PHYSIOLOGICAL adjustments to slowly developing anemia are so successful that anemic patients characteristically present themselves with only minor complaints of fatigability, weakness, or dizziness, despite severe reductions of the hematocrit to 15 per cent or less. These adjustments are largely cardiovascular.

Oxygen transport is maintained by a marked augmentation of blood flow through most parts of the body as a result of peripheral vasodilatation and increased cardiac output. Oxygen uptake by the tissues is more efficient. Initially the compensation for the reduction of the red cell mass is adequate and effective, but, ultimately, limitations become apparent. Congestive heart failure may develop, possibly as a result of myocardial anoxia, and renal dysfunction may appear, with azotemia, proteinuria, and isosthenuria.

The renal circulation has been found to play an important role in the cardiovascular adjustments during fever, fear, orthostasis, and shock. In acute blood loss and shock active renal arteriolar constriction appears to divert blood from the kidney to regions such as the heart and brain where it is more urgently required. The present study indicates that, in chronic anemia, a similar active renal vascular response occurs and probably interferes with renal function.

SUBJECTS AND METHODS

The subjects of this study were 15 patients with severe chronic anemia. Eight were proved cases of pernicious anemia in relapse who responded to therapy with liver extract. The other 7 suffered from anemia due to other causes: 2 had paroxysmal nocturnal hemoglobinuria, 2 had bleeding duodenal ulcers, and 1, bleeding hemorrhoids. One patient had lymphatic leukemia, proved by hematological study and subsequent postmortem examination, and 1 was anemic as a result of iron deficiency.

The sexes were about equally divided, although females dominated the group with pernicious anemia, 6 to 2, while males outnumbered females among those with secondary anemia by 6 to 1. The age range was wide, ranging from 24 years to 72 years, but a third of the cases were more than 60 years of age. This preponderance of older subjects appeared to have little influence upon the results.

Without exception these patients had been moderately active until the time of admission to the hospital. Most complained of dyspnea on exertion and a moderate degree of dizziness and faintness on standing. The anemia and the symptoms referable to it were of at least two weeks' duration, and in most instances had been present for several months. It seems safe to assume that all patients were physiologically adjusted to the severe grades of anemia they presented.

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.
An effort was made to exclude subjects in whom factors other than anemia might have interfered with renal function, but it is possible that other processes were active in 3. In 1 patient with pernicious anemia, L. M., a persistent arterial hypertension was found. It should be noted that there has been no evidence of progression of the hypertensive disease over a three year period of observation and that cardiac, ocular, or cerebral involvement has not occurred. While it is possible that in the 2 subjects with paroxysmal nocturnal hemoglobinuria the prolonged excretion of hemoglobin might have produced renal parenchymal damage, the renal functional changes were in general agreement with those of the other cases (table 1).

All subjects were studied in the fasting basal state, following the ingestion of 1500 to 2000 cc. of water to provide adequate urine flow. Kidney function was measured with the technics devised by H. W. Smith and his co-workers, summarized by Goldring and Chasis8 in their monograph, Hypertension and Hypertensive Disease. Glomerular filtration rate was determined as the mannitol* or inulin clearance; and effective renal plasma flow, as the diodrast clearance. Effective renal blood flow was calculated from the diodrast clearance and the hematocrit. Tubular function was studied by saturation technics,8 the maximal tubular excretory capacity with diodrast (diodrast Tm) and maximal tubular reabsorptive capacity with glucose (glucose Tm). Analyses were performed upon plasma filtrates, prepared according to the method of Fujita and Iwatake,9 and diluted aliquots of urine. Diodrast, mannitol, and inulin were determined by methods outlined by Goldring and Chasis;8 glucose, by that of Nelson.10

Although all subjects were studied thoroughly from the hematological point of view, and, in many instances, followed for a period of years in the Hematology Clinic, only the hematocrit values will be presented in this paper. These values were obtained by centrifuging oxalated blood in Wintrobe tubes in duplicate, at 3000 revolutions per minute for 60 minutes.

