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Hypoproteinemia in surgical patient

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HYPOPROTEINEMIA

IN

THE SURGICAL PATIENT

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INTRODUCTION

Hypoproteinemia is an abnormal decrease in the amount of protein in the blood.

During the past few years much clinical and experimental work has been done on this subject, especially its relationship to the surgical patient.

The emphysis which surgeons have placed on correcting dehydration and electrolyte loss before and after operation have often been accompanied by failure to consider the mechanism invalued in keeping the fluids in the blood vessels.

Data will be presented demonstrating the value of an adequate protein balance in the pre and post operative care of surgical patients.

The history of this subject is all recent, most of it being in the last decade. Its recent prominence can be correlated with the recent rapid advancement in the field of Biochemistry because it is upon the blood chemistry that our clinical investigation is based.

PHYSIOCHEMICAL REVIEW

The plasma proteins may be divided into fibrinogen, the other globulins, and albumin.

The origin of fibrinogen is ascribed by Whipple and his co-workers (24) to the liver. They state that this action is extremely rapid, a matter of hours. They have found that the content of fibrinogen in plasma was reduced by measures that caused reduction of hepatic tissue.

The origin of serum albumin and globulin is not known. It is thought however not to be an independent process and may be controlled by different influences.

Whipple and his co-workers (24) have published data concerning the rate of regeneration of the total plasma proteins. They found that after the plasma proteins had been reduced by plasmapheresis, regeneration of the globulin occurred more rapidly than that of albumin. In man albumin can be regenerated at the rate of at least 25 grams per day.

That the maintenance of a minimal plasma protein concentration is essential to life has been demonstrated by Whipple and his co-workers (24). The symptoms of extreme depletion of plasma proteins resembles those of surgical shock. They include collapse, fall in temperature, and increase in the rate of breadknown of body protein.

The increase protein catabolism indicates the probability that injury to some of the tissue cells had occurred. The nature of this injury, and the part which the plasma proteins normally play in preventing it, we do not know.

The plasma proteins do not appear to serve as sources of nutrition to the tissues. The inability of proteins to penetrate the vessel walls appear to render them unsuitable as tissue nutrients, a role for which the amino acids are better adapted. The principle functions of the plasma proteins aside from the clotting property of fibrinogen, appear to be the maintenance of the physical and physiochemical state of the blood. The proteins also promote the mobility of the corpuscles, since these settle more rapidly in plasma than in Ringers solution, despite the greater viscosity of the plasma.

The known role of paramount importance is their maintaining the fluid balance between the blood and the intercellular tissue spaces and serous cavities.

Sterling (24) first measured the osmotic pressure of plasma proteins dialized against physiological saline solution. He pointed out that the osmotic pressure of plasma crystaloids, although relatively large (5000 or 6000 mm. of Hg.) as compared with that of the proteins (30 mm.) is of little influence on the fluid distribution, because the crystalloids can pass through the vessel walls with the water.

It was also learned that normal serum separated from its own protein free filtrate by a membrane, develops a pressure of 21 to 29 mm. of mercury due to the serum colloids which can not diffuse through the membranes. This is called by some authors the "oncotic pressure".

The oncotic pressure is roughly but not exactly proportional to the concentration of total proteins in pathological plasma. The plasma protein in diffusion equilibrium with the relatively protein free saline solutions in the tissue spaces must, in accordance with present physiochemical theory attract water from the spaces by osmotic forces of two origins; (1) the molal concentration of non diffusible protein in the plasma, causing an osmotic pressure similar to that of an equal number of sugar molecules, and (2) the unequal distribution of diffusible ions, chiefly Na, Cl and HCO 3, between plasma and the fluids in the tissue spaces.

The theory presented to explain the interchange of fluid between the blood stream and the tissues in health and disease is as follows. At the arterial end of the capillary the hydrostatic force is greatly in excess, therefore fluids pass into the tissue. As the blood advances in its course the blood pressure falls rapidly, the oncotic pressure rises very slowly, because of the hemoconcentration that has resulted from loss of blood water at the arterial end of the capillary, until eventually it exceeds the hydrostatic pressure, and at the venous end of the capillary the flow of the fluid is reversed, passing from the tissues to the blood. The predominent direction of fluid exchange between blood and tissue spaces must, according to this conception , depend upon the relative magnitudes of hydrostatic and oncotic pressures throughout the full course of the blood in the capillaries.

Factors which reduce hydrostatic pressure or increase oncotic pressure in the capillary bed will promote absorption of fluids from the tissue spaces into the blood stream; while influences which increase hydrostatic pressure or diminish oncotic pressure will favor transudation and the development of edema.

The total blood proteins have been found to vary between 6.5 and 8.5 Gm. per 100 cc. Figures within this range are considered normal by Peters and Van Slyke (24).

ETIOLOGY

Moschcowitz (20) classifies the etiology of hypoproteinemia in the following manner.

