THE ESTIMATION AND CONTROL OF POST-OPERATIVE DEHYDRATION, WITH THE AID OF HEMOGLOBIN AND PLASMA PROTEIN DETERMINATIONS [1]

By BENJAMIN WHITE SEAMAN AND ERIC PONDER

(*From the Nassau Hospital, Mineola, N. Y.*)

(Received for publication February 23, 1943)

INTRODUCTION

The purpose of this paper is to describe certain changes in hemoglobin and plasma protein concentration which occur after major surgical operations, and to show how hemoglobin and plasma protein determinations can be used as a guide to the maintenance of pre- and post-operative water balance.

There are two essentially different ways of ascertaining a patient's water balance from day to day. The first is to keep intake and output records. This may be simple, the intake by mouth being balanced against the loss by urine, feces, and drainage, with an estimated figure for loss by skin and lungs; or it may be elaborate, as when it takes "metabolic water" into account. Under hospital conditions, it is always approximate, and an error in the estimate for one day is carried forward to the next, and so any daily errors tend to be cumulative. The second method consists in making daily hemoglobin and plasma protein estimations, and comparing each value with the value for the day before. Since hemoglobin formation is a slow process, any increase of the figure for one day over that for the day before can be taken as evidence of a corresponding degree of dehydration.

This method of estimating dehydration is not new, for Scudder (1), Foote and Gerst (2), Rhoads, Wolff, and Lee (3), and others have used it clinically. By an extension of the same idea, daily blood studies allow us to follow variations in plasma protein concentration, and, provided we have certain additional data, to draw conclusions from the variations. To interpret properly the results of plasma protein measurements, for example, we need simultaneous measurements of hemoglobin concentration, for any changes in the water content of the blood, as shown by decreases or increases in the hemoglobin values, necessarily lead to changes in the protein concentrations, and so have to be allowed for.

The observations in this paper are largely based on the study of a series of 31 partial gastrectomies and 24 partial colon resections, but some explanation is required about the arrangement of material. Originally, we were interested in the post-operative hypoproteinemia which occurs after partial gastrectomy, partial colon resection, and similar major operations (Section III). In order to interpret the results of measurements of plasma protein concentration, we found that we had to take account of the state of the water balance, and this led to the investigations described in Section II. Finally, the method of following the state of the water balance by means of daily hemoglobin determinations involves a knowledge of the probable extent of the post-operative fall in hemoglobin, and this led to the experimental work described in Section I.

METHODS

1. *Blood samples.* The samples of blood (5 to 7 cc.) are taken from a vein into small bottles containing heparin. When an intravenous infusion is to be given, the needle is inserted on a 10 cc. syringe, the blood sample withdrawn, leaving the needle in place, and the infusion is started through the needle; in this way, the samples are always obtained before the infusion is begun. The laboratory determinations are started as soon as possible after the withdrawal of the blood, which may be kept in the refrigerator for a few hours without the results being affected.

2. *Hemoglobin determinations.* These are made photometrically as acid hematin with the Klett-Summerson photometer. This method has been chosen for its convenience rather than for its absolute accuracy, which leaves something to be desired because the color takes a variable time to develop fully, and even when fully developed does not give hemoglobin values which agree absolutely with the results of iron determinations (Ponder (4) and Barkan (5)). When dealing with the blood of the same individual from day to day, however, the method is accurate to ± 2 per cent, provided the tubes containing

[1] Part of this work was carried out with the aid of a grant from the Simon Baruch Foundation.

the acid hematin are allowed to stand until maximum color is developed. This may take several hours. Visual determinations of hemoglobin by the acid hematin method, and using the Sahli hemoglobinometers often seen in clinical laboratories, are quite inadequate.

The errors attached to the red cell count, even if done in duplicate, are too great to allow of red cell counting being used to follow the changes which take place after hemorrhage or which accompany dehydration (Berkson, Magarth, and Hurn (6)).

The results of blood loss at operation and the effects of dehydration can also be followed by hematocrit determinations, but these are subject to no smaller error than are determinations of hemoglobin concentration. Reference will be made below to the use of blood density measurements as a guide to increase or decrease in hemoconcentration.

3. *Plasma protein determinations.* These are found from the plasma density as determined by the falling drop method (Scudder (1)), and again this method has been chosen for its convenience rather than for its absolute accuracy, which has been called into question by Looney (7). The results which it gives can be shown to agree, however, with the results of gravimetric determinations to within ± 0.1 per cent of plasma protein concentration, and this is good enough for our purpose. A thermostatically controlled apparatus is preferable to Scudder's model, and this is constructed of a glass cylinder, 20 inches by 5 inches, controlled to $\pm 0.05°$ C. by a Lolag heater and a mercury-toluol regulator, both of which go the entire length of the cylinder. The cylinder contains a tube in which the drop of plasma falls through a brombenzene-xylene or a brombenzene-kerosene mixture, suitable for the determination of its density. Measurements of density made by the falling drop method are very satisfactory, although they may not have the high degree of accuracy sometimes implied. The limits of significance in the absence of lipemia are not less than ± 0.1 gram per cent of plasma protein concentration.

Measurement of whole blood density is less satisfactory and more difficult to interpret, for the whole blood density is dependent on the density of the plasma, of the red cells, and of the white cells, and on the partial volume of each. Being made up of three partial volumes with their associated densities, any one of which may vary, the changes in the density of whole blood are not unequivocal measures of variations in the degree of hemoconcentration, and ought not to be relied upon.

SECTION I

The post-operative fall in hemoglobin

The hemoglobin and the plasma protein concentrations of a normal person in water balance are constant within narrow limits from day to day,[2] and both increase if a state of dehydration supervenes. Any attempt to use hemoglobin and plasma protein concentrations as a guide to post-operative intravenous therapy, however, must take into account the fact that surgical operations are accompanied by a variable blood loss, and that this is followed by a fall in hemoglobin concentration. Comparatively little attention has been paid to this post-operative fall, although it has often been remarked that the hemorrhage which takes place at the average operation is usually underestimated. One would expect at first sight that the post-operative fall, which reaches its maximum between the second and the fourth post-operative days, would be proportional to the amount of blood lost, and the following experiments were carried out to see if this is so.