RESULTS

Table 1 summarizes the results of the various tests of renal function in the 15 subjects. All the values collated in table 1 are averages of two or more determinations. As a rule, three or more figures were obtained but in several instances values were discarded for technical reasons. All figures are expressed in terms of the surface area of ideal man (1.73 M.2) in order to minimize differences attributable to variation in size. With 4 exceptions, all subjects were studied prior to treatment. Two and three transfusions had been given to L. T. and M. B., respectively, during the week prior to the renal function test. Two patients with pernicious anemia had received liver extract: K. Mc. for two weeks and M. Ch. for nine days.

Seven patients (table 2) were studied prior to and, on various occasions, after

* Mannitol, ampuled in 25 per cent sterile solution, was supplied for use in this study through the courtesy of the Medical Research Division of Sharp and Dohme, Inc., Philadelphia, Pennsylvania. Inulin (10 per cent in sterile solution), manufactured by William R. Warner and Company, New York, and diodrast (35 per cent in sterile solution), manufactured by the Winthrop Chemical Company, New York, were used in this study.
Each datum in columns 5 to 11 represents the average of two or more clearance periods and is corrected to 1.73 sq. M. Glomerular filtration rate denotes values of mannitol and inulin clearances; effective renal plasma flow, values of diodrast clearances.

### Table 1.—Renal Function in Chronic Anemia

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Body Surface</th>
<th>Glomerular Filtration Rate (G.F.R.)</th>
<th>Effective Renal Plasma Flow (E.R.P.F.)</th>
<th>F1ldostrin (Tm) (mg./lit.)</th>
<th>Glucose (Tm) (mg./lit.)</th>
<th>Blood Pressure</th>
<th>Arterial Blood</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. M.</td>
<td>57</td>
<td>F</td>
<td>M</td>
<td>1.40</td>
<td>1.18</td>
<td>609</td>
<td>19.0</td>
<td>699</td>
<td>12.8</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>K. Mc.</td>
<td>63</td>
<td>F</td>
<td>M</td>
<td>1.63</td>
<td>1.06</td>
<td>604</td>
<td>13.7</td>
<td>320</td>
<td>26.4</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>M. C.</td>
<td>57</td>
<td>F</td>
<td>M</td>
<td>1.48</td>
<td>1.38</td>
<td>311</td>
<td>16.8</td>
<td>440</td>
<td>20.3</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>R. deV.</td>
<td>65</td>
<td>M</td>
<td>M</td>
<td>1.67</td>
<td>1.01</td>
<td>575</td>
<td>20.8</td>
<td>695</td>
<td>15.1</td>
<td>Pernicious anemia; diabetes mellitus</td>
</tr>
<tr>
<td>A. K.</td>
<td>72</td>
<td>M</td>
<td>M</td>
<td>1.89</td>
<td>1.79</td>
<td>457</td>
<td>17.2</td>
<td>580</td>
<td>21</td>
<td>Pernicious anemia; arteriosclerotic cardiovascular disease</td>
</tr>
<tr>
<td>M. Ch.</td>
<td>37</td>
<td>F</td>
<td>M</td>
<td>1.66</td>
<td>1.37</td>
<td>523</td>
<td>26.3</td>
<td>646</td>
<td>19.0</td>
<td>Pernicious anemia; essential hypertension</td>
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<tr>
<td>L. M.</td>
<td>62</td>
<td>F</td>
<td>M</td>
<td>1.80</td>
<td>1.80</td>
<td>381</td>
<td>18.4</td>
<td>528</td>
<td>27.7</td>
<td>Pernicious anemia; lymphatic leukemia</td>
</tr>
<tr>
<td>H. C.</td>
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<td>F</td>
<td>M</td>
<td>1.62</td>
<td>1.19</td>
<td>553</td>
<td>21.4</td>
<td>703</td>
<td>34</td>
<td>Pernicious anemia; arteriosclerotic cardiovascular disease</td>
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<tr>
<td>L. T.</td>
<td>24</td>
<td>M</td>
<td>M</td>
<td>1.77</td>
<td>1.76</td>
<td>203</td>
<td>12.8</td>
<td>277</td>
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<tr>
<td>L. G.</td>
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<td>M</td>
<td>M</td>
<td>1.78</td>
<td>1.76</td>
<td>752</td>
<td>10.1</td>
<td>887</td>
<td>26</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>H. Cu.</td>
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<td>M</td>
<td>M</td>
<td>1.71</td>
<td>1.74</td>
<td>640</td>
<td>14.6</td>
<td>816</td>
<td>31</td>
<td>Chronic blood loss —hemorrhoids</td>
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<td>M. B.</td>
<td>31</td>
<td>M</td>
<td>M</td>
<td>1.96</td>
<td>2.11</td>
<td>501</td>
<td>22.1</td>
<td>672</td>
<td>68</td>
<td>Chronic blood loss —duodenal ulcer</td>
</tr>
<tr>
<td>H. S.</td>
<td>38</td>
<td>F</td>
<td>M</td>
<td>1.72</td>
<td>1.58</td>
<td>528</td>
<td>15.1</td>
<td>648</td>
<td>34</td>
<td>Iron deficiency</td>
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<tr>
<td>B. K.</td>
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<td>F</td>
<td>M</td>
<td>1.50</td>
<td>1.44</td>
<td>716</td>
<td>19.9</td>
<td>877</td>
<td>415</td>
<td>Lymphatic leukemia</td>
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<tr>
<td>J. S.</td>
<td>53</td>
<td>M</td>
<td>M</td>
<td>1.86</td>
<td>1.25</td>
<td>123</td>
<td>42</td>
<td>387</td>
<td>32</td>
<td>Chronic blood loss —duodenal ulcer</td>
</tr>
</tbody>
</table>

