STUDIES ON HYPOPROTEINEMIA. II. FAMILIAL IDIOPATHIC DYSPROTEINEMIA

By F. Homburger, M.D., and M. L. Petermann, Ph.D.

The present paper describes a new familial syndrome characterized by subtle disturbances of the qualitative relationships of the components of the blood plasma proteins and by a number of clinical disturbances.

The patients comprising this study provided a unique opportunity to investigate mechanisms of the homeostasis of plasma proteins in individuals not afflicted with any of the common pathologic causes affecting the metabolism of plasma proteins. Studies were thus possible on the homeostasis of plasma proteins, i.e., the factors which maintain uniformity or stability at the "normal" levels.

In view of the many factors which tend to unbalance the equilibrium of plasma proteins this homeostasis is remarkably effective, yet little is known regarding its mechanisms. The known facts may be summarized as follows: Deviations from the norm (euproteinemia) may result in hypoproteinemia, hyperproteinemia, "dysproteinemia" and "paraproteinemia"—the last two terms meaning a disproportion between components usually occurring in blood plasma (dysproteinemia) and the presence of proteins not usually found in blood (paraproteinemia). A combination of any of these disorders with each of the others is of course possible. Thus, in multiple myeloma hyper-, para-, and dysproteinemia may coexist, and gastric cancer may cause hypo- and dysproteinemia (hypoaalbuminemia). A similar picture is found in nephrosis. In Addison's disease, one may find dysproteinemia with normal total protein levels or with hyperproteinemia, and in dehydration hyperproteinemia may exist without disturbance of the proportional relationship of plasma components. With the exception of dehydration and of the production of Bence Jones' protein in multiple myeloma, the mechanisms causing these disturbances are poorly understood. Even in the relatively simple case of hypoproteinemia the mechanisms are complex. It may occur because the circulating blood is inadequately supplied with protein or because too much of it escapes. Insufficient protein enters the blood stream in malnutrition or intestinal malabsorption or in defective synthesis of proteins (liver disease, Cushing's syndrome). Protein
STUDIES ON HYPOPROTEINEMIA

is lost in excess from the blood stream in nephrosis,5 in altered vascular permeability, as in burns,6 or with excessive catabolism of proteins, as in hyperthyroidism,7 uncontrolled diabetes mellitus8 and pyrexia.

A more complex type of hypoproteinemia which persists in the presence of tissue protein repletion occurs in patients with gastric cancer,9 in chronic tuberculosis,10 and in certain types of kidney disease.11 In another group of cases the hypoproteinemia is unexplained and is therefore designated idiopathic hypoproteinemia.12-16

It appears from the preceding discussion that a theory of simple depletion alone cannot explain all of these phenomena.20,21 Although many aspects are still but little understood, an approach to some of them is possible in favorable circumstances.

In the patients studied by us, a number of physiologic factors governing the homeostasis of single protein components have been observed. There were none of the usual systemic disorders leading to changes of the protein pattern and, except for the dysproteinemia and idiopathic hypoproteinemia in some cases, the individuals were healthy.

A detailed description of the clinical syndrome is necessary for the proper interpretation of the experiments to be described.

PART I. THE CHARACTERISTICS OF THE SYNDROME AND ITS FAMILIAL ASPECTS

After the clinical studies described below, it became evident that the subjects studied presented a new syndrome, for which the name "familial idiopathic dysproteinemia" is proposed. The syndrome is characterized by the familial occurrence of edema of the legs, with ulcers in the males and functional vascular changes in the females, by dysproteinemia of variable types and sometimes discernable only by electrophoresis, by a number of congenital malformations and by a high incidence of stillbirths. No etiologic factor was found.

Methods of Study

A complete history was taken in each available member of the family and checked against that given by every other member; a complete physical examination was made of each available member. Whenever possible, routine studies of renal, hepatic,* cardiovascular (including oscillometric studies by means of the Collins oscillometer), gastrointestinal and adrenal12-17 function were carried out. In the case of some patients special tests were employed. These included liver biopsy through an abdominal incision in one case (Case 8) and muscle biopsies for study of blood vessels in two cases (Cases 5 and 8), as well as measurements of the renal clearance of glucose, para-aminohippuric acid and mannitol.28-30 Glucose tolerance tests31 and nitrogen, phosphorus and potassium balance studies32 were performed on the metabolic ward.

The total plasma protein concentration was measured by Kjeldahl analysis and corrected for non-protein nitrogen. Plasma volumes were estimated by the Evans blue method.33 The volume of the extracellular fluid space was estimated by the use of thiocyanate.34 The electrophoretic technic used in this study has been described elsewhere.35 Unless otherwise specified, a veronal-citrate buffer at pH 8.6 and ionic strength 0.10 was used. Electrophoresis was performed on samples of plasma obtained from the patients.* In the liver function tests the following methods were employed: measurement of hippuric acid excretion,36 retention of bromsulfalein,37 cephalin flocculation test38 and thymol turbidity test.39

* In the liver function tests the following methods were employed: measurement of hippuric acid excretion,36 retention of bromsulfalein,37 cephalin flocculation test38 and thymol turbidity test.39
TABLE 1.—Nitrogen, Phosphorus and Potassium Balance Study during 18 Days. See also Fig. 3.

<table>
<thead>
<tr>
<th>Date</th>
<th>Average N intake per day</th>
<th>Average N output* per day</th>
<th>N Utilized per day</th>
<th>K Utilized per day</th>
<th>P Utilized per day</th>
<th>Total Plasma Protein Gm. per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/1</td>
<td>28.0 Gm.</td>
<td>24.5 Gm.</td>
<td>3.5 Gm.</td>
<td>6.2 mM.</td>
<td>145 mg.</td>
<td></td>
</tr>
<tr>
<td>11/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stool 0.85-2.7 Gm. per day.

TABLE 2.—Case 8. Tabulation of Total Protein Concentration, Albumin Concentration and Protein Intake from December, 1945, to October, 1947.