A. Hypoproteinemia due to loss of protein

1. By way of kidneys
2. By way of the intestinal tract
3. By anasarca
4. By loss of blood

B. Hypoproteinemia due to deficient formation or destruction of plasma protein.

C. Hypoproteinemia due to insufficient intake of protein.

Any one of these factors may be the cause of the depletion of proteins, or there may be a combination of these factors.

Attention has been repeatedly called to the association of hypoproteinemia with edema (19). Hypoproteinemia has been observed repeatedly as a result of excess loss of protein, decreased consumption of nitrogenous foodstuffs and increased protein wastage. However there has been cases reported which do not appear to be due to any of these three causes.

In one of these cases (19) it appeared that the patient had no difficulty in the digestion and absorption of protein as evidenced by his urinary and fecal nitrogen excretion and by the effect of changes in diet as reflected in the non-protein nitrogen partition of the blood. There was no evidence of increased protein wastage.

The degree of hypoproteinemia found in this case with a normal albumin globulin relationship is unusual. There was also no evidence of alterations in the inorganic constituents of the blood in this case.

The essential abnormality seems to be in the mechanism of synthesis of plasma proteins. This was emphasized by the failure of protein feeding to influence the level of the plasma proteins.

The origin of the plasma proteins is poorly understood. The weight of the evidence at hand indicates that fibrinogen is formed in the liver and that the liver, intestinal wall and blood forming organs are probably sites of origin for other plasma proteins. It is of interest to note that in this patient there was a suggestion of a disturbance of liver function. It is thought by Myers and Taylor (19) to be conceivable that the defective formation of plasma proteins here is due to altered liver function. However they conclude that hypoproteinemia in a patient with chronic edema, low plasma proteins and reduced colloid osmotic pressure, which were uninfluenced by protein feeding, would indicate a deficiency in the formation of plasma proteins.

Melnick and Cowgell (17) after their series of experiments on the loss and lack of protein conclude that both are factors in producing hypoproteinemia but think that there is also an impairment of, or an injury to, a specific mechanism responsible for the formation of serum protein. They think that this may play an accessory or primary role in the persistence of the hypoproteinemia.

SURGICAL ASPECTS OF HYPOPROTEINEMIA

In all surgical interventions the first and primary requisite is the preparation of the patient for the operation.

Moynihan (23) many years ago, stated that "surgery has been made safe for the patient; now the patient must be made safe for the operation".

In order that the patient may be made safe for surgery it is necessary to prepare the patient before operation in order that all functions of the body be brought near the basal physiologic line.

If the patient is not prepared certain complications may be expected. One important factor and the first to be discussed is slowness or lack of wound healing and wound disruption.

The rupture of abdominal wounds with or without evisceration is an old story. Even with the development of modern septic technic and a more intelligent handling of tissue, this complication continues to occur in from 1 to 3% of all abdominal operations.

Starr and Nelson (6) found it in .61% of their cases after laporatomy. Fincke reported an incidence of 1.1%; Meleney and Howes of from 1 to 2%, and Eleason and Mc Laughlin of .27%. Sokolov reported an incidence in Europe of from 2 to 3%.

That this complication occurred in wounds which were not infected, in which hemostasis was good, in which trauma to the tissues and tension were minimal and in which unusual strain was obviated suggested that additional factors of a general character might be playing a part in the disruption of certain abdominal wounds.

The fact that the majority of these cases occurred after operation on the upper part of the gastro-intestinal and biliary tracts is significant. It is thought that mechanical factors play a larger part in the disruption of these cases. Ravdin and his co-workers (6) believe that they have an explanation for the disruption of the wounds in certain cases and a method for control.

Ravdin (6) says that during his work on motility of the gastro-intestinal tract as the effect of hypoproteinemia it was necessary that certain abdominal operations be performed. In a high percentage of dogs with well advanced hypoproteinemia evisceration or breakdown of the wound occurred after laporatomy. That this occurred after the same painstaking technic with silk sutures that they had used for many years is even more important.

Their method of study in the dog was as follows: The serum protein was reduced to the desired level by low protein diets and plasmaphersis. Then the animal was anaesthetized with ether and an 8 cm. incision was made in each rectus muscle. The peritoneal cavity was always opened and incisions were made the same lenght and in the same part of the abdominal wall. The wounds were then closed the same way, the same aseptic technic being employed on both sides.

After operation the serum proteins were maintained at a low level and biopsy specimens were taken from the wound on the seventh and fourteenth post operative days. The animals in which gross infection developed were excluded from the studies.

Ravdin and his co-workers (6) found in a series of eleven dogs disruption of the wound or a failure of the wound to heal during a hypoproteinemic state was observed eight times, an incidence of 72%. Tissue was removed from four of the dogs for study at intervals of seven days.

It was noticed that at the time the incisions were made the tissue was paler than normal and frequently looked as though a local anaesthetic had been recently injected. When the second biopsy was taken it was found in four cases that the wound was no healed although the edges were approximated in all cases.