Average values—female
- Glomerular Filtration Rate: 117 ml./min. per cent.
- Effective Renal Plasma Flow: 594 ml./min. per cent.
- F1ldostrin (Tm): 982 mg./lit.
- Glucose (Tm): 42.6 mg./lit.
- Blood Pressure: 23.0 mm. Hg.
- Arterial Blood: 303 mm. Hg.

Average values—males
- Glomerular Filtration Rate: 104 ml./min. per cent.
- Effective Renal Plasma Flow: 534 ml./min. per cent.
- F1ldostrin (Tm): 673 mg./lit.
- Glucose (Tm): 33.0 mg./lit.
- Blood Pressure: 19.7 mm. Hg.
- Arterial Blood: 416 mm. Hg.

The last observation. On the whole, follow-ups such as these proved difficult to obtain since the subjects refused to return to the hospital for study when they...
felt completely well. The follow-up studies summarized in Table 2 covered various periods of time ranging from two weeks to about three years of observation.

**Effective renal blood flow**

The most striking functional alteration during chronic anemia regardless of etiology was the reduction of effective renal blood flow. This alteration in effective whole blood flow was associated with a much smaller change in the effective renal plasma flow, the latter always falling in the lower portion of the normal range. On the average, the effective volume of whole blood flowing through the kidney fell from a normal figure of 1209 ml./min. to 654 ml./min., or 46 per cent in males, and from 982 ml./min. to 673 ml./min., or 31.8 per cent in females. The diodrast clearance or effective renal plasma flow, on the other hand, decreased in males by 25.2 per cent from the normal figure of 697 ml./min. to 522 ml./min., and in females by 10.5 per cent from 597 ml./min. to 534 ml./min. The clearance method

<table>
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<td>699</td>
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<td></td>
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<td>23.0</td>
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<td>31.0</td>
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<td>13.9</td>
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<td>76.1</td>
<td>422</td>
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<td>715</td>
<td>37.0</td>
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<td>14.1</td>
<td>120/70</td>
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<td>18.4</td>
<td>528</td>
<td>18.4</td>
<td>31.4</td>
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<tr>
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<td>93.3</td>
<td>388</td>
<td>23.6</td>
<td>578</td>
<td>18.4</td>
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<td>13.9</td>
<td>138/74</td>
</tr>
<tr>
<td></td>
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<td>90.0</td>
<td>520</td>
<td>14.6</td>
<td>680</td>
<td>16.5*</td>
<td>41.3</td>
<td>13.9</td>
<td>138/74</td>
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<td>M. C.</td>
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<td>58.0</td>
<td>351</td>
<td>16.8</td>
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<td>31.0</td>
<td>14.2</td>
<td>20.3</td>
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<td>8/3/43</td>
<td>74.6</td>
<td>316</td>
<td>22.9</td>
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<td>705</td>
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<td>14.6</td>
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<td>110/70</td>
</tr>
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<td>13.3</td>
<td>724</td>
<td>28.2</td>
<td>25.5</td>
<td>24.2</td>
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<td>752</td>
<td>10.1</td>
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<td>26.0</td>
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<td>15.1</td>
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<td>594</td>
<td>20.2</td>
<td>836</td>
<td>30.6</td>
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<td>30.6</td>
<td>104/70</td>
</tr>
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<td>528</td>
<td>15.1</td>
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<td>34.0</td>
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<td>579</td>
<td>16.6</td>
<td>685</td>
<td>36.2</td>
<td>19.0</td>
<td>15.1</td>
<td>120/60</td>
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<tr>
<td></td>
<td>6/18/43</td>
<td>93.4</td>
<td>635</td>
<td>14.7</td>
<td>936</td>
<td>45.0</td>
<td>20.7</td>
<td>33.2</td>
<td>114/70</td>
</tr>
</tbody>
</table>
may be used to measure renal plasma flow only if 90 to 100 per cent of the diodrast (or sodium p-aminohippurate) in the blood traversing the kidneys is removed. Since there is evidence that the extraction of diodrast or p-aminohippurate is not reduced during anemia, these values are probably accurate and valid.