The loss of blood at operation was measured by a method similar to that of Gatch and Little (9). All sponges, towels, etc., stained with the patient's blood are soaked for some hours in a pail containing 15 liters of cold water, and then, after wringing out, in a second pail containing 10 liters of cold water. A 15 cc. sample from the first pail, added to a 10 cc. sample from the second, gives a solution of hemoglobin to which 30 cc. of 2 per cent HCl is added to make a solution of acid hematin. This is matched photometrically against a solution of acid hematin made from the patient's blood, obtained immediately pre-operatively. The blood loss, in cc., is calculated from the result, and is corrected for the patient's body weight by being expressed as the loss in cc. per 70 kgm. of body weight.

Determinations of the patient's post-operative hemoglobin concentration (venous blood) are made each morning at the same time for 3 or 4 days. Typically, the values fall to a minimum, usually reached on the third post-operative day, and the difference between the original value and the minimum value obtained constitutes the post-operative fall in the patient's hemoglobin. This fall is expressed as a percentage of the original hemoglobin concentration.

For the observed fall to be a reflection of the amount of blood lost, three conditions have to be met. (*1*) The patient must be in water balance at the time of operation. In any cases of doubt, 2 pre-operative samples should be taken, the first, 24 hours before operation, and the second, just

[2] Smith (8) has shown that no real diurnal variations in red cell count and hemoglobin level occur, although there may be small differences from one day to another over long periods.

before the patient is anesthetised. The hemoglobin concentration in the 2 samples should not differ by more than ± 2 per cent, but if there is appreciable pre-operative dehydration, due to restriction of fluids the night before, the second sample will show a higher hemoglobin concentration than the first. Under such circumstances, the concentration in the first sample should be taken as the initial value from which the post-operative fall in hemoglobin is estimated; but the second concentration should be used in calculating the blood lost at operation. Unrecognised pre-operative dehydration would be a very important source of error in these experiments, for if the patient is dehydrated before operation, the post-operative fall will reflect not only the effects of blood loss, but also the effect of correcting the dehydration. (*2*) Similarly, post-operative dehydration would mask the fall in hemoglobin and its effects; but if the post-operative course of the patient is satisfactorily controlled as regards water balance (see Section II), the fall in hemoglobin will usually reach its maximum on the second or third post-operative day, and the true value of the maximum fall can be found without difficulty if daily observations of hemoglobin concentration are made and properly interpreted. The smallest value of the hemoglobin concentration observed during the first 4 post-operative days should be used in calculating the post-operative fall. (*3*) The effects of blood loss cannot be studied by these methods if there has been hemorrhage shortly before operation, because under such circumstances the pre-operative hemoglobin level is not that of a steady state, nor if hemorrhage occurs into the tissues either pre- or post-operatively; this last condition is sufficient to exclude the use of these methods in most cases involving extensive tissue injury.

The rate at which the hemoglobin concentration falls after bleeding is shown in Figure 1, which is based on the average values found during the first 3 days following (*a*) loss of 1029 cc. of blood per 70 kgm. of body weight, by vein (blood donors; data of Ebert, Stead, and Gibson (10); 6 cases); (*b*) loss of 520 cc. per 70 kgm., by vein (blood donors, 7 cases); and (*c*) loss of 230 cc. per 70 kgm. during partial gastrectomy. These are all average values, and inspection of the data which make them up shows considerable individual variation (as noted by Fowler and Barer

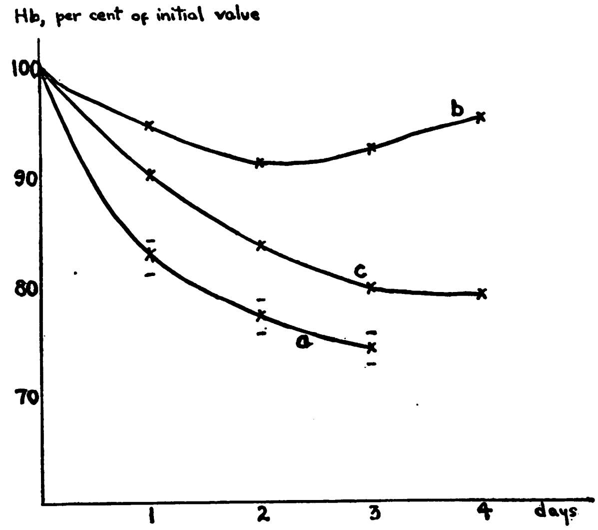

FIG. 1. AVERAGE HEMOGLOBIN VALUES AFTER (a) LOSS OF 1029 CC. OF BLOOD PER 70 KGM. OF BODY WEIGHT, BY VEIN; (b) LOSS OF 520 CC. PER 70 KGM. BY VEIN; (c) LOSS OF 230 CC. PER 70 KGM., AFTER PARTIAL GASTRECTOMY

The extent of variation met with is indicated by the short horizontal lines on curve a.

(11), and by others who have worked on the same subject [8]). The purpose of the figure is to show that the post-operative fall in hemoglobin follows a smooth curve, and that it is virtually complete by the third post-operative day. It will be seen in Section II that an appreciation of the extent and course of the post-operative fall in hemoglobin is necessary in the consideration of post-operative dehydration, which shows itself as an interruption in the smooth course of the curve.

The unexpected result of plotting the post-operative fall in hemoglobin against the quantity

[8] Fowler and Barer give the fall in hemoglobin found 24 hours after removal of an average of 550 cc. of blood by vein, and call attention to the great variations (4-fold) encountered. Their average value is shown as a double circle in Figure 2. Martin and Meyers (12) give the fall in hemoglobin which occurs "directly after" the loss of about 500 cc. of blood by vein; their average value is shown in Figure 2 as a square. It is less than Fowler and Barer's value; and our value, represented as a large cross in the figure, lies in between the two. Unquestionably, there is great variation, but the apparent discrepancy in the various values may be partly due to the way in which they were obtained; it is, for example, by no means certain that the true minimum value will be found if the observations are made at 24-hour intervals only (this will be plain if one looks at the course of the top curve in Figure 1).

