STUDIES ON HYPOALBUMINEMIA PRODUCED BY PROTEIN-DEFICIENT DIETS

II. RAPID CORRECTION OF HYPOALBUMINEMIA WITH AN AD LIBITUM MEAT DIET*

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The practical problem of restoring protein deficiency induced by diet has been studied experimentally by Weech (1) and his coworkers who found a definite regeneration (in the following order of efficacy) when beef serum, egg white, meat, liver, or casein was added to the diet of dogs. For example, after a 3 week depletion period, these workers observed an almost complete return to normal when 5 gm. per kilo per day of beef chuck was added to the diet for 10 days. This was about twice the rate of regeneration in other experiments in which half this amount of meat was given.

In surgical and other patients suffering from hypoproteinemia of dietary origin restoration of serum protein must often be achieved in a relatively short period of time. It has seemed important, therefore, to determine how fast the serum protein can be restored to normal when much larger amounts of protein are given. This was the purpose of the present experiment.

Methods

Five dogs were fasted for 3 weeks; however, they were allowed water ad libitum and some of them were given Ringer's solution by gavage. At the end of 3 weeks they were started on the regeneration diet, which consisted solely of raw lean horse meat given ad libitum; i.e., sufficient meat was offered so that some of it was left at the end of each 24 hour period. This was then subtracted from the total to record the amount actually eaten.

Technical Methods.—Hematocrits were determined on heparinized blood. Plasma proteins were then determined and fractionated by methods already described (2). The blood volume was determined by using the Evan's blue dye T-1284 according to a simplified technique as follows:

The method for the determination of plasma volume in dogs was adapted from that described by Gibson and Evelyn (3). The main difference was the use of the Klett

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photoelectric colorimeter instead of the Evelyn apparatus employed by these workers. Many of these details were worked out in the Department of Physiology of the Washington University Medical School, and the authors are indebted to Miss Rolf for her help in applying them to our purposes.

An initial heparinized blood sample was first obtained. Through the same needle a 200 mg. per cent saline suspension of Evans blue was injected, the total dose being 1 mg. of dye per kilo of body weight. To insure the accurate introduction of the calculated amount of dye a 3 way-stop-cock and an 18 inch rubber tubing of small diameter connected with a syringe barrel was employed. After the initial blood sample was drawn saline was allowed to flow by gravity from the syringe barrel into the dog's vein to test the position of the needle in the vein. This assured, the dye solution was added by pipette under the surface of the saline solution. Toward the end of the injection small portions of saline were added to wash the last remnants of dye from the tubing into the vein. The initial time of mixing (zero point) was considered to be the time of the first saline washings.

Samples of heparinized blood for dye estimation were taken subsequently at recorded intervals of approximately 15, 25, and 35 minutes from the initial (zero) time. All blood samples were centrifuged for 30 minutes at 3000 R.P.M. 1 cc. of plasma from each of the 4 samples was measured into test tubes and 5 cc. of saline added. After the contents of the tubes were mixed, readings were immediately made on the Klett photoelectric colorimeter using 620 and 540 filters; the two filters are used to correct for any hemolysis present in the dye samples. The blank dye-free plasma was set at zero. The correct R for each sample was calculated according to the formula which is nearly the same as that used by Gibson and Evelyn (3):

\[ R = \frac{(R_{200}) \times 20 - (R_{sal})}{19.5} \]

The corrected R values for each of the 3 samples were then plotted against time and a line was drawn through these points and carried back to zero.

The concentration of dye (as mg. per cc.) for the R at zero time was read off a previously prepared graph which established the relationship between R and the concentration of dye. This graph was made by setting up several series of tubes each containing a known amount of dye and 1 cc. of plasma, made up to 6 cc. with saline. Because we found such dilute solutions of Evans blue to be unstable, a fresh 1 mg. per cent saline solution was made from the 200 mg. per cent dye solution each time a series was to be read. A straight line always resulted at least in the range of dye concentration used in our experiments.

The plasma volume in cubic centimeters was then calculated by dividing the milligrams of dye injected by the milligrams of dye present in 1 cc. of plasma at zero time.

