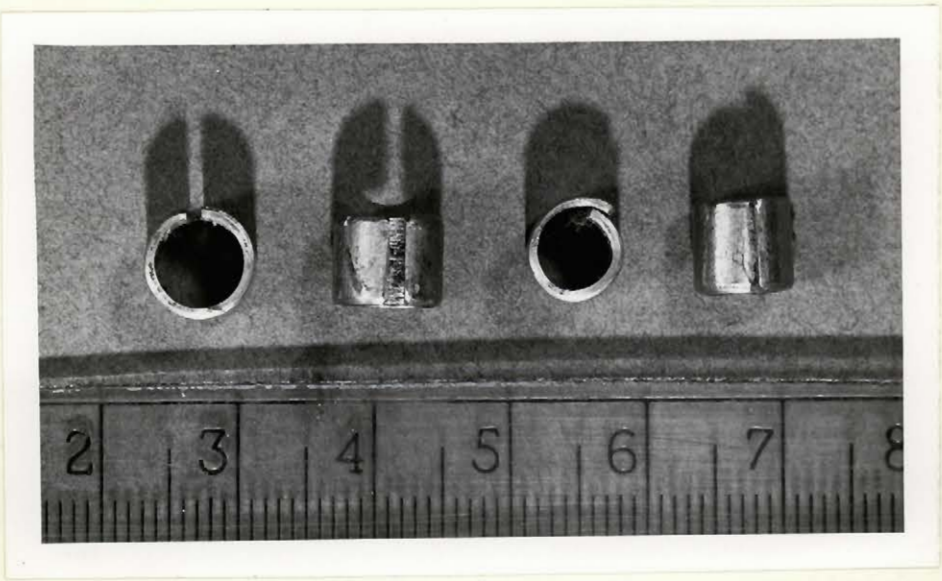


FIGURE 8.

Stainless steel ring used for inferior vena cava constriction.

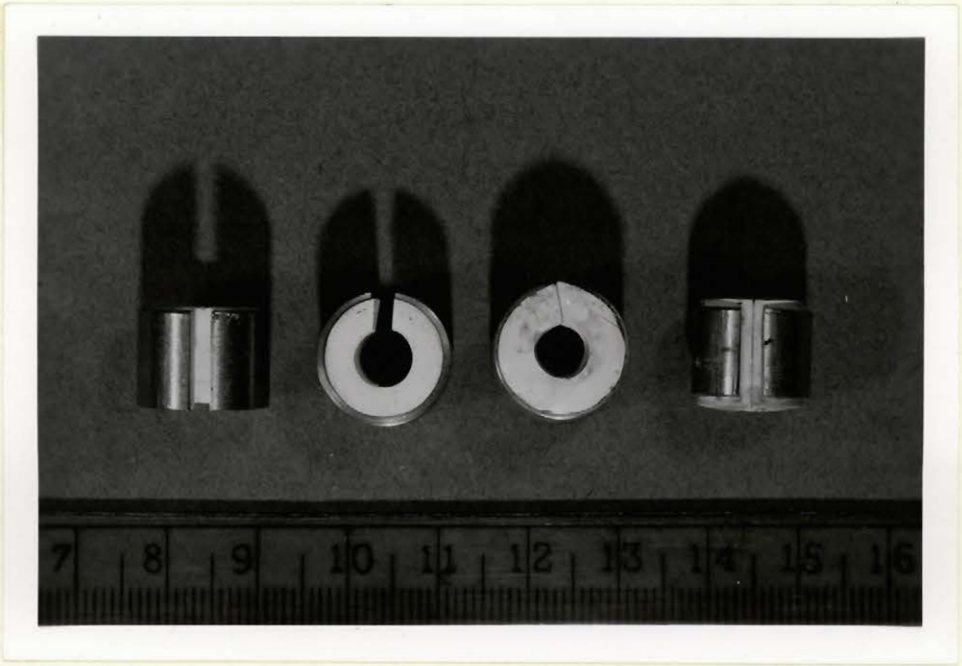


FIGURE 9.

Ring containing ameroid used for inferior vena cava constriction.

As will be described later, some animals underwent a second operative procedure at this time; the others were returned to their cages. They were given the diet as above when tolerated, usually within twenty-four hours of the operation. Within two to three weeks, all survivors developed detectable ascites with the exception of a few of those who had the relief procedure performed at the same time as the chest operation.

## II. Surgical Treatment of Ascites

The following operations were used on randomly selected dogs in an attempt to relieve their ascites:

1) Polythene prosthesis in peritoneal cavity with drainage to the exterior - 6 dogs.

2) Prosthesis in peritoneal cavity with drainage to retropubic space

   a) Polythene prosthesis - 10 dogs

   b) Silicone rubber prosthesis - 6 dogs

3) Omentopexy - 15 dogs

4) Omentopexy followed by splenectomy at a later date - 4 dogs

5) Ileoentectropy - 9 dogs

### Description of Prostheses

Prostheses, using either polythene plastic or silicone rubber, were constructed manually with the assistance of those companies

which have been acknowledged.

Both types of prosthesis combine the principle of a sieve with multiple perforations through which the ascites is to drain from the peritoneal cavity. This sieve is either flat or concave, with a diameter of seven to eight centimeters, and containing two hundred or more perforations. The sieve leads into a chamber about one to two centimeters in depth and from this the fluid is funneled out through a hollow tube of the same material. Around the periphery of the sieve-collector is a thin rim of plastic or rubber by which the prosthesis is anchored to the parietal peritoneum of the anterior abdominal wall, the perforated surface facing the abdominal viscera.

In an attempt to prevent coagulation of ascitic protein on the surface of the plastic prosthesis, it was silicone-coated. In addition, some dogs were given parenteral parenzymol (Horner) for the same purpose. The results of this will be discussed in a succeeding section.

The polythene prosthesis is illustrated in Figures 10 and 11, and the silicone rubber one in Figures 12 and 13.

Implantation of the Prosthesis

Under nembutal anesthesia, the peritoneal cavity was opened in the midline suprapubically and the ascites drained. The

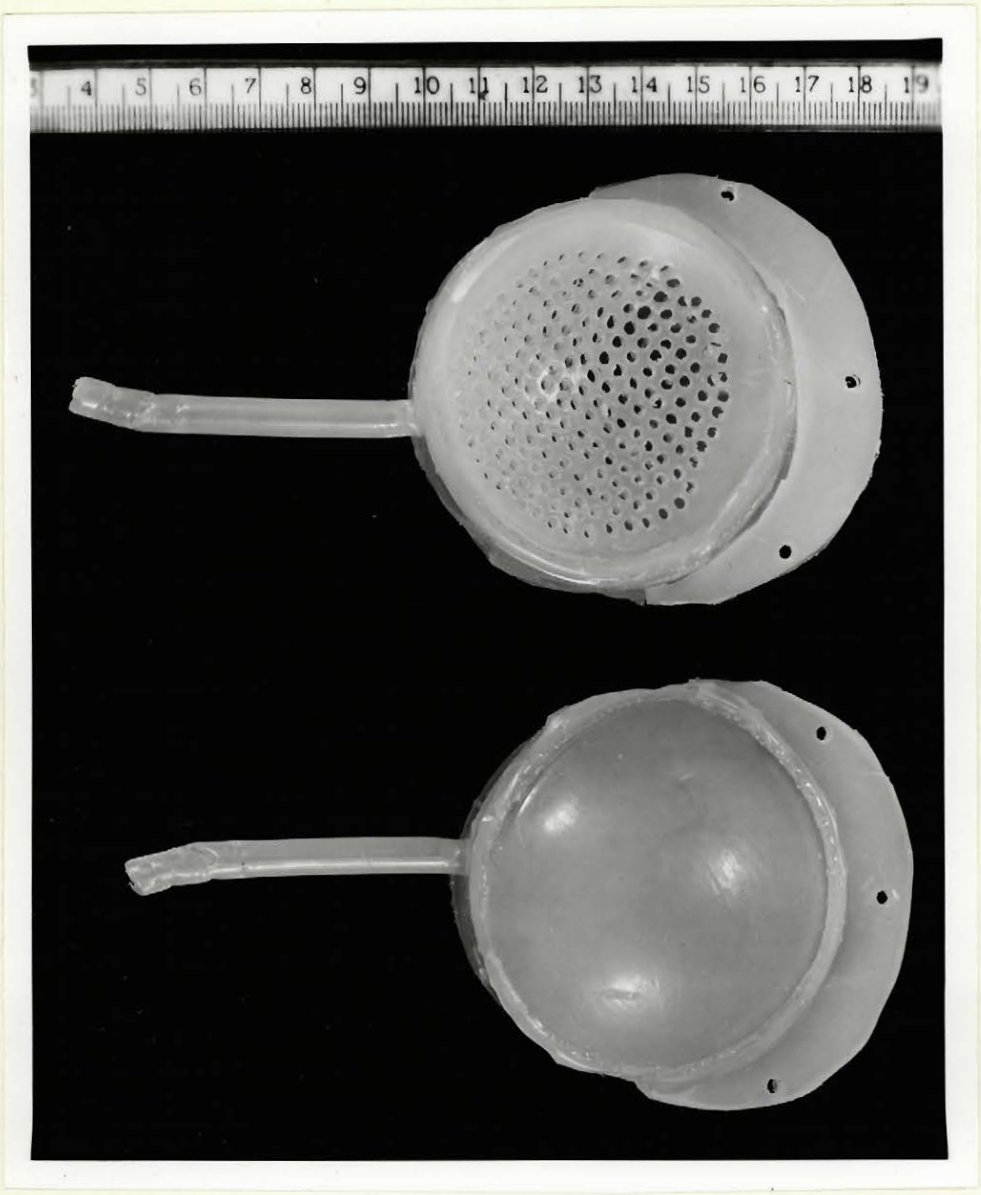

FIGURE 10.

Front and rear views of polythene prosthesis.


FIGURE 11.

Side view of polythene prosthesis.


FIGURE 12.

Front view of two different-sized silicone rubber prostheses


FIGURE 13.

Side view of two prostheses shown
in Fig. 12.

omentum was delivered into the wound and resected as close to the stomach and spleen as possible. The prosthesis, which had previously been cold sterilized in formalin and then aqueous zephiran for at least twenty-four hours, was then inserted into the peritoneal cavity in front of the viscera. The perforated surface faced the viscera, while the solid posterior wall was against the parietal peritoneum of the anterior abdominal wall. The rim of the prosthesis was then anchored to this peritoneum. The conducting tube was dealt with in two different ways in the three different series. In the first, it was led through a stab wound in the anterior abdominal wall lateral to the midline. There it was anchored with a rubber bag tied to it to collect the draining ascites. In the other two series, the tube was anchored to the extraperitoneal fat of the retropubic region. The peritoneum was then closed around the drainage tube. The abdominal wall was closed in layers, using cotton for deeper sutures, and stainless steel wire for the skin.

Postoperatively the animals were given antibiotics and diet as tolerated. Where dehydration appeared, intravenous fluids and parenteral vitamins were given.

Omentopexy

The dog does not have the same space of Retzius as is present in man. The peritoneum does, however, pass from the

anterior wall of the bladder down into a prevesical space, then forwards above the urethra and then up on the posterior surface of the anterior abdominal wall. Extraperitoneally in this region, fatty areolar tissue, blood vessels and lymphatics are abundant. It was this space into which the conducting tube of the prosthesis in the first series and the omentum in this series were placed.

The abdomen was opened in the midline suprapubically and the omentum was anchored to the extraperitoneal retropubic fat. The peritoneum was sutured around the omentum, and the abdomen was then closed in layers as above.

Splenectomy

In a series of four dogs, the abdomen was opened in the midline of the epigastrium. The spleen was easily delivered into the wound. A large splenic vein was isolated and portal pressure measured using a saline manometer. Splenectomy was then performed and the abdomen closed in layers in the usual fashion.

Ileoentectropy

The midline abdominal incision was again made and the omentum was resected close to the stomach. The terminal ileum was then delivered into the wound, and a three-to-four inch loop with

its mesentery and blood supply intact was excluded from the rest of the small intestine. End-to-end anastomosis of the ileum was performed, and the defect in the mesentery was closed. The excluded loop was then opened close to its antimesenteric border, following which hemostasis was obtained. The serosal surface of the excluded segment was then abraded as was a suitable area of the anterior parietal peritoneum. The loop was then sutured, serosa to peritoneum, to this region. Antibiotic powder was placed in the peritoneal cavity, and the incision closed in layers without drainage.

During the course of the operation, the dogs were given previously collected non-crossmatched blood, and autogenous ascitic fluid or glucose in water or saline, up to a total volume of one to two litres. Postoperatively, until the return of peristalsis they were given parenteral fluids with vitamins and antibiotics, progressing to fluids and then solid food by mouth.

III. Evaluation of Operative Procedures

The protein of the ascitic fluid, which is predominantly albumin and globulin, is derived from the body reserves. Determinations of plasma proteins were done as an index of the effect of thoracic inferior vena cava constriction, and then plasma and ascitic fluid proteins in an attempt to determine the value of

the experimental relief operation. The Kjeldahl and salting-out techniques were the methods employed for these estimations.

Ascitic fluid also contains large quantities of electrolytes lost to the body when in the peritoneal cavity or when removed by paracentesis or external drainage. The quantities of sodium and potassium in ascitic fluid samples were determined in our laboratory using the internal standard flame photometer, while chloride values were established by Sendroy's Iodometric Chloride Titration Method.

It became apparent early in the course of this work that clinical evaluation of the volume of ascites as a guide to the usefulness of a specific procedure was grossly inadequate and very inadcurate. Neither the appearance of the animals nor their weights, which were inconstant, could be considered as exact evaluation. It was therefore decided to make use of some labelling substance to measure the volume of ascites and also the rate of absorption of ascitic fluid. For this prupose, the diazo dye, Evan's Blue or T-1824, was used. After injection into the peritoneal cavity, it reaches an equilibrium within thirty to sixty minutes. Removal of samples after this period of time allows for easy calculation of ascitic fluid volumes (7). In addition, at low concentrations of dye (0.004%), T-1824 migrates entirely with albumin, each mole of albumin binding eight to fourteen moles of dye. At 0.098% concentration, the Evan's Blue moves into the circulation with albumin, alpha and beta globulins (195).

Evan's Blue once absorbed into the circulation, disappears from the circulation in two phases in the dog and rabbit. Phase I, lasting about 30 minutes in the dog, is characterized by an early rapid decrease in plasma dye concentration, amounting to about 0.70 ± 0.04% per minute. The second phase, lasting between 60 and 240 minutes, is marked by a slower disappearance rate, 0.078 ± 0.01% lost per minute. The reticuloendothelial system is involved in Phase I only, and blockage by thorotrast or T-1824 will slow the initial rate of disappearance (97). The rate of disappearance of the dye from the circulation was not taken into account in any of the calculations.

Evan's Blue (Warner-Chilcott) was obtained in lots of 25 ampoules. Each ampoule contained 5.0 cc. of a 0.5% solution (equivalent to 0.452% of the anhydrous tetra sodium salt) of dye in water (25 mgm. dye per ampoule).

After removing samples of blood and ascitic fluid from the lightly anesthetized dog, a known quantity of Evan's Blue dye (40-75 mgm) was injected into the peritoneal cavity. Samples of both blood and ascitic fluid were then taken at half-hour intervals for a period of two hours. All specimens were heparinized (Upjohn) in order to prevent coagulation. Weights of the dogs were recorded, and the hematocrit determined. At the end of the two-hour period, a smaller known quantity (10 mgm.) dye was injected intravenously, and blood samples were taken at ten and twenty minutes after injection.

The optical density of each sample was obtained from the galvanometer reading on the Evelyn Photoelectric Microcolorimeter. The T-1824 concentration was determined from the optical density by using a "K" (calibration constant) value, after the method of Gibson and Evelyn (88). Galvanometer readings (G) were obtained for a number of known concentrations of T-1824 in dog plasma and ascites by setting up in duplicate a number of known standards to cover the galvanometer scale from five to ninety-nine. The photometric density (L) of the sample solution was analogous to the optical density as measured on a spectrophotometer. It was obtained from the formula $L = 2 - \text{Log } G$, and the value for K was obtained from the formula $K = \frac{L}{C}$. K was found to be constant for all the G readings, indicating that the technique was logarithmic and in accordance with the laws of Beer and Lambert.