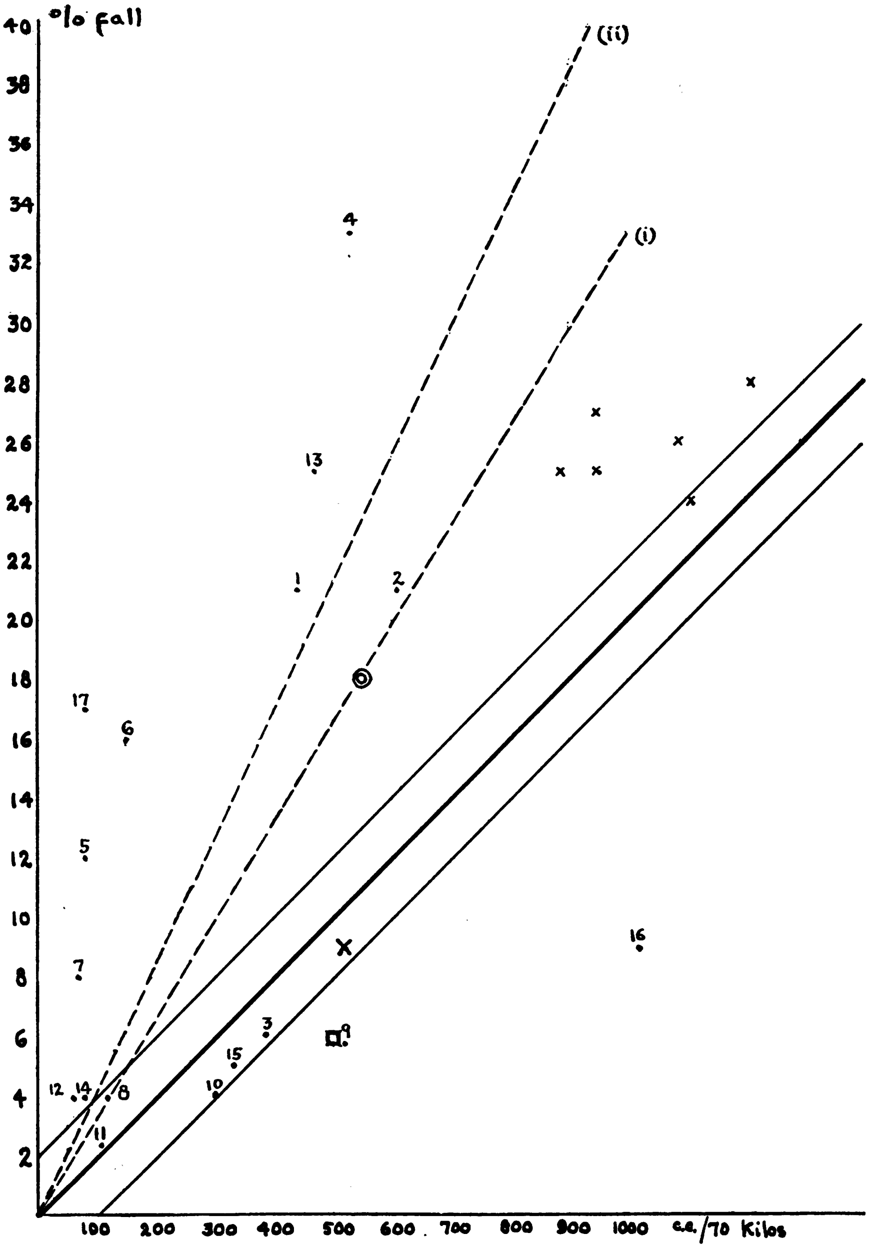

FIG. 2. MAXIMUM POST-OPERATIVE PERCENTAGE FALL IN HEMOGLOBIN, PLOTTED AGAINST THE BLOOD LOSS AT OPERATION

Small cross, blood loss by vein (data from Ebert, Stead, and Gibson); large cross, blood loss by vein (our data); double circle, blood loss by vein (data from Fowler and Barer); square, blood loss by vein (data from Martin and Meyers). Numbered points, 1, 2, 3, mastectomy; 4, 5, 6, partial gastrectomy; 7, 8, 9, 10, hysterectomy; 11, 12, cholecystectomy; 13, partial colon resection; 14, colostomy; 15, Manchester operation; 16, Caesarean section; 17, pyloroplasty. The heavy line denotes the "expected" relation between hemoglobin fall and blood loss. For explanation of other lines, see text.

of blood lost is shown in Figure 2. The straight line represents the relation which would obtain if the blood lost were replaced by the transfer of fluid from the tissues to restore the volume of the vascular system to its original value (0.07 of the body weight), and the 2 lines parallel to it mark the limits of the allowable experimental error (± 2 per cent). Each point represents the result of a separate determination of blood loss and maximum hemoglobin fall, those shown by crosses being the data of Ebert, Stead, and Gibson for blood donors, that shown by a double circle being the average value of Fowler and Barer for blood donors after 24 hours, that shown by a square being the average value of Martin and Meyers (12), and the remainder being our own material, selected from about five times as many cases as go to make up the figure, but in such a way as to illustrate the more important points.

It will be seen that some of the points lie along the theoretical line within the limits of experimental error, but that a larger number do not, the post-operative fall in hemoglobin being greater than would be expected from the amount of blood lost. In some cases, the discrepancy is very great (*e.g.,* points 4, 13, or 17). Of the explanations which can be put forward to explain this result, three are of particular interest.

(*a*) Following blood loss, water enters the vascular system from the tissues to restore the blood volume, and Ebert, Stead, and Gibson have found that the quantity of circulating plasma, 3 days after a hemorrhage of about 1000 cc. from a vein (in blood donors), is approximately the same as the initial plasma volume, *i.e.,* that the volume of circulating blood after hemorrhage is quickly restored to its original value. After such a hemorrhage, the maximum fall in hemoglobin observed is approximately the same as, or only a little greater than, that to be expected on the basis of the blood lost (see Figure 2). It is possible, however, that the blood loss at operation is complicated by a general loss of vascular tone, so that the volume of the vascular system 3 days afterwards is not the same as it was initially, but greater. Such an increase might be brought about, in part at least, by an increase in the volume of the spleen, and there are other blood depots, such as the skin plexuses, which might contribute towards the change in volume. More specifically, if V_1 is the volume of the vascular system in cc. before hemorrhage and V_2 the volume after, and if the blood loss in cc. is L, we have the relation

$$\frac{F_2}{F_1} = \frac{V_1}{V_2} \cdot \frac{V_2 - V_1 - L}{L} \qquad (1)$$

in which 100 F_1 represents the post-operative hemoglobin fall, in per cent, which would result from the loss L without any change in vascular volume, and 100 F_2 the fall which would appear if the volume were to increase from V_1 to V_2 linearly with loss L. The dotted lines in Figure 2 show the relation which would obtain between the observed post-operative fall and the quantity of blood lost if the vascular system were to increase from 5 liters to 6 liters (line i) and from 5 liters to 7 liters (line ii). Even such large changes in volume would be insufficient to account for many of the observed points (*e.g.,* points 4, 13, or 17).