**FINDINGS AND COMMENTS**

The main results of the experiment are recorded in Table I, which shows that after a 3 weeks fast the ad libitum meat diet resulted in a complete regeneration in 1 week of both the concentration of serum albumin and the total amount
thereof. Indeed the total circulating albumin increased well above normal, although this was undoubtedly a reflection of the increased plasma volume which accompanied the fall in red cell volume (hematocrit). There was very little further increase in the albumin during the 2nd week of the regeneration period. The fall in body weight and its subsequent rise, though a little more pronounced, roughly paralleled the behavior of the serum albumin. The red cell volume decreased but slightly during the fast; during the regeneration period it fell markedly, a reflection of the tremendous increase in the plasma volume. The serum globulin, unchanged during the fast and for the 1st week of the regeneration period showed a pronounced increase in the 2nd week.

The amount of meat ingested by the animals was surprisingly large and averaged 250 gm. per kilo per day; i.e., the dogs consumed one-fourth of their body weight each day. Inasmuch as meat is composed of one-fifth protein the actual protein intake was 50 gm. per kilo of body weight per day. It was interesting to note that this large amount was eaten even during the last days of the experiment; i.e., when body weight and serum protein had returned to normal.

These findings indicate first, the tremendous amount of protein which a depleted dog will ingest, and second, the rapidity with which such a high protein intake will lead to a complete correction of hypoproteinemia induced by a

### TABLE I

Changes during a 3 Week Fast and during 2 Weeks of an ad Libitum Meat Diet

<table>
<thead>
<tr>
<th>Dog</th>
<th>Initial</th>
<th>After 3 wks.</th>
<th>After 4 wks.</th>
<th>After 5 wks.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kg.</td>
<td>gm. per cent</td>
<td>gm.</td>
<td>gm. per cent</td>
</tr>
<tr>
<td>E6</td>
<td>5.6</td>
<td>48.8 2.65</td>
<td>2.75</td>
<td>4.3</td>
</tr>
<tr>
<td>E2</td>
<td>7.4</td>
<td>48.7 3.46</td>
<td>2.78</td>
<td>5.4</td>
</tr>
<tr>
<td>F3</td>
<td>8.5</td>
<td>45.1 3.39</td>
<td>2.90</td>
<td>6.8</td>
</tr>
<tr>
<td>S9</td>
<td>8.0</td>
<td>51.1 3.26</td>
<td>2.17</td>
<td>6.4</td>
</tr>
<tr>
<td>S2</td>
<td>13.4</td>
<td>35.3 3.14</td>
<td>3.52</td>
<td>10.3</td>
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</table>

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</thead>
<tbody>
<tr>
<td></td>
<td>8.0</td>
<td>49.0</td>
<td>6.8</td>
<td>45.2</td>
<td>2.69</td>
</tr>
<tr>
<td></td>
<td>13.9*</td>
<td>10.92</td>
<td>1.96</td>
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<tr>
<td></td>
<td>2.82</td>
<td></td>
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* Estimated.

Abbreviations: wt, body weight; hem., hematocrit; alb., plasma albumin; glob., plasma globulin; T. A., total plasma albumin.

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3 weeks fast. The practical inference is obvious and points the way toward rapid relief of clinical hypoproteinemia by the administration of sufficient protein. This is suggested in the accompanying study from this laboratory (2) in which a partition of about 30 to 1 was found in the distribution of dietary nitrogen loss or gain between tissue and serum proteins respectively; in other words evidence was presented showing that the body tissues will take up 30 gm. of nitrogen for every gram which goes to the regeneration of serum protein. This explains why large amounts of protein are needed to correct hypoproteinemia. The present findings are corroborative in that they indicate that if the protein intake is unusually large (in this case 50 gm. per kilo per day) regeneration of serum proteins will be complete within a week. We have no data as to whether this return to normal might not have occurred within a few days. However, a continuation of the high protein intake, i.e. during the 2nd week did not raise the albumin level any further though for some reason it did instigate an increase of the globulin fraction during this last period.

The failure of the red cells to regenerate as shown by the fall in the hematocrit is not surprising in view of the well known fact that restoration of red cells requires a number of weeks. From the practical point of view this is not a serious deficiency inasmuch as the important clinical manifestations of protein depletion are concerned with the plasma and not with the erythrocyte portion of the blood. The increase in the plasma volume during the regeneration period (from an average of 748 to 897 cc. during the 4th week) was probably the reason for the particularly pronounced fall in the red cell volume during this time.

SUMMARY

Serum albumin depletion, induced by a 3 weeks fast, was completely corrected within 1 week by the ingestion of a diet consisting solely of meat administered ad libitum. The average protein intake was 50 gm. per kilo of body weight per day. A 2nd week of the same diet produced no further increase in serum albumin though it did lead to an increase in the globulin fraction.

BIBLIOGRAPHY