Standardization was repeated for each new lot of dye, and the K value was checked for each dog.

Maximum absorption of light by albumin labelled with T-1824 is about 620 mu. and the absorption of oxyhemoglobin, the pigment most commonly released in the plasma, is very low in this region, so that amounts of hemoglobin which can be detected visually are necessary to cause error in the Evan's Blue estimate. A correction for hemoglobin may be made using a 540 mu. filter, but tedious corrections for hemolysis are eliminated except in grossly hemolyzed

samples by using T-1824 (96). In the present experiments, corrections for hemoglobin were not made as grossly hemolyzed specimens were discarded.

IV. Autopsy

All animals used in this experiment have been autopsied with particular attention to the chest cavity and lungs, the liver, the peritoneal cavity and its contents, and the prevesical space. Histological slides have been made of suitable material to provide additional means of interpreting the results.

# CHAPTER VIII.

## RESULTS

### Constriction of the Inferior Vena Cava

A total of 70 dogs underwent the operation of thoracic inferior vena cava constriction. In 46 the small ring was applied, while in 24, the size of the vessel permitted the use of the larger ring containing ameroid. The hygroscopic material absorbed water so that it circumferentially constricted the vessel by about 50 - 60% of its original diameter, similar to the smaller ring.

All dogs which survived this procedure developed ascites within two to three weeks of the operation. Loss of body protein and tissue mass was evident within about one week after constriction. Twenty-three dogs showed impairment of wound healing in the chest incision, ranging from slight breakdown of the suture line to complete separation of the skin with purulent exudation.

Total plasma protein before operation ranged from 5.16 - 8.78 gms%, with a mean of 6.74 gms% (S.D. = 0.85). Albumin levels were from 2.87 - 5.92 gms% with a mean of 4.49 gms% (S. D. = 0.65). The globulin levels of the plasma varied in the dogs between 0.22 and 3.81 gms% with a mean value of 2.25 gms%. (S.D. = 0.88). Postoperatively, the total proteins were decreased to a range of 4.22 - 7.94 gms%; the mean was 5.43 gms%. (S.D. = 0.94). Albumin levels ranged from 1.96 - 4.52 gms%, with a

mean of 3.12 gms% (S.D. = 0.61); the globulins varied from 1.23 - 4.40 gms%, with a mean of 2.31 gms% (S.D. = 0.72). (Tables IX and X).

| DOG NUMBER | TOTAL PROTEIN | ALBUMIN | GLOBULIN |
|---|---|---|---|
| 1 | 6.65 | 4.96 | 1.69 |
| 2 | 6.80 | 5.06 | 1.74 |
| 3 | 6.67 | 5.17 | 1.50 |
| 4 | 5.85 | 3.73 | 2.12 |
| 5 | 6.36 | 4.75 | 1.61 |
| 6 | 6.25 | 4.11 | 2.14 |
| 7 | 6.52 | 4.52 | 2.00 |
| 8 | 6.42 | 3.82 | 2.60 |
| 9 | 5.84 | 2.87 | 2.97 |
| 10 | 7.74 | 4.62 | 3.12 |
| 11 | 7.81 | 4.60 | 3.21 |
| 12 | 5.35 | 4.50 | .85 |
| 14 | 5.93 | 4.61 | 1.32 |
| 15 | 7.42 | 5.05 | 2.37 |
| 16 | 6.77 | 4.06 | 2.77 |
| 17 | 7.08 | 4.95 | 2.13 |
| 18 | 6.38 | 4.88 | 1.50 |
| 19 | 6.62 | 4.67 | 1.95 |
| 20 | 6.02 | 4.35 | 1.67 |
| 22 | 7.95 | 4.79 | 3.16 |
| 23 | 8.06 | 4.46 | 3.60 |
| 25 | 6.26 | 3.16 | 3.10 |
| 26 | 6.92 | 3.70 | 3.22 |
| 27 | 6.80 | 4.20 | 2.60 |
| 28 | 6.97 | 5.06 | 1.91 |
| 29 | 5.64 | 5.42 | .22 |
| 30 | 5.76 | 5.25 | .51 |
| 31 | 5.76 | 3.33 | 2.43 |
| 32 | 5.64 | 5.35 | .29 |
| 33 | 7.94 | 5.41 | 2.53 |
| 34 | 7.14 | 4.97 | 2.17 |
| 35 | 8.58 | 5.13 | 3.45 |
| 36 | 6.87 | 4.79 | 2.08 |
| 37 | 7.50 | 4.51 | 2.99 |
| 38 | 7.25 | 4.47 | 2.78 |
| 39 | 5.50 | 4.36 | 1.14 |
| 41 | 6.26 | 4.68 | 1.58 |
| 42 | 6.45 | 4.60 | 1.85 |
| 43 | 6.97 | 4.35 | 2.62 |
| 44 | 6.70 | 3.64 | 3.06 |
| 45 | 6.81 | 5.17 | 1.64 |
| 46 | 5.53 | 4.00 | 1.53 |
| 47 | 7.72 | 4.84 | 2.88 |
| 48 | 7.39 | 3.86 | 3.53 |
| 49 | 6.48 | 5.92 | .56 |
| 50 | 5.44 | 3.14 | 2.30 |
| 51 | 5.77 | 3.51 | 2.26 |
| 53 | 6.19 | 4.49 | 1.70 |
| 54 | 6.36 | 3.84 | 2.52 |
| 55 | 5.70 | 3.64 | 2.06 |
| 56 | 5.16 | 4.27 | .89 |
| 57 | 6.34 | 3.12 | 3.22 |
| 58 | 7.06 | 4.75 | 2.31 |
| 59 | 8.66 | 5.10 | 3.56 |
| 60 | 7.05 | 5.22 | 1.83 |
| 61 | 6.04 | 3.90 | 1.14 |
| 62 | 5.90 | 4.60 | 1.30 |
| 63 | 7.09 | 4.95 | 2.14 |
| 64 | 7.50 | 3.91 | 3.59 |
| 65 | 7.93 | 5.36 | 2.57 |
| 67 | 7.65 | 4.37 | 3.28 |
| 69 | 8.78 | 5.39 | 3.39 |
| 70 | 6.35 | 4.97 | 1.38 |
| 71 | 8.04 | 4.67 | 3.37 |
| 72 | 7.76 | 3.97 | 3.81 |

TABLE IX.

PREOPERATIVE PLASMA PROTEIN LEVELS
(Grams/100 ml)

PLASMA PROTEIN LEVELS AFTER INFERIOR VENA CAVA CONSTRICTION ( GRAMS/ 100 ML. )

| DOG NUMBER | TOTAL PROTEIN | ALBUMIN | GLOBULIN |
|---|---|---|---|
| 3 | 4.76 | 2.32 | 2.44 |
| 4 | 5.00 | 2.89 | 2.11 |
| 8 | 7.10 | 2.70 | 4.40 |
| 48 | 4.40 | 2.83 | 1.57 |
| 66 | 6.41 | 3.95 | 2.46 |
| 63 | 7.94 | 4.52 | 3.42 |
| 22 | 4.71 | 3.37 | 1.34 |
| 20 | 5.90 | 3.63 | 2.27 |
| 46 | 5.34 | 2.72 | 2.62 |
| 47 | 5.47 | 3.32 | 2.15 |
| 37 | 5.03 | 3.29 | 1.74 |
| 45 | 6.00 | 3.82 | 2.18 |
| 57 | 5.00 | 2.61 | 2.39 |
| 58 | 4.96 | 3.51 | 1.45 |
| 59 | 5.57 | 1.96 | 3.61 |
| 7 | 4.96 | 3.50 | 1.46 |
| 10 | 4.64 | 2.39 | 2.25 |
| 14 | 6.29 | 3.06 | 3.23 |
| 17 | 5.01 | 3.05 | 1.96 |
| 18 | 4.22 | 2.99 | 1.23 |

TABLE X.

## Characteristics of the Ascitic Fluid

Measurements of the volume of ascites were carried out in most animals. In some the volume was estimated only. The range was wide, varying from 50 - 7,000 ccs. (Table XI). Specific gravity was determined with the hydrometer and ranged from 1010 to 1026. The color of the fluid was usually yellowish-grey in color, and clear to slightly opalescent.

Protein determinations were done on 17 samples of ascitic fluid from dogs which underwent IVC constriction alone. Total protein ranged from 1.94 - 4.86 gms%, with a mean value of 3.49 gms% (S.D. = 0.78). The albumin varied between 0.54 and 2.94 gms%, the mean value being 2.07 gms% (S.D. = 0.66). Globulin values in untreated dogs' ascites ranged from 0.71 - 2.21 gms%, with a mean of 1.42 gms% (S.D. = 0.51). (Table XII).

Electrolyte concentrations in the ascitic fluid were determined in 10 samples. Sodium ranged from 140.0 - 154.7 meq./l., with a mean of 148.8 meq./l. (S.D. = 5.03). Potassium levels ranged from 3.00 - 4.57 meq./l., the mean value being 3.62 meg./l. (S.D. = 0.55). The chloride levels had a mean content of 113.6 meq./l., ranging from 98.9 - 120.6 meq./l. (S.D. = 6.07). (Table XIII).

## Operations Performed for Relief of Ascites

Six different operations were performed on randomly selected

ASCITES VOLUMES CALCULATED BY EVAN'S BLUE DILUTION MEASUREMENTS

I. INFERIOR VENA CAVA CONSTRICTION ALONE

| DOG NUMBER | DOG WEIGHT (lbs.) | VOLUME (mls.) |
|---|---|---|
| 1 | 25 | 1300 |
| 7 | 34 | 2300 |
| 10 | 32 | 52 |
| 14 | 32 | 700 |
| 17 | 38 | 490 |
| 18 | 38 | 3000 |
| 20 | 30 | 2800 |
| 22 | 45 | 5500 |
| 37 | 51 | 5218 |
| 46 | 27 | 1368 |
| 47 | 35 | 1250 |
| 48 | 17 | 732 |
| 58 | 32 | 182 |
| 61 | 32 | 1608 |

II. "CORRECTIVE" OPERATION PERFORMED AT SAME TIME AS IVC CONSTRICTION

| DOG NUMBER | OPERATION | WEIGHT (lbs.) | VOLUME (mls.) |
|---|---|---|---|
| 41 | Polythene to prevesical space | 30 | 97 |
| 33 | Omentopexy | 30 | 2954 |
| 35 | " | 60 | 467 |
| 38 | " | 30 | 3268 |
| 39 | " | 25 | 667 |
| 43 | " | 22 | 338 |
| 44 | " | 24 | 944 |
| 50 | " | 20 | 756 |
| 51 | " | 18 | 262 |
| 72 | Silicone rubber to prevesical space | 40 | 1645 |

III. "CORRECTIVE" OPERATION PERFORMED AFTER IVC CONSTRICTION

| DOG NUMBER | OPERATION | WEIGHT (lbs.) | VOLUME (mls.) |
|---|---|---|---|
| 20 | Omentopexy | 34 | 1487 |
| 20 | " | 34 | 1852 |
| 47 | " | 30 | 3760 |
| 35 | Omentopexy plus splenectomy | 42 | 2892 |
| 44 | " | 28 | 1382 |
| 37 | Ileo-entectropy | 52 | 6422 |
| 63 | Silicone rubber to prevesical space | 37 | 1412 |

TABLE XI.

PROTEIN LEVELS IN ASCITIC FLUID AFTER INFERIOR VENA CAVA CONSTRICTION
( GRAMS /100 ML.)

| DOG NUMBER | TOTAL PROTEIN | ALBUMIN | GLOBULIN |
|---|---|---|---|
| 3 | 3.43 | 1.94 | 1.49 |
| 4 | 2.27 | 0.54 | 1.73 |
| 48 | 3.89 | 2.26 | 1.63 |
| 66 | 4.64 | 2.94 | 1.70 |
| 7 | 2.95 | 1.76 | 1.19 |
| 10 | 1.94 | 1.23 | 0.71 |
| 14 | 3.78 | 2.49 | 1.29 |
| 17 | 3.54 | 2.32 | 1.22 |
| 18 | 3.89 | 2.54 | 1.35 |
| 37 | 3.61 | 2.04 | 1.57 |
| 45 | 4.41 | 2.58 | 1.83 |
| 58 | 3.25 | 2.31 | 0.94 |
| 63 | 4.86 | 2.65 | 2.21 |
| 20 | 3.93 | 2.83 | 1.10 |
| 46 | 3.33 | 1.85 | 1.48 |
| 47 | 2.70 | 1.00 | 1.70 |
| 22 | 2.92 | 1.88 | 1.04 |

TABLE XII.

ELECROLYTE COMPOSITION OF ASCITES ( MILLIEQUIVALENTS / LITRE )

| Sodium | Potassium | Chloride |
|---|---|---|
| 150 | 3.57 | 110.6 |
| 147.1 | 4.00 | 117.5 |
| 154.7 | 4.43 | 112.0 |
| 153.1 | 3.14 | 117.3 |
| 146.5 | 3.57 | 117.5 |
| 153.1 | 4.57 | 115.0 |
| 151.3 | 3.43 | 115.0 |
| 150.6 | 3.00 | 120.6 |
| 140.0 | 3.00 | 98.9 |
| 141.1 | 3.52 | 111.9 |

TABLE XIII.

dogs in an attempt to ameliorate the ascites. These are listed in Table XIV, which also includes the number of animals on which each procedure was used. Thus, a total of 52 operations were performed on 47 different dogs. The other animals either died or were sacrificed after undergoing inferior vena cava constriction alone; the causes of their deaths are included in Table XXIII.

All dogs which died less than two weeks after the "corrective" operation designed to relieve their ascites are listed in Table XV. The two week period is of significance in that at least that time is required for ascites to appear, and for the definitive operation to begin its desired improvement effects. The time that the relief operation was performed is listed in Table XVI. From combining these two, it is found that 29 out of the 47 animals did not survive long enough to properly evaluate the effects of operation. The days that each animal survived are listed in Table XVII. At first glance it appears that one can analyse readily the comparative survivals of dogs after each of the various operations. This is not possible because exact statistical analysis is precluded as many of the ameliorative procedures were performed at the same time as the inferior vena cava constriction. Less accurate examination of the figures as a group is possible, and certain trends are demonstrated.

OPERATIONS PERFORMED FOR RELIEF OF ASCITES

| OPERATION | DOGS' SERIES NUMBERS | TOTAL NUMBER OF DOGS |
|---|---|---|
| Polythene to exterior | 1,7,10,14,17,18,23 | 7 |
| Prosthesis to prevesical space | | |
| a)Polythene | 22,24,26,27,29,31,36,41, 52,56 | 10 |
| b)Silicone rubber | 61,63,69,70,71,72 | 6 |
| Omentopexy | 20,25,30,32,33,35,38,39, 42,43,44,46,47,50,51 | 15 |
| Omentopexy plus splenectomy later | 35,44,47,51 | 4 |
| Ileo-entectropy | 37,40,45,53,55,57,58,59, 60 | 9 |

47 dogs underwent 52 operations; one dog required a second operation after biting off the tube to the exterior from the polythene prosthesis within the peritoneal cavity.

TABLE XIV.

DOGS DYING WITHIN TWO WEEKS OF "CORRECTIVE" OPERATION

| TIMING OF OPERATION | TYPE OF "CORRECTIVE" PROCEDURE EMPLOYED | | | | |
|---|---|---|---|---|---|
| | Polythene to exterior | Polythene to prevesical space | Silicone rubber to p.v. space | Oment-opexy | Ileo-entect-ropy |
| Same time as IVC constriction | 0 | 6 | 3 | 2 | 0 |
| Later than IVC constriction | 7 | 1 | 1 | 1 | 5 |
| Before IVC constriction | 0 | 1 | 0 | 0 | 1 |
| TOTALS | 7 | 8 | 4 | 3 | 6 |

TABLE XV.

TIME OF PERFORMANCE OF "CORRECTIVE" OPERATION

| TIME | TYPE OF OPERATION | | | | |
|---|---|---|---|---|---|
| | Polythene to exterior | Polythene to p.v.space | Silicone rubber to p.v.space | Omento-pexy | Ileo-entectropy |
| Same time as IVC constriction | 0 | 7 | 4 | 12 | 1 |
| Later than IVC constriction | 7 | 2 | 2 | 3 | 7 |
| Before IVC constriction | 0 | 1 | 0 | 0 | 1 |
| TOTALS (47) | 7 | 10 | 6 | 15 | 9 |

TABLE XVI.