(*b*) The second possibility is that the activity of the hemapoietic system is depressed post-operatively, so that red cell production is reduced or even arrested for a period which may amount to days. Since the life of the red cell is variously estimated as from 20 to 60 days, or even longer, the daily rate of new red cell production in the steady state must be between 5 per cent and 1.7 per cent (or less) of the total number, or of the hemoglobin concentration, but a hemoglobin deficit of from 5 to 15 per cent in excess of that due directly to the blood loss might accumulate in 3 post-operative days. Taken alone, however, even such a complete arrest of hemapoiesis would not be sufficient to account for all the post-operative falls of hemoglobin observed (*e.g.,* such points as 4, 13, or 17).

(*c*) Some of the greatest disproportions found between the amount of blood lost and the fall in hemoglobin have occurred in cases in which 4 grams of sulfanilamide were placed in the abdominal cavity after partial gastrectomy, partial colon resection, and similar operations, and this makes it necessary to entertain the possibility of a hemolytic anemia having been caused by the drug (see Watson and Spink (13); Machella and Higgins (14)). It should be emphasised, however, that sulfanilamide cannot be held responsible for most of the discrepancies between blood loss and hemoglobin fall which are observed, for in most cases which make up Figure 2, the drug was not used, and in the case of one of the greatest falls in relation to the amount of blood lost (point 6), no sulfanilamide was employed. The possibility of some other hemolytic process contributing to the result must, however, be admitted.

Further investigation will be necessary before we can bring independent evidence to decide whether a change in the vascular volume is involved, as suggested in the first explanation, and before we can offer any hypothesis as to the mechanism by means of which the hemapoietic system becomes depressed, as suggested in the second explanation. Meanwhile it is sufficient to remark that both explanations involve the idea of a temporary post-operative depression of function, of vascular tone on the one hand, and of hemapoietic activity on the other, and it will be shown below (Section III) that a post-operative fall in plasma protein concentration occurs also, out of all proportion to the quantity of blood lost.

It will be observed from Figure 2 that the same fall in hemoglobin does not result from the same blood loss, even for the same type of operation. As judged from the patient's post-operative course for the first few days, we have observed that the operation seems to be less well tolerated when the hemoglobin fall is great in relation to the amount of blood lost (*e.g.*, the case corresponding to point 4, 13, or 17) than when it is not, and this observation suggests that the "mild post-operative shock" which follows certain major operations, and which is recognised as being something of an idiosyncrasy, may be the result of just such depressions of vascular tone, hemapoietic activity, and plasma protein production (see Section III) as we have suggested, to account for the experimental results in Figure 2 and Table III. We have also observed that the hemoglobin fall in relation to blood loss is usually greater after intraperitoneal operations than after operations such as mastectomy, thyroidectomy, etc., but much further investigation will be necessary before points such as this can be established one way or another.[4]

The principal conclusion of this Section is that the post-operative fall in hemoglobin concentration follows a regular curvilinear course, and that the extent of the fall is frequently much greater than would be expected on the basis of the quantity of blood lost.

SECTION II

The regulation of post-operative fluid balance

We shall consider one case in detail, in order to illustrate the way in which measurements of hemoglobin and plasma protein concentrations can be used as a guide to intravenous therapy. For the purposes of this paper, this selected case pre-

[4] An extreme instance of a lack of correspondence between the amount of blood lost and the resulting hemoglobin fall is found after Caesarean section, and is illustrated by point 16 in Figure 2. Although the blood loss is usually great (500 to 1000 cc.), the fall in hemoglobin which follows is typically quite small. Most of the blood is apparently extraneous to the maternal circulation, and so is not missed.

TABLE I

24-hour period	Hemoglobin	Proteins	Intake		Clinical course
			By vein	By mouth	
	grams per cent	*grams per cent*	*cc.*	*cc.*	
0	11.3	6.6	3000		Loss at operation, 220 cc. Until the 3rd day, the post-operative fall in hemoglobin and in plasma protein concentration was according to expectation.
1	10.6	6.3	3000		
2	9.7	6.1	3000		
3	12.9	6.8	3500		Period during which there was an extensive peritoneal transudate. Water balance disturbed and corrected.
4	13.2	6.8	4000		
5	11.6	6.4	2500	160	
6	9.9	6.2	2000	465	
7			1500	870	Period of dehydration, patient taking inadequate fluids by mouth.
8				1230	
9	14.4	6.8		1480	
10	13.3	6.7	3000		On fluids by mouth from this time on, maintaining good water balance.
11	10.5	6.4	2000	690	
12	9.9	6.3			

sents 4 post-operative periods to be considered, and in reading the description, reference should be made to Table I.

Case 1. This patient, a woman of 41 years and weighing 122 lbs., had such an extensive scirrhus carcinoma of the cardiac half of the stomach as to make total gastrectomy necessary. Before operation her hemoglobin concentration was 11.3 grams per cent, and her plasma protein concentration was 6.6 grams per cent. She was in good water balance on the day of her operation. The total gastrectomy was performed with a blood loss of 220 cc.

We now follow her post-operative course as set forth in Table I.

In the course of the first 2 post-operative days, the patient's hemoglobin concentration fell from the original 11.3 grams to 9.7 grams per cent. For a blood loss of 220 cc., and with a daily intravenous intake of 3000 cc., this fall in hemoglobin is within the limits of expectation, and the fall in plasma protein concentration which accompanied it (from 6.6 grams to 6.1 grams per cent) calls for no special comment.

On the third post-operative day, the patient complained of a tenseness in the abdomen, and, while physical examination did not yield any positive information, the increase in the hemoglobin concentration (to 12.9 grams per cent) and the increase in the plasma protein concentration (to 6.8 grams per cent) showed that some disturbance of the patient's water balance had occurred. The amount of infusion was increased to 3500 cc. and on the evening of the same day, it became evident what the trouble was. A profuse, clear, peritoneal exudate made itself evident through the drain; and although the quantity could not be measured, it is certain that the patient lost at least 2000 cc. by this route.

We next enter the period from the 3rd to the 6th post-operative day, during which the patient's intravenous intake was increased in order to compensate for the loss by drainage. On the 6th post-operative day, her hemoglobin was 9.9 grams per cent and her plasma protein concentration was 6.2 grams per cent. During this 3-day period, our patient's water balance had been restored by the quantity of fluid given by vein. The drainage from the peritoneal cavity became steadily less; it was probably due to transudation, low in protein, from the large surface exposed in the course of the resection.