The tissue was unhealthy looking and serous fluid could be clearly expressed from the wound even as late as the fourteenth day after the abdominal incision. The tissue around the site of incision was edematous, glistening and pale and the bleeding was not as great as would have been expected in a normal wound which had been cut at right angles for a biopsy. There was no apparent attempt at union of the wound. It seemed as though the two surfaces were merely loosely approximated by the sutures and the serous material was interposed, keeping the surface bathed in a solvent which prevented even the sticky adherence found in very early sterile wounds.

In the sections taken from the skin, muscle, fascia and omentum at the first operation there was evident intracellular edema.

In the later sections taken there was little difference with the exception that the tissue edema was a little more prominent. Fibroblastic proliferation was found only occasionally in the seven day section, indicating a marked delay in fibrolblastic regeneration. On the fourteenth day fibroblasts were seen but in decreased numbers. The whole histologic picture was that of a marked delay in tissue repair.

Ravdin and his associates (6) do not wish to imply that disruption of all abdominal wounds is associated with hypoproteinemia or a protein dietary deficit. A knowledge of the simplest principles in surgery would show that many factors must be taken into consideration. But when all these factors have been considered and controlled there will remain wounds whose failure to heal must be due to general more widely acting causes. It is into this group that wounds of animals or patients with hypoproteinemia must fall.

Harvey and Howes (16) have done some experimental work on the effect of high protein diet on the velocity of growth of fibroblasts in the healing wound. Histology has taught us that the first step in the healing of uninfected wounds in which the tissues are maintained in close approximation is the restoration of their continuity by the proliferation and maturation of connective tissue. This multiplication and growth of the fibroblasts form the cicartix. A function of this is the change in the tensile strength of the healing wound which can scarcely be dependent upon else than the increase in the number of the fibrolblasts and the degree of condensation of the connective tissue.

In the experimental work done here normal rats were used which had been on normal diets. An incision was made in the stomachs of these rats and then the wounds were closed. The rats were then put on different diets, some were on normal diets, the others on high protein diets. Six animals were sacrificed at daily intervals from one to fourteen days. Their stomachs were then inflated to measure the tensile strength.

It was found from these experiments that the latent period preceding the initiation of growth in the healing wound in the stomach of a rat is not affected by a high protein diet, but once growth has started its velocity is distinctly increased by a high protein diet. As a result of this the maximum strength of a healing wound is reached some two days earlier than in the case on the standard diet.

Clark (15) of John Hopkins Hospital has also worked out some experiments on the effect of diet on the healing of wounds. He used dogs as his experimental animals. From his experiments in which the certain length incision was made in the animals and each dog or group of dogs put on a different diet, he concluded as follows.

The length of the quienscent period of wound healing is affected by diet. It varies from zero in protein fed dogs to six days in fat fed dogs. The date of final healing differed by about five days, between the protein and fat fed dogs. He also noted that the periods of contraction of the wounds and epidermization was not effected.

The second surgical aspect to be discussed is protein loss in severe burns.

That large amounts of blood plasma are lost into burned areas has long been known; its measurement, experimentally, has shown that it may be very extensive. It is also generally realized that it is the prime, if not the only factor in the blood concentration of burned patients. Weiner, Rowlette and Elman (25) state that its significance in therapy has not been sufficiently emphasized.

In a series of forty patients with severe burns, the degree of blood concentration was roughly estimated by the erythrocyte count. It was found that very rapidly often within an hour or two the red cells increased to values of over 6,000,000 and in a few cases over 8,000,000 per cmm.

The serum protein of such blood when examined soon after admission was usually normal or a little low. This in itself indicates an actual or relative loss of blood protein when one considers the marked concentration as shown by the high erythrocyte count. The degree of this loss in serum protein is apparent if we compare the average figure in these burned patients which was 6% with a serum protein of 10% or more which occurs in the concentrated blood due to extreme dehydration from vomiting, diarrhea etc.

In a number of patients treated with large amounts of saline and glucose solutions a falling serum protein was noted. In a few of these in which 5 to 8 liters of fluids were given daily there was a maked subcutaneous edema of the unburned skin. In these cases the return of serum protein was slow, in many cases requiring weeks.

In a number of severely burned patients intravenous blood plasma was given. Under the influence of this treatment the concentration of the erythrocytes was rapidly reduced and subcutaneous edema was relieved.

These observations led the workers to believe that loss of serum protein is a serious result of extensive burns, and that the store of body protein is not sufficient to restore rapidly this loss when only water, glucose and electrolytes are administered. In severe burns large amounts of proteins are needed. It is believed that the best way to give these proteins is by the injection of blood plasma.

The next aspect of hypoproteinemia to be discussed is edema with special reference to the gastro-intestinal tract. It is upon this subject that most of the experimental work has been done.

