HYPOPROTEINEMIA AND ITS RELATION TO SURGICAL PROBLEMS *

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DURING the past two decades innumerable papers have been written on the fluid and electrolyte loss in persistent vomiting, in diarrhea, following extensive superficial burns, and in many other conditions, but until very recently, with the exception of the papers dealing with shock following trauma, very little has appeared in clinical literature on the important part that an adequate concentration of the plasma protein plays in keeping fluid in blood vessels. No consideration of fluid and electrolyte loss and their restitution is sufficient unless the plasma protein is simultaneously considered. The present symposium on a surgical program is evidence of the recognition by surgeons of the importance of plasma volume in a wide variety of conditions. The clinical and experimental conditions to be briefly considered in this paper may seem to be unrelated. Indeed, in some cases the studies were initiated independently. Nevertheless, a common factor would seem to appear as an important casual agent in each. This factor is the protein of the body available to meet the body's demands under the prevailing conditions.

General Considerations.—Many of the patients coming to the surgeon for operation have, as a result of restriction of diet resulting from a variety of causes, from visceral injury, or from excessive plasma loss, a reduction not only in the concentration of plasma protein but also in the total available plasma protein. In fact, a reduction in the total plasma protein usually occurs before a reduction in the concentration takes place. Even though the concentration of the plasma protein is normal when the patient is first seen, it frequently falls sharply when fluids are administered in attempting to overcome an existing dehydration. Observations we have made strongly support the concept that there is no such thing as a critical level of the plasma protein at which edema becomes manifest. As soon as the plasma protein falls below the normal concentration, fluid begins to leave the vessels resulting first in a latent, and, finally, when the accumulation of fluid in the tissues is great enough, in an evident edema.

Weech and Ling[1] have shown that the administration of large amounts of neutral sodium salts, such as sodium chloride, will intensify the edema normally occurring at the same level as the plasma protein. Thus, frank edema may be present in patients receiving excessive amounts of salt solution, whose plasma protein concentration is well above the so-called critical level of edema of 5.2 Gm. per cent. In the presence of hypoproteinemia, attempts to restore a normal fluid and electrolyte balance, without at the same time

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increasing the colloid osmotic pressure by adding to the plasma protein, too frequently result only in adding to the extravascular fluid reservoirs.

Although the final pictures may be similar, the primary factors involved in hypoproteinemia in many conditions are, of course, quite dissimilar. In extensive superficial burns the hypoproteinemia is the result of the excessive loss of plasma protein into the tissues. The hypoproteinemia associated with hepatic disease is no doubt due to a defect in protein synthesis, while the hypoproteinemia encountered in gastric and duodenal ulcer and cancer results frequently from protein restriction in the diet. Thus, while a "loss or lack"[2] of protein accounts for many instances of hypoproteinemia, alterations from the normal of protein synthesis are also a factor in some conditions.

The evidence now available shows that in starvation or on diets low in protein the protein content of certain viscera, especially the liver,[3] is markedly reduced. Whatever the cause of the reduction in total plasma protein, it is unlikely that this reduction is not also associated with at least a partial depletion of the important stores of rapidly mobilizable protein of the body. In protein undernutrition the tissue stores of protein may suffer before hypoproteinemia is excessive. The stores of protein mobilized under these conditions have been designated by Whipple[4] as "labile protein."

When adequate protein feeding is begun the depleted stores of visceral protein must be at least partly replenished during the period of plasma protein regeneration. Tissue and plasma protein depletion and regeneration must, therefore, under many conditions go on simultaneously, the one complementing the other. In dogs which we had kept on an extremely low protein intake and further reduced their protein reserves by plasmaphereses, we obtained evidence which suggests that intravenously injected plasma protein was used for replenishment of protein stores depleted during the period of protein starvation.

During undernutrition, tissue protein is protected in part as long as carbohydrate and fat are available for energy requirements. The sparing action of carbohydrate on protein is too well known to require further discussion.

The many references in surgical literature to tissue regeneration upon a diet composed entirely of carbohydrate demonstrate a fundamental lack of knowledge of cell regeneration, for tissue growth requires protein components, the amino-acids, or larger aggregates, for building material.

