Hemodynamic Alterations in Hemorrhagic Fever

By George Entwistle, Captain, M.C., and Edward Hale, Captain, M.C.

The cardiac output during the shock phase of hemorrhagic fever was very low. Increases in mean arterial pressure resulted from therapy with albumin or norepinephrine. With the former, this increase was associated with an increased cardiac output; with the latter, an increase in peripheral resistance. During the hypertensive phase, patients were found to have an increased cardiac output if they were also oliguric, and a relatively normal cardiac output if diuresis had begun. Some of the hypertensive patients presented the clinical syndrome of the "hyperdynamic state"; this occurred almost exclusively during the oliguric phase and was associated with high cardiac output and metabolic acidosis.

The patient severely ill with hemorrhagic fever progresses through a prolonged course of rapidly changing phases of the disease, each with its own peculiar clinical state and physiologic problems. During this course there are violent fluctuations in a variety of physiologic adjustments. The initial febrile phase is fairly sudden in onset and lasts 4 to 5 days. Widespread capillary damage becomes evident late in the febrile phase and is manifested by leakage of plasma from the blood vessels and by the development of some hemoconcetration. In 30 per cent of the cases, a phase of hypotension or shock lasting 24 to 36 hours follows the febrile phase and is accompanied by further hemoconcentration and continued plasma leakage. When hypotension is no longer a clinical problem, anuria or oliguria and their complications become prominent and characterize the next phase. At this time maintenance of fluid and electrolyte balance may be a particular problem. Late in the oliguric phase hypertension may be marked and complicated by pulmonary edema, and some patients show marked sensitivity to small alterations in fluid balance. Diuresis usually begins on the eleventh to thirteenth day of the disease, is marked for 2 or 3 days, and gradually the urine volume falls as the patient enters convalescence. Early in the diuretic phase electrolyte imbalance may again occur and at times is difficult to manage. Normal renal function returns completely within 45 days in most cases.

The mortality of epidemics from 1951 to 1954 averaged about 5 per cent, and most deaths occurred in the shock or oliguric-hypertensive phases of the illness. Much work to clarify the physiologic problems of the different phases is available in the recent literature.

Extensive physiologic studies were carried out on patients ill with hemorrhagic fever at the 48th Surgical Hospital, in the fall of 1953. As part of this over-all investigation, a hemodynamic study was performed, and is the subject of the present report. The previous year a preliminary study of similar nature was performed, and this was reported recently by Cugell, who found that the cardiac index was increased during the febrile and hypertensive phases, and low normal or decreased during the period of hemoconcentration.

Methods

All observations were made on hospitalized United Nations personnel. Forty-three patients were studied. Nine were control subjects, and consisted of hospitalized soldiers who had recovered from mild medical illnesses, such as infectious mononucleosis or upper respiratory infections. The other 34 patients had hemorrhagic fever. All studies were done with the patients in the recumbent position and in the overnight fasting state, except for patients in shock who were studied at the onset of their shock phase. The measurements were begun within 30 minutes after the diagnosis of shock had been made and the ward physician had decided to start therapy. This therapy was postponed in patients being studied until initial data had been gathered. Since all patients in this phase had marked anorexia and some degree of vomiting, they were also for the most part in the fasting state.

Arterial pressure was measured directly through an inlying Courmand needle, placed usually in the femoral artery. Mean arterial pressure was recorded
through an electromanometer connected with a direct-writing electrocardiograph. Venous pressure was measured through a thin-walled 18-gage needle connected to a saline manometer. The "zero" level in all patients was taken to be 10 cm. above the dorsal spine with the patient in the supine position. Occasional use was made of an antecubital vein.

Cardiac output was measured by the indicator-dilution technic with Evans blue dye. Accurately calibrated syringes were used to inject a fixed amount of dye (varying from 2.4 to 2.7 ml of T-1824, 26 mg per ml). The dye was injected through the indwelling 18-gage venous needle and serial samples of blood were taken at 2- to 4-second intervals from the intraarterial needle. A minute amount of liquid heparin was placed in each of the collecting test tubes.

The serial samples were continued for a total of 1 to 3 minutes. Thereafter 6 blood samples were taken at 5-minute intervals to determine plasma volume. Plasma concentration of T-1824 was measured with a Coleman junior spectrophotometer. Dye-tinged plasma standards were calibrated individually for each study during the first part of this investigation. When it became obvious that the optical density of the plasma dye standard was remaining constant, the same standard optical density was used for all patients subsequently studied, with periodic checks to assure that the base standard was maintained.

The total blood volumes (TBV) were calculated from the equation:

\[
TBV = \frac{\text{Plasma volume}}{100 - (\text{Hct} \times 0.96)} \times 100.
\]