SURVIVAL OF DOGS AFTER VARIOUS OPERATIVE PROCEDURES

| OPERATION | SURVIVAL (DAYS) |
|---|---|
| Polythene to exterior | 1,2,3,9,3,5,8 (31)# |
| Polythene to prevesical space | 15,12,6,10,3,10,13,23,19,2 (113)# |
| Silicone rubber to prevesical space | 1,25,4,16,11,11 (68)# |
| Omentopexy | 27,14,6,13,30,130,33,60,150,21,86,30,40, 44,76 (760)# |
| Ileo-entectropy | 44,2,13,8,60,2,14,1,9 (153)# |
| IVC constriction alone | 1,25,22,30,27,15,8,27,18,1,1,13,33,1,5,0, 21,30,1,9,12,10,0,4,7 (331)# |

# represents total for group

TABLE XVII.

The external drainage of ascites by means of the polythene prosthesis inserted within the peritoneal cavity with a conducting tube to the outside was associated with the shortest periods of survival. The animals which survived 5, 8 and 9 days all received daily infusions of fluid and electrolytes on an empirical basis. Each of the animals had no ascites at autopsy; the bag collecting the ascites contained some fluid, but most had drained to the outside via the fistula created by the tube and by leaking around it.

The use of polythene or silicone rubber with the conducting tube to the prevesical space was associated with longer survival. These groups, however, show no difference between them. The results of the operations with regard to the ascites volumes and the effects of the prosthesis will be reviewed later.

The group of dogs which underwent omentopexy survived longer than any others, while those which survived the operation of ileo-entectropy are intermediate in position.

Most of the figures for inferior vena cava constriction alone are useful. These dogs lived on the average probably as long as any group other than those on which omentopexy was performed.

Protein Levels After "Corrective" Operations

Plasma and ascites proteins were examined in all dogs which survived for at least two weeks after the definitive procedure to

relieve ascites was performed. Each operation cannot be considered separately as the numbers of animals in each group was too small.

The total plasma protein of dogs after relief procedures ranged from 3.76 - 8.84 gms% with a mean of 5.30 gms% (S.D. = 1.32). Albumin levels ranged from 2.24 - 3.60 gms%, with a mean of 2.80 gms% (S.D. = 0.47). Globulins varied from 1.30 - 5.52 gms%, the mean being 2.50 gms% (S.D. = 1.19). (Table XVIII).

POSTOPERATIVE PLASMA PROTEIN LEVELS AFTER "CORRECTIVE" OPERATION PERFORMED AT SAME TIME AS INFERIOR VENA CAVA CONSTRICTION ( GRAMS/ 100 ML. )

| DOG NUMBER | OPERATION | TOTAL PROTEIN | ALBUMIN | GLOBULIN |
|---|---|---|---|---|
| 33 | Omentopexy | 4.84 | 3.35 | 1.49 |
| 35 | " | 5.22 | 2.73 | 2.49 |
| 38 | " | 4.98 | 2.24 | 2.74 |
| 39 | " | 4.90 | 3.60 | 1.30 |
| 42 | " | 8.84 | 3.32 | 5.52 |
| 43 | " | 5.11 | 2.58 | 2.53 |
| 44 | " | 5.38 | 2.77 | 2.61 |
| 51 | " | 5.00 | 2.68 | 2.32 |
| 41 | Polythene to prevesical space | 5.02 | 2.48 | 2.54 |
| 72 | Silicone rubber to prevesical space | 3.76 | 2.26 | 1.50 |

TABLE XVIII.

The progression of plasma proteins in those dogs which survived longer was also determined by examining samples taken at two-week intervals. The total protein range was 4.23 - 7.72 gms%

with a mean of 5.58 gms% (S.D. = 0.97). The mean albumin value was 2.60 gms%, with variation between 2.08 and 3.09 gms% (S.D. = 0.31). Globulins ranged from 1.51 - 4.88 gms%, the mean being 2.98 gms% (S.D. = 0.84). (Table XIX).

PROGRESSION OF PLASMA PROTEINS AFTER CORRECTIVE OPERATION ( GRAMS/ 100 ML.)

| DOG NUMBER | OPERATION | TOTAL PROTEIN | ALBUMIN | GLOBULIN |
|---|---|---|---|---|
| 22 | Polythene to prevesical space | 5.82 | 3.09 | 2.73 |
| 20 | Omentopexy | 4.72 | 2.60 | 2.12 |
| 20 | " | 5.69 | 2.64 | 3.05 |
| 20 | " | 4.23 | 2.72 | 1.51 |
| 35 | " | 4.71 | 2.08 | 2.63 |
| 35 | " | 5.52 | 2.43 | 3.09 |
| 35 | " | 7.04 | 2.72 | 4.32 |
| 42 | " | 7.72 | 2.84 | 4.88 |
| 44 | " | 5.16 | 2.79 | 2.37 |
| 47 | " | 5.43 | 2.49 | 2.94 |
| 47 | " | 4.94 | 2.12 | 2.82 |
| 51 | " | 6.26 | 2.94 | 3.32 |
| 63 | Silicone rubber to prevesical space | 4.80 | 2.15 | 2.65 |
| 37 | Ileo-entectropy | 4.91 | 2.57 | 2.34 |
| 55 | " | 6.99 | 3.04 | 3.95 |
| 58 | " | 5.34 | 2.36 | 2.98 |

TABLE XIX.

The ascites total protein range in those dogs which underwent the "corrective" operation at the same time as IVC constriction was 2.91 - 3.95 gms% (mean = 3.53 gms%; S.D. = 0.33). The albumin levels varied from 1.68 - 2.26 gms% (mean = 1.97 gms%;

S.D. = 0.33). Globulins ranged from 0.86 - 2.23 gms%, the mean value being 1.56 gms% (S.D. = 0.42). (Table XX).

**ASCITIC PROTEIN LEVELS AFTER "CORRECTIVE" OPERATION PERFORMED AT SAME TIME AS INFERIOR VENA CAVA CONSTRICTION (GRAMS/ 100 ML.)**

| DOG NUMBER | OPERATION | TOTAL PROTEIN | ALBUMIN | GLOBULIN |
|---|---|---|---|---|
| 41 | Polythene to prevesical space | 3.75 | 1.74 | 2.01 |
| 33 | Omentopexy | 3.35 | 2.26 | 1.09 |
| 35 | " | 3.67 | 1.95 | 1.72 |
| 38 | " | 3.29 | 1.68 | 1.61 |
| 39 | " | 3.95 | 3.09 | 0.86 |
| 43 | " | 3.39 | 1.70 | 1.69 |
| 44 | " | 3.79 | 2.08 | 1.71 |
| 46 | " | 3.33 | 1.85 | 1.48 |
| 57 | " | 3.91 | 1.68 | 2.23 |
| 72 | Silicone rubber to prevesical space | 2.91 | 1.72 | 1.19 |

TABLE XX.

Ascites total protein progression after "corrective" operations was such that the range of values was from 2.73 - 4.17 gms%, with a mean of 3.33 gms% (S.D. = 0.56). The albumins fell into the 1.14 - 2.07 gms% range; the mean value was 1.59 gms% (S.D. = 0.24). Globulins ranged from 0.99 - 2.38 gms%, with a mean of 1.74 gms%. (S.D. = 0.41). (Table XXI).

PROGRESSION OF ASCITIC PROTEINS AFTER "CORRECTIVE" OPERATION (GRAMS/100 ML)

| DOG NUMBER | OPERATION | TOTAL PROTEIN | ALBUMIN | GLOBULIN |
|---|---|---|---|---|
| 37 | Ileo-entectropy | 2.94 | 1.55 | 1.39 |
| 55 | " | 3.67 | 1.80 | 1.87 |
| 63 | Silicone rubber to prevesical space | 2.52 | 1.53 | 0.99 |
| 20 | Omentopexy | 3.42 | 1.50 | 1.92 |
| 20 | " | 3.96 | 1.89 | 2.07 |
| 20 | " | 4.11 | 1.73 | 2.38 |
| 35 | " | 2.76 | 1.49 | 1.27 |
| 35 | " | 3.27 | 1.45 | 1.82 |
| 35 | " | 3.98 | 1.65 | 2.33 |
| 44 | " | 3.04 | 1.59 | 1.45 |
| 47 | " | 3.16 | 1.31 | 1.85 |
| 47 | " | 2.73 | 1.14 | 1.59 |
| 51 | " | 4.17 | 2.07 | 2.10 |

TABLE XXI.

The Incidence and Volume of Ascites After "Corrective" Operations

I. Omentopexy

Of 12 dogs surviving longer than two weeks after this procedure, 9 had ascites, while 3 did not. Three of those which had abdominal accumulations had only a small volume of ascites. One dog with ascites also had a pleural effusion at autopsy.

II. Omentopexy followed by Splenectomy Later

All four animals which underwent splenectomy later had ascites. In three, the volume at autopsy was minimal, while in the fourth, the amount was moderate. Only one of those dogs which had a small quantity of ascites after omentopexy also had

splenectomy. The other two were animals whose ascites was apparently decreased by splenectomy.

III. Polythene Prosthesis with Drainage to Exterior

As stated above, none of these animals showed any ascites at autopsy; neither did any survive two weeks postoperatively.

IV. Polythene Prosthesis with Drainage to Prevesical Space

Only three of this series lived the required two-week period. All of these dogs showed only minimal ascites at autopsy.

V. Silicone Rubber Prosthesis with Drainage to Prevesical Space

Only two of this group survived the arbitrary two-week period required to evaluate the efficacy of the operation. Both of these animals showed massive volumes of ascites at autopsy.

VI. Ileo-entectropy

Three of this series survived two weeks or longer after operation . Two of these showed large volumes of ascites, while the third only had a minimal collection of fluid. Two dogs also had a pleural effusion at autopsy.

Calculated volumes of ascites appear in Table XI. These were determined from optical density readings after removal of samples from the peritoneal cavity. A measured amount of Evan's Blue dye had previously been injected into the peritoneal cavity.

The formulas used for calculations follow:

a) For calculation of concentration of dye in ascites:

$$\frac{\text{Optical Density (O.D.)}}{\text{Constant (K)}} = \text{Concentration (milligrams/litre)}$$

b) For calculation of ascites volume:

$$\frac{\text{Quantity of Dye Injected (mg)}}{\text{Concentration in Ascites (mg/l)}} = \text{Volume of Ascites (litres)}$$

The Absorption of Ascites

A total of 23 series of determinations was performed on dogs with ascites.

Simple calculations using the dog's weight, concentration of dye in the plasma, concentration of dye in ascites, and plasma volume permitted a determination of the volume of ascites absorbed per hour.

I. Determination of Plasma Volume - after intravenous injection of dye:

a) $\frac{\text{Optical Density of Sample (O.D.)}}{\text{Constant (K)}}$ = Concentration of Dye in Plasma (mg./l)

b) $\frac{\text{Quantity of Dye Injected (mg)}}{\text{Concentration of Dye in Plasma (mg/l)}}$ = Plasma Volume (litres)

II. Determination of Volume of Ascites Absorbed:

$$\frac{\text{Concentration of Dye in Plasma (mg/l/hr) x Plasma Vol. (l.) x 1000}}{\text{Concentration of Dye in Ascites (mg/l) x Weight of Dog (lbs.)}}$$

= Volume of Ascites Absorbed (mls./lb/hr)

The values obtained by these computations are found in Table XXII. The marked variation between dogs and even within the same dog from time to time does not permit statistical analysis.

THE ABSORPTION OF ASCITES LABELED WITH EVAN'S BLUE DYE BY DOGS UNDER NEMBUTAL ANESTHESIA

| DOG NO. | OPERATION | DOG WT. (LBS.) | CONCENTRATION OF DYE IN ASCITES (MGR./L.) | CONCENTRATION OF DYE IN PLASMA (MGR./L.) | PLASMA VOLUME (MLS.) | VOLUME OF ASCITES ABSORBED (MLS./LB./HR.) |
|---|---|---|---|---|---|---|
| 48 | IVC constriction alone | 17 | 100.0 | 1.673 | 651 | 0.64 |
| 47 | " | 35 | 30.6 | 3.560 | 1094 | 0.41 |
| 61 | " | 32 | 62.8 | 1.905 | 1495 | 1.43 |
| 58 | " | 32 | 329.3 | 3.390 | 598 | 0.19 |
| 37 | " | 51 | 7.7 | 3.750 | 1242 | 11.85 |
| 46 | " | 27 | 52.9 | 1.510 | 893 | 0.94 |
| 20 | Omentopexy | 32 | 26.9 | 1.769 | 972 | 2.00 |
| 20 | " | 34 | 21.5 | 2.099 | 1015 | 2.91 |
| 33 | " | 30 | 13.4 | 1.247 | 894 | 2.76 |
| 35 | " | 60 | 85.6 | 3.740 | 809 | 0.59 |
| 38 | " | 30 | 12.3 | 0.854 | 1075 | 2.50 |
| 39 | " | 25 | 58.8 | 1.768 | 1196 | 1.28 |
| 43 | " | 22 | 99.6 | 1.300 | 898 | 0.48 |
| 44 | " | 24 | 768.0 | 2.090 | 767 | 0.89 |
| 47 | " | 35 | 30.6 | 3.560 | 1094 | 0.41 |
| 50 | " | 20 | 64.5 | 1.550 | 760 | 0.94 |
| 51 | " | 18 | 162.5 | 3.915 | 552 | 7.98 |
| 35 | Omentopexy & splenectomy | 42 | 34.4 | 2.665 | 1550 | 2.86 |
| 44 | " | 28 | 71.5 | 0.780 | 1105 | 0.44 |
| 37 | Ileo-entectropy | 52 | 11.2 | 2.083 | 1723 | 6.06 |
| 41 | Polythene to p.v. space | 30 | 276.5 | 3.384 | 544 | 0.35 |
| 63 | Silicone rubber to p.v. space | 37 | 6.7 | 1.484 | 1269 | 7.64 |
| 72 | " | 40 | 59.5 | 3.355 | 956 | 1.31 |

TABLE XXII.

Pathology Associated with Production and Relief of Ascites

I. The Liver after IVC Constriction (Figs. 14, 15 and 16)

All livers were enlarged and engorged with blood. Grossly, the cut surface showed evidence of passive congestion, with red central areas and paler lobular structure around them. Even those animals which did not have ascites showed this pattern. In no dog was excessive hepatic fibrosis present. Microscopically, the congestion was found to be most marked at the periphery of the liver, in the subcapsular areas. Fatty degeneration, with some loss of liver cells, edema, especially of centrilobular tissue and fading out toward the portal triad regions, was present to a variable degree in all sections examined. In addition, gram positive rods, probably Clostridia, were present in many sections. Small bile plugs, insufficient to interfere with function, were also scattered through many specimens.

The severity of changes was related to the duration of time after constriction of the vena cava. In no case was healing evident, but progression of the lesions was found in serial examinations of liver tissue from the same animals.

II. Wound Healing

Delay and actual failure of wound healing was evident in a large number of animals.