Hypoproteinemia and Its Effect on Gastro-intestinal Motility.—As Starling[5] pointed out many years ago, the osmotic pressure of the plasma crystalloids, although large when compared with that of the plasma protein, is of minor importance in keeping fluids in blood vessels, for the crystalloids pass freely in either direction through the walls of blood vessels. As the plasma protein concentration falls from the normal 7.0 to 7.5 Gm. per cent the osmotic pressure exerted by the plasma is reduced and fluid begins to leave the vessels, causing at first a latent and finally, when the increase of extravascular fluid is great enough, an evident edema. Jones and Eaton[6] and Jones,

Eaton and White[7] first called attention to certain complications which may occur during hypoproteinemia and its accompanying edema.

The papers of Jones, Eaton and White,[6, 7] and those which we have published,[8, 9, 10] focused attention on the importance of nutritional edema in gastro-intestinal surgery. The increase in subcutaneous fluid in hypoproteinemia is but one manifestation of a widespread increase in tissue fluid and the gastro-intestinal tract is not exempted from this process. Mecray, Barden, Frazier and I[8, 9, 10] have shown that even when the gastro-intestinal tract of the dog is intact, a reduction in the plasma protein concentration will result in a marked increase in the normal gastric emptying time and a further delay in cecum appearance time. We have in a number of instances after operation upon our own patients, and in patients operated upon by other surgeons, found that the retardation of gastric emptying time may be so prolonged as to simulate a technical defect in the anastomosis. We have, in fact, come to the conclusion that so-called "vicious circle" more often results from a disturbance in the normal movement of fluids than from technical defects of the new anastomosis.

In dogs, which many months previously had had a pylorectomy with restoration of gastro-intestinal continuity by the Pólya technic, a reduction in the plasma protein by diet and plasmaphereses results in a marked increase in gastric emptying time. The roentgenographic appearance in these dogs, following the barium meal, is similar to that observed in many of the patients who supposedly have retention from a defect in the anastomosis after a similar operation.

The prolonged interference with a normal diet which many of the patients coming to operation for gastric and duodenal ulcer and gastric cancer have had, results, frequently, in varying degrees of undernutrition. The total caloric intake and the composition of the diet have very often been inadequate. The protein starvation may be the result of a self-imposed diet, but we have been impressed with the frequency with which hypoproteinemia has been observed while patients were under supposedly competent medical care. In man, the problem has been further complicated by the fact that there are frequently associated deficiencies in certain of the important accessory foodstuffs which affect gastro-intestinal motility and pattern.

Hypoproteinemia intensifies the edema of trauma naturally occurring at the site of gastro-intestinal suture. Under normal conditions of fluid exchange the edema of trauma begins to disappear 48 to 72 hours after operation, but in the presence of hypoproteinemia it continues to increase during this period, resulting in a mechanical impediment to the forward progress of the gastric contents.

Furthermore, when gastric contents pass into the small bowel the progress is further restricted by a coincidental, though less marked, decrease in small intestinal motility.

Surely, the convalescence of these patients will be smoother and the incidence of untoward complications will be reduced if nutritional deficits

are, if possible, corrected prior to operation, or as soon as possible after operation.

I shall not discuss the many methods which may be employed both before and after operation to correct protein deficiency. At present we have found that the most rapid means of correcting it is by repeated plasma transfusions. These are well tolerated and rarely associated with the postinjection reactions so frequently observed after employing serum. We believe that it is better to administer small amounts of plasma repeatedly, over a long period, than to inject large amounts during a very short period. When more time is available and after operation upon patients whose "labile stores" of protein are thought to be very low, the orojejunal method, which Stengel and I[11, 12] have described, is useful and practical. Although we have used varying amounts and combinations of amino-acids, intravenously in these patients, we have as yet no significant data that their administration in this manner will lead to the rapid synthesis of plasma protein. Even though we have, in a few instances, in the dog and in man obtained a positive nitrogen balance for a brief period, we have never observed a significant rise in the plasma protein concentration or the total plasma protein unless these substances were placed directly into the gastro-intestinal tract. Is the older viewpoint, that the gastro-intestinal mucosa conditions the amino-acids for protein-building stores, perhaps the correct one?