The collected group of females showed a considerably smaller average change in effective renal plasma flow than the males. This difference was also observed with regard to the values for whole blood flow, glomerular filtration rate, and maximal tubular capacities. Whether this difference in response represents a true sex difference cannot be said upon the basis of this small series. Since most of the women had pernicious anemia it is possible that the typical functional pattern is less striking in pernicious anemia. However, B. K., a female with a severe secondary anemia of several months' duration, also presented high figures. No correlation between the extent of renal hemodynamic change and duration of symptoms was found.

In view of the fact that cardiac output is almost always increased in anemia of this severity it follows that the fraction of cardiac output passing through the kidneys fell markedly. This decrease was not only relative to blood flow elsewhere in the body, but absolute, since the fall in renal blood flow was considerably larger than the change in the head of pressure in the renal artery. Thus, the average mean arterial pressure (calculated according to the method of Bögr and Wezler) fell only 7.8 per cent, or from an average normal figure of 90 mm Hg. to 83 mm. Hg. in both men and women, excluding L. M. Consequently, it is probable that active vasoconstriction within the renal vascular bed accounted for the reduction of blood flow.

Following treatment, the renal blood flow slowly improved as the hematocrit returned toward normal (table 2). This increase was clearly related to the hematocrit since the effective renal plasma flow (or diodrast clearance) showed relatively little change. Indeed, on two occasions (E. M. and H. C.) where determinations were made at short intervals, the effective renal plasma flow actually fell during recovery from anemia despite a rise in effective renal blood flow. In most cases the effective renal plasma flow tended to increase slightly as recovery progressed. It should be noted that the arterial pressure did not increase.

**Glomerular filtration rate and the filtration fraction**

In more than half the subjects the glomerular filtration rate was below the normal range; in only 2 was it higher than the normal mean value. On the average it fell from a normal figure of 113 ml./min. in males to 89 ml./min. and 117 ml./min. to 107 ml./min. in females. The filtration fraction or percentage of plasma filtered at the glomerulus fell into the lower portion of the normal range or below it in nearly every case.

As anemia responded to treatment the glomerular filtration rate tended to increase, although on several occasions it fell sharply during the early phase of recovery (table 2). The filtration fraction showed relatively little change. In most instances (best seen in E. M., H. C., and H. S.) it remained low. In 3 patients the filtration fraction returned toward the normal mean value but did not exceed it.
Tubular function

The maximal rate of tubular diodrast excretion (diodrast Tm) was determined in 10 subjects, 7 of whom had pernicious anemia. This value, normally 1.8 mg./min. in men and 0.8 mg./min. in women, was depressed significantly in 9 subjects; 22.5 per cent in females, and 39 per cent in males. This reduction could not be attributed to a failure to attain sufficiently high plasma concentrations of diodrast, for the load* of diodrast presented to the tubules for excretion, in 8 of the 10, was greater than 2.0 mg. for each unit of Tm. In H. C. and M. B. the load/Tm ratio was 1.44 and 1.77 respectively, probably sufficient to assure saturation.