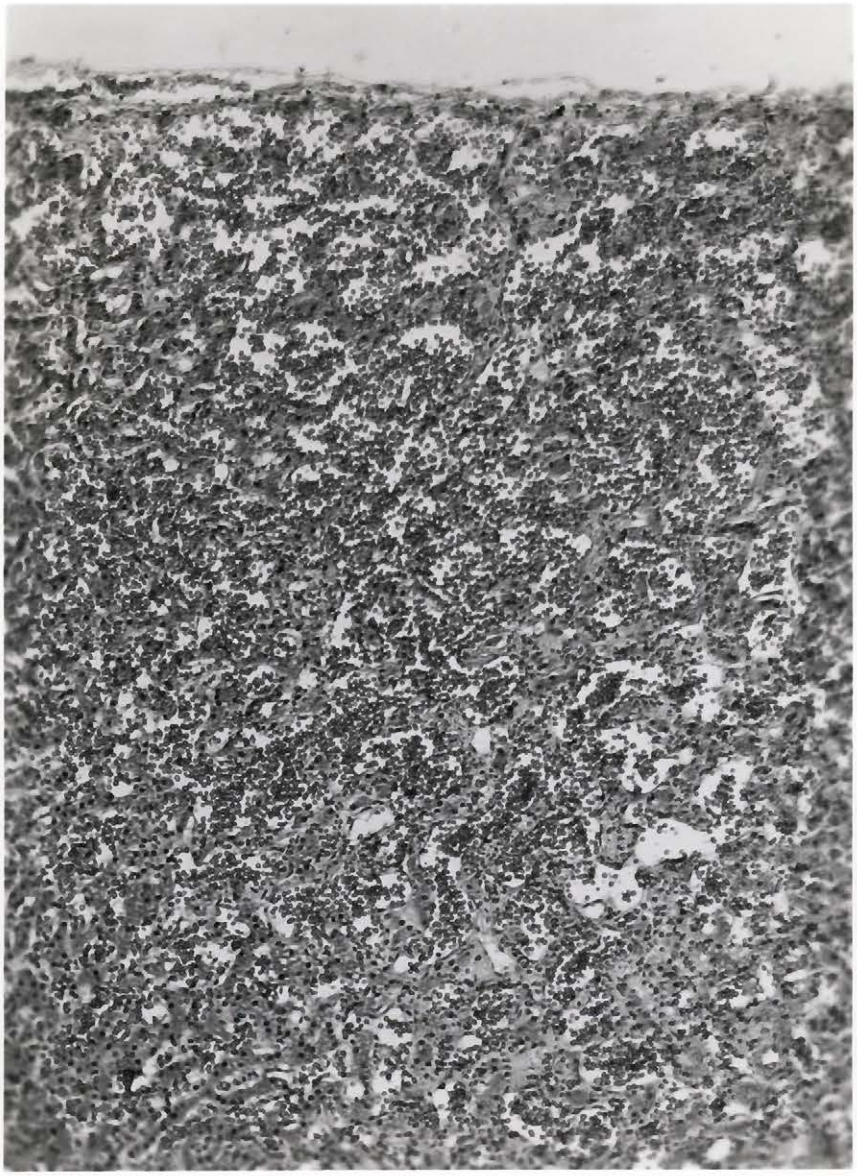

FIGURE 14.

Liver - subcapsular congestion and degeneration after IVC constriction. (x 115).

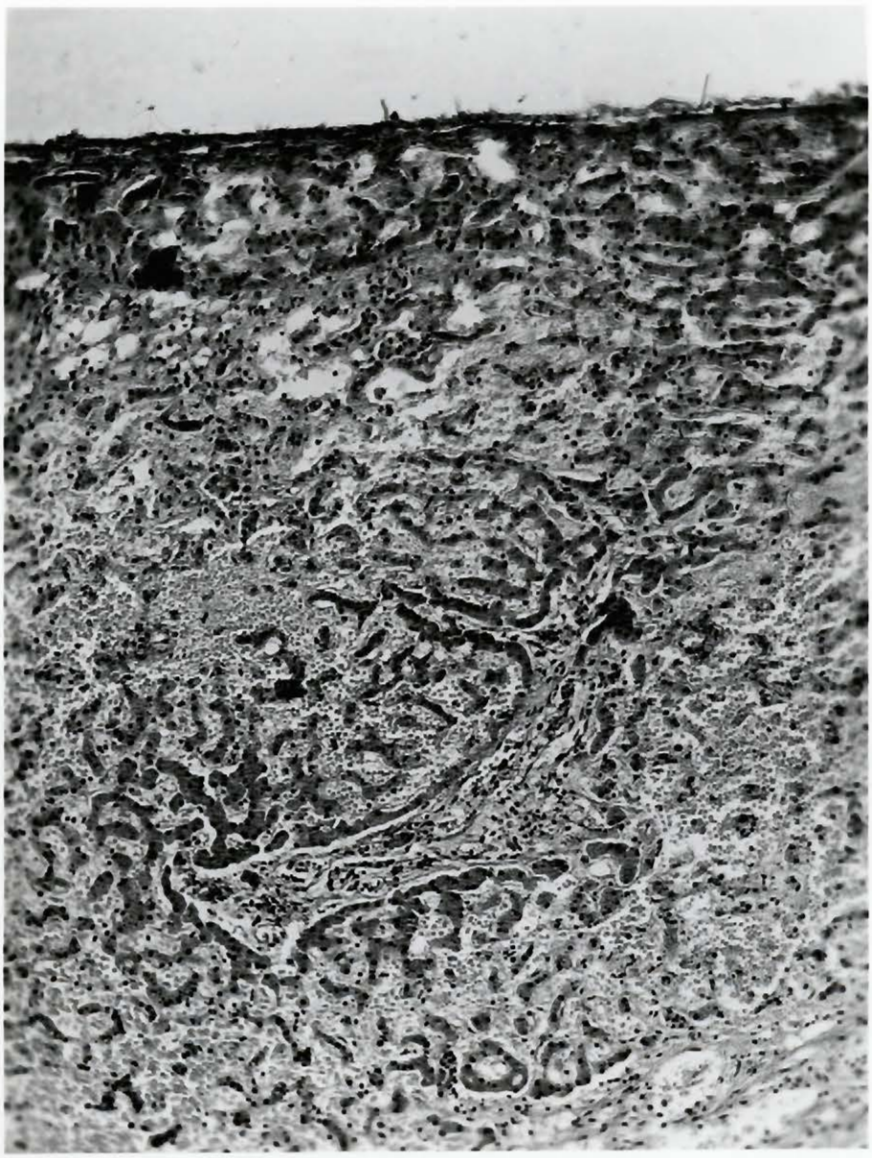

FIGURE 15.

More extensive loss of liver architecture after IVC constriction. (x 100).

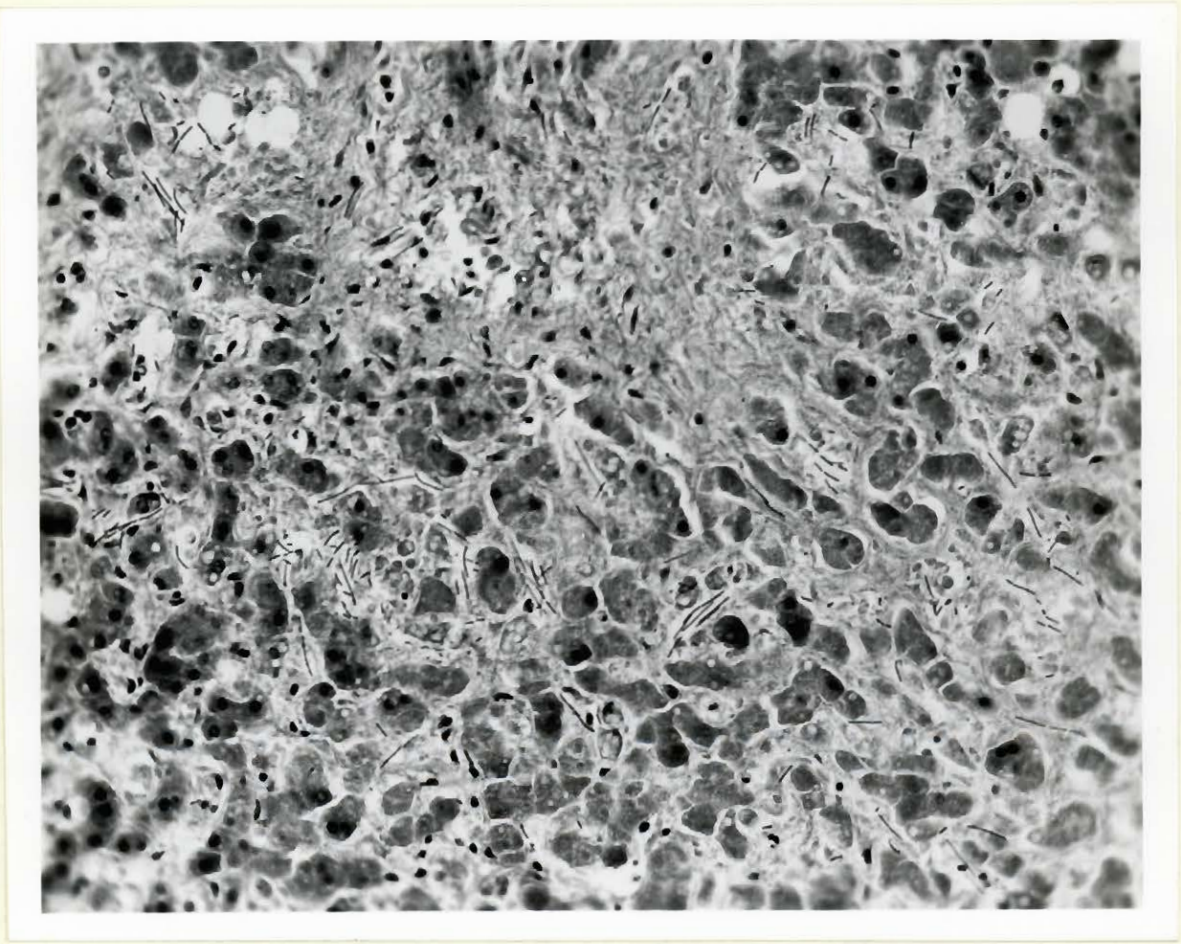

FIGURE 16.

Bacteria and degenerated liver parenchyma after IVC constriction. (x 200).

As mentioned earlier, many skin incisions, especially thoracic in location, showed impaired union with separation of skin edges and infection. This spreading of the wound and breakdown of tissue usually did not occur until at least one week after operation.

Similar delays were noted in the case of many animals which underwent abdominal procedures. Thus, for example, the omentum was not well adherent in many dogs, nor had union of serosa to peritoneum after ileo-entectropy taken place within periods of time to be expected after surgical intervention. Evisceration through abdominal wounds also occurred in three dogs at a later date than the complication usually takes place (8, 20 and 23 days post-operative).

III. The Portal Venous Pressure after IVC Constriction

In all four dogs which underwent splenectomy, the portal venous pressure was measured in a large splenic vein at the time of operation. These were 148, 160, 180 and 400 mm. of saline, with no correlation between the pressure reading and the volume of ascites.

IV. The Collateral Circulation after IVC Constriction

Within about two weeks after constricting the vena cava, large venous collaterals became evident. These were most marked on the anterior abdominal wall. Other prominent veins appeared

in the deeper tissues of the abdonimal wall, the mesentery and omentum, and the lower thoracic wall. All bled under increased pressure when cut.

V. The Omental-Retropubic Fat Junction (Figs. 17 and 18)

The reparative process here showed much variation. Most prominently, minimal to moderate chronic inflammation was apparent, especially in relation to sutures and necrotic fat cells. Most union was only fibrinous even after prolonged periods of lying in continuity. These areas were readily disrupted, the omentum separating easily from the prevesical fat. In some regions, an area of necrosis separated the two tissues, while in other regions a suggestion of joining by fibrosis and capillaries, and widely dilated blood vessels were seen. No dilated lymphatics were evident.

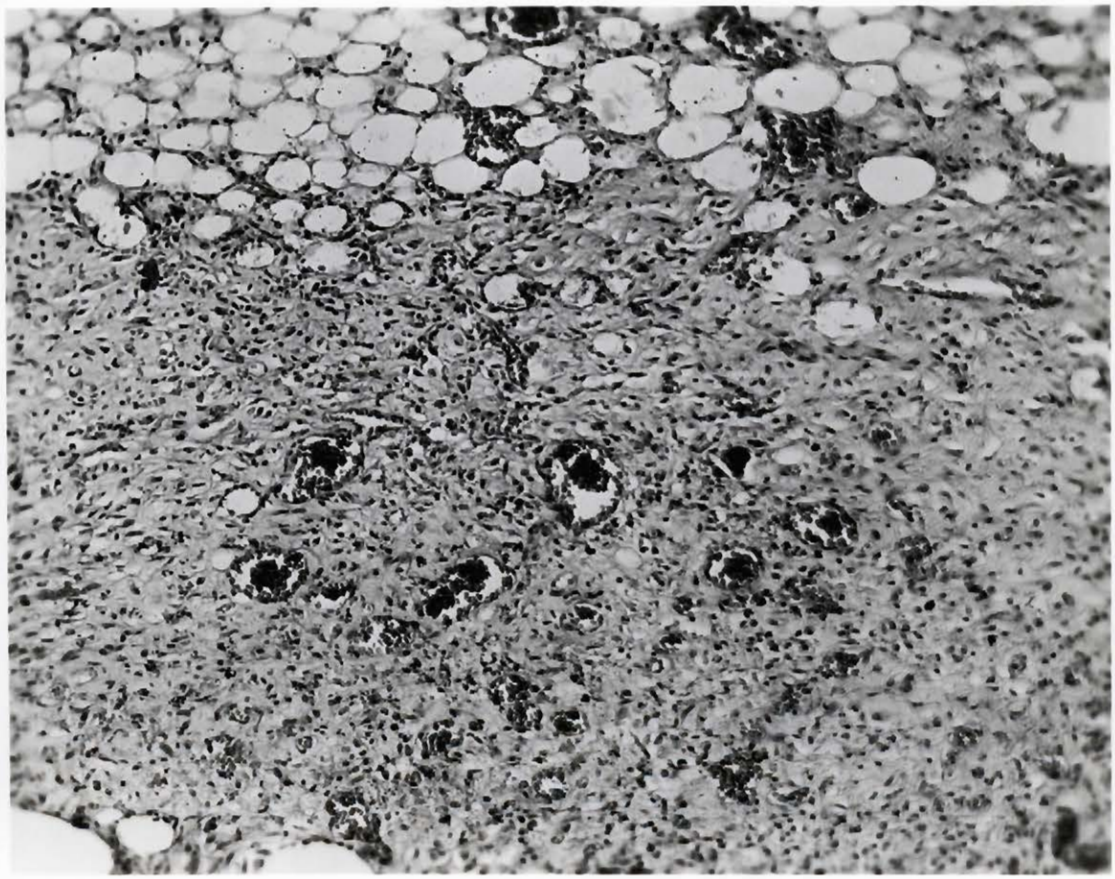

FIGURE 17.

New blood vessels in organizing scar tissue
at site of omental-retropubic fat anastomosis.
(x 100)

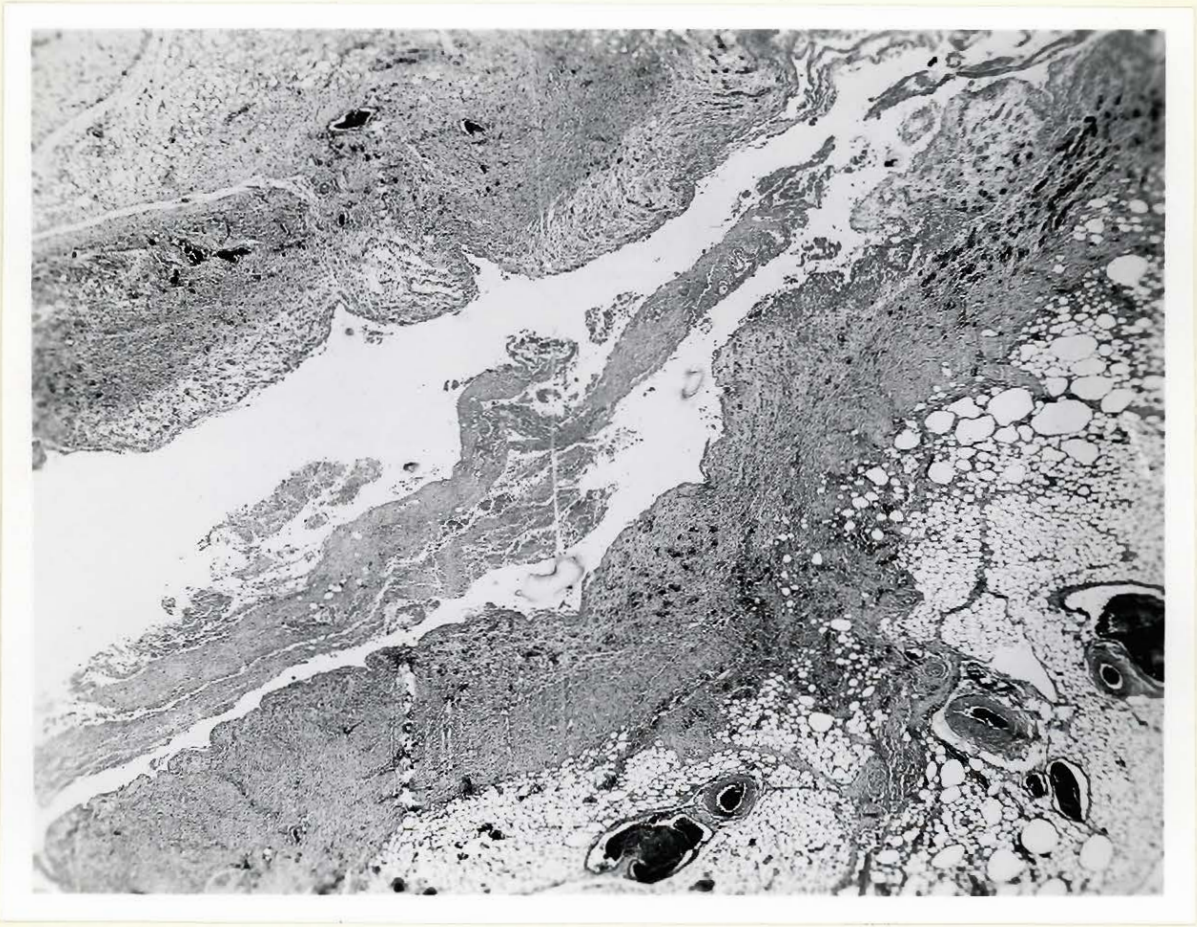

FIGURE 18.