Wound Healing.—In a study of wound healing which Smelo[13] made in my department, in 1935, he concluded that "factors other than the local dressing appear to play the dominant rôle in determining the rate of wound healing." Anderson,[14] continuing these studies, stated that "the healing of granulating wounds under normal conditions, as determined by precise volume measurements, occurs according to a regular geometric curve which may be expressed as a function of area and time, by the mathematic equation presented by Carrel[15] and DuNoüy[16] for the normal cicatrization of clean surface wounds."

That disruption is still encountered in wounds free from infection, in which hemostasis was excellent, in which trauma to tissues and tension was minimal, and unusual strain obviated, strongly supports the concept that other factors of a general character play an important part in the failure of certain wounds to heal. That purely local factors may intensify the factors of a biologic character will not be doubted by anyone who has carried on investigations in this field.

We have shown that dogs which have been made hypoproteinemic by prolonged feeding of a low protein diet and plasmapheresis have a marked delay in fibroblastic proliferation and thus wound healing is retarded. The hypoproteinemia in our animals was but one manifestation of the protein starvation of the dogs. Although at first we were inclined to attribute the delay in fibroblastic proliferation to the presence of edema, we are now convinced that the mechanism is associated with a profound disturbance in protein metabolism, the hypoproteinemia being only an easily measurable indi-

cator of the extent to which the so-called "labile stores" of protein have already suffered.

It is well known that cellular repair and regeneration require protein, for in the absence of an adequate amount of certain essential animo-acids growth cannot take place. Admont Clark[17] has shown that on a diet high in protein there was no quiescent period in the repair of wounds, and Harvey and Howes[18] have shown that such a diet causes accelerated fibroblastic proliferation. Without adequate building stores repair cannot take place.

A protein deficiency is of course not the only mechanism resulting in wound disruption. Sokolov[19] and Lanman and Ingalls[20] have shown that a vitamin C deficiency is also an important biologic factor in this complication. These two nutritional disturbances are frequently found in patients who come for operations for gastric ulcer and cancer, duodenal ulcer, and biliary tract disease. That plasma may be employed to restore depleted protein stores was indicated in the experiments in which we gave large amounts of plasma, as much as 2,400 cc. during a two-week period, to hypoproteinemic dogs that had been on a low protein diet for some days. The amount of plasma which we administered intravenously was more than six times the calculated plasma volume of the animal, but the plasma protein concentration never exceeded the original normal level for the dog. With the restoration of a normal serum protein concentration and, very likely, a more nearly normal store of tissue protein, the wounds promptly healed. Addis,[3] and Holman, Mahoney and Whipple[21] have shown that plasma protein can be utilized to replenish the depleted stores of tissue protein, and it is this purpose we believe that the excess protein, we injected, fulfilled.

When all the local factors favoring wound disruption are controlled, there will remain wounds whose failure to heal must be due to more widely acting causes such as hypoproteinemia and a reduction in "labile protein" stores, and deficiencies in important accessory foodstuffs.

Protein and Its Influence in Preventing Visceral Injury.—In a study of the protective action of oxygen against liver injury, when certain hepatotoxic anesthetics were employed, our attention was directed to the relation of the dietary regimen to the susceptibility of the liver to damage by these same agents. That a diet high in carbohydrate is protective and that a diet high in fat induces maximal susceptibility of the hepatic cells when the liver is exposed to chloroform, has been repeatedly confirmed since the original reports by Opie and Alford.[22] Experiments which Goldschmidt, Vars and I[23] have reported strongly suggest that glycogen *per se* does not protect the liver from the injurious effects of chloroform. Chemical analyses of the livers of animals following various diets, which were considered adequate and where feeding was prolonged, together with histologic evidence of changes in the cytology of the liver cells, have provided data which must lead to a realignment of our concept of the mechanism by which diet protects the liver or increases its susceptibility. It furthermore may, by inference, lead to certain conclusions on the effect of diet on regeneration.

The data which Goldschmidt, Vars and I[23] obtained conclusively demonstrated that, regardless of the reasons for the toxic action of chloroform upon the cells of the liver, the incidence and degree of injury increases with increases in the concentration of lipid in the liver. The data reveal no evidence that the level of hepatic glycogen *per se*, at the time of anesthesia, influences the toxic action of chloroform.

The hypothesis which assumes that glycogen *per se* is effective in protecting the liver against the action of chloroform received no support from our experiments. The data on the incidence and severity of damage to the liver with high and low contents of glycogen were essentially the same where the content of lipid was similar. There can be no doubt but that the susceptibility of the liver to injury by chloroform is markedly enhanced by the presence of small increments of fat.