Jones and his associates (3) have performed numerous experiments on animals postoperatively. They have produced experimentally the edema by measures simulatin those not infrequently practiced on patients undergoing operations. The production of edema appeared to depend on certain factors. These factors in order of importance seem to be, nitrogen starvation, general malnutrition, sepsis, the administrations of somewhat excessive amounts of water and sodium chloride, serous drainage, major surgical procedures and general anaesthesia. They believe that edema may readily occur in the presence of normal volumes.

Jones and Eaton (2) have presented a series of 34 patients, 26 of whom showed some edema. They were treated by the generally accepted surgical procedures. The surgical procedures included gastro enterostomy with or without gastric resection, appendectomy and drainage, cholecystoduodenostomy, surgical drainage of sepsis and exploratory laporatomy.

A consideration of their data indicates that nutritional or inanition edema may readily occur as a complication of many surgical procedures. The majority of the patients observed were undernourished prior to operation because of malignancy, pyloric obstruction and similar conditions. Actual vomiting and loss of appetite contributed to such a situation.

Following a surgical procedure in every instance the process of undernutrition was continued for several days by the very nature of the operation performed. In addition the situation was further aggrivated by the administration of relatively large amounts of water and salt. In these cases the amount of fluid administered during the first few days after operation for gastric diseases was 3,000 cc. per day. With this was given from 15 to 21 grams of salt. The average daily intake of sodium chloride for a normal person does not exceed 5 to 6 grams a day. In these cases the blood chlorides were never low but were always abnormally high as a direct result of the administration of sodium chloride.

In the group of patients with gastroduodenal disease there is little doubt but what the immediate surgical intervention plus necessary limitations of all food and an excess administration of water and salt were the factors involved in the production of edema.

The average amount of serum protein noted at the time of the development of edema was 5.2 Gm. per hundred cc. which is well below the critical level for the development of edema. The range was between 3.7 and 5.8 Gm. in these cases during the period of edema. The lowering of the serum protein was due first to malnutrition and second to subsequent dilution of the plasma by excessive amount of fluid. It would seem that the retention of water in the tissues was dependent on the altered osmotic relations as a result of the foregoing factor, plus the addition of excessive amounts of sodium chloride, resulting in a movement of sodium to the tissue along with the water. Such an hypothesis is in accord with the results obtained in numerous experimental observations by Moore and Van Slyke.

In one case discussed prior to operation the serum protein was apparently at a normal level (6. 5 Gm. per hundred cc). Such an apparently normal figure is not uncommon in association with dehydration and may give a false sense of security. Once a slight excess of fluid has been given the serum protein drops rapidly. Under the observation of Jones and Eaton (2) it has dropped from 6.2 Gm. to 4.4 Gm. in eight days. In this case as soon as diuresis was established the edema disappeared rapidly and the serum protein rose. In this same series three cases of potential edema following an operation for appendicitis were reported. In these cases there was no undernutrition before operation but following operation the excessive administration of fluids and salt was very striking. For the first five days after operation these patients were given approximately 2600 cc. of fluid per day. It is quite possible that an intake of 2.5 liters of fluid was advisable in view of the elevated temperature with constant loss of water but there is little reason to warrent the administration of over 19 Gm. of salt a day for nearly a week. It is possible that the lowering of serum protein in this case was due solely to dilution by excessive fluids especially by the intravenous route. Experimental work by Beard and Blalock as shown by Jones and Eaton (2) would indicate that this may be a partial explanation of this phenomena.

There are two other factors which may have contributed to the lowering of the serum protein and the development of edema. In each instance because of the localized peritonitis associated with a gangrenous appendix, drainage was necessarily established and was profuse. Here then was a cause for the lowering of serum protein, namely, loss of serum protein by actual drainage. Jones (2) states that he has not noticed edema in simple cases of appendicitis where no drainage is needed that is if the serum protein was normal. He also states that his own animal experiments would seem to indicate that drainage alone will apparently act as a factor in lowering the protein content of the blood and in the development of edema. It is also conceivable that sepsis even if localized and properly drained may cause a greater generalized capillary permeability with the escape of fluid into the tissues.

In one case reported in this series the mechanism for the production of edema differed from the preceding cases and was of some interest. No element of under-nutrition was present. In this case there was a tremendous loss of protein associated with a hemorrhage which dropped the red blood cell count to about 1,000,000 although surgical intervention immediately after a hemorrhage from a duodenal ulcer is not usually indicated, continous bleeding occasionally necessitates an operation. Under such circumstances the administration of fluids and salt that is a normal consequent of gastro-intestinal surgical procedures might have resulted in edema or more serious problems.

One might ask what is the actual critical level for serum protein at which edema begins to develop. Van Slyke (24) and others have shown that a level of 5.5 plus or minus .3 Gm. per 100 cc. constitutes the point where fluid begins to leave the blood and accumulates in the tissues.