Failure of attachment after omentopexy - fibrin separating omentum and retropubic fat. (x 25).

VI. Ileo-entectropy (Figs. 19 to 23)

Despite abrasion of the contiguous surfaces, fibrous union of the serosa of the excluded loop of ileum with the peritoneum was mainly confined to the areas surrounding suture points. Microscopically the bowel wall showed variable degrees of chronic ileitis extending from the mucosa through to the muscle coats. Chronic serositis and edema of the serosa were evident in many areas. The junction zones varied from fibrin and cellular deposits to poorly formed edematous collagen with feeble connective tissue; some areas, however, showed mature fibrous tissue with scattered inflammatory cells within it and large numbers of blood vessels.

Sound healing at the site of the bowel anastomosis was present in all animals.

VII. The Use of the Prosthesis

In 3 dogs the prosthesis and small bowel were adherent to each other by fibrin. (Fig. 24). Most of the other sieve portions of the polythene and silicone rubber showed fibrin plugging of many of the perforations. Clot was also present within the chambers of many prostheses as well as within their conducting tubes. Siliconizing the polythene before insertion into the dogs did not prevent clot formation, nor did injections of parenzymol exert any benefits.

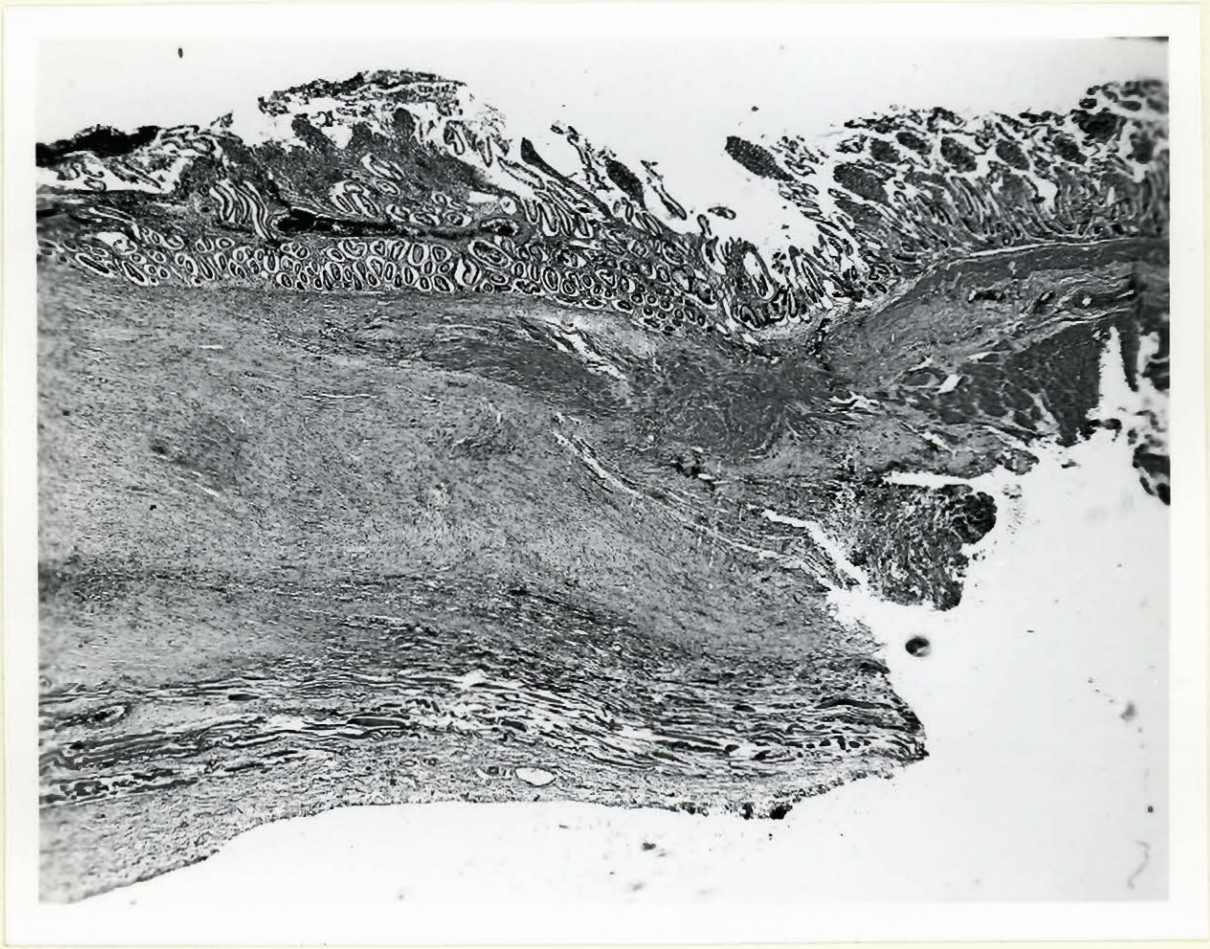

FIGURE 19.

Ileo-entectropy: Fusion of serosa to abdominal parietes at left; failure of fusion at right. (x 25).

FIGURE 20.

Ileo-entectropy: Organizing fibrous tissue at serosal-peritoneal junction. (x 100).

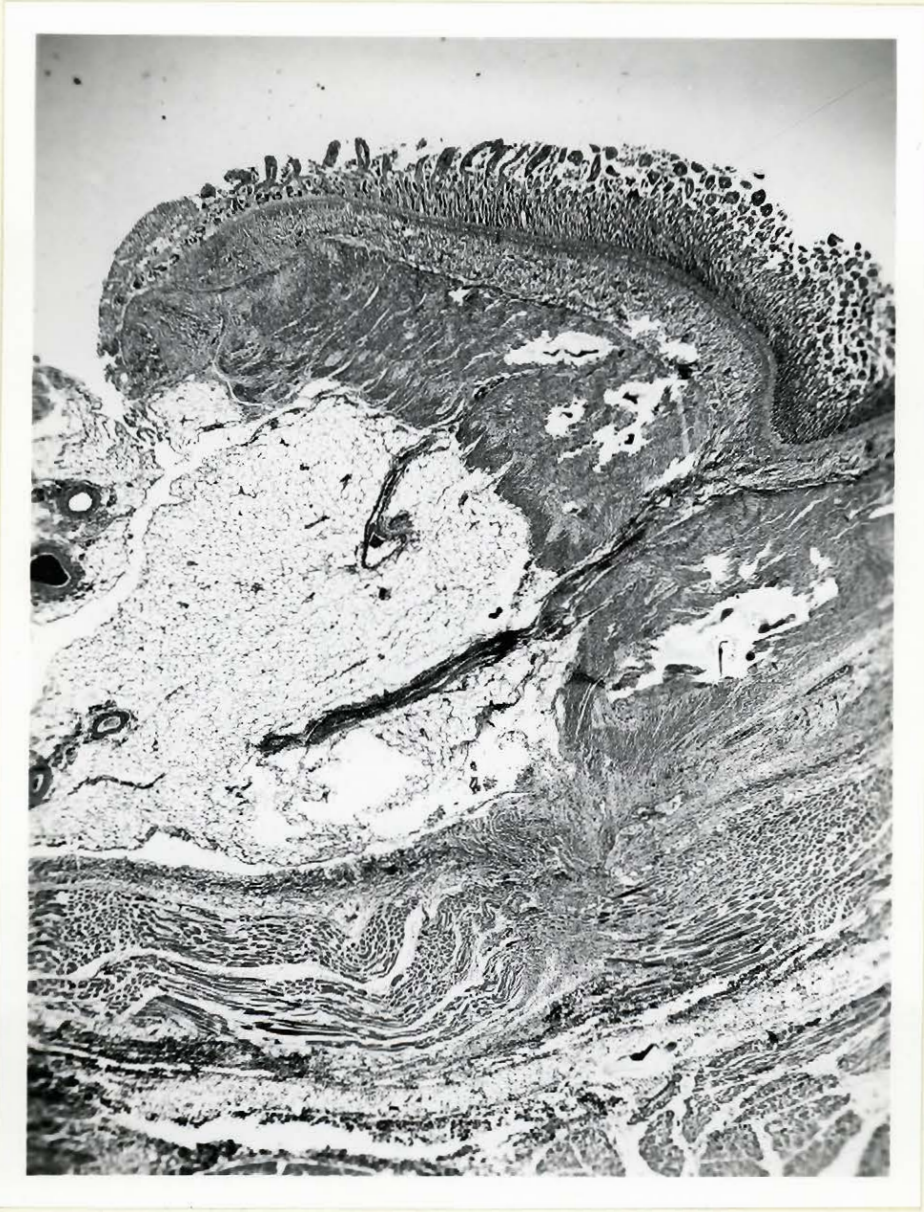

FIGURE 21.

Ileo-entectropy - interposition of areolar tissue between bowel and peritoneum. (x 20).

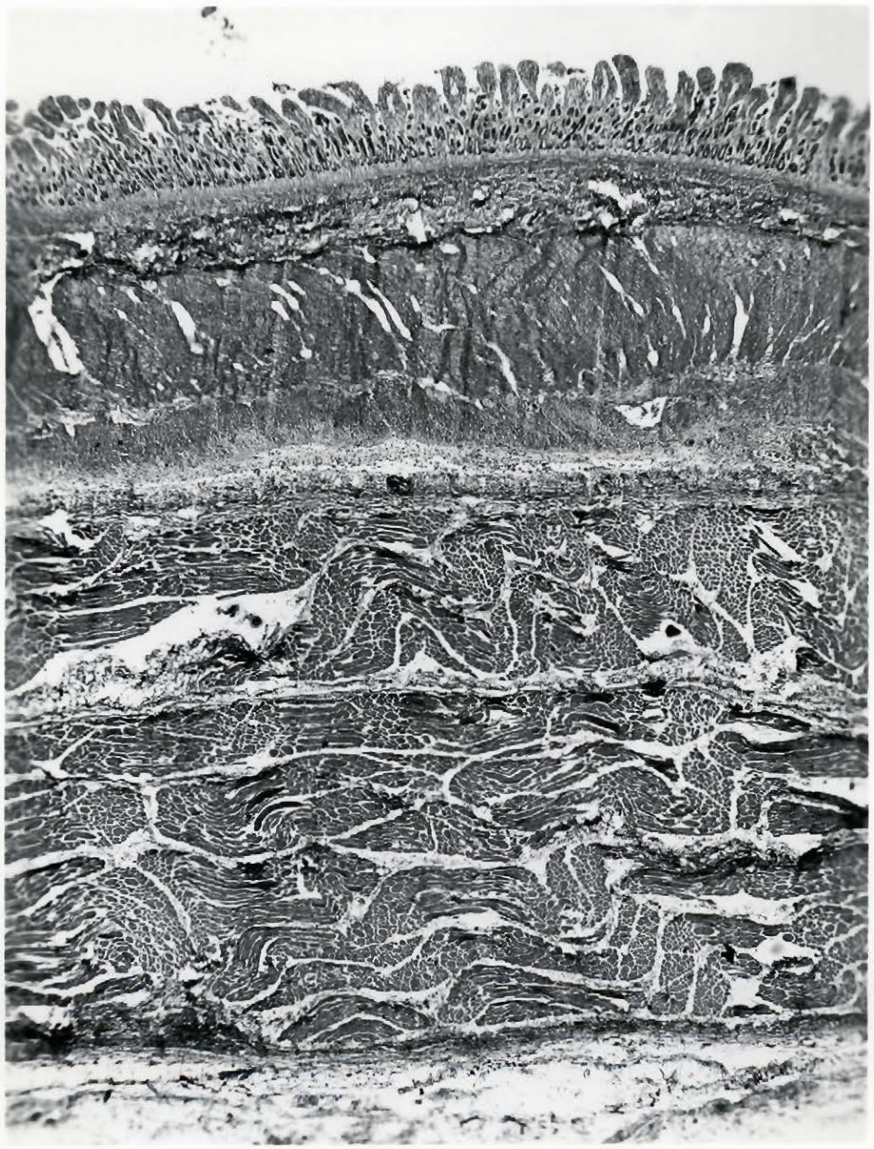

FIGURE 22.

Ileo-entectropy: Fibrin and edematous collagen at serosal-peritoneal junction. (x 25).

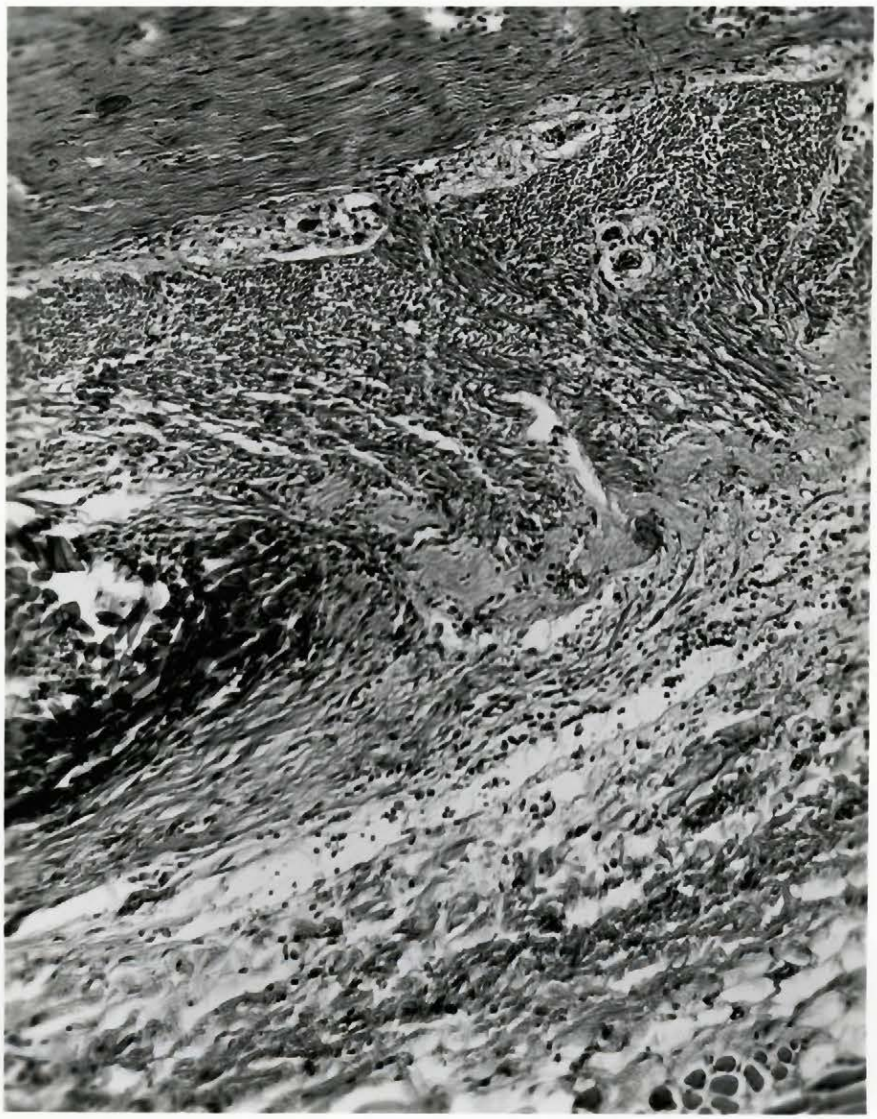

FIGURE 23.