On the other hand, when animals had been fed diets with a relatively high or low content of protein in the rations, and where the lipid concentration was similar, a striking protection was observed in the rats which had been provided 17 per cent or more of their total calorific value from protein. The significant difference is to be found in the severity of the cellular changes, for in the high protein group areas of necrosis in the liver were found in but 41 per cent of the rats, while in the low protein group extensive necrosis was present in 88 per cent of the rats. Although a high protein diet did not markedly influence the total incidence of hepatic injury, it decidedly reduced the degree of injury. The protective action of protein revealed itself even in animals with a high concentration of hepatic lipid and a low concentration of hepatic glycogen. The incidence of hepatic injury in starved rats was compared with that which was found in fed animals with the same initial hepatic fatty acid concentration. The extent and severity of the damage to the liver in the starved animals was almost maximal and nearly as great as that which we had observed in fed animals with approximately 50 per cent concentration of hepatic lipid.

That a high carbohydrate dietary regimen is efficacious in preventing liver injury is agreed to by every clinician who has administered such a diet in patients with hepatic disease. It would seem that the explanation of its action must lie in some concomitant effect produced by large deposits of hepatic glycogen. Rosenfeld[24] has found that under many conditions of the body, depletion of hepatic glycogen is followed by an increase in fat in that organ and vice versa. Opie and Alford[22] suggested that the necrosis produced by chloroform, phosphorus and similar substances is perhaps the anatomic expression of advanced disintegration of body protein. Carbohydrate may, therefore, also be of value in limiting the necrosis due to these agents, by exerting its recognized function of sparing body protein.

The comparative protective value to the liver of foodstuffs against necrotizing anesthetics resolves itself, therefore, into the positive action of dietary protein versus the increased susceptibility to injury with increments in the hepatic lipid. In contrast to the indirect protection afforded by carbo-

hydrate the protection afforded by protein would seem to be a direct one, perhaps related to some intrinsic value of the protein itself.

The data which we have collected have led us to postulate that a liver high in lipid content and low in protein is maximally susceptible to injury; a liver low in fat and high in protein is maximally protected from injury. Carbohydrate is advantageous only if, during its deposition in the liver, fat is displaced and if, as a result of an adequate store of hepatic glycogen, hepatic protein is spared.

Protein stored or elaborated into the body tissues may serve to protect the hepatic cells or to offer protein for regeneration should damage occur. The increased susceptibility of the starved animal is in our opinion chiefly a matter of depletion of its easily mobilizable protein stores.

Even so great an advocate of the carbohydrate protective concept as George Whipple[25] has recently confirmed our findings, and his associates[26] have extended them, for they have shown that a high protein dietary regimen protects the liver from the necrotizing effects of arsphenamine. It is highly likely that a protein deficiency in the organism, frequent in surgical patients, either with or without hypoproteinemia, may lead to hepatic and other visceral injury following the use of a wide variety of hepatotoxic agents.

The evidence which we have brought forth, fortified by the recent investigations of Miller and Whipple,[25] and his associates, Messinger and Hawkins,[26] makes it highly probable that a carbohydrate-protein diet should be given in the future before operation wherever possible, and begun again after operation as soon as the gastro-intestinal tract will tolerate food.

Johnson, Vars, Zintel and I[27] have found that in the dog with a high lipid content in the liver, a diet consisting of approximately 72 per cent of the calories as carbohydrate, and 28 per cent as protein, was twice as efficient in reducing the concentration of hepatic lipid as carbohydrate alone given in the same number of calories per kilogram per day. If minimal visceral injury is to be conditioned and repair facilitated, an adequate amount of protein must be added to an otherwise satisfactory caloric intake.

CONCLUSIONS

An attempt has been made to demonstrate that a protein deficiency may be of serious significance in surgical patients. The reduction of the plasma protein, both in concentration and total amounts, frequently is associated with a reduction in the amount of protein stored in certain viscera. A reduction in the concentration and total amounts of the plasma protein as well as the so-called "labile stores" of body protein may result in the failure of a newly formed gastro-enteric or intestinal anastomosis to function normally, to impairment of normal fibroblastic proliferation and to increased susceptibility of certain viscera to damage by hepatotoxic agents.

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