In 1931 Lepora (14) made a study of water and chloride metabolism in dogs during the development of low serum protein edema. The sites of deposit of water and chloride were determined by analysis of tissue obtained from sacrificed animals. A known diet was fed to the dogs the blood was removed every day from 1 to 7 days and was deprived of its plasma, the cells being injected back into the dog. At a suitable time the dogs were sacrificed. In these dogs edema was found to occur consistently when the serum protein concentration was below 4 Gm. per 100 cc. This is the equivalent of 5.5 Gm. per 100 cc. in man. The occurrence of edema was associated with retention of sodium chloride and water. The skin contained most of the water while the most of the retained chloride was found in the muscle. It was concluded from this that the edema which occurs in dogs rendered hypoproteinemic is a sodium edema which is facilitated by the presence of a low serum protein concentration and exaggerated by increasing the sodium chloride and water intake of the animals.

Ravdin (4) states that it is not uncommon to experience the disappointment after what is considered a technically perfect operation for gastro or duodenal ulcer or gastric malignancy, the newly provided stoma has failed to function. This has been noted after a variety of surgical procedures and it makes little difference whether the Billroth I or II operations are used or whether any of the many modifications are used. The interference with normal gastric emptying and the prolonged loss of fluids and electrolytes may be so serious as to cost the patient his life.

Even when this outcome does not occur the surgeon is faced with the problem of deciding whether reoperation is necessary. The secondary operation is attended by a higher risk than the primary operation and likewise a delay may seriously reduce the chances of a secondary operation.

There have been many theories as to the origin of the cause of this retardation in gastric emptying. The most recent one is that of hypoproteinemia and is more than a theory since it has been substantiated by many experiments carried out by Ravdin.

These workers have found that following any resection or anastomosis there is a certain amount of edema associated with the trauma of the operation. They also state that under favorable conditions the excess of extracellular fluid returns to the circulation and the edema of trauma disappears. They have observed in certain cases where the edema, gastric retention and regurgitant vomiting continue long past the time when the edema of simple trauma could produce and obstruction at the stoma site. In these cases the decision must be made whether or not to reoperate. It was found that in this type of patient there was usually some dietary deficit, at time due to medical treatment and at times due to self restricted diets because of pain or vomiting or both. Although it is not evident when the patient is first observed, there is in such instances an actual serum protein deficiency. The coincidental dehydration often masks your hypoproteinemia and you do not recognize the condition until the fluids and electrolytes have been restored to normal. Thus the administration of large amounts of sodium chloride intensifies the edema. The role of the blood proteins in maintaining the delicate state of balance by which fluids are kept in blood vessels is well known. The colloid osmotic pressure which they exert provides the mechanism for preventing rapid fluid loss from the circulating blood. When these serum proteins are increased above the normal level there is a pulling of the fluids into the blood vessels and when they are decreased below normal the fluids leave the blood vessels.

Ravdin (4) concluded that the edema of trauma was accentuated and greatly prolonged by a hypoproteinemia insufficient to cause edema by itself. But if the serum proteins are below the edema level this with the administration of large quantities of fluids and salt may result in gastro-intestinal and subcutaneous edema which acting together with the edema of trauma prevents gastric emptying. It is also his opinion that the delayed empting of the stomach after operations of the Billroth I and II type is due much more often to edema than to the technical defects of anastomosis.

Ravdin (4) in his experiments produced hypoproteinemia in a dog with all other parts of his diet given in plentiful amounts. He concluded that as the serum proteins fell the gastric emptying time as determined by fluoroscopic observations increased. This finding was confirmed in both the operated and unoperated dogs. He also found that the gastric emptying time in the hypoproteinemic dogs could be speeded up by withholding all fluids for 36 to 48 hours, the fluid restriction causing a temporary increase in the serum protein concentration.

Ravdin (4) states that in animals the condition can be produced by simple restriction of protein but it is his belief that in man it is a more complicated process involving vitamin deficiency.

It is interesting to note that with the exception of the papers by Jones and Eaton in 1933 and the papers by Ravdin in 1935 the importance of nutrutional edema effecting the gastro-intestinal tract is not stressed by writers on gastro-intestinal surgery. On several occasions Mecray and his associates (11) have noticed cases which in their post operative pictures mimics in every way a technical defect in anastomosis.

The following is a single case history which is typical of the many covered in writing this thesis.

Case History.

"W. S., male, age 42, was admitted to the surgical division of the hospital on September 18, 1933 with a diagnosis of duodenal ulcer. The roentgen studies had disclosed a marked pyloric obstruction. Restriction of food intake had resulted in a loss of 48 pounds in weight. There was no evidence of peripheral edema. The patient on the contrary showed definite evidence of dehydration".

"On admission his hemoglobin was 102% and the plasma proteins were 7.8Gm. per 100 cc. A pylorectomy was performed with reconstruction of the gastro-intestinal continuity by the Polya technic. Subsequent to operation the patient was given normal saline solution intravenously and siphon drainage to the stomach was instituted".