### Table 1. Hemodynamic Studies in Hemorrhagic Fever

<table>
<thead>
<tr>
<th>Stage of disease &amp; no. pts.</th>
<th>Day of disease</th>
<th>Hematocrit</th>
<th>Cardiac index (L./M.Y. min)</th>
<th>Peripheral* resistance</th>
<th>Venous pressure (cm. water)</th>
<th>Pulse rate</th>
<th>Mean arterial pressure (mm. Hg)</th>
<th>Plasma volume (ml./Kg.)</th>
<th>Blood volume (ml./Kg.)</th>
<th>Red cell mass (ml./Kg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>9</td>
<td>44.8±3.61</td>
<td>3.61</td>
<td>19.1</td>
<td>12.0</td>
<td>75</td>
<td>75.6</td>
<td>41.3</td>
<td>70.1</td>
<td>28.8</td>
</tr>
<tr>
<td>Shock</td>
<td>13</td>
<td>56.7±8.01</td>
<td>0.98</td>
<td>±5.70</td>
<td>±5.00</td>
<td>±19</td>
<td>64.2</td>
<td>±7.8</td>
<td>73.3</td>
<td>31.8</td>
</tr>
<tr>
<td>Hypertensive oliguric</td>
<td>6-14</td>
<td>36.3±4.24</td>
<td>0.52</td>
<td>±11.47</td>
<td>±2.79</td>
<td>±23</td>
<td>62.7</td>
<td>±5.79</td>
<td>60.7</td>
<td>25.8</td>
</tr>
<tr>
<td>Hypertensive diuretic</td>
<td>11-16</td>
<td>38.9±7.02</td>
<td>3.55</td>
<td>29.4</td>
<td>±12.40</td>
<td>±13</td>
<td>±11.08</td>
<td>±6.50</td>
<td>±8.40</td>
<td>±2.91</td>
</tr>
<tr>
<td>Normotensive diuretic</td>
<td>12-26</td>
<td>41.5±6.49</td>
<td>0.87</td>
<td>±11.04</td>
<td>±1.86</td>
<td>±14</td>
<td>±4.38</td>
<td>±9.71</td>
<td>±14.26</td>
<td>±6.74</td>
</tr>
</tbody>
</table>

* Expressed in units (mean arterial pressure — venous pressure).
† Mean values and standard deviation.
were derived from the hematocrit change, with the assumption that the red cell mass had not changed.

**Results**

In table 1 the patients are grouped according to the usual phases of the disease (febrile, shock, oliguric, diuretic, and convalescent). A group of postfebrile patients was added to obtain data on patients who had recovered from shock, but had not yet developed hypertension. Furthermore, the hypertensive patients were divided into 2 groups, depending on the presence or absence of diuresis. This division was carried out to investigate the possible relationship between diuresis (or its absence) and the hemodynamic alterations of the hypertensive phase. Serial observations were done in a number of patients studied in more than 1 phase of the disease and the data on these patients are presented in table 2.

**Febrile Phase.** Results are summarized in table 1 for the 5 patients in the febrile phase of hemorrhagic fever. Their average hematocrit value is higher than that of the control patients. This difference is due mainly to the high value observed in 1 febrile patient who was studied on the sixth day of his disease. This patient had marked hemoconcentration (hematocrit 64 per cent) although his blood pressure was normal at the time of the study. He developed hypotension a few hours later. The average cardiac index for the 5 febrile patients is the same as that for the control patients (table 1, fig. 1), despite an average oral temperature of 102 F. for the febrile patients.

If the data from the 5 febrile patients are arranged in order of day of disease when the patient was studied, there appears to be a progressive fall in cardiac output during the febrile phase.

**FIG. 1.** Cardiac index in serial stages of hemorrhagic fever. Ordinate, cardiac index (L./min./M.²); abscissa, number of patients.

<table>
<thead>
<tr>
<th>Day of Disease</th>
<th>Oral Temperature (°F)</th>
<th>Cardiac Index L./M.²/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>104.2</td>
<td>5.21</td>
</tr>
<tr>
<td>3</td>
<td>104.0</td>
<td>3.16</td>
</tr>
<tr>
<td>5</td>
<td>102.0</td>
<td>3.13</td>
</tr>
<tr>
<td>5</td>
<td>100.4</td>
<td>2.99</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
<td>2.90</td>
</tr>
</tbody>
</table>

This fall may be related to the subsidence of fever. Unfortunately, no patients were studied serially during the febrile phase. There is a relative bradycardia throughout the febrile phase, associated early in the fever with a high cardiac output that progressively falls to normal. The peripheral resistance is low. Except for the 1 patient with hemoconcentration, the plasma volume, blood volume, and red cell mass are comparable to those found in normal patients.

**Shock Phase.** Thirteen patients were studied in the shock phase. These patients had temperatures ranging from 99.6 to 105 F. orally, but in 8 of these patients the temperature was below 102 F. During the shock phase there is a noticeable increase in the venous hematocrit and a corresponding reduction in the plasma volume (table 1). The red cell mass, however, is unchanged. The most striking change was the significant reduction in cardiac output ($p < .01$) that was associated with a significant increase in peripheral resistance ($p < .01$) (tables 1 and 2, fig. 1). Although there were some patients with a normal peripheral resistance in the face of reduced cardiac output, the mean peripheral resistance of this group of patients was significantly elevated compared to normal patients ($p < .01$) (table 2, fig. 2).

Patients with hemorrhagic fever who go into shock can be roughly divided into 3 clinical categories on the basis of hematocrit, pulse rate, and peripheral skin temperature. The majority of patients show warm dry skin, only slight increase in pulse rate and hematocrit, and
they are usually given norepinephrine intravenously and may be successfully carried through the shock phase with this treatment alone. Other patients present marked hemococoncentration, tachycardia, and cool, often moist skin; they are treated initially with 1 to 2 units of albumin. No other treatment may be needed. The interpretation is that, in the latter group, reduction in blood (plasma) volume contributes more to production of shock than in the former group, where insufficient peripheral vasoconstriction predominates. The third group is comprised of patients who initially do not obviously fall into the 2 categories just described. The third group