"Plasma" means the 975 cc. of plasma injected at that time containing 6.15 Gm. of protein per 100 ml. Notice that the actual (electrophoretically measured) albumin is considerably lower than that measured by the Howe method. The "Howe albumin" roughly corresponds to the sum of the electrophoretic albumin plus the globulins.22

<table>
<thead>
<tr>
<th>Date</th>
<th>Albumin Gm./100 ml.</th>
<th>Electrophoresis</th>
<th>Howe</th>
<th>Total Plasma Protein Gm.</th>
<th>Protein Intake Gm./day</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/1</td>
<td>5.28</td>
<td>3.57</td>
<td>3.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/4</td>
<td>4.31</td>
<td>3.23</td>
<td>3.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/13</td>
<td>4.58</td>
<td>3.18</td>
<td>3.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/47</td>
<td>3.75</td>
<td>3.17</td>
<td>3.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/30</td>
<td>6.15</td>
<td>2.75</td>
<td>2.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/30</td>
<td>5.49</td>
<td>3.05</td>
<td>3.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/21</td>
<td>5.83</td>
<td>3.05</td>
<td>3.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/28</td>
<td>6.01</td>
<td>2.79</td>
<td>2.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/2</td>
<td>5.27</td>
<td>2.68</td>
<td>2.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/11</td>
<td>5.13</td>
<td>2.68</td>
<td>2.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/8</td>
<td>4.95</td>
<td>2.68</td>
<td>2.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/8</td>
<td>4.70</td>
<td>2.68</td>
<td>2.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/5</td>
<td>5.16†</td>
<td>2.68</td>
<td>2.68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Plasma vol. 3000 ml. † Plasma vol. 2160 ml.
STUDIES ON HYPOPROTEINEMIA

in the postabsorptive state. Since values for the various protein components given as percentages may be misleading when the total protein concentration is low, the concentration of each component is given in grams per 100 ml. of plasma. The amino acids of plasma and urine were studied by chromatograms on paper, and no abnormalities were found.

The composite family history is indicated in the genealogic table in figure 1. The strong physical resemblance between some of the members of the family is evidenced in figure 2.

The mother, now 70 years old and a cardiac patient, had suffered from ankle edema since the age of 50. There were consistently large families on her side as well as on her husband’s, in both their generation and the preceding one. In contrast to that, she had only 6 living offspring out of 11 pregnancies. The stillborn fetuses were described as edematous, about 7 months old, and “uremic poisoning” was given as the presumed cause of death. A stillbirth also occurred in the subsequent generation, presumably in the third month of pregnancy. No information was obtained regarding this fetus.

The father’s family history reveals 3 surviving brothers, one with long-standing edema of the legs, presumably due to varicose veins, and 1 with prominent floating ribs. The father had edema of the legs, at times severe enough to be incapacitating; he underwent a number of operations for “varicose veins.” He died of “dropsy” at the age of 52, following a cholecystectomy. He had a double vortex pilorum, a malformation recurring in several of his offspring (“V” in fig. 1).

Eighteen members of the family are included in the present study. Eleven of these were examined at home and blood taken for electrophoresis (Cases II H, II M, 4, 6, 10, 11, 12, 14, 15). Five were hospitalized (Cases 1, 5, 7, 8, and 9) for studies lasting from 1 day (Case 1) to 1 year (Case 8). Two were not seen (Cases II N and 2), the histories being obtained from relatives.

In 9 of these subjects ankle edema was present. It is of interest to note that none of the patients who were prepubertal or at puberty (Cases 10, 11, 12, 14, 15) had ankle edema, even though dysproteinemia existed in 3 of them (Cases 11, 12, and 14). The onset of edema in all of those affected had always been after puberty. Some form of dysproteinemia was found in all patients with edema. Of 7 adult males, 4 had ulcers of the legs or a history thereof.

The following physical signs were found: All adult males in generation III (Cases 3, 5, and 6) had ulcers of the legs at some time in their adult life. All adult females in generation III (Cases 4, 7, and 8) had low oscillometric indices in the upper extremities. Protruding floating ribs were seen in 11 subjects (Cases 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, and 22).

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Date</th>
<th>BSP</th>
<th>T.T.</th>
<th>C.F.</th>
<th>H.A.</th>
<th>P.T.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>12/245</td>
<td>30% (NYH)</td>
<td>&lt;1.7</td>
<td>o-1+</td>
<td>&gt; 1 Gm.</td>
<td>88.7%</td>
</tr>
<tr>
<td>12/45</td>
<td>1% (R. I.)</td>
<td>.60</td>
<td>o-1+</td>
<td>1.075</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/47</td>
<td>Negative Hepatitis</td>
<td>3.10</td>
<td>4 +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/13</td>
<td>3.45</td>
<td>4 +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/23</td>
<td>3 +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/3</td>
<td>3 +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/12</td>
<td>1.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/18</td>
<td>.40</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/47</td>
<td>0</td>
<td>.60</td>
<td>0</td>
<td>1.075</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/46</td>
<td>4%</td>
<td>.15</td>
<td>0</td>
<td>1.4038</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

T.T.—Thymol turbidity test.  NYH—New York Hospital
C.F.—Cephalin flocculation.  R.I.—Rockefeller Institute
H.A.—Hippuric acid excretion test.
Double vortices pilorum existed in 4 individuals, 3 males and one female (Cases 1, 5, 9 and 15), scattered through 3 generations.

Laboratory Studies (Tables 5 and 8)

Laboratory studies revealed the following: Hypoproteinemia existed in 4 cases (Cases 5, 8, 9 and 14), ranging from 4.7 Gm. per 100 ml. to 6.0 Gm. per 100 ml. (The normal range in our 13 controls was from 6.1 Gm. per 100 ml. to 7.9 Gm. per 100 ml.) Dysproteinemia was found in 10 cases (Cases 5, 6, 7, 8, 9, 11, 14, 15, II L and II M). The changes found in the mother (Case 1) and in one of her daughters (Case 7) may be insignificant, and in Case 6 the marked abnormalities reverted to normal after 6 months. In all the others, dysproteinemia was present beyond doubt. A single component was altered in 7 instances (α₂, in Cases II L, II M, 7 and possibly Case 5; albumin in Case 9 and possibly Case 1; and γ-globulin in Cases 11 and 14).* Two plasma components or more were altered in 3 cases (Case 5, albumin, α₂, and γ-globulin); Case 6 showed α₂ and β markedly changed on one occasion on repeated analyses in two different buffers. Six months later, no abnormalities were uncovered by electrophoresis. Case 8 repeatedly had a low albumin and exceedingly low γ-globulin values. In Case 14 there was a low γ-globulin and a low albumin.)*

<table>
<thead>
<tr>
<th>Table 4.—Kidney Function Tests in Case 5 and Case 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manitol (glomerular filtration) ml./min.</td>
</tr>
<tr>
<td>Normal Range</td>
</tr>
<tr>
<td>Case 5</td>
</tr>
<tr>
<td>Case 8</td>
</tr>
</tbody>
</table>

This represents a wide variety of alterations in the concentration of individual components of plasma protein with only one combination of changes (albumin and γ-globulin) occurring in more than one patient.

Routine clinical laboratory findings were normal in all subjects studied. Blood chemical examinations other than plasma protein levels (vide supra) were within normal limits. There was a tendency to hypochlorhydria in the 3 subjects studied (Cases 5, 7 and 8) and no response to histamine in one case (Case 5) but proteolytic enzymes were present in the gastric juice of all patients. The hematologic examination gave a normal picture; there was a tendency to low white counts but none fell below the normal range.

Urine examinations were consistently normal and no proteinuria could be demonstrated by any of a number of methods.