After the morning of the 7th day, the patient was given fluids by mouth only. The daily hemoglobin and plasma protein determinations were now discontinued. As it turned out, the intake was inadequate, and a state of dehydration supervened. On the 8th day, her temperature was slightly raised, and she complained of nausea. Her hemoglobin concentration on the 9th post-operative day had increased to 14.4 grams per cent, and an estimation of the CO_2-combining power of her plasma gave a value of 37 volumes per cent.

This state of acidosis and dehydration was relieved by 3000 cc. of intravenous fluid on the 10th day, and 2000 cc. on the 11th day. After the 11th day, the patient was able to maintain her water balance by taking fluids by mouth.

This case has been described at some length, not only because it illustrates the use of hemoglobin concentration determinations as a measure of the extent of dehydration, but also because it leads to conclusions which are reached quite generally in the cases of dehydration in our experience.

1. A simple rule for regulating the intravenous water requirements of a patient post-operatively is to estimate the probable daily hemoglobin level, the post-operative fall in hemoglobin being more or less characteristic of the type of operation, and then to give the smallest amount of fluid which will keep the hemoglobin from rising above the estimated level for the day. In practice, this is done by ordering an infusion of 1500 cc. twice daily, taking the blood sample through the intravenous needle before the infusion is started, and then increasing or decreasing the amount of fluid according to the result obtained. In this way, the dangers of giving too much or too little fluid are avoided, and the daily requirement is found without reference to water balance sheets, etc. The method is more flexible than those which depend on records of intake and output. These records may be very difficult to keep, for the patient may, for example, be drinking water with a Levine tube operating with suction, losing fluid by drainage, and sweating freely, all at the same time; the daily hemoglobin determinations nevertheless enable one to maintain a good water balance, and if one is in doubt, the determinations can be made more frequently, *e.g.*, before each infusion rather than only once a day. We do not mean by this, of course, that daily intake and output records should not be kept, and we have kept them routinely in all the cases of this series. The result has been to show, however, that the water requirements as judged from the repeated hemoglobin determinations agree with those as judged from the balance sheets, if about 30 cc. per sq. M. per hour is allowed for loss by skin and lungs. This is about 75 per cent of what is usually allowed, and the result is that 3000 cc. per day, given in 2 equal infusions of 1500 cc., is usually sufficient for the average adult (70 kilos., 1.9 sq. M.) receiving nothing by mouth, provided that he is in good water balance to begin with. After

partial gastrectomy, even with a Levine tube inserted, it is usually sufficient to give an infusion of 1500 cc. during or immediately after operation and another infusion of 1500 cc. the same evening, these to be followed by 2 infusions of 1500 cc. each the next day. On the 2nd and 3rd post-operative days, when the patient usually tolerates 30 cc. per hour by mouth, 2500 cc. by vein is sufficient, and thereafter, the amount of the infusion is decreased as the intake by mouth increases. With this allowance of water, which is at the lower limit of the variable requirements found by Maddock and Coller (15), the patient can be expected to excrete 1200 to 1500 cc. of urine. It should be emphasized, however, that these quantities apply only if the patient is in good water balance pre-operatively, and when no complications arise.[5]

[5] It should be emphasised that this paper is concerned with the quantity of intravenous fluid to be given, and not with the kind of infusion. From a clinical standpoint, however, our procedure is more complex than this paragraph conveys. Generally speaking the patients fall into one of two categories. 1. When considerable dehydration is present and has to be corrected, we use infusions of 5 per cent glucose in saline, for infusions of glucose in water can correct dehydration in a transitory manner only, since they set up only a transitory osmotic gradient. All the cases which go to make up Figure 3 were treated in this way. 2. When the patient is in approximate water balance and when the problem is merely the maintenance of this balance (as in most of our post-operative material), we go half-way towards following Coller and his school by giving 5 per cent glucose in water as the morning infusion, and an equal amount of glucose in saline in the evening. This keeps the daily intake of NaCl down to 15 grams or less, and the arrangement seems to work well over short periods (a few days). Over longer periods, and when the problem is still merely maintaining balance in a patient already in approximate water balance, we reduce the NaCl intake still further and rely on infusions of 5 per cent glucose in water, supplemented by infusions of 5 per cent glucose in saline when indicated by falling values for blood Cl. This is our present practice, but we ought to remark that our own experimental results leave us dissatisfied with the currently accepted views regarding the relation between the amount of Cl given by infusion and the blood Cl levels. The situation seems to be much more complex than is generally recognised.

We also supplement our daily observations by making determinations of the CO_2-combining power of the patient's plasma. If the CO_2-combining power falls, we use M/6 sodium lactate and 5 per cent glucose instead of glucose in saline or glucose in water. There is no doubt but that sodium lactate is more immediately effective in correcting acidosis than is glucose in saline.

2. The plasma protein concentration is increased in dehydration (Drew, Scudder, and Papps (16)), but not in proportion to the increase in hemoglobin concentration, and when dehydration is relieved by infusions, the plasma protein and hemoglobin concentrations do not fall proportionately. Dehydration may therefore mask a hypoproteinemia, but there seems to be no reliable way of calculating what the protein concentration will be when the dehydration is overcome.

3. It is a familiar observation that an infusion is more effective in reducing hemoglobin concentration when dehydration exists than when it is absent, and in suitable cases one finds a clear quantitative relation between the fall in hemoglobin which each liter of infusion produces and the degree of dehydration existing at the time.

Case 2. A woman of 63 years, weighing 123 lbs., fell down stairs, injuring her back, lower ribs, and left knee. For a month afterwards, she had pain in her back and difficulty in raising her arms above her head. A month later (January 29th) she fell again, this time sustaining a compression fracture of the 3rd dorsal vertebra. This was reduced on January 31st, and a plaster jacket was applied. Two days later, the patient became nauseated; on February 5th, her temperature rose to 103° F. and her pulse to 130, while she complained of abdominal pain, and vomited. Wangensteen suction was started, and when the jacket was removed on February 6th, the patient was found to have all the signs of intestinal obstruction. On the morning of February 7th, her hemoglobin was 13.4 grams per cent; she received an infusion of 2680 cc. (glucose in saline) during the next 24 hours, and on the following morning, her hemoglobin was 11.5 grams per cent. During the next 24 hours, she received 3000 cc. of saline-glucose, which reduced the figure to 10.1 grams per cent; another infusion of 3000 cc. during the following 24 hours brought her into a state of water balance with a hemoglobin concentration of 9.65 grams per cent, as shown by the fact that further daily infusions of 2200 to 2500 cc. did not bring about any further reduction. The rest of the course of the patient's illness has no bearing on the subject of this paper. The patient turned out to have an intestinal obstruction; on this being relieved, an uninterrupted recovery followed.