"On the nineteenth day after operation there was no evidence that the stoma was functioning. At this time the serum proteins were 5.1 Gm. per 100 cc. and roentgen studies showed almost complete obstruction at site of the stoma. Peripherial edema was present. At this time a Levine tube was passed through the patients stoma and vigorous protein therapy was instituted. Repeated blood transfusions were given. Within three days there was marked clinical improvement. The roentgen studies on the 29th post operative day disclosed a normally functing stoma".

Mecray (11)noted that it is exceedingly difficult to refrain from doing a secondary operation when roentgenographic evidence of obstruction is obtained. In this case a regime which tended to restore the plasma proteins resulted in their rapid rise and complete disappearance of the supposed technical defect of the anastomosis. Mecray and his associates (11) report observing a similar condition as early as 1928. In this patient restriction of fluid intake and blood transfusions resulted in a functioning stoma.

It occurred to Mecray (11) that many or most of the patients who were subjected to secondary operations after surgical procedures for gastric or duodenal ulcer or malignancy might in rality be examples of a profound disturbance of plasma proteins with the state of edema affecting the site of the anastomosis.

It also seemed important to him to test the hypothesis that a relation existed between gastric retention and nutritional state. Experimental work was carried out by Mecray and his co-workers (11) and it was found that in dogs there was direct relationship between hypoproteinemia and gastric emptying time.

There are several possible explanations for the observed delay in the gastric emptying time in hypoproteinemic patients and animals. First the reduced vitality may diminish the gastric activity. Second the edema of the gastric tissues may interfere with effective muscle contractions. Third and most likely is the reduction in size of the stoma coincident with the edema may interfere with emptying so as to result in the observed retention.

Ravdin, Borden and Frasier (5) are now studying the motility and pattern of the small intestine of the dog with hypoproteinemia. In these animals there is a very definite retardation of the barium in its passage through the small intestine though it is not of the same degree of retardation as the gastric emptying.

Ravdin and Rhoads (13) suggest that in cases of edema of the gastro-intestinal tract after operation that gum acacia in many instances gives a satisfactory result by reducing the edema. In concentration above 8%, it is hypertonic and will temporarily draw fluids from the circulating blood. However there seems to be two sides to this question. In March 1938 Heckel and his associates (21) found that the injection of gum acacia in dogs has lowered the plasma proteins. Two mechanisms have been suggested as a cause of this. First the liver cells become ingorged with gum acacia and are not able to produce the necessary amount of plasma proteins to supply the normal demand or the other possibility is that with the injection of the gum there is an increase in the colloids of the bood and the more readily removable colloid, plasma protein, is taken out of the blood stream in an attempt to return the plasma volume and colloid oncotic pressure to normal limits. They conclude that the intravenous use of gum acacia is not without danger. In considering the observations made it is believed that serum protein determinations should be made during the preoperative period with a normal fluid and salt balance. If the serum level approaches the critical level for edema the patient should receive one or more transfusions of whole blood or serum. It is better to maintain the patient in the state of mild dehydration and hypochloremia than to push water and salt to the point where tissue edema is accentuated and prolonged.

The fourth surgical complication to be discussed is liver damage from anaesthesia in hypoproteinemic patients. Goldschmidt (10) and his associates in their experiments concluded that the severity of damage to hepatic cells by chloroform increased progressively with an increase in the concentration of lipids in the liver and since the absence of protein intake predisposes to fat deposition in the liver there is a definite relationship between low protein intake and liver injury from chloroform. They found that a high protein diet previous to anaesthesia with chloroform reduces the incidence of hepatic cellular necrosis.

TREATMENT

Observations which have been made on hypoproteinemic animals and human beings have led to the investigation of methods by which hypoproteinemia could be corrected prior to operation and controlled afterwards. In these studies investigation has been made of the effect of diet, the intravenous administration of amino acid mixtures, jejenal and rectal administration of a peptone hydrolysate and intravenous injection of serum either in the normal state or after lyophilization and regeneration.

The first method of treatment discussed will be diet. A high carbohydrate, high protein diet given by mouth is the most satisfactory means of supplying the nutritional requirements of the surgical patient. Whenever possible this method should be used. However, it is frequently impossible to get the patient to take sufficient calories by mouth prior to operation, either because of anorexia or because of pain or obstruction and the very nature of the surgical procedure often precludes the oral intake of food for a period afterward. The oral route is also the best one available for the administration of the necessary accessory foodstuffs, the vitamins. The diet which has been found most satisfactory is approximately 70 to 80% of carbohydrate, 20 to 30% of protein and 5 to 10% of fat.

It is important to remember that while in many surgical patients the deficiency in the reserve protein stores of the body and that in the serum protein may not be equally severe, a serious deficiency in the reserve store may and does often coexist with a serious shortage in the serum protein.