The renal clearance studies (table 4) and the adrenal function tests gave normal responses. All liver function tests (table 3) gave negative results excepting in Case 8, in which liver functions were disturbed in the course of a severe homologous serum hepatitis. This was followed by a return to normal function as measured by

* Interpretation of the electrophoretic data in Cases 14 and 15 was difficult because of cloudiness caused by a meal being taken before venipuncture. The patterns were fairly normal for children of this age,37 except for the changes noted.
the tests. In Case II L, there was a history of alcoholism and clinically liver disease could be suspected but no liver function tests could be carried out.

Muscle biopsies showed normal blood vessels and lymphatics (fig. 4) and the special stains and numerous sections studied on the liver biopsy material taken from Case 8 failed to reveal any morphologic change (fig. 4).

**TABLE 5.—Tabulation of Plasma Protein Components as Determined by Electrophoresis. The values falling outside our normal range are italicized. See also Fig. 3.**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Normal Av.</th>
<th>Normal Range</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Protein</td>
<td>6.99</td>
<td>6.10-7.88</td>
<td>0.508</td>
</tr>
<tr>
<td>Plasma Proteins in Grams/100 ml.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.81</td>
<td>3.22-4.39</td>
<td>0.292</td>
</tr>
<tr>
<td>a1</td>
<td>0.42</td>
<td>0.28-0.54</td>
<td>0.072</td>
</tr>
<tr>
<td>a2</td>
<td>0.61</td>
<td>0.37-0.81</td>
<td>0.062</td>
</tr>
<tr>
<td>b</td>
<td>0.87</td>
<td>0.61-1.09</td>
<td>0.137</td>
</tr>
<tr>
<td>p</td>
<td>0.41</td>
<td>0.31-0.59</td>
<td>0.076</td>
</tr>
<tr>
<td>g</td>
<td>0.78</td>
<td>0.61-0.99</td>
<td>0.108</td>
</tr>
</tbody>
</table>

* Values outside the normal range are italicized.
† Specimen partially clotted.
§ Veronal buffer, ionic strength 0.10, pH = 8.6.
¶ Serum.
¶¶ Phosphate-chloride buffer, ionic strength 0.1, pH = 7.7.
¶¶¶ Veronal-citrate buffer with 0.2 M NaCl added; pH = 8.2.

**Part II. Studies on the Nature of the Defects of Protein Homeostasis in Familial Idiopathic Dysproteinemia**

The following studies were made on the nature of the alterations of the plasma proteins:

1. A nitrogen balance study was made in Case 8. This patient was maintained in positive nitrogen balance for a considerable length of time; during this period her total circulating plasma protein was measured repeatedly.
2. In the same patient, the rate at which the increased albumin concentration returned to normal following the intravenous injection of human albumin was determined by measuring plasma volume and albumin concentration before and after the injection of human serum albumin.

3. In the same case, the rate at which γ-globulin concentration returned to normal following the injection of plasma containing a normal amount of γ-globulin was determined. This was possible because the initial concentration of γ-globulin in the plasma was very low. Nine hundred and seventy-five ml. of pooled plasma were injected and the γ-globulin concentration before and after the plasma infusion was followed by electrophoretic studies and also by immunologic methods to be reported later. The results of the electrophoretic procedures were subjected to certain calculations before evaluation.

## Table 6

The Disappearance of Injected Plasma Protein Components in Case 8, with Special Reference to γ-globulin (see text). Plasma protein concentration in Grams/100 cc.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Total Protein</th>
<th>Albumin</th>
<th>a1</th>
<th>a2</th>
<th>γ1</th>
<th>γ1 corr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/27/47 pre-inj.</td>
<td>5.31</td>
<td>2.75</td>
<td>0.59</td>
<td>0.81</td>
<td>0.90</td>
<td>—†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.49</td>
<td>2.96</td>
<td>0.52</td>
<td>0.76</td>
<td>—†</td>
</tr>
<tr>
<td>1/27/47 2 hrs. post-inj.</td>
<td>6.01</td>
<td>3.05</td>
<td>0.56</td>
<td>0.89</td>
<td>0.92</td>
<td>—†</td>
</tr>
<tr>
<td>1/28/47</td>
<td>5.83</td>
<td>2.79</td>
<td>0.46</td>
<td>0.82</td>
<td>0.85</td>
<td>—†</td>
</tr>
<tr>
<td>1/29/47</td>
<td>5.27</td>
<td>2.65</td>
<td>0.52</td>
<td>0.76</td>
<td>0.81</td>
<td>—†</td>
</tr>
<tr>
<td>Plasma Pool</td>
<td>6.15</td>
<td>3.32</td>
<td>0.45</td>
<td>0.60</td>
<td>0.70</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* γ1 is the globulin component of serum which has the mobility of fibrinogen. (Biophysical studies on blood plasma proteins IV. Separation and purification of a new globulin from normal human plasma. Deutsch, H. F., Alberty, R. A., and Gosting, L. J., J. Biol. Chem., 165: 31-25, 1946.)

† Serum.

4. In the same patient, the effect on the plasma protein concentration of the acute withdrawal of 500 ml. of blood and reinjection of the cells into the donor was studied (protein subtraction test). After a base-line sample had been taken, 500 ml. of blood were removed, centrifuged in a closed system and the red cells separated from the plasma. The cells were suspended in 10 per cent dextrose solution to make a total volume of 500 ml. and immediately re injected. The plasma protein concentration was then followed.

* From the data of Perlmann and Kaufman and of Armstrong, Budka and Morrison, it may be calculated that the γ-globulin values obtained under the conditions used in these experiments (2.15 per cent protein and ionic strength 0.15) are 15 per cent too low. Further correction was made for variation in nitrogen content and refractive index increment among the various plasma protein components. Since these corrections increase the γ-globulin concentration of normal plasma from 6.8 to 8.0 grams per liter, an additional correctional factor of $\frac{8.0}{6.8}$ has been applied here. The total correction is thus $1.15 \times \frac{8.0}{6.8} = 1.47$. 
The ability of this patient to form certain antibodies was tested in collaboration with Drs. M. Heidelberger, E. A. Kabat and A. Bendich. The formation of antibodies against pneumococcus polysaccharides was tested in Dr. Heidelberger's laboratory by the method he has described. The formation of anti-A isohemagglutinin was tested by Drs. Bendich and Kabat, using an antigen (A agglutinogen) that has been assayed with positive results in 9 normal adults.

Results

1. A considerable amount of nitrogen, phosphorus and potassium were retained by this patient during the 18 days of the balance study (table 1, fig. 5). The concentration of the plasma protein, however, remained the same throughout this period. Table 2 further demonstrates that throughout two years of observation, her plasma protein remained low while her protein intake had been high.

2. Figure 6 shows that this patient initially retained slightly more injected albumin than a normal control of the same age and sex but that the slope of the disappearance curve was parallel to that in the normal subject.