Maximal tubular glucose reabsorption (glucose Tm) was measured in 7 patients; 4 with pernicious anemia and 3 with anemia of varying etiology. Unlike diodrast Tm, glucose Tm fell within the normal range in every subject, except one (R. deV.). It is of interest that this patient suffered from diabetes mellitus in addition to per-

<table>
<thead>
<tr>
<th>Subject</th>
<th>Glucose Load (mg./min.)</th>
<th>Glucose Tm (mg./min.)</th>
<th>Load/Tm</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. S.</td>
<td>463.0</td>
<td>346.6</td>
<td>1.34</td>
</tr>
<tr>
<td>M. Ch.</td>
<td>479.9</td>
<td>442.4</td>
<td>1.08</td>
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<tr>
<td>R. deV.</td>
<td>362.0</td>
<td>214.5</td>
<td>1.69</td>
</tr>
<tr>
<td>A. K.</td>
<td>432.0</td>
<td>314.8</td>
<td>1.37</td>
</tr>
<tr>
<td>B. K.</td>
<td>610.0</td>
<td>359.6</td>
<td>1.73</td>
</tr>
<tr>
<td>L. G.</td>
<td>648.0</td>
<td>362.6</td>
<td>1.55</td>
</tr>
<tr>
<td>J. S.</td>
<td>647.5</td>
<td>415.9</td>
<td>1.53</td>
</tr>
<tr>
<td>H. C.</td>
<td>675.0</td>
<td>404.0</td>
<td>1.68</td>
</tr>
</tbody>
</table>

nicious anemia. With one exception (M. Ch.—1.08) the glucose load/Tm ratio exceeded 1.2, indicating the probability of effective saturation loads.

*Loading of the tubular transfer mechanisms must be in excess of their capacity if accurate measurements of Tm are to be made. The load of glucose reaching the tubules for reabsorption (mg./min.) may be calculated as the arterial plasma concentration of glucose (mg./ml.) multiplied by the filtration rate (ml./min.). The diodrast load (mg./min.) is the plasma concentration of diodrast (mg./ml.) times the effective renal plasma flow (ml./min.) less the quantity of diodrast filtered at the glomerulus (plasma concentration of diodrast [mg./ml.] multiplied by the filtration rate [ml./min.] and by a factor of 0.72 to correct for protein-binding). Since high plasma levels of diodrast must be used in the determination of diodrast Tm, the effective renal plasma flow is estimated from the filtration fraction, determined during a control study, and the filtration rate, observed during Tm determination.

All measurements of diodrast and glucose Tm are tabulated in tables 3 and 4. These figures are presented as they were obtained, without correction for body surface, together with the loads and load/Tm ratios. It can be seen that, with few exceptions, the ratios exceeded 1.0 for diodrast and 1.2 for glucose, the lower limits of adequate loading set down by Smith.13 In the one instance (M. Ch., table 3) where the glucose load/Tm ratio was low, the Tm value was quite high and probably correct. In H. C. (table 4), with ratios of 1.44 and 1.91 for diodrast, the Tm values measured at different times agreed closely despite the divergence of ratios. M. B. (table 4), with a diodrast load/Tm ratio of 1.77, had the highest diodrast Tm observed.
On 5 occasions (E. M., L. M., M. C., H. C., and H. S.) diodrast Tm was determined at different times after treatment was started. In 2 (E. M. and H. S.) there was a definite change toward the normal value. The others revealed no significant change. In 1 of these (H. C.) only twelve days had elapsed and there was evidence, in the renal hemodynamic pattern, of continuing renal functional abnormality despite hematologic cure. In another (M. C.) the hematocrit increased from 20.3 per cent to 29.7 per cent without any change in diodrast Tm.

**DISCUSSION**

It has been found that a characteristic and reversible renal functional abnormality develops in chronic anemia. Both effective renal plasma flow and glomerular filtration rate are reduced significantly, the latter to a somewhat greater extent in each case so that the filtration fraction (percentage of plasma filtered at the glomerulus)
tends to fall slightly. The most striking change is the marked reduction of effective whole blood flow through the kidneys. Since systemic arterial pressure does not change significantly while cardiac output increases, it is evident that active vasoconstriction occurs within the renal vasculature. In addition to the renal hemodynamic adjustment during anemia, abnormalities of renal tubular activity appear. The maximal excretion of diodrast is diminished while maximal glucose reabsorption remains unchanged. This dissociation indicates a local dysfunction of tubular cells rather than the destruction or inactivation of nephrons.