Ileo-entectropy: Organization of granulation tissue in relation to suture (x 115).

FIGURE 24.

Fibrinous adhesion between bowel and silicone rubber prosthesis.

Only the bowel showed deleterious effects of the prosthesis. Compression was evident in many animals, but only in one did frank gangrene of a loop of intestine result. Small amounts of congestion of the bowel wall in short segments also was present in a few animals.

Minimal protrusions of segments of bowel wall and mesentery through perforations in the prosthesis occurred in many cases. (Fig. 25). Microscopically these nodules were localized areas of edema with some degeneration of bowel wall muscle. (Fig. 26 and 27).

The collecting tube excited little reaction in the prevesical fat. Hemorrhage and necrosis at the tip was present in some cases - this would heal ultimately by fibrosis. Granulomatous inflammation was also present in scattered areas in the fat, consisting of large numbers of plasma cells, and cells intermediate between plasma cells and macrophages containing eosinophilic inclusions within their cytoplasm. Large numbers of new blood vessels and fibroblasts also were present in some regions, signifying that scar formation would probably be the ultimate result (Figs. 28 and 29).

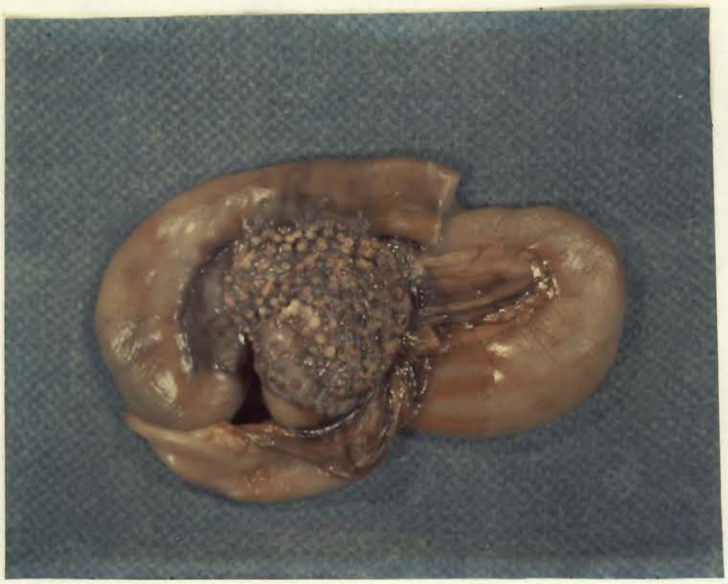

FIGURE 25.

Protrusion of mesentery through perforations of prosthesis.

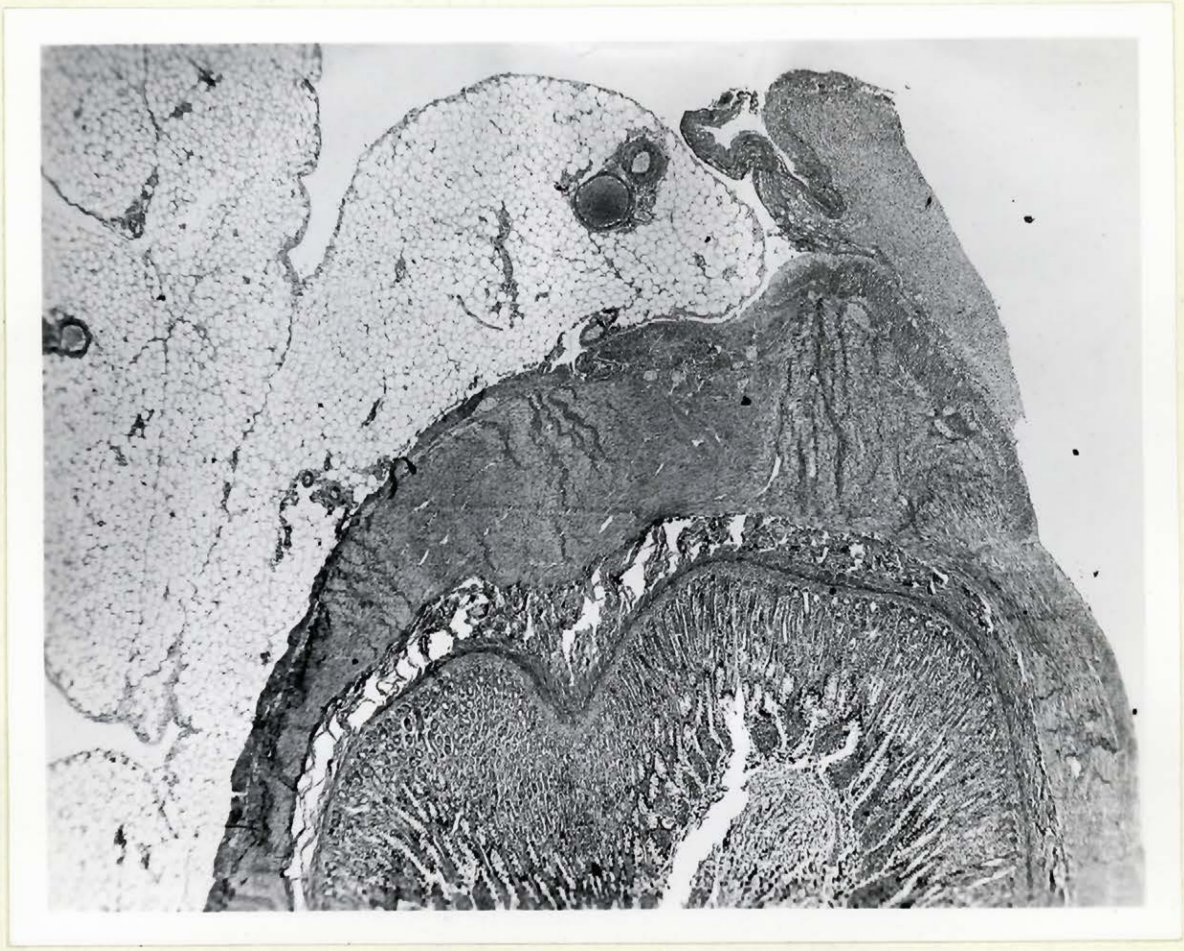

FIGURE 26.

Segment of bowel wall protruding through prosthesis perforation (x 25).

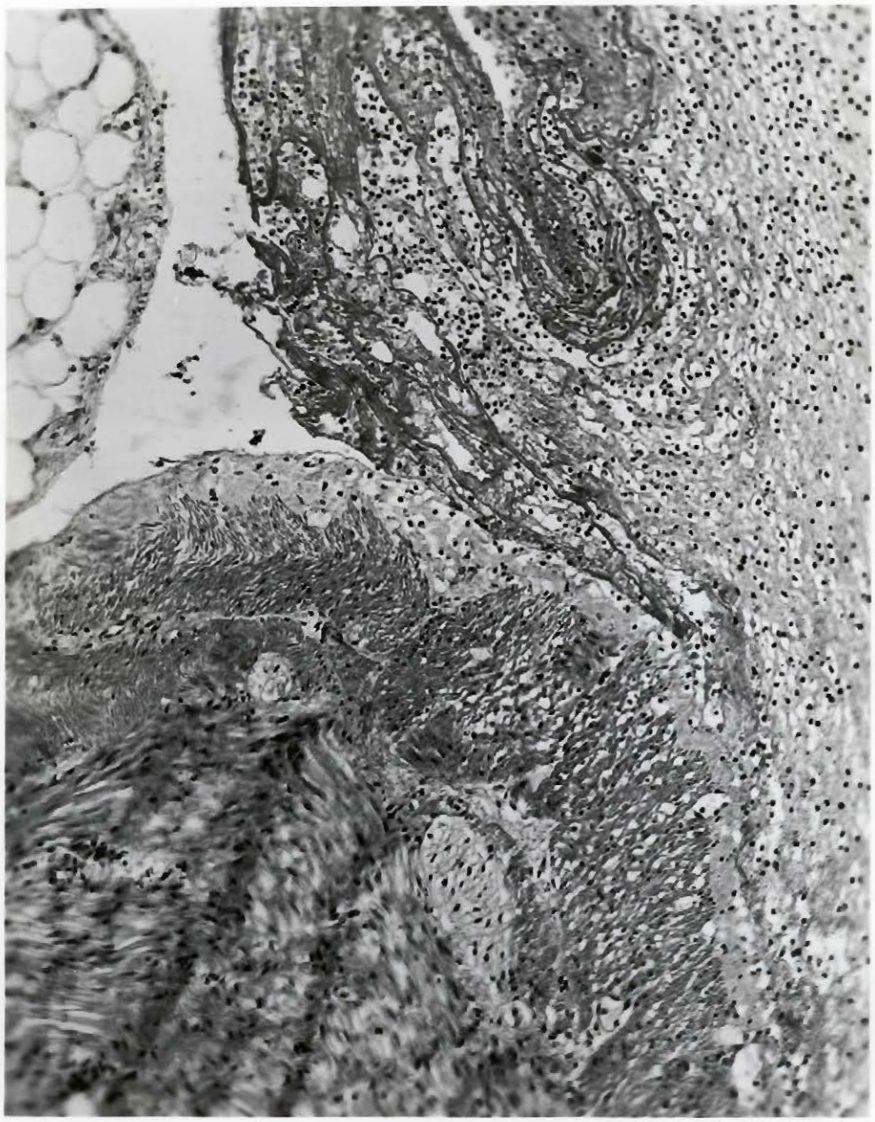

FIGURE 27.

Fibrin deposition, edema and degeneration of bowel at site of protrusion through prosthesis perforation. (x 100).

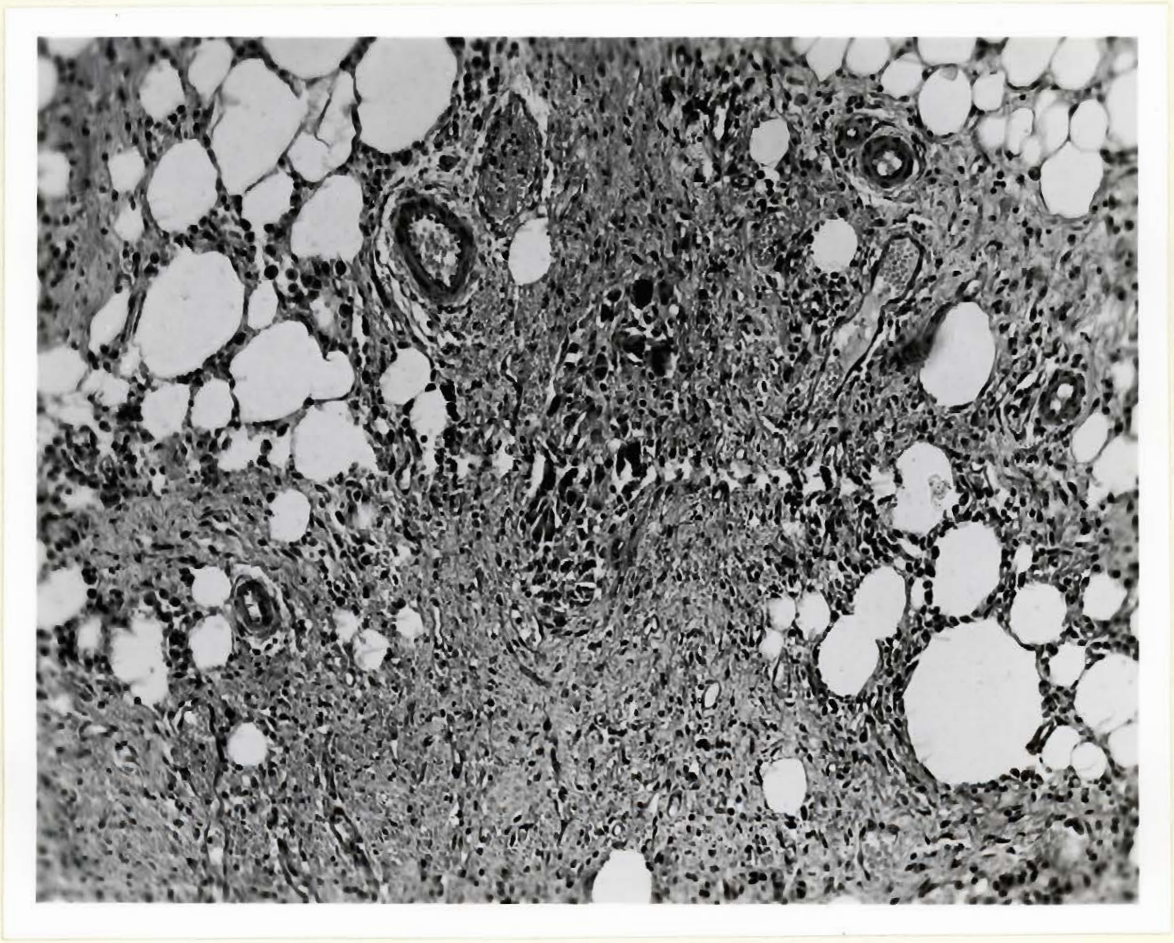

FIGURE 28.

Granulomatous reaction at tip of prosthesis in retropubic fat. (x 115).

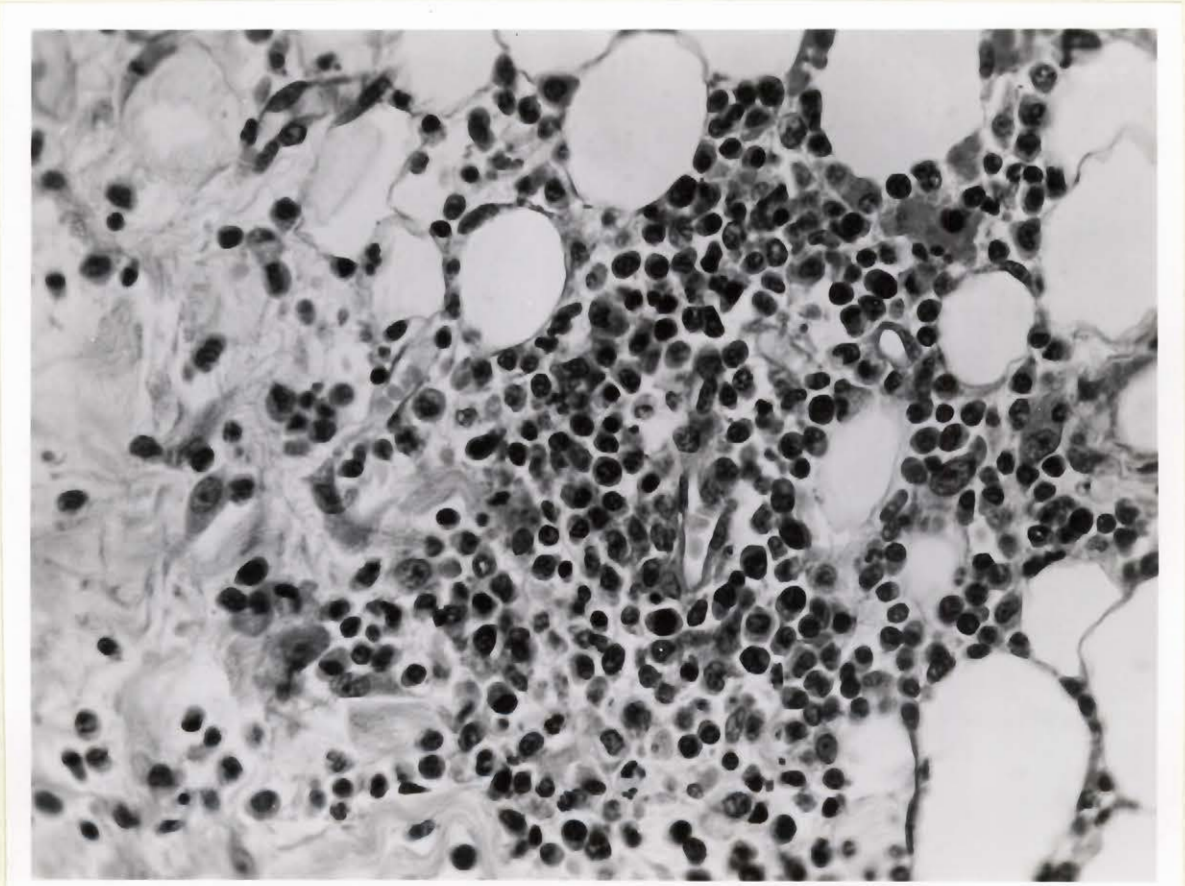

FIGURE 29.