3. The rate of disappearance of the injected γ-globulin as measured by the immunologic methods was rapid, with a half-life of immunologically specific circulating γ-globulin of 3–5 days. The disappearance rate as determined by electrophoresis (table 6) was slower but agreed with the immunochromatic results within the limits of error of the electrophoretic method, which is large for the measurement of such a small component.

4. The result of the protein subtraction test was obscured by the fact that the sample taken 24 hours after bleeding was hemolyzed, due to difficulties in venipuncture in this patient; consequently, the extent of the fall of the plasma protein concentration following plasmapheresis could not be evaluated. There was a clear-cut increase of plasma protein 48 hours after bleeding, even more marked than that found in normal individuals (fig. 7).

5. The production of antibodies against pneumococcus polysaccharides was definitely weak and no anti-A isohemagglutinin was formed following the injection of an agglutinogen.

In summary, one patient (Case 8) failed to elevate her reduced plasma protein level while maintained in positive nitrogen balance by a high protein intake. She showed no defect in her ability to handle injected human albumin and in her ability to regenerate plasma protein following acute withdrawal. Studies on the rate of disappearance of injected γ-globulin were inconclusive. No antibody response was obtained to 2 specific antigens.

Discussion

Although the presenting features of this syndrome are the marked edema in males and females and ulcers of the legs in males, in no case was the amount of albumin or total protein lowered to the extent that is usually required to produce edema. Therefore, the pathogenesis of this part of the syndrome must be sought elsewhere, such as in a defect of the vascular system, since adrenal and renal mechanisms were found to be intact. In view of the multiple congenital malforma-
tions uncovered in this family, one is tempted to consider a constitutional inferiority of the vascular system. However, systemic humoral mechanisms affecting the vascular system have not been excluded. The lowered oscillometric indices in the arms of 3 females and the markedly hypoplastic veins in one of them tend to strengthen this concept, even though muscle biopsies in 2 patients did not show morphologic vascular changes.

The existence of a clinical entity wherein such cryptogenic edema is coupled with subtle changes in the proportion of electrophoretic components of the blood plasma has been established; it is to be expected that more such cases will be found. In this event, the family history should be carefully investigated, as the familial occurrence of this disorder was the most striking feature of this group of patients. The co-existence of congenital malformations, frequent stillbirths (mother Rh positive), and dysproteinemia coupled with constitutional inferiority of the vascular system suggest very strongly the possibility of genetic etiologic mechanisms. This assumption seems even more likely in view of the known hereditary transmission of hemophilia and fibrinogenopenia, both of which appear to be mediated through a lack of certain components of the plasma proteins. The hereditary mechanisms governing hemagglutinins, another type of plasma protein component, are well established.

Table 7.—Blood Groups and Types of the Subjects Studied. Data obtained by Dr. Philip Levine,*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Group</th>
<th>D</th>
<th>C</th>
<th>E</th>
<th>c</th>
<th>Negative Positive</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>heterozygous</td>
</tr>
<tr>
<td>II H</td>
<td>O MN</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>II L</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>heterozygous</td>
</tr>
<tr>
<td>II M</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>heterozygous</td>
</tr>
<tr>
<td>II N</td>
<td>A MN</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>3</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>4</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>5</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>6</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>7</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>8</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>9</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>10</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>11</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>12</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>13</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>14</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
<tr>
<td>15</td>
<td>O MN</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>homozygous</td>
</tr>
</tbody>
</table>

* The help of Dr. Levine in our study is thankfully acknowledged.
‡ Homozygous and heterozygous refer only to the antigenic constitution of the C factor and on statistical probability also to the D factor. No abnormal antibodies were found in the plasma of the wife of this patient 6 months after a stillbirth.
STUDIES ON HYPOPROTEINEMIA

The connection between appearance of edema and puberty, as well as the frequency of stillbirths without Rh immunization (table 7), suggest the possibility of sex hormone disturbance. This may or may not have etiologic or pathogenic significance.

So far, the etiology of the syndrome as well as the pathogenesis of the edema remain obscure. We feel that all known organic causes have been eliminated.

Some information, however, has been gained on the pathogenesis of the disturbed homeostasis of plasma proteins. The pictures observed electrophoretically were (with the possible exception of Cases 7 and 11) striking and significant. In some cases (Cases 6 and 8), the analyses were run in a variety of buffers, so as to exclude changes in mobility of the protein that might be due to an abnormal affinity for citrate iron.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Serum Calcium</th>
<th>Serum Inorganic Phosphorus</th>
<th>Serum Phosphatases in units</th>
<th>Serum Cholesterol</th>
<th>Serum Sodium</th>
<th>Serum Potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg./100 cc.</td>
<td>mg./100 cc.</td>
<td>Ac.</td>
<td>Alk.</td>
<td>Total</td>
<td>Free</td>
</tr>
<tr>
<td>5</td>
<td>10.8</td>
<td>3.40</td>
<td>0.46</td>
<td>3.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>10.9</td>
<td>4.22</td>
<td>—</td>
<td>1.2</td>
<td>159</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>9.8-10.5</td>
<td>3.13</td>
<td>0.46</td>
<td>3.5</td>
<td>134</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Sugar</th>
<th>Hgb. Gm./100 cc.</th>
<th>RBC 10⁶</th>
<th>WBC</th>
<th>Poly. %</th>
<th>Ly. %</th>
<th>E %</th>
<th>M %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>63</td>
<td>11.3</td>
<td>4.1</td>
<td>4200</td>
<td>68</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>90</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>105</td>
<td>13.6</td>
<td>4.3</td>
<td>6900</td>
<td>86</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

In the case of the mother (Case 1), the slight hypoalbuminemia observed at first examination had disappeared on the second examination, nearly a year later. There is some question whether the lowered albumin may not have been due to congestion of the liver, as the patient had signs of cardiac infarction at that time. In Case 6, the marked changes that had been found in two different buffers at the first examination had disappeared on second examination. The patient still had marked ankle edema but the ulcers of the legs present when the first blood had been drawn had healed.

Some of the plasma protein patterns were most unusual. We are aware of only 2 cases in adults that resemble the pattern found in Case 8 (fig. 3). In one case this marked defect of the γ-globulin was on a nutritional basis, and in a second case liver disease was not ruled out and there was a history of chronic alcoholism. Two additional comparable patterns have been reported in children, one of them a definite case of idiopathic hypoproteinemia.

The statistical significance of the changes in γ-globulin in Cases 5 and 8 has been
analyzed in comparison with a group of 13 normal individuals by Dr. J. W. Tukey, Princeton University, and his comments follow:

"The 13 normal cases have a mean γ-globulin (in Gm./100 ml.) of 0.78 and a standard deviation of 0.106. This compares well with Dole's\textsuperscript{54} mean of 0.74 and standard deviation of 0.151 (for 15 cases). If we are prepared to assume that the distribution of amounts of γ-globulin in normal persons follows the so-called normal or Gaussian law, we can set tolerance limits of the form (sample mean) ±\(K\) (sample standard deviation) in such a way that there is a 75 per cent probability that 999 normal cases in 1000 fall between these limits. Values of \(K\) are tabulated for different numbers of cases and different probability levels in Eisenhart, Hastay and Wallis\textsuperscript{55} at pages 102-107. For 13 cases and the probability levels chosen above \(K = 4.059\).