The diet should if possible be given in amounts adequate to maintain energy requirements and at the same time provide for tissue regeneration. There is no doubt that the oral route can be used more frequently than it now is used.

It is of primary importance that where operation is not of an emergency character and where evidence of a nutritional deficit exists an attempt should be made to improve this condition before operation. The caloric requirements in these patients usually exceed the regular three meal a day diet of the average hospital. When given close record should be kept of how much the patient has eaten so that the actual caloric intake is known. During the period of oral feeding the intravenous use of glucose is of value more for the effect it has on sparing protein stores than for any other reason.

However when there is no contra indications to oral feedings the patient can take adequate calories by mouth and the intravenous route is not needed.

The orojejunal method of feeding is one of the most popular forms of feeding. If the nutritional state is extremely hazardous in a major operation it is at times wise to perform a jejunostomy to feed the patient.

When X Ray evidence indicates pyloric obstruction in these patients drainage of the stomach for several days, by the Wangensteen method frequently results in the disappearance of some of the edema associated with the obstruction o that the Abbott tube will pass into the jejunum. This Abbott tube is pulled down into the first loop of the jejunum in the later stages of the operation so that after operation the suction from the stomach can be done through one lumen and feeding into the jejunum through the other lumen. The patient may be fed for 30 minutes and rested for 30 minutes and after peristalic activity becomes normal it is possible to feed 45 minutes of each hour.

It is of course obvious that such a program is efficacious only when there is no lesion present which prevents the formation of serum proteins when the components are offered in the diet.

Stengel (8) reports some controlled patients in which operation was performed but no attention was paid to the nutrition. In these cases the serum protein was 6.5 Gm. per 100 cc. Two weeks following the operation the serum proteins had dropped to 4.3 Gm. per 100 cc.

In those patients receiving the orojejunal feeding the serum protein was from 7.3 to 7.7 Gm. per 100 cc. , before the operations. They fell to 6.1 to 6.6 after the operation but were restored 6.7 to 6.9 Gm. per 100cc. within 5 to 8 days after the operation and were held at this level. We can see that this type of feeding is advantagious when there is no interference with the protein regenerating mechanism.

Much reference has been made to high protein diets. What is a high protein diet and how much protein does a person need? This is a much discussed subject and depends upon the many variable factors involved.

The term biologic value has been adopted by the authors (22) to express this nutritive suitability, and proteins are classed as of high or low biologic value according to the completeness with which they supply all the amino acids necessary for the construction of the body tissue.

At the top of the list among those of unusually high value, stand the proteins of milk and eggs, those of meat are also of high biologic value. This superiority of meat proteins is enhanced by the fact that their "coefficient of digestibility" is high. They yield on digestion 95 to 100% of their nutritive value while the vegetables proteins yield 80% at the most. The plant proteins are of distinctly lower biological value.

"Just as a chain is as strong as its weakest link, so is a protein as valuable as the building stone which it provides in smallest amount"(22). Thus the plant proteins must be supplemented by proteins from a different source.

Mans need for a liberal ration of protein is today generally recognized. By liberal is meant an amount well in excess of his theoretic needs, such an amount as the more prosperous races, in their long experience, have instinctively chosen. This amount should be 100 Gm or more daily. These proteins should be of high biologic value in which proteins of meat, eggs and milk find first place.

The second form of treatment to be discussed is the use of peptone hydrolysate. This is a partially hydralyzed peptone which can be put into solution with water to which various amounts of glucose may be added. In addition sufficient amounts of sodium chloride may be added to maintain the plasma chloride concentration. At least 1,500 calories per 24 hours, may be given in this way without difficulty. One reason for its frequent use is that there is usually some disturbance in enzyme production in the operated cases and this feeding mixture is partially digested so that it may be easily absorbed from the jejunum. Another reason for its use is that the authors Ravdin and Stengel (1) have become convinced that at present the most efficacious method of meeting the protein requirements of the patients is some type of alimentary feeding. A completely satisfactory method would in addition provide carbohydrate, fat, and salt and sufficient fluid to obviate the simultaneous administration of fluids and salt by the paraenteral routes. This peptone hydrolysate used for orojejunal feeding is a peptic, pryptic digest of beef peptone. Concentrations of protein in the solution calculated on the basis of total nitrogen varies from 4 to 10%. As a rule from 65 to 90 Gm. of protein and from 200 to 300 Gm. of dextrose are fed daily. This method of feeding was carried out by Ravdin (1) in 20 cases with good results. When the jejunal method is not possible one may at times resort to the rectal method of administration of the hydrolysate. Rhoads and Stengel (9) and their associates have investigated the problem of the absorption of split protein by isolated loops of colon. They concluded that the amino acids were readily absorbed from the chronic isolated loops of the large bowel of the dog. There was also some evidence that the higher split products of protein were absorbed from such loops. In these experiments an increase in the concentration resulted in an increase in the amount absorbed in a given time. The absorption was however less in the large intestine than in the small intestine. Of the materials used the protein hydrolysate was absorbed more rapidly than was the amino acid mixtures.