Plasma cells and macrophages containing eosinophilic granules in retropubic fat. (x 425).

VIII. Causes of Death

The causes of death are tabulated in Table XXIII. Most striking is the fact that emaciation and dehydration alone contributed to 30 deaths, while shock and anesthesia and infection played a large part in 15 deaths each.

Deaths due to distemper occurred early in the experiments almost exclusively, before beginning universal immunization of dogs admitted to the animal house. At least one animal developed the disease despite the use of vaccine.

Evisceration, in 2 cases from the thorax and in three from the abdomen, led to the deaths of 5 dogs.

The use of too large a prosthesis probably contributed in large measure to the deaths of 5 dogs, although only one showed frank gangrene of the intestine due to the extrinsic pressure on its blood supply.

Hemorrhage into the mesentery of the terminal intestine after ileo-entectropy with the production of massive gangrene was the cause of death in one dog.

In only three dogs was the cause of death unknown. Presumably inanition and electrolyte disturbances played some role.

CLASSIFICATION OF CAUSES OF DEATH

| OPERATION PERFORMED | SHOCK & ANESTHESIA | EMACIATION & DEHYDRATION | INFECTION # | DISTEMPER | EVISCERATION | PROSTHESIS TOO LARGE | HEMORR - HAGE INTO MESENTERY | UNKNOWN |
|---|---|---|---|---|---|---|---|---|
| Polythene to exterior | 0 | 7 | 1 | 0 | 0 | 2 | 0 | 0 |
| Polythene to prevesical space | 0 | 3 | 2 | 2 | 2 | 2 | 0 | 2 |
| Constriction IVC only | 8 | 7 | 8 | 6 | 0 | 0 | 0 | 0 |
| Silicone rubber to P.V. space | 0 | 5 | 2 | 0 | 0 | 1 | 0 | 0 |
| Omentopexy | 4 | 3 | 2 | 0 | 0 | 0 | 0 | 1 |
| Omentopexy & splenectomy later | 0 | 2 | 0 | 0 | 2 | 0 | 0 | 0 |
| Ileo-entectropy | 3 | 3 | 0 | 1 | 1 | 0 | 1 | 0 |
| TOTALS | 15 | 30 | 15 | 9 | 5 | 5 | 1 | 3 |

# in addition, 23 dogs showed impaired skin healing, with minimal to marked local infection

TABLE XXIII.

# CHAPTER IX.

## DISCUSSION OF RESULTS

### The Production of Ascites in Dogs

The dogs used in this experiment were suitable for the production of ascites. 50-60% constriction by a stainless steel or ameroid ring resulted in detectable fluid accumulation after two to three weeks.

Some dogs died early in the postoperative period. Anesthetic complications such as overdosage and inadequate pulmonary ventilation with cardiac irregularities probably caused the death of some animals. Others probably died as a result of constriction of the vena cava to too great an extent. Insufficient venous return with pooling of blood in the liver and irreversible shock, non-hemorrhagic in type, probably killed these animals (123). The necessity of preventing collapse secondary to vena cava constriction has been observed. Technical errors may have resulted in too much constriction, however, with loss of the animal.

Although a plain band was satisfactory to constrict the vessel, a ring containing ameroid was employed. Some vessels were too large in diameter to allow adequate constriction by closing the small ring; incomplete closure of the band would have permitted the vessel to slip out, while complete closure would have occluded the vein to too small a fraction of its original size. The ameroid ring was useful; both in vitro and in vivo it absorbs

water which closes it wholly circumferentially but only partially internally. An interesting study of ascites formation would have resulted had the ameroid closed gradually and completely.

Berman and Hull (16) have described the nature of ascites produced in dogs by IVC constriction. The ascites was straw-colored with a specific gravity of 1016, total protein concentration about 3.2 gms%, albumin 1.4 grams% and globulin 1.8 grams%. These values are different from the means obtained in our series of animals where the total protein averaged 3.49 grams%, the albumin 2.07 grams%, and the globulin 1.42 grams%. Using the standard deviation, however, each value obtained in our series compares very favorably with those of Berman and Hull. The difference in figures may be related to the initial plasma protein levels, for the concentration of proteins in ascites varies with the plasma concentrations, the fluid generally containing a protein level equivalent to about 60% that of the serum (231). Sodium, chloride and potassium levels in their series were 157.8 meq/litre, 122 meq/litre and 4.3 meq/litre respectively, while in our laboratory the figures obtained averaged 148.8 meq/litre, 113.6 meq/litre and 3.62 meq/litre respectively. Once again, one standard deviation would bring the results closer together.

Berman and Hull found that bacteriological smear and culture of ascites in their animals were negative for bacteria. Red blood cells were present in concentration of about 600/$mm^3$, and about 2000

white blood cells/$mm^3$, all polymorphonuclear leucocytes, were found. These examinations were not performed in our laboratory.

The ascites resulting from IVC constriction is non-persistent. According to Parsons and Holman, it appears after seven days, begins to decrease by the twentieth day, and is completely absent after 140 days (177). Although a few of our dogs lived this long, nevertheless none had lost their ascites at the time of death or sacrifice. Furthermore, rather than decreasing, the ascites increased in volume with time, probably related in part to the progressive hypoproteinemia that developed. The emaciation and decreased plasma proteins that occur with IVC constriction were noted in our animals.

The volume of ascites formed by dogs of 9-13 kilograms in weight is usually about 2000-3000 ccs. every two to three weeks. Our dogs had 52-5500 ccs. of ascites at the time of measurement with Evan's Blue Dye. Volumes are influenced by dietary content of sodium chloride and protein (10, 11, 154, 156); the variation in results may be due to this.

One other aspect of experimental ascites production must be noted before concluding this discussion. Although no figures are available from the literature, it appears from our series that ascites production is associated with a reasonably high death rate. Numerous causes may be listed, which may act early or

late in the postoperative period. These include shock, distemper, pneumonia, empyema, skin ulcerations, wound infection and disruption, hemorrhage, pleural effusion, lung congestion, liver impairment with low albumin and emaciation, and dehydration. All of these, plus the difficulties related to animal care before and after operation, all contribute to the problems of the experimental surgery of ascites.

Some Effects of Plasma Protein Depletion

The hypoproteinemia incident to ascites formation has been noted. The source of the protein in the ascitic fluid is the plasma which in turn depletes the tissues. This emaciates the animal, as was evident very soon after IVC constriction in our series, even before fluid accumulation became detectable. The lethargy of our dogs was marked, as well as anorexia and weakness probably due to compression of abdominal and thoracic viscera by the accumulating fluid, as well as to the protein depletion which impairs the digestive processes.

Delayed wound healing and increased susceptibility to infection were also noted in many dogs. The incidence of these complications was much higher by random observation of our animals compared with other dogs operated on by others in this laboratory.

The ability to withstand other stresses, such as anesthesia and trauma of other operations, distemper infection, etc., was also diminished in our hypoproteinemic dogs.

The Changes in the Liver Produced by IVC Constriction

The pathological changes produced in the liver by supradiaphragmatic vena cava constriction have been reported in numerous papers (16, 24, 30, 166, 242). Although function tests other than proteins may remain unchanged, subacute and chronic passive congestion of the liver is marked. After about six days of caval constriction, mitoses and increased connective tissue elements are present around the central veins; by 41 days, marked distension of subcapsular venous sinusoids is apparent, with much fibrosis around central veins and with newly formed vascular spaces in this scar tissue. After about 85 days, the fibrosis ceases to increase.

The lymphatics of the liver, including those in the capsular and subcapsular locations, are markedly dilated; the lymph volume is increased five to twenty times, the hepatic lymph flow increasing even before ascites appears.

The liver acts as a buffer against the same changes occurring in the remainder of the portal area, where only moderate passive congestion and slightly excessive lymph production occurs.

Gage and his associates (87) reversed the changes in the liver by means of hepatopexy, as vascular adhesions overcame the effects of the IVC constriction.

The livers of the dogs in our series resembled those of human subacute passive congestion due to any cause. Marked congestion, especially in capsular and subcapsular regions, was noted.

Centrilobular degeneration with edema, fatty metamorphosis, and loss of parenchymal tissue in progressive sequence occurred in all animals, being most severe in those dogs which survived longest. Reticulin fibres were well preserved, and no evidence of increased fibrosis was found. Even those dogs which were apparently cured of their ascites by operation showed these changes. No especial significance may be attached to the presence of small intrahepatic bile plugs nor to the presence of bacteria in the liver (22).

Although the livers of long-term survivors were abnormal, nevertheless the changes themselves were not imcompatible with survival nor with complete healing with return to normal architecture. Even at the time of sacrifice, however, no dogs showed any suggestion of repair. This would be in keeping with the presence of ascites in most of the dogs at autopsy. The collateral circulation, either that which should develop naturally after prolonged IVC constriction, or that induced by surgical interference, was apparently not sufficient to overcome the anoxic and protein deprivation changes which the liver sustained.

The Operation of Omentopexy

The successful use of the space of Retzius by Kolb and Lorbek (127), Kopf (128) and Steinhardt and Saexinger (220) prompted the use of a similar procedure in dogs, both for omentopexy

and implantation of the prosthesis.

Although the same hiatus does not exist in the dog, nevertheless a retropubic extraperitoneal space is present. This area is rich in blood vessels and lymphatics, and appeared suitable for use to drain ascites.

In man a rich venous plexus in the retropubic region carries blood back to the internal iliac veins. (Fig. 30). Although too small for direct anastomosis, nevertheless, adhesion formation between tissues placed there with the structures already present would serve as a suitable route for collateral circulation between the portal and systemic venous systems. Accordingly, the omentum has been sutured to the prevesical space.

The lymphatics of the retropubic region form a fine network connecting with the bladder neck and posterior vagina and cervix in the female (186). The lymphatics of the anterior bladder wall converge and are directed toward the middle third of the lateral border of the bladder in the region of the middle vesical artery. These trunks merge with those from the posterior wall, and after passing through intercalating nodes, the lymph makes its way to the external iliac, hypogastric, common iliac and paraaortic nodes, and finally into the thoracic duct via the main trunks of the posterior abdominal wall (201). These pathways provide a route for drainage of ascites once it is successfully conducted to this region (Fig. 31).

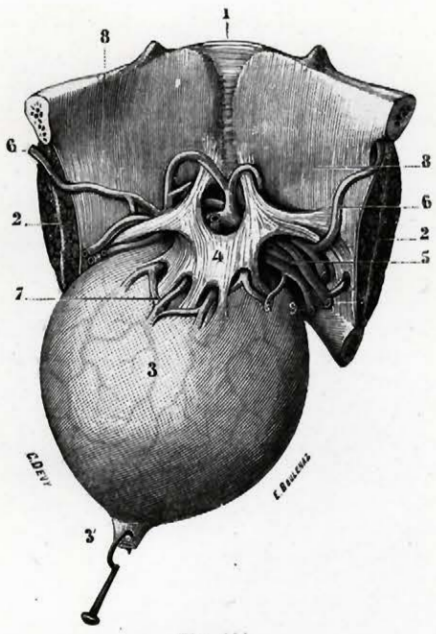


Fig. 484.

Les veines antérieures de la vessie et le plexus de Santorini.

(La vessie a été fortement érignée en bas et un peu à gauche.)

1, symphyse pubienne, vue par sa face postérieure. — 2, muscles obturateurs interne et externe. — 3, vessie, vue par sa face antérieure, avec 3', l'ouraque. — 4, ligaments pubo-vésicaux. — 5, plexus de Santorini. — 6, 6', anastomoses des veines obturatrices. — 7, veines vésicales antérieures. — 8, 8, fascia pelvien, recouvrant les muscles obturateurs internes et releveurs de l'anus. — 9, veines honteuses internes.

FIGURE 30.

Veins Anterior to Bladder and Santorini's Plexus.
( J. L. Testut: Traite D'Anatomie Humaine,
Volume IV, 7th Ed., Doin, Paris, 1921-23,
p. 487. )

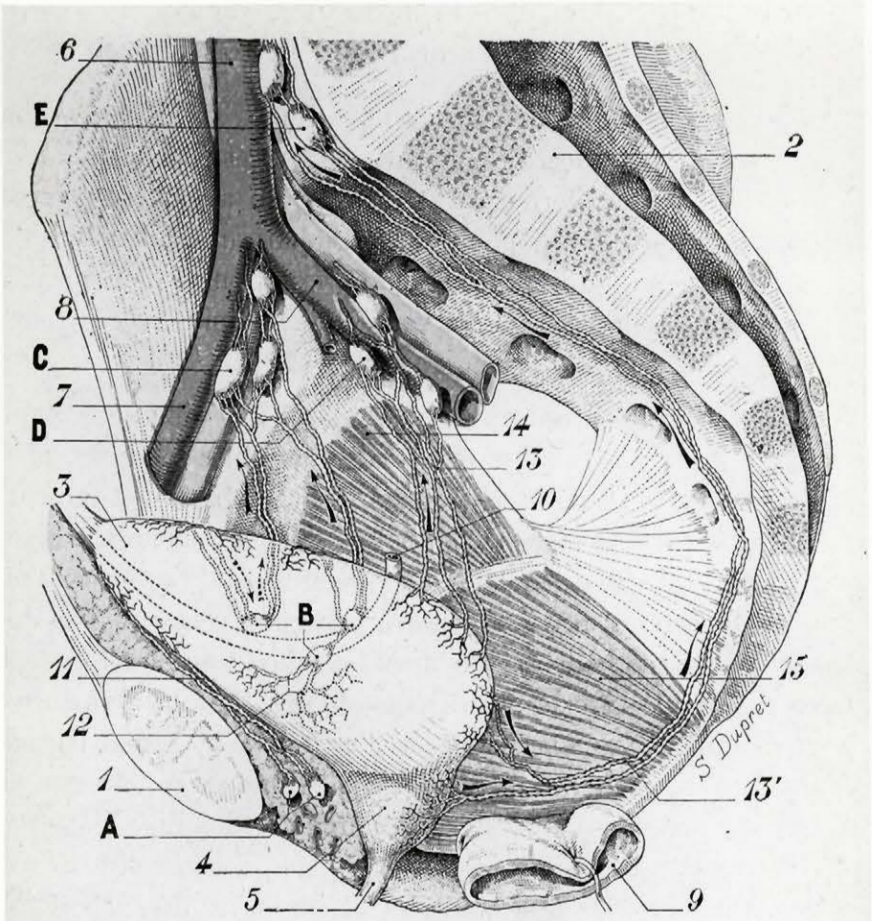


Fig. 486.

Lymphatiques de la vessie avec leurs ganglions (*schématique*).

1, symphyse pubienne. — 2, colonne sacro-coccygienne. — 3, vessie. — 4, prostate. — 5, urèthre. — 6, artère iliaque primitive. — 7, artère iliaque externe. — 8, artère iliaque interne ou hypogastrique. — 9, rectum. — 10, artère ombilicale. — 11, lymphatiques antérieurs. — 12, lymphatiques latéraux, vus en pointillé ; ils sont continués en dehors de la vessie par d'autres lymphatiques allant des ganglions latéraux aux ganglions iliaques externes. — 13, 13', lymphatiques postérieurs. — 14, obturateur interne. — 15, releveur de l'anus.

A, ganglions prévésicaux. — B, ganglions vésicaux latéraux, vus en pointillé sur le côté droit de l'organe. — C, ganglions iliaques externes. — D, ganglions hypogastriques. — E, ganglions du promontoire.

FIGURE 31.

Lymphatics and Lymph Nodes of Bladder.

( J. L. Testut: Traite D'Anatomie Humaine, Volume IV, 7th Ed., Doin, Paris, 1921-23, p. 487. )

The operation of omentopexy was performed in a total of 15 dogs. There were 12 animals which survived longer than two weeks after operation. Of the survivors, 3 showed no ascites, 2 showed minimal accumulations, and 6 developed large volumes. Survivals after omentopexy were also on the average longer than after any other operative procedure. Total proteins, albumins and globulins, pathological changes in the liver and volumes of ascites did not revert more toward normal, however, than would be expected by chance occurrence.