"It seems reasonable to suppose that, while the distribution of γ-globulin may be somewhat skew, with a longer tail toward higher values, the distribution of the logarithm of γ-globulin will be symmetrical, or skewed toward low values. Thus, if we set tolerance limits based on both γ-globulin and on the logarithm of γ-globulin, and then use the outermost limits, we are likely to have a reasonable chance of being conservative. The results are as follows:

\[
\begin{array}{|l|c|}
\hline
\text{Assumption} & \text{Range with 75\% probability of covering 999 in 1000} \\
\hline
gamma-globulin normally distributed, & 0.34 to 1.11 \\
\text{Logarithm of } \gamma\text{-globulin normally distributed,} & 0.43 to 1.37 \\
\text{Conservative recommended.} & 0.34 to 1.37 \\
\hline
\end{array}
\]

It will be noticed that the single determination on Case 5 and all 5 determinations on Case 8 fall outside the conservative limits."

The occurrence of such extreme changes is convenient, since by the simple administration of normal plasma one is able greatly to increase the concentration of the deficient plasma component and may then follow its disappearance from the circulation. In Case 8 the injected γ-globulin disappeared rather rapidly and a mechanism seemed to exist that maintained the γ-globulin at its set level far below normal. In an unpublished case of Dr. E. Shorr, with a sprue-like syndrome, complicated by a history of an earlier disease of the lymphoid tissue, a similar curve of disappearance of γ-globulin was obtained (an autopsy later revealed generalized giant follicular lymphoblastoma). The "half-life of the immunologically specific γ-globulin" was considerably shorter than the "half-life of the glycine labeled γ-globulin" as measured by Rittenberg and Shemin (quoted in ref. no. 45). It is impossible for us to offer an interpretation of these facts at the present time.

Evidence was obtained, however, that in one patient (Case 8), a defect existed in the fabrication of circulating antibody against pneumococcus polysaccharide and A agglutinogen. A similar defect in synthesis, combined with a homeostatic mechanism set for subnormal levels, may exist for other components. Following the
injection of albumin, its concentration returned to the subnormal preinjection level at a normal rate,* whereas in Case 7 plasma protein infusions resulted in one instance in a normal protein level for several weeks.

In 2 cases the general condition of the patient was improved by the administration of plasma and the edema tended to regress even though the initial hypoproteinemia had been moderate (Cases 7 and 8). In Case 5 no beneficial effect was observed following plasma infusion.

The failure of one patient to increase the plasma protein concentration while repleting tissue protein (Case 8) resembled the condition found in hypoproteinemic patients with gastric cancer," tuberculosis" and certain types of renal disease."

**SUMMARY**

1. A new syndrome, idiopathic familial dysproteinemia, is described in 4 adult members of one generation, in 2 of their paternal uncles and in 4 members of the second generation. The syndrome is characterized by hypoproteinemia and/or abnormalities in the electrophoretic patterns of the blood plasma (dysproteinemia). These are accompanied in the adult by peripheral vascular changes (ulcers of the legs in the men, low oscillometric indices in the women) and edema. There are also malformations of the thoracic cage and of the occipital hair distribution in some of the cases.

2. The idiopathic nature of the disease was ascertained in some of the patients by study of the nutritional history, of the renal, hepatic and adrenal functions, and of the response to a high-protein diet under controlled conditions.

3. In one case detailed studies of the mechanisms of plasma protein regulation resulted in findings that indicate a disturbance in the production of certain protein components. The disappearance rate of injected albumin and the rate of replacement of acutely withdrawn plasma protein were normal.

4. The clinical and physio-pathologic significance of this syndrome and the possible role of genetic factors are discussed.

**APPENDIX: CASE HISTORIES**

**(Generation II, Fig. 1)**

1. This white woman, aged 70, is the mother and grandmother respectively of some of the other patients herein described.

Chief complaint: swelling of ankles since age of 50, accentuated in the last five years. There was dyspnea, orthopnea and tachycardia. Past History: five years ago, there was an increase in ankle edema with progressive fatigue, dizziness and headaches. Her family physician found an elevated blood pressure.

Physical examination: B.P. 135/95, pulse 90. There was a moderately enlarged liver, obesity, ankle edema, and rales in both lung fields. Laboratory findings: the electrocardiogram showed signs of recent infarction and auricular fibrillation; the urines were negative; the blood picture was negative. The liver function tests were as follows: prothrombin time, 81 per cent; cephalin flocculation and thymol turbidity, negative. Protein studies have been described above.

Course: the patient was not hospitalized and was doing well under routine care by her local physician when last heard from.

* Dr. F. Albright reports recent metabolic studies in an isolated case of idiopathic hypoproteinemia demonstrating an increased rate of combustion of injected albumin.
H. White woman, aged 65, only surviving sister of preceding patient, was examined in her home. Her past history was negative. She has 4 children, who are in excellent health.

Physical examination: negative except for a B.P. of 160/100 which was not causing any symptoms.

L. An obese white male of 63, one of 3 surviving brothers of husband of Case 1. He was examined at his home and was rather vague about his past history. Twelve years ago he had swelling of the ankles and later an attack of gout. He admitted a fairly high alcoholic intake. Physical examination revealed telangiectasis on face and thorax, and pityriasis rosea on thorax. The edge of the liver was palpable 3 finger-breadths below the costal margin in the mid-clavicular line. The floating ribs were markedly prominent.

M. A white male aged 72, brother of preceding. He had always been in good health, except for an episode of pulmonary tuberculosis in early life, until 5 years ago, when he began to suffer from back pain which became intolerable. Studies at Johns Hopkins and in other university hospitals failed to reveal any etiology except osteoarthritis of the spine and an exploratory laminectomy was negative. Physical examination revealed a well-developed and well-nourished white male bedridden with severe back pain. There was a scar of an old lumbar laminectomy, and the left wing of the sacrum seemed more prominent than the right and was tender on palpation. There were markedly prominent floating ribs. On the right hand there was a Dupuytren's contracture. The remaining physical examination was negative. Complete laboratory studies could not be done but serum phosphatases and phosphorus were within normal limits.

N. A third brother of the 2 preceding patients is said to have suffered from edema of the legs during all his adult life. Unfortunately it was not possible to reach him personally at the time of this study.