The normal value for glucose Tm indicates that all the glomeruli continue to function and to provide glucose for reabsorption by the tubules. Hence it is evident that vasoconstriction does not entail shunting of blood away from renal parenchyma or the cessation of flow in any significant portion of the renal vascular bed. Vasoconstriction may be more intense in some areas but this phenomenon is not manifest in the data presented above. To detect activity of this character, titration studies would be required.

Since blood continues to perfuse all the glomeruli, the filtration fraction may be used as a means of evaluating the site of vasoconstriction in the kidney. Accepting the hypothesis that filtration equilibrium is approximately reached across the glomerular membrane, a fall in both filtration fraction and renal blood flow implies increased afferent arteriolar resistance. The filtration fraction denotes the extent to which the plasma proteins are concentrated by filtration, and since the plasma oncotic pressure is equal to the hydrostatic pressure in the capillaries at equilibrium, the filtration fraction is a function of the equilibrium pressure. The slight reduction in filtration fraction therefore indicates a slight fall in equilibrium pressure. In some subjects the equilibrium pressure apparently remained at a normal level. This means that the difference of pressure between the renal artery and the point of filtration equilibrium changed very little despite a marked reduction of blood flow. Hence, the resistance between these points, to which the afferent arterioles make the largest contribution, increased in a manner roughly proportional to the reduction of blood flow. In addition, the equilibrium pressure is the head of pressure at the beginning of the postglomerular vascular bed. In view of the smaller reduction in filtration fraction than in renal blood flow, it may be concluded that the forces opposing perfusion increased, possibly as a result of efferent arteriolar vasoconstriction. Consequently, it is probable that both afferent and efferent arteriolar vasoconstriction occur in chronic anemia, and since the filtration fraction tends to fall it may be surmised that afferent vasoconstriction is the more prominent.

The reduction of blood flow through the kidneys is presumably a homeostatic

*The reduction of effective renal blood flow relative to the glucose Tm implies a diffuse and widespread renal ischemia during chronic anemia. However, no consistent change in the perfusion of functioning excretory tissue was observed. The effective renal blood flow/diodrast Tm ratio was elevated in 3 patients, reduced in 3, and normal in 3 (table 1). During recovery, the ratio increased in 3 individuals (E. M. and L. M., table 2) and remained unchanged in 3 others. Hence, no conclusion can be reached regarding the relationship between diodrast Tm and blood flow, although it is possible that they may have varied independently.
200 RENAL FUNCTION DURING CHRONIC ANEMIA
device by which blood is diverted to tissues with less resistance to oxygen lack.
The amount of blood thus spared is considerable. Normally 1200 ml of blood pass
through the renal vascular bed each minute in men. The average reduction to 600
ml observed in this series of patients (males) indicated a diversion of 600 ml of
blood per minute. Actually the saving was much greater, for the kidney might
have been expected to participate in the general vasodilation. This phenomenon
is not peculiar to chronic anemia for it occurs in traumatic shock, orthostasis, and
Addison’s disease. A reduction of the effective circulating blood volume is a
common denominator in these otherwise diverse conditions, but it is impossible at
present to attribute renal vasoconstriction to this factor. Since the kidney is sub-
ject to direct stimulation only by the arterial pressure, blood composition, and,
possibly, the nervous system, there is no obvious point d’appui at which effective
hypovolemia alone might excite renal vasomotion. Blood volume alteration, as
such, would not influence renal blood flow except through some intermediate
secondary effect. Certainly, a secondary change in the arterial pressure cannot be
adduced as the immediate cause, since the mean pressure may rise (as in orthostasis)
or fall (as in shock). The possible role of humoral or neural activity resulting from
a reduction of the circulating blood volume remains to be elucidated.