Expressing each figure for hemoglobin as a percentage of 9.65 grams per cent, the patient's hemoglobin concentration when in water balance (her "equilibrium value"), we get Table II:

TABLE II

Day	Hemoglobin	Hemoglobin, per cent of equilibrium value	Intravenous water (W)	Change	Effectiveness = change/W
	grams per cent		*liters*	*per cent*	
1	13.4	137	2.680	19	7.1
2	11.5	118	3.000	14	4.7
3	10.1	104	3.000	4	1.4
4	9.7	100			

The difference between the hemoglobin, expressed as a percentage of the equilibrium value, and 100, is a convenient measure of the degree of dehydration, and if we plot it against the effectiveness of the infusion as shown in the last column of the Table, we get the points marked by circles in Figure 3, which show that the effectiveness of each liter of infusion in reducing the hemoglobin concentration becomes greater as the dehydration becomes greater. This relation suggests a similar treatment of data which we have accumulated in the course of these studies, and in which we know (*A*) the hemoglobin concentration before an infusion of *W* liters per day, in 2 more or less equal amounts, (*B*) the hemoglobin concentration approximately 24 hours afterwards, and (*C*) the hemoglobin equilibrium value for the patient, *i.e.*, the value to which he settles down as water balance is restored. Each point entered on Figure 3 is based on such data, obtained from cases in which dehydration had resulted from persistent vomiting or restriction of water by mouth, and in which water balance was being restored, preparatory to operation, by daily infusions. In preparing the Figure, the daily intake was corrected for the weight of the patient when this was more or less than 70 kgm.

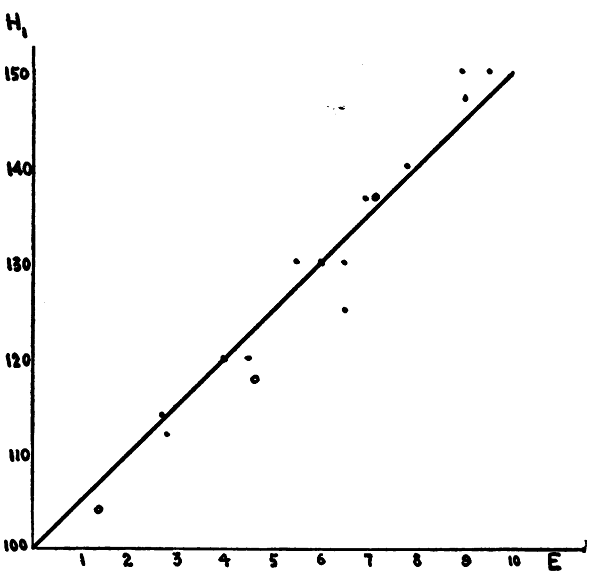

FIG. 3. EXTENT OF DEHYDRATION, H_1, PLOTTED AGAINST THE EFFECTIVENESS, E, OF A 3000 CC. INFUSION

The circles are the points taken from Table II. For further explanation, see text.

It will be observed that the points tend to lie along a straight line, which is the line given by expression (*2*), below. The situation can now be considered from a more general point of view. Suppose that on a given day a dehydrated patient of 70 kgm. has a hemoglobin concentration of H_1, that he receives *W* liters of infusion during the course of the next 24 hours, but nothing by mouth, and that at the end of the time his hemoglobin concentration is H_2. Suppose further that H_0, the equilibrium value to which he settles down as he approaches good water balance, is known. Then $(H_1 - H_0)$ is a measure of the extent of the dehydration, and $(H_1 - H_2)$ is a measure of the effectiveness of the infusion, and when *W* is in the neighborhood of 3.0, the relation between them is given by the line in Figure 3, or by

$$(H_1 - H_2)/W = k \cdot (H_1 - H_0) \qquad (2)$$

where *k* has the value 0.2.[6] This relation holds, irrespective of whether the hemoglobin values are

[6] The value of the constant, 0.2, is of peculiar interest. Suppose that we have an isolated system of 5 liters of blood (the average volume of the circulating blood for a person of 70 kgm.) with a hemoglobin concentration of 100 per cent, and that in some way water were abstracted (as in dehydration) so as to reduce it to 4 liters; the hemoglobin would rise to 125 per cent. If one liter of water were added, the effect (H_1-H_2) would be related to the extent of dehydration by expression 2 with $k = 1.0$. Suppose this 1 liter to be supplied by the infusion, the remainder of which is excreted. In our experimental results, $k = 0.2$, which means that the addition of each liter of retained water is 1/5th as effective *in vivo* as it would be in an isolated system, or, to put it another way, that the volume involved in the processes of dehydration and rehydration *in vivo* is 5 times the volume of the circulating blood itself. The simplest way of accounting for this result is to suppose that the process of dehydration removes extracellular fluid, one quarter of which (the blood plasma) lies inside the vascular compartment, and three quarters (interstitial fluid) lies outside the vascular compartment. There is recent evidence that the water losses from these two compartments are roughly

expressed in grams per cent or in percentages of the equilibrium values (as in Table II), and provides an approximate relation between the effectiveness of an infusion and the degree of dehydration of the patient to whom it is administered. It is therefore at least a partial answer to the problem of how much intravenous fluid should be given when water balance records are not available, because it tells us what change in the hemoglobin value will be produced per liter of infusion, under specific conditions which can be defined. It will be noticed that the relation between effectiveness and the extent of dehydration is derived from the observation of what happens in a considerable number of cases, without involving any assumptions regarding transfers of fluid between blood, interstitial fluid, and the intracellular fluid.

4. The same expression as is used to describe the relation in Figure 3 can be used to find the extent of dehydration in a patient for whom the hemoglobin equilibrium value is unknown, as is illustrated numerically in the following case.