The father of some of the patients described and the husband of Case 1 died at the age of 52 from "dropsy," following a cholecystectomy. He had edema of the legs at an early age and at times had to use crutches. Repeated vein ligations had to be done for "phlebitis" of the legs. There are no hospital records to substantiate this history. He had a double vortex pilorum. His family history was not contributory. He had had 6 brothers and one sister, and there was a history of tuberculosis at an early age in 1 of these individuals.
3. A white male of 48, tall and thin with grey hair, looking somewhat older than his chronologic age. He had had mumps, measles and chicken pox but remembered no diseases in adult life other than an episode of "phlebitis" 3 years ago, with a small ulcer of the leg. Physical examination showed markedly prominent floating ribs, a blood pressure of 120/60, and 1 plus pitting edema of both ankles. The skin over the ankles and the lower part of the calves was thin and atrophic. There was a dark brownish discoloration on the external and internal aspect of the right ankle. Body hair was scant. The remaining physical examination was negative.

4. The history of this well-developed, stout woman, sister of preceding patient, was negative. She has enjoyed remarkably good health, except for vasomotor disturbances of hands and feet with episodes of cold and clamminess. Physical examination revealed normal blood pressure but exceedingly low oscillometric indices (1-2) in both arms. There was marked prominence of the floating ribs. There was mild edema of the ankles, less evident than in the photograph shown in figure 2.

5. (MH 8492-SKI 163) White man aged 41, brother of the preceding patient. His chief complaint, swelling of the legs, started an unknown number of years ago, and the patient has been using elastic stockings ever since. In 1944, large ulcers appeared on the right lower calf and caused what was termed a deep phlebitis. Saphenous vein ligation was then performed. The right leg has persistently remained more swollen than the left one.

The past history contained a story of swelling of both legs at the age of 8 months, followed by atrophy, making walking impossible until the age of 19 months. In the absence of persistent sequelae, it was difficult to accept the diagnosis of "poliomyelitis" then made. There were numerous episodes of infectious
diseases, 4 recurrent bronchopneumonias between 1909 and 1911, tonsillectomy in 1925, appendicitis
with peritonitis in 1931. The patient gained a great deal of weight from 1939 to 1946, when he weighed
275 lbs. He was 6 ft. 7 in. tall. He lost 50 lbs. on a reducing diet but regained 20 lbs. on the well-balanced
food intake he had had for several months before admission.

Physical examination revealed a white male of tall build. He wore shoes size 14; his feet were thus large
even for his stature. Physical examination was negative except for pitting edema of both legs with
brownish discoloration around the ankles, bilaterally. There was an abdominal scar in the lower qua-
drant. The floating ribs were protruding and there was a double vortex pilorum. There was complete
edentia. The visual acuity was poor bilaterally and there was an early cataract on the right eye (Dr. B. F.
Payne). The ophthalmologist found the fundi and visual fields bilaterally normal.

Laboratory studies: chest x-ray was negative and no anomalies were seen in lateral pictures of the
skull.

Basal metabolic rate: several tests were done but the patient was resistant to the procedure and the
results, while within normal limits, were inconclusive.

Hematology: hemoglobin, 12.7 Gm. White blood cells: 3,850, filamented 44 per cent, nonfilamented
4 per cent, eosinophiles 3 per cent, monocytes 3 per cent, lymphocytes 46 per cent

Serology: Mazzini tests were negative.

Urinalysis: urines showed no protein on repeated tests, and no other abnormal findings.

Gastric analysis: showed no free acid before or after histamine. Liver function tests: these were all
negative and the results are shown in table 3.

Renal function tests: showed no evidence of renal damage (see table 4). Cardiovascular tests: blood
pressure 115/85, pulse 75, temperature 98.7. Electrocardiograms were negative. The oscillometric read-
ings of arms and legs were normal. The circulation times by decholin were 20 seconds, by ether 15 seconds.
The venous pressure was 16 cm. of water. Chemical studies of blood are shown in table 7 and are within normal limits. The disturbances of the plasma protein pattern are shown in table 5. In this case there was mild hypoproteinemia and a marked disturbance of the globulin fractions.

Histopathologic studies: serial sections of muscle revealed no morphological anomalies of blood vessels (Dr. S. Spitz) (fig. 4).

Course of disease: the patient remained in the hospital for one week only. He left to resume his work as a travelling salesman. The only functional study on his protein metabolism was the administration of 75 Gm. of albumin intravenously. The test could not be carried out completely because of a severe pyrogenic reaction with chills and high temperature. However, about one-third of the injected dose was still present in the circulation after 24 hours.

6. This white man aged 38 was seen at his home. He suffered from boils on his head in infancy and had whooping cough at the age of one year. At the age of 8 (1918), he had influenza, followed by chicken pox and roseola. At the age of 15, he had a serious attack of mumps and later on episodes of chronic appendicitis. He was always subject to skin rashes and is sensitive to poison oak. A dark brownish discoloration of both ankles made its appearance at the age of 15. At the age of 20 (1930), the first ulcers of
the leg appeared and kept him bedridden for six months. Ulcers of the legs recurred in 1935, 1938, 1939, 1940, 1941, 1942, 1946 and 1947, taking each time from some weeks to several months to heal. Physical examination revealed brownish discoloration around both ankles, hypertrophy and desquamation of the skin in these areas, prominent floating ribs and no other changes.

Laboratory studies, other than electrophoresis of blood, were not performed.

7. (MH 86268-SKI 8) This patient is a white married woman of 33. She is the sister of Case 8 and her family history has been described above. She is the mother of 2 children aged 3 and 9 years (Cases 14 and 15).

Chief complaint: swelling of ankles of several years' duration. The patient had been hospitalized for this two years ago and was told that she had a "lymphatic condition." She has had measles, whooping cough and chicken pox but, like her sister, never mumps. She has not lived with her sister for eleven years.

Two years before her admission to this hospital, she felt that she was "too fat" (145 lbs.) and reduced on a regime of low dietary intake, dexedrine and thyroid. She has continued to take $\frac{1}{2}$ to 1 gr. daily of thyroid since then with no particular indication. Once her weight had stabilized at 132 lbs., she returned to a well-balanced and adequate food intake and did not regain her overweight.

There was no history of any disease during her adult life except for the swelling of her ankles, which dates back to about the age of 16. This was complicated at one time by phlebitis following an infection of a toe. Systemic review revealed that she had always had "cold and clammy" extremities, recurrent mild headaches, and constipation. Her menstrual history was normal, except for menorrhagia for several months following her second pregnancy. Both deliveries were at term and normal.

Physical examination: completely negative, except for the protrusion of the floating ribs, resembling that found in some of the other siblings who were studied, and for the marked edema of the ankles. There was also blue discoloration and coolness of the hands and feet. The oscillometric measurements in arms and legs were extremely low.

Laboratory studies: Chest x-rays were within normal limits. X-rays of the bones showed no anomalies. There was a small calcified area in the mid-pelvis, possibly a mesenteric node or urethral calcification.

Basal metabolic rate: $-17, +1, -10$.

Hematology: see table 7.

Serology: Mazzini, Kahn and Kline tests negative.

Urinalysis: urines were negative and no albumin was found at any time.