The volumes of ascites absorbed per hour per pound of body weight are not amenable to statistical analysis for the same dog will absorb at different rates at different times. In addition, the depth of anesthesia effects the rate of absorption and probably was not exactly the same for each observation. Insufficient control and postoperative studies were done on each dog to allow for averages and statistical evaluation of results.

In summary, about 50% of animals were benefitted by omentopexy. This figure approximates averages of human cases derived from review of the literature. The retropubic space, however, does not seem to offer advantages over any other part of the abdominal parietes, when compared with other reported series.

The Use of Splenectomy

The encouraging although short-term result obtained recently in a local hospital by splenectomy in a case of postnecrotic

cirrhosis with intractable ascites prompted its use in our dogs. Furthermore, many successes have been reported in the literature with the use of the procedure in human beings (107, 151).

Four dogs which had undergone previous omentopexy with failure to relieve their ascites, probably at least partially related to failure of omental-retropubic fat adhesion, were subjected to splenectomy. At the time of operation, portal venous pressures were measured, closely approximating values reported after IVC constriction in dogs (111). Indeed, in these animals, omentopexy had also failed to relieve the portal hypertension which probably aids localization of fluid to the abdomen.

Although splenectomy was of no benefit in Milne's series of dogs (161), nevertheless at autopsy at least 2 of the 4 animals in our small series were apparently improved thereby. The added operation was very traumatic, however, in that 2 of the dogs eviscerated postoperatively and required sacrifice. Biochemical and pathological evidence of improvement in the other two dogs is lacking. This deters from further speculation concerning the mechanisms of ascites production and its surgical relief.

The Drainage of Ascites by Means of a Prosthesis

The successful reports of drainage of ascites by means of various buttons encouraged the author to design a similar device.

One of the reasons for failure of those used thus far was fibrin-plugging of the lumen. It was believed that a sieve-like prosthesis with multiple perforations might overcome this difficulty. Obstruction of the holes was expected, but perhaps a longer time would be required before complete failure of drainage would take place. The use of materials such as polythene or silicone rubber which are relatively innocuous was considered. In addition, by means of the connecting tube, a fistula would be created, whereby fluid might pass into the retropubic space even after the perforations had sealed.

In our dogs, at least half of the perforations did become plugged with fibrin. In addition, many of the prostheses and collecting tubes contained clot at the time of autopsy. The use of silicone-coating and injections of parenzymol did not prevent this. Furthermore, the tip of the tube excited a granulomatous reaction in the surrounding tissue. This would have healed by fibrosis in all probability had the animals survived sufficiently long. The silicone rubber should have prevented clotting in view of the natural non-wetting characteristics of the material, but such was not the case. In addition, the fibrous reaction around the tube would probably have resulted in formation of the same type of pseudo-pocket which develops after the use of buttons in human cases of chronic ascites.

Another problem related to the use of the prosthesis is its size. In many of our dogs, some evidence of pressure on the bowel was noted. Very few showed gross congestion, however, and only one developed gangrene of the intestine. This problem would be overcome easily in future trials by the use of a smaller prosthesis.

Drainage to the exterior was effective for the short survival period which the 7 dogs lived after operation. Most of the drainage was around the tube, however, in that the rubber collecting bags contained only a small volume of ascites, while the surrounding skin was always wet. Significant also is the fact that those animals which received parenteral fluids and electrolytes lived longer then those which did not. In view of the known quantities of electrolytes, protein, and water that is lost as ascites per day, this is not surprising. Our experience is contrary to that of Ferguson (78, 79) and Mulvany (164) where transvesical drainage of ascites did not result in detectable changes in body proteins and electrolytes. Although not conclusive, our results would suggest that in dogs at least, the external drainage of ascites is not well tolerated.

The dogs survived longer after drainage to the prevesical space. Three which lived more than two weeks with the polythene in place showed minimal ascites, while the two which had the rubber prosthesis both showed massive ascites at autopsy.

There was no significant difference, however, between the biochemical and pathological examinations performed on these dogs.

Ileo-entectropy

Nine dogs were subjected to the operation of ileo-entectropy. One dog sustained the operation at the same time as IVC constriction, and survived longer than two weeks, one which was operated before constriction died less than two weeks afterward, while 5 of 7 which underwent ileo-entectropy about 2 - 3 weeks after the thoracic procedure died shortly thereafter. Only one death due directly to technical error (hemorrhage into mesentery), was noted. Three died postoperatively probably due to shock and anesthesia, one required sacrifice because of distemper, one eviscerated and was sacrificed, and three died of emaciation and dehydration.

These results are presented in detail here because of the support with which Neumann and his associates' work has been received. Many surgeons have spoken of it with enthusiasm without realizing the high mortality rate after operation in the reported series. In our hands, the death rate was also high. Our dogs were as poor surgical risks as any human patients who are considered suitable candidates for the operation. It would be interesting to read of other reported series when these appear in order to compare this aspect of ileo-entectropy.

Of the three "long-term" survivors, one showed a small volume of ascites at autopsy; the other two had large quantities of fluid. The pathological examination of the everted loop of ileum and of the adjacent serosa help to explain in part at least the apparent failure of the operation as carried out here. Only in that dog which survived for 60 days was the segment completely adherent to the peritoneum throughout its length; minimal ascites was present. A longer loop might have prevented ascites completely. This animal also showed chronic ileitis in this loop. Comparison with human cases of chronic enteritis makes one question whether this loop could function adequately if the benefit of operation is due to absorption of ascites through the bowel wall. New vessels in the scar tissue may serve as a source of collateral circulation with, therefore, less formation of ascites rather than increased absorption being the key factor.

Examination of the other specimens revealed adherence only near points of suture, with fibrinous and cellular deposition bordering the separated serosa and peritoneum. Here perhaps continuous bathing by fluid would prevent adhesion formation between the bowel and parietes before individual organization of the fibrin layers occurred. Under this circumstance, failure of the operation would be imminent. Other pitfalls of the operation have already been outlined in preceding chapters.

The Use of Evan's Blue Dye to Study Ascites

The literature reports use of Evan's Blue for investigation of ascites formation. Clinically, T-1824 is used to measure plasma volumes; it has also been used to measure volumes of ascites.

Our method is a crude and simple one for assessing ascites absorption. Although it does not permit precise numerical data to be derived from it without improvements, nevertheless it does offer approximate measurements which can be compared from animal to animal. Certain refinements are necessary before our technique can be used to provide reliable data. The volume of dye that was injected in this experiment was only roughly estimated. A more accurate measurement would involve the use of pipettes to deliver the dye. A side-tube attachment through which a measured volume of saline could be run in to wash all the injected dye into the peritoneal cavity or circulation is also needed.

The nature of the Colorimeter used for determining the optical density of the removed specimens requires a large volume of dye in those dogs with a large volume of ascites. Too great a dilution of the injected Evan's Blue when measuring the amount that has been absorbed into the circulation increases the possibility of technical errors in the readings.

It has been stressed that anesthesia affects absorption from the peritoneal cavity. Changes in lymph flow and rate and depth of respiration occur in the anesthetized animal. It is

extremely difficult to assess the depth of anesthesia with the accuracy required for precise observations. For comparative purposes, however, the use of a mechanical respirator set at a uniform rate would probably improve the experimental conditions. Another variable exists, however, which is more difficult to control. As different dogs react differently to the same amount of anesthetic per pound of body weight, it would be best to perform the experiments on unanesthetized animals. Their exercise levels would have to be carefully controlled in this situation because of the effects of activity on respiration, lymph flow and absorption. This necessitates prior training of the dogs.

In order to assess the rate of absorption of ascites both before and after operations designed to relieve the condition, dog differences within themselves and between animals must be taken into consideration. The best manner of overcoming this difficulty is the performance of several Evan's Blue studies before ameliorative surgery and then several more afterwards on the same dog. By establishing mean values before and after operation, figures would become available for statistical analysis. This was not possible and has not been done on our series.

Accurate calculations would also require determination of the rate of disappearance of Evan's Blue from the circulation.

For the numerous reasons outlined above, therefore, our results may be presented only, without subjecting them to statistical analysis. The method of determining absorption rates

by means of T-1824 is recommended, however, provided cognizance is taken of the variables mentioned.

Statistical Evaluation of Results

Although not many definite conclusions may be drawn from our investigations due to many factors (sample sizes, arbitrary yet standard definition of survival period, lack of adequate controls, etc.) nevertheless some of our data is amenable to statistical analysis.

Analysis of variance has been applied to our results obtained for plasma albumin levels before and after IVC constriction. A value of $t = 6.29$ was obtained (D.F. = 18; P = 0.05, $t = 2.10$). Thus, a significant difference exists between the figures for pre- and postoperative albumin levels.

Comparison of serum albumin levels after IVC constriction alone with those obtained in those dogs which had a relief operation performed at the same time as IVC constriction reveals no significant difference although the means are different. The F ratio was 0.79, the t value = 0.89, while for P = 0.05, that value for n = 28 is 2.048. Thus, the numerical difference in albumin obtained is no greater than would be expected by chance.

For reasons outlined previously, survivals, ascites volumes, rates of absorption of ascites, and ascites proteins before and after ameliorative surgery cannot be subjected to analysis.

Table XXIV is a compilation to demonstrate those two-week survivors which benefitted from the "corrective" operations as compared with those which did not, in terms of the presence of ascites at autopsy. "Improved" signifies minimal or absent ascites, while "not improved" indicates those dogs which had large effusions. Analysis gives a $X^2$ value of 0.0052, while for $n = 3$, $P = 0.05$, $X^2 = 7.81$. Therefore, although our results at face value give a cumulative improvement of 50%, they are no better than would be expected by chance. The figure of 50% approximates closely figures which appear in the literature for all types of operations for the relief of ascites, but the factor of so small a series makes it impossible to state that our results were significant. No significant difference from chance findings does not mean not significant, however, for use of a larger series might have revealed significance.

DIMINISHED VOLUME OF ASCITES AT AUTOPSY AFTER "CORRECTIVE" OPERATIONS
( TWO WEEK SURVIVORS )

| OPERATION | IMPROVED | NOT IMPROVED | TOTAL |
|---|---|---|---|
| Omentopexy | 6 | 6 | 12 |
| Omentopexy plus splenectomy later | 2 | 2 | 4 |
| Drainage to prevesical space | 3 | 2 | 5 |
| Ileo-entectropy | 1 | 2 | 3 |
| TOTALS | 12 | 12 | 24 |

TABLE XXIV.

Application to Human Ascites

Before applying or rejecting the experimental procedures used in this study, one must be satisfied that the mechanisms of ascites formation in human beings are comparable to the conditions used in the laboratory. IVC constriction with hepatic congestion appears analogous to cases of human ascites secondary to congestive heart failure, constrictive pericarditis, the Budd-Chiari syndrome, and cirrhosis wherein outflow block to the hepatic venous system is operative. The ascites secondary to carcinomatosis, peritonitis, nephritis and nephrosis, however, require the implication of other factors.

Another problem is related to the nature of the ascites which results from IVC constriction. Human ascites, unless of extremely high protein content, does not coagulate (22). On the other hand, most of our samples clotted in vitro while many showed evidence of coagulation in vivo when the prosthesis was used. There may be a difference in the physical chemistry of ascites between the two species, and so one of the difficulties encountered in the use of the prosthesis may be overcome.

Although similar morphologically, the prevesical space may differ functionally between animal and man. The space of Retzius in the human being may be more active in absorbing ascites. Trials of drainage to this region should be pursued further.

The prosthesis should not be abandoned before adequate tests of its value in man. The important feature to appreciate from animal use is the relative harmlessness of the device. The pressure effects observed will probably be overcome by differences in anatomy between the dog and man and by altering its size and shape in such a way as to conform to the requirements of the human pelvis.

That something must be done for the individual crippled by chronic ascites is undeniable. What to do in terms of surgery is the question. Operations such as omentopexy, splenectomy and the implantation of prostheses should have a low morbidity and mortality and should be considered first in surgical management. Better risk cases or patients in whom the procedures mentioned have failed are probably candidates for the more severe operation of ileo-entectropy.

# CHAPTER X.

## SUMMARY

The mechanisms which lead to the formation of ascites constitute an important aspect of the problem of its surgical relief. Numerous factors have been elucidated in an attempt to explain its pathogenesis. Although most clinicians prefer to ascribe one cause to any one sign, ascites is too complex a condition to allow for adequate explanation by means of a single etiology. A combination of factors, some well established, and some still under investigation, must be used to describe the mechanisms of ascites formation. Thus, certain factors which cause generalized retention of salt and water, such as hypoproteinemia and antidiuretic substances, act in concert with those which contribute to the localization of fluid within the abdomen, such as hepatic congestion, portal hypertension, lymphatic blockage, low tissue resistance and increased capillary permeability.

About one-half of all patients debilitated by chronic ascites will improve on intensive medical treatment. Rest, a nutritious diet, salt and water restriction aided by diuretics, both osmotic and saliuretic, hormones and hormone-suppressing agents, all contribute to the amelioration of ascites. The therapeutic use of radioactive and other chemotherapeutic agents will aid many patients impaired by carcinomatous effusion.

The surgeon is beckoned when medical management and even paracentesis have failed to relieve the patient for a prolonged period. These individuals, furthermore, are the most debilitated poor-risk cases. Their underlying disease, protein depletion, electrolyte disturbances, impaired cardio-respiratory status, and perhaps anemia, all modify the surgeon's approach to therapy. Minimal operations, such as visceropexies of various types which improve collateral circulation, and "button" procedures for internal drainage of ascites, take precedence over more severe undertakings such as shunt operations and bowel resections including ileo-entectropy. By careful selection of cases, however, a low complication rate from surgery should occur, and the maximum number of patients will benefit. With procedures now in use, the figures for surgical intervention approach the 50% improvement level.

The ascites produced in dogs by supradiaphragmatic inferior vena cava constriction bears many features in common with human accumulations. For this reason, the dog is a suitable animal for experimental investigation of mechanisms of formation and surgical means of relieving ascites. Great care and skill are required, however, in maintaining the severely depleted ascitic dog. One disadvantage of evaluation of procedures by their use in dogs is the fact of spontaneous disappearance of ascites

produced by IVC constriction after about three to four months. The establishment of collateral circulation as occurs with vein constriction offers a lead to the development of surgical techniques for human use. Operations which provide artificial by-pass routes such as adhesion-formation and shunting procedures would be analogous to the development of collaterals after IVC constriction in dogs. Whether these collaterals be produced by visceropexy, direct vessel anastomoses, vessel ligations or ileo-entectropy is not important. The most significant feature to be applied from animal experimentation for use in human surgery is the benefit derived, with, at the same time, the least morbidity and mortality.

In this laboratory an attempt has been made to evaluate some of the procedures for relief of ascites reported in the surgical literature. An original prosthesis has also been devised to drain ascites to the exterior or to the retropubic space. As much as possible, and subject to the limitations of animal research, comparisons between omentopexy, omentopexy with later splenectomy, drainage to the exterior or to the prevesical space, and ileo-entectropy have been made. Conclusions from the experiments are few, but, optimism is high concerning the use of omentopexy or of a prosthesis leading to the retropubic space of man to drain chronic ascites.

# CHAPTER XI.

## CONCLUSIONS

1. Inferior vena cava constriction by 50 - 60% of its original diameter is a satisfactory method of producing ascites in dogs. The complications of the procedure have been discussed.

2. Hypoproteinemia, emaciation and dehydration are important causes of death of the experimental animals; careful attention to nutrition may prolong survival.

3. In our laboratory, omentopexy to the retropubic space and omentopexy with later splenectomy have been the most effective procedures to relieve ascites in dogs. This statement is based on the volume of ascites present at autopsy. Reasons for failures have been outlined.

4. The external drainage of ascites is not well tolerated by dogs. Fluid and electrolyte losses may be of significance.

5. A polythene or silicone rubber prosthesis draining ascites to the prevesical region may benefit some experimentally ascitic dogs.

6. A refined prosthesis similar to the one used in the dogs is worthy of further trial, with a view to its ultimate use in human cases of chronic ascites.

7. The operation of ileo-entectropy may improve some ascitic dogs. The mortality has been high in our series.

8. Pathological and biochemical evidence of benefit from relief operations has not been obtained.

9. Evan's Blue Dye is a useful label for measuring plasma volumes, ascites volumes, and rates of absorption of ascites. Simple calculations provide values for these parameters.

10. Definite and significant conclusions form this experiment would require a larger series of studies, with certain modifications as described.

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