Case 3. A robust man of 50 years, weighing 167 lbs., was admitted at 3:45 p.m. on March 1st, in a state of dehydration following persistent vomiting due to a stenosing pyloric ulcer. His hemoglobin was 18.2 grams per cent, and his plasma protein concentration 8.9 grams per cent. These values, and particularly the plasma protein value, are characteristic of dehydration, but in themselves do not tell us its extent, as the patient's normal equilibrium hemoglobin concentration is unknown. He received an infusion of 3000 cc. in the first 24 hours after admission, one infusion of 1500 cc. being given at 4 p.m. the same afternoon, and another of 1500 cc., the following morning. At 4 p.m. on the afternoon of March 2nd, the patient's hemoglobin was found to be 15.7 grams per cent. The difference (H_1-H_2) is 18.2–15.7, or 2.5, and this divided by 0.2 and by W ($= 3$) gives 4.16, which is the difference (H_1-H_0). Thus H_0, the equilibrium value for the patient's hemoglobin, is 14.04 grams per cent, and the extent of the dehydration which resulted in the admission value of 18.2 grams per cent for the hemoglobin concentration is no longer in doubt. A further infusion of 3000 cc. in 24 hours should have been sufficient, by the same kind of calculation, to reduce the hemoglobin content of 15.7 grams per cent by $(15.7-14.3)/5 \times 3 = 1.0$ gram per cent, or to 14.7. Actually, the hemoglobin on the afternoon of March 4th, after such an infusion had been given, was 14.4 grams per cent, and this turned out to be the equilibrium value which the patient maintained for several days with an intravenous intake of 2500 cc. per day. He was thus in good water balance on the day of his partial gastrectomy, March 7th, and his operation was followed by an interrupted convalescence.

proportionate (Mellors, *et al.* (20)). This 1:4 ratio of volumes would provide a k of 0.25 for a retention of 1 liter of water, and the observed value, 0.2, probably indicates that a little less than 1 liter is retained when the dehydration is such as to raise the hemoglobin to 125 per cent.

5. Since the effectiveness per liter increases as the degree of dehydration increases, infusions of 3000 cc. or so are more effective in cases of dehydration than appears at first sight, and it is certain that the amount of intravenous fluid required to overcome a state of dehydration is less than the usually estimated 2500 cc. per day plus the number of liters of water deficit which the patient is supposed to have, clinical signs of dehydration appearing when the deficit is about 3500 cc. Presumably the reason for this is that the water loss of a dehydrated patient decreases with the extent of dehydration, so that it becomes possible to sustain life for weeks on an intake by mouth of as little as 600 cc. per day (Richards and Banigan (17)).

The conclusion of this Section is that the extent of dehydration can be estimated by making daily determinations of hemoglobin concentration, and that a linear relation exists between the extent of dehydration and the effectiveness of an infusion in relieving it.

SECTION III

Post-operative plasma protein concentration

For about 2 hours after a hemorrhage of about 1000 cc. from a vein, the plasma protein concentration falls sharply because of the transfer of a protein-poor fluid from the tissues to the bloodstream; thereafter, protein as well as water is transferred, so that the plasma protein concentration levels off to about 93 per cent of the initial value and remains unchanged for at least 72 hours (Table III, row 1, data of Ebert, Stead, and Gibson); our experience confirms their results. If a smaller amount of blood is withdrawn, the fall in plasma protein concentration is less, *e.g.*, when an average of 250 cc. is removed by vein, the value for the plasma protein concentration at the end of 72 hours is approximately 98 per cent of the initial value (Table III, row 2).

In order to compare the fall in plasma protein concentration which occurs after partial gastrectomy and partial colon resection with the foregoing figures, it is necessary to be sure that the values are not falsified by the effects of dehydration. This means that we can use only values of plasma protein concentration for which there are corresponding hemoglobin values, and only values for cases in which the post-operative fall in hemoglobin occurs uninterruptedly and in accordance with expectation based on the extent of the blood loss at operation. These are severe conditions. It is certain that the great majority of post-operative plasma protein values in the literature do not meet them, and from our series of 55 cases we have been able to select only 14 partial gastrectomies and 10 partial colon resections which do. The results in these cases are shown in Table III as means accompanied by their standard errors, as there is considerable individual variation.

TABLE III

Loss by	Plasma protein concentration, per cent of initial*			
	Day 1	Day 2	Day 3	Day 4
Vein 6 cases approx. 1000 cc.	93.9 ±1.11	92.6 ±1.40	92.3 ±0.55	
Vein 6 cases approx. 250 cc.	98.1 ±0.72	97.9 ±0.91	97.7 ±0.63	
Partial gastrectomy 14 cases approx. 250 cc.	96.7 ±1.32	95.6 ±1.24	90.4 ±0.96	89.6 ±1.17
Partial colon resection 10 cases approx. 250 cc.	97.3 ±1.70	94.3 ±1.46	93.2 ±1.03	93.0 ±1.28

* The initial values were: 7.0 grams per cent for the 1000 cc. donors, 6.8 grams per cent for the 250 cc. donors, 7.0 grams per cent for the partial gastrectomies, and 6.9 grams per cent for the partial colon resections.

At least 2 conclusions emerge from this Table. (*1*) The falls in plasma protein concentration after partial gastrectomy and after partial colon resection are substantially the same, but they are much greater than the fall which follows the loss of the same amount of blood by vein; indeed, the post-operative falls approximate that which follows the loss of about 1000 cc. by vein, or 4 times the amount lost at operation. This observation has its counterpart in the observation that the post-operative fall in hemoglobin is also greater than would be expected on the basis of the blood lost (Section I). (*2*) The post-operative fall in plasma protein concentration pursues a different course from that following the loss of blood by vein. In the latter case, the fall is sudden and complete within a few hours (Ebert, Stead, and Gibson, confirmed by our own observations), whereas after partial gastrectomy and partial colon resection, the fall is steady and slow, being complete only after 3 or 4 days, at which time the post-operative fall in hemoglobin is complete also. The mechanisms underlying the 2 phenomena are therefore almost certainly different. In the case of hemorrhage, the fall is due to the transfer of a large amount of protein-poor fluid from the tissues, whereas the post-operative falls, over and above that which would correspond to the amount of blood lost, seem to be due to a depression of the mechanism which keeps the plasma proteins at a constant level.[7] This conclusion should be considered in relation to observations made in 1938 by Chanutin, Hortenstine, Cole, and Ludewig (18), who found that the serum proteins undergo complex changes after simple laparotomy in the rat, the serum albumin falling about 10 per cent immediately after operation, and serum globulin and the fibrinogen rising. Chanutin, Hortenstine, Cole, and Ludewig say that their results are "difficult to explain unless one assumes that tissue damage reduces the stimulus to albumin formation," and this is essentially the conclusion to which our results point, although we are dealing with total plasma protein rather than with the albumin fraction only. The post-operative fall in plasma protein concentration also seems to be related, in point of time at least, to the post-operative inhibition of hemapoiesis, referred to in Section I, and, like it, may be connected with the inhibition of hemoglobin formation which occurs, apparently as a result of a disturbance of the