Gastric analysis: fasting free acidity was 14 units and total acidity 34 units. This rose following histamine to 55 and 73 units respectively.

Liver function tests: bilirubin, cephalin flocculation, thymol turbidity tests and bromsulfalein retention all gave normal results.

Cardiovascular tests: electrocardiograms were normal.

Circulation times: dextroin 16 seconds, ether 13.5 seconds. Venous pressure measured 17 cm. of water. The oscillometric indices have been discussed.

Chemical studies of the blood fell within normal limits. The anomalies of the blood plasma proteins of this patient are shown in table 5.

Course of disease: this patient was able to remain in the hospital for only three days. A most remarkable fact was her response to the infusion of 15 Gm. of human albumin. Even though no diuresis occurred, her ankles decreased markedly in size during the night following the infusion. She was given one liter of human plasma before leaving the hospital and it was rather striking that the total protein level remained above 7 Gm. per 100 ml. for nearly one month. In spite of this, however, the ankle edema returned to its previous extent about 2 weeks after discharge.

8. (MH 83651-SKI 130) This patient was a white girl of 31, a personnel manager, who was born and lived most of her life in the South. She came to work in New York City several years before her admission to Memorial Hospital. Since the age of about 16 she has suffered from swelling of the ankles and legs and from occasional facial edema.
Family history: as described above.

Past history: the patient had the usual childhood diseases except mumps. She had repeated colds, four episodes of "pneumonia" as a baby, and underwent tonsillectomy at the age of 13, which failed to decrease the frequency of colds and sore throats. There is a history of shoulder pains, suffered as a small child, and the patient still occasionally experiences dull pains in her shoulder girdle.

The systemic review reveals that she suffers from occasional headaches, especially whenever she has one of her frequent colds. For a short period in 1944, she had daily elevation of temperature, but no lesions were seen on x-ray of the chest and the temperature became normal. She was often rather tired and her swollen ankles were at times attributed to a "cardiovascular" disorder, for which no objective evidence was ever obtained. She has had gingivitis and occasional gastrointestinal uppers. In the past two years, she has had nocturia occasionally once a night and there was usually some urgency for urination. There was no history or evidence of venereal infection. She started to menstruate at the age of 13 and had a 30-day regular cycle, periods lasting 5 days and slight abdominal pains preceding menstruation, with occasional mastodynia at the same time. There was no history of disturbed endocrine function. She was allergic to various foods, which caused urticaria to appear; she showed fairly severe urticarial reactions following the administration of plasma. There was no history of severe gastrointestinal or hepatic disorder.

Physical examination revealed a well-nourished white girl of 3½ of asthenic habitus. Blood pressure 105/76, pulse 95, temperature 99 F. The skin was moist and warm. In places, especially over the upper and lower extremities, there was some bluish discoloration (vasodilatation). There was mild seborrhea of the face and scalp. The hair was soft and brown. The finger- and toe-nails were exceedingly thin and soft, and detached from the nailbed at their tips to a more marked degree than is usually seen; all the nails showed longitudinal ridges.

The bones appeared to be of normal size and configuration, except for the floating ribs, which protruded more than is usually the case from the thorax. The joints were free from swellings or inflammation and no visible deformities were present.

Fig. 5.—Estimated Protein Distribution, Case 8. Cross hatched areas show daily nitrogen retention, cumulative nitrogen retention in last column, presumably retained for protoplasm synthesis. Solid line at 2.8 Gm. shows normal amount of plasma protein nitrogen. (Seven Gm. protein per 100 ml. plasma = 1.12 Gm. nitrogen. This value times "normal" plasma volume of 2500 ml. = 2.8 Gm.) Full columns show amounts of circulating protein nitrogen found in patient.
There was no enlargement of lymph nodes. The ears, nose and throat were normal, the tonsils were absent. No anomalies were found in the eyes or extraocular muscles. The tongue showed slightly atrophic papillae and there was some loosening of the gums from the teeth, which were in good repair. The trachea was in the midline. The thorax was symmetrical and clear to percussion and auscultation; the floating ribs protruded unduly. The breasts were small but firm and glandular tissue was distinctly palpable.

The cardiovascular system was normal on physical examination, except for the peripheral veins, which were extremely small, hardly visible even in infra-red photographs or palpable in the antecubital fossae, even though there was no excess of subcutaneous fat. There was also striking blue discoloration of hands and feet. The oscillometric examinations of arms and legs showed markedly reduced oscillations, a finding which was to be expected in the edematous legs but which was also marked in both arms. There was pitting edema of both ankles and calves up to the knee.

The abdomen was soft and slightly protruding; there was no tenderness on palpation and no masses were felt. The gynecological examination revealed a normal vulva and vagina, a small uterus in the midline, retroverted and flexed but freely mobile, and normal annexae. The rectal examination was negative. The neurological examination was completely negative.

Laboratory studies: chest x-rays were repeatedly negative. Studies of all bones including the skull showed normal structure and bone age and specifically no signs of decalcification. A gastrointestinal series was negative. The only positive x-ray finding was a congenital lumbarization of the first sacral vertebra.

**Fig. 6.—Albumin Addition Test in Case 8**

**Fig. 7.—Protein Subtraction Test**
Basal metabolic rate: +7, on two occasions.

Hematology: from November, 1946, to November, 1947, 20 blood counts were done. The hemoglobin varied from 12 Gm. to 15.6 Gm., the red blood cells were 4.1 and 4.3 millions (they were not counted in all blood examinations). The white count varied from 4,750 to 6,900; filamented polynuclear cells from 59 per cent to 81 per cent, non-filamented forms from 1 per cent to 15 per cent, eosinophiles from 1 per cent to 7 per cent, monocytes from 1 per cent to 5 per cent and lymphocytes from 9 to 26 per cent. Hematocrists varied between 38 and 41. Metamyelocytes were seen on a few occasions. Sedimentation rates were repeatedly normal. Blood group and type are shown in table 7.

Serology: Mazzini, Kline and Kahn tests were repeatedly negative. Heterophile and Abortus Bang agglutination tests were negative.

Urinalysis: urines were acid except on one occasion. No albumin was ever found either by the routine nitric acid test or with other precipitants such as sulfosalicylic acid, trichloroacetic acid, heat coagulation, etc. The centrifuged sediment contained occasional leukocytes and rare epithelial cells, never any red cells.

Stool examination: the appearance of the stools was normal. They were well formed, negative for fat, blood and undigested muscle fibers. No parasites were found. The daily fecal nitrogen excretion never exceeded 10 per cent of the intake. The fecal fat excretion was below 1 per cent of the intake.

Gasometric analysis: this showed no free acid in a fasting sample and 18 units of total acidity. After histamine there were 34 units of free and 40 units of total acidity. On another occasion there were 64 units of total and 48 of free acidity following histamine, and pepsin was repeatedly found to be present by digestion test.