Among the many things that have been used in the treatment is lyophile and normal serum. This lyophile serum is prepared by drawn blood being centrifuged so as to separate the cells from the serum. After lyophilization the residues are stored in the refrigerator until required, at which time they are regenerated to hypertonic or normal concentrations by the addition of sterile water. The lyophile process of preserving plasma described by Flasdorf and Mudd (7) provides plasma in such a state that it can be shipped to isolated communities and kept for months at refrigerated temperature for immediate use. This serum is administered intravenously by the drip method. The author (1) has found this method efficacious for temporary elevation of serum protein.

Thompsen (7) and his associates have used lyophile serum in their experiments on hypoproteinemic animals. These animals were given 300 cc. of lyophile plasma daily for six days, then 150 cc. the following four days. It was found by frequent biopsy specimens that the dogs which had received the lyophile plasma showed much more normal wound healing than did the controlled animals. In these experiments the lyophilized plasma was shown to have two merits when given as a intravenous hypertonic solution. First it rapidly replenishes the protein deficit and, secondly if given in a hypertonic solution it rapidly increases the osmotic prèssure of the blood thus efficiently overcoming any tissue edema that might be present.

Ravdin and Stengel (1) have found that in the use of this serum there have been some very annoying reactions characterized by chills and fever with their associated phenomena. Until the cause of these reactions is ascertained lyophile serum they believe will have a limited usefulness. For a number of patients the authors have used repeated blood transfusions or if the cell count was normal, normal serum alone. Both these materials are at times very helpful and can be utilized more frequently than they now are.

The last and most recent type of treatment to be discussed is the intravenous use of amino acids. Protein as a source of parenteral alimentation can be given only in the form of amino acids, aside of course from the use of matched blood in transfusions or plasma alone. Amino acids represent the form in which protein food enters the blood stream from the intestinal tract after appropriate digestion and absorption. We therefore speak of the use of protein as amino acid metabolism.

Elman (18) in his work on intravenous injection of amino acids in dogs found that healthy starving dogs subjected to a single severe hemorrhage revealed a much more striking regeneration of serum protein in 6 to 24 hours when treated by intravenous injections of a complete mixture of amino acids and glucose than when treated with glucose alone. His findings suggest that the amino acids introduced in this way are utilized in the regeneration of serum protein. Clinical observations in patients unable to take proteins by mouth have given similar results.

Elman and Weiner (12) think that amino acids should be just as suitable for intravenous injection as is dextrose since they are soluble and non-toxic in ordinary amounts.

Of the twenty-one or more amino acids which make up the usual protein foods only nine or possibly ten are essential. Thus by supplying an adequate amount of these nine amino acids the nitrogenous needs of the body should be met. This experiment was first carried out in rats and proved satisfactory enough to warrent its use in human cases.

The amino acids used in all the studies here were obtained from acid hydrolysis of casein. In this, all of the essential amino acids were presumably present except tryptophan which was destroyed during the hydrolysis. Therefore to make the mixture complete 2% of tryptophan was added. At times 2% cystine or methionine were also added because of the low concentration of these acids.

In these dogs the rate of intravenous injection was important. If given too fast diarrhea often occurred with vomiting. To determine whether these acids were being utilized studies on nitrogen balance were carried out. It was found that if incomplete mixtures of amino acids were used the nitrogen balance was not achieved. This was even true when tryptophan and cystine were withheld and injected eight hours after the injection of the basic mixture.

In the control, hypoproteinemic dogs showed no regeneration of serum protein in 24 hours but if the amino acids were injected intravenously definite evidence of an increase in serum protein was obtained within 6 hours.

The greatest problem when these acids were going to be used in humans was whether or not they would cause any reactions. For this reaason small doses were used at first. They produced no demonstrable effect so that .5 to 2 Gm. per kilogram of body weight was finally used.

Usually each liter contained 20 Gm. of amino acids and 80 Gm. of dextrose. It was found that better results were obtained when glucose was given in conjunction with the acids. If given slowly over a period of 2 hours the amino acids did not spill over into the urine and produced no objective reactions. There was no elevation of temperature or pulse rate. Some patients noticed a sense of warmth which was evident in a slight peripheral vasodilitation. In this series studied by Elman and Weiner (12) only eight patients received the amino acids intravenously in large amounts.

The results were sufficiently promising to justify the hope that further use will produce added evidence that this method of alimentation not only is harmless but results in active and rapid systhesis of tissue and other proteins.

SUMMARY

The important role that protein balance plays in the surgical patient is only beginning to be appreciated by the profession.

Much interesting clinical and experimental data is being collected, and from this comes increasing information about this problem.

Much work remains to be done but it offers a field worthy of further intensive laboratory and clinical research.

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