[7] The nature of this mechanism is obscure. It should be pointed out, however, that the mere intravenous feeding is not sufficient to bring about the protein falls shown in Table III. We have had several cases in which the plasma proteins showed a precipitous fall; in 3 cases, this occurred a few days after operation, and we had reason to believe that the fall corresponded to the formation of intraperitoneal exudate (as in Case 1, above). In 4 cases in which intravenous therapy had to be continued for over 2 weeks because of complications, a considerable fall in the plasma protein concentration was observed (as low as 5.6 grams per cent in one case). These cases were not included in compiling Table III.

metabolism of hemoglobin-building, under conditions in which toxic material is absorbed (see Whipple (19)).

In conclusion, something ought to be said about the relation of these results to "post-operative shock." It is a matter of general clinical observation that some patients tolerate operations better than others do, as shown by their behaviour and reactions during the first few post-operative days, and also that some operations are followed by a greater degree of prostration than others, although shock, in the currently accepted sense, is not demonstrable by lowered blood pressure values. This condition, which is difficult to describe exactly but which must be very familiar, is often referred to as "mild post-operative shock," and perhaps the phrase is used somewhat loosely. It might be better to borrow Alvarez' expression, and refer to it as post-operative "constitutional inadequacy," the inhibitions of hemoglobin production and of plasma protein production described in this paper being two of the "inadequacies" which can be demonstrated experimentally.

SUMMARY

1. After major surgical procedures, the post-operative fall in hemoglobin concentration follows a regular curvilinear course over a period of from 2 to 4 days when complications are absent, but the extent of the fall is often much greater than would be expected on the basis of the amount of blood lost at operation. The most likely explanation for this is that there is a post-operative inhibition of hemoglobin formation and hemapoiesis, although changes in vascular volume and even hemolytic processes may contribute to the result.

2. Since the post-operative fall in hemoglobin concentration follows a regular curvilinear course, a simple rule for regulating the water requirements of a patient post-operatively is to estimate the probable daily hemoglobin level, being guided by the general shape of the curve, and then to give the smallest amount of intravenous fluid which will keep the hemoglobin from rising above the estimated level for the day. This procedure gives results which are more simply obtained, and which we believe to be more dependable, than those which may be expected from the intake and output records kept under the average hospital conditions.

3. An approximately linear relation exists between the effectiveness of an infusion and the extent of the dehydration present. This relation enables one to estimate the extent of the dehydration present in any given case from the effect produced by a measured volume of infusion.

4. After partial gastrectomy and partial colon resection, the plasma protein concentration falls to a much greater extent than would be expected from the amount of blood lost at operation. It is suggested that this post-operative fall in plasma protein concentration is largely due to a disturbance of the physiological mechanism which maintains the steady state, and that this disturbance bears a relation to the inhibition of hemapoiesis which occurs at about the same time (see 1 above).

We wish to thank Dr. Peyton Rous and Dr. F. A. Coller for reading and revising the manuscript.

BIBLIOGRAPHY

1. Scudder, J., Shock: Blood Studies as a Guide to Therapy. J. B. Lippincott Company, Philadelphia, 1940.
2. Foote, M. N., and Gerst, G. R., Practical application of the falling drop method for determining surgical prognosis. Am. J. Surg., 1940, **50**, 316.
3. Rhoads, J. E., Wolff, W. A., and Lee, W. E., The use of adrenal cortical extract in the treatment of traumatic shock of burns. Ann. Surg., 1941, **113**, 955.
4. Ponder, E., Errors affecting the acid and alkali hematin methods of determining hemoglobin. J. Biol. Chem., 1942, **144**, 339.
5. Barkan, G., Hemoglobin estimation with undiluted reduced blood. J. Lab. and Clin. Med., 1941, **26**, 1823.
6. Berkson, J., Magarth, T. B., and Hurn, M., The error of estimate of the blood cell count as made with the hemocytometer. Am. J. Physiol., 1940, **128**, 309.
7. Looney, J. M., The relation between specific gravity of blood serum and its protein concentration. J. Lab. and Clin. Med., 1942, **27**, 1463.
8. Smith, C., Normal variations in erythrocyte and hemoglobin values in women. Arch. Int. Med., 1931, **47**, 206.
9. Gatch, W. D., and Little, W. D., Amount of blood lost during some of the more common operations. J. A. M. A., 1924, **83**, 1075.
10. Ebert, R. V., Stead, E. A., Jr., and Gibson, J. G., Jr., Response of normal subjects to acute blood loss. Arch. Int. Med., 1941, **68**, 578.

11. Fowler, W. M., and Barer, A. P., Rate of hemoglobin regeneration in blood donors. J. A. M. A., 1942, **118**, 421.

12. Martin, J. W., and Meyers, J. T., The effects of blood transfusions on donors. J. Lab. and Clin. Med., 1935, **20**, 593.

13. Watson, C. J., and Spink, W. W., Effect of sulfanilamide and of sulfapyridine on hemoglobin metabolism and hepatic function. Arch. Int. Med., 1940, **65**, 825.

14. Machella, T. E., and Higgins, G. M., Anemia induced in rats by means of sulphanilamide. Am. J. M. Sc., 1939, **198**, 804.

15. Maddock, W. G., and Coller, F. A., Water balance in surgery. J. A. M. A., 1937, **108**, 1.

16. Drew, C. R., Scudder, J., and Papps, J., Controlled fluid therapy. Surg., Gynec., and Obst., 1940, **70**, 859.

17. Richards, P., and Banigan, J. J., How to Abandon Ship. Cornell Maritime Press, New York, 1942.

18. Chanutin, A., Hortenstine, J. C., Cole, W. S., and Ludewig, S., Blood plasma protein in rats following partial hepatectomy and laparotomy. J. Biol. Chem., 1938, **123**, 247.

19. Whipple, G. H., Protein production and exchange in the body. Am. J. M. Sc., 1938, **196**, 609.

20. Mellors, R. C., Muntwyler, E., and Mautz, F. R., Electrolyte and water exchange between skeletal muscle and plasma in the dog following acute and prolonged extracellular electrolyte loss. J. Biol. Chem., 1942, **144**, 773.