Liver function tests: these are shown in table 3. An intravenous glucose tolerance test was normal.

Renal function tests: shown in table 4. Measurements of renal blood flow, glomerular filtration and tubular re-absorption were within normal limits. Cardiovascular tests; electrocardiograms were normal.

Circulation time by decholin was 2.2 seconds, by ether 10 seconds. The venous pressure was 20 cm. of water. The oscillometric studies have been discussed.

Tests of adrenal function: a Robinson, Power and Kepler procedure clearly indicated the absence of Addison’s disease. The same result was obtained by the Cutler, Power, Wilder test, as well as by that described by Reform-Membrives, Power and Kepler. Chemical studies of blood were within normal limits.

Histopathologic studies: a liver biopsy was performed in local anesthesia through an abdominal incision (Dr. G. C. Child, III) and slides showed normal hepatic tissue (Dr. S. Spitz). A muscle biopsy (rectus abdominis), taken at the same time and examined in serial sections, showed no muscular or vascular anomalies.

Repeated vaginal smears (Dr. A. Carter) showed changes as seen in normal ovulatory menstrual cycle.

The anomalies found in the blood plasma protein patterns are shown above (table 5). The total protein was consistently low (Kjeldahl determinations) and the γ-globulin as measured by electrophoresis was the lowest value seen for that protein in this laboratory.

Course of disease: since November, 1946, this patient has had 5 hospitalizations, some for study and one for severe hepatitis, probably homologous serum jaundice due to large amounts of plasma given her. In the interim between admissions, she worked as secretary at the hospital and had her meals from the research diet kitchen. Her plasma protein remained low throughout the period of observation, exceeding 6 Gm. per 100 ml. only once, following the administration of large amounts of plasma. There were two periods during which she had mild temperature elevations in the afternoon, for which no cause could be found and which, in one instance, promptly receded following the administration of 50,000 units of penicillin every four hours for three days. The second episode subsided spontaneously; during it there was some swelling and reddening over the second joint of the third finger of the right hand, accompanied by itching and interpreted by some observers as possibly a rheumatic manifestation, by others as a urticarial phenomenon. The latter hypothesis seemed more likely, as there was no elevation of the sedimentation rate and as the lesion disappeared rapidly under pyribenzamine therapy. In the absence of other signs, the explanation suggested by some of these febrile and allergic episodes as manifestations of disseminated lupus erythematosus seemed unlikely. The patient’s course was otherwise uneventful except for the fact shown in table 2, that in spite of high protein intake her plasma protein concentration remained low.

On May 1, 1947, the patient left for the South, on a low salt, high protein diet. She returned on June
13, 1947, with marked jaundice, anasarca and prostration. Liver functions were disturbed and her plasma protein level was at its lowest point (3.6 Gm. per 100 ml.). There were ascites and bilateral hydrothorax. Concentrated human plasma and albumin were given and a marked diuresis resulted. There was a dramatic increase of plasma volume and a fall of the extracellular fluid space as measured by thiocyanate. This change was so pronounced that pulmonary edema resulted and had to be treated actively (tourniquets on extremities, morphine). Following the re-establishment of her usual protein level of 5 Gm. per 100 ml. the patient improved rapidly while on a high protein diet and could be discharged on July 27, 1947. In October, 1947, all liver function tests measured gave normal results.

(Generation IV, Fig. 1)

9. (MH 89947-SKI 390) This white boy aged 19 is the son of Case 3. He is a well-developed, healthy individual, at present a member of a military academy, where he has to undergo a rigid biannual physical examination. He has had chicken pox, mumps, whooping cough and measles. At the age of 7 he underwent a tonsillectomy. He had an injury to his right leg at the age of 12, which healed slowly. Other minor abrasions sustained in the course of sports healed at a normal rate.

Physical examination was negative, except for the existence of a double vortex on the occiput.

Liver function tests were negative (thymol turbidity 0.25 ml., bromsulfalein 2 per cent, bilirubin 0.51 mg. [0.29 indirect, 0.22 direct, 0.11 delayed direct], hippuric acid excretion 1.49 Gm., cephalin flocculation negative).

A P.S.P. excretion test was within normal limits.

10. A white boy aged 16, just entering puberty, brother of preceding patient. He had mumps and chicken pox but not measles. In 1939, he suffered an attack of "intestinal influenza." Physical examination was negative except for prominent floating ribs.

11. This 13 year old boy had had measles and ascariasis, and has frequent colds. There was mild acne vulgaris. Physical examination was negative.

12. A well-developed white girl of 17, sister of the preceding patient. She had had chicken pox and measles but not mumps. There were no serious illnesses. Physical examination showed marked prominence of the floating ribs. Blood pressure was 125/75 and the oscillometric index in the arms was above 5.

13. This patient could not be reached.

14. This boy, aged 4, is the brother of Case 15 and the son of Case 7. He had a history of repeated colds and refractory infections of the toes. At the time of this examination he was apparently in good health. He had a double vortex pilorum and prominent floating ribs. Blood was taken for electrophoretic analysis. The blood group and type are shown in table 7.

15. This girl of 7 is the daughter of Case 7. She had none of the usual childhood diseases excepting repeated colds. Apparently she has always been in excellent health. Physical examination revealed a well-developed child, with prominent floating ribs and a double vortex pilorum. Blood was taken for electrophoretic analysis. The blood group and type are shown in table 7.

ACKNOWLEDGEMENTS

We wish to acknowledge the courtesy of Dr. E. Shorr and Dr. E. A. Burkhardt, who referred to us the first patient of this group. Several members of the staff of Memorial Cancer Center have helped in this study. The authors wish to thank Drs. E. McCabe and J. B. Trunnell for assistance in the clinical management of the patients; Dr. Aurelia Potor, for performing the renal and adrenal function studies; Dr. N. F. Young, who supervised laboratory procedures; Dr. H. J. Tagnon, who performed the liver function tests, assisted by Miss P. Nichols; Dr. C. G. Child, III, for performing the biopsies; Dr. S. Spitz, for the pathological interpretations and Dr. E. C. Reifenstein, Jr., for advice in preparing the graphs and manuscript.
STUDIES ON HYPOPROTEINEMIA

REFERENCES


10. Go Tui: Personal communication.


22. Maisner, J. G., Baitz, J. I., Marion, D. F., and Hollands, R. A.: A comparative evaluation of the newer liver function tests—comparison of the intravenous hippuric acid test, the cephalin-cholesterol flocculation test, the colloidal gold test and a serial bromsulphthalein test with the oral hippuric acid test and the Rosenthal bromsulphthalein test. J. Dig. Dis. 9: 13-29, 1942.


F. HOMBURGER AND M. L. PETERMANN


STUDIES ON HYPOPROTEINEMIA


STUDIES ON HYPOPROTEINEMIA. II. FAMILIAL IDIOPATHIC DYSPROTEINEMIA

F. HOMBURGER and M. L. PETERMANN