The clearance and Tm values showed a tendency to return to normal during
treatment and after the return of the blood picture to normal. The release of renal
vasoconstriction and the correction of the intracellular defect responsible for the
lessened capacity to transfer diodrast at high plasma levels, apparently paralleled,
in a general way, the clinical and hematologic improvement. In contrast, the
emergency treatment of shock results in a return of the cardiac output and blood
pressure to normal before any change in renal hemodynamics occurs. This lag be-
tween systemic and renal circulatory responses was not demonstrable in most in-
stances of chronic anemia, possibly because improvement was slower. Where the
anemia was rapidly corrected, as in H. C., by multiple transfusions of blood,
marked renal vasoconstriction and depressed diodrast Tm continued to be apparent
several days after the return of the hematocrit to normal.

It is interesting that a somewhat similar pattern of renal functional change has
been described in diffuse glomerulonephritis. The glomerular filtration rate is
reduced in this disorder presumably by glomerular damage and destruction. Since
filtration decreases more than the renal blood flow the filtration fraction falls.
Unlike anemia, there is little evidence that renal vasoconstriction is important.
Indeed, hyperemia as a result of vasodilation may be a prominent finding. It
is probable that anemia may intensify this pattern of renal functional change, but
it should be emphasized that anemia is not concerned with the initiation or per-
petuation of the typical alterations in clearance values during the course of diffuse
glomerulonephritis.

The findings of this study may throw light upon certain manifestations of chronic
anemia. Edema occurs in a large number of cases on some basis other than decreased
plasma oncotic pressure or increased venous pressure. Salt and water are retained
and the withdrawal of salt from the diet is frequently followed by loss of body
weight and reduction of edema. In view of the consistent change in renal function
observed in the present study, it may be suggested that edema is secondary to renal retention of water and salt, possibly attributable to a glomerulotubular imbalance indicated in the reduction of the filtration rate/glucose Tm ratio. The reduction of the urea clearance and the development of azotemia may be attributed to a reduction of glomerular filtration rate, which may be quite severe (M. C., L. M., L. T., table 1).

The renal functional changes, in general, are nonspecifically related to chronic anemia. Patients with pernicious anemia showed a less marked deviation from normal, on the average, but since this group was made up largely of females, the possibility of a sex difference cannot be excluded. The circulatory adjustments are made independently of the cause of anemia and it is not surprising that the renal circulatory phenomena should follow suit.

Although hypertension may be produced experimentally by constricting the renal arteries and reducing the flow of blood through the kidneys, hypertension does not usually develop in the course of chronic anemia, even when renal ischemia is marked. There is no reason to believe that the circulatory adjustments of anemia prevent elevations of the blood pressure, since hypertensive emotional responses are easily evoked and the blood pressure may rise as the result of some other disease process, such as glomerulonephritis, in spite of severe anemia. Pre-existing hypertension persists, as in L. M., with very little change. These facts are opposed to the view that renal ischemia is an important causal factor in human hypertension.

SUMMARY

1. Renal function has been studied quantitatively in 15 patients with chronic anemia, 8 of whom were proved to have pernicious anemia. In 7 the anemia was secondary to chronic blood loss, iron deficiency, paroxysmal nocturnal hemoglobinuria, and leukemia. The effective renal plasma flow and glomerular filtration rate were measured by clearance technics; and tubular function, by saturation methods (diodrast Tm and glucose Tm).

2. The effective renal plasma flow, the glomerular filtration rate, and the filtration fraction (percentage of plasma filtered at the glomerulus) were reduced slightly below the normal values in most subjects. The effective renal whole blood flow was always greatly reduced, by 46 per cent on the average in males and by 31.8 per cent in females.

3. Since arterial pressure was not significantly depressed it was concluded that renal vasoconstriction occurs in chronic anemia, possibly as a homeostatic device for the diversion of blood to tissues more sensitive to oxygen lack. The relatively small reduction of filtration fraction implies afferent and efferent arteriolar vasoconstriction with dominance of the afferent arterioles. These changes were shown to be reversible, a return to normal values paralleling the return of the blood picture to normal.

4. Diodrast Tm was reduced significantly in 9 of 10 patients while the values of glucose Tm were normal in 6 of 7 patients. The normal values for glucose Tm indicated continued operation of all glomeruli and implied the absence of shunting or of cessation of blood flow in any significant portion of the kidney. The fall in
diodrast Tm, which appeared to be reversible in 2 of 4 individuals, was interpreted as evidence of intracellular dysfunction rather than destruction or inactivation of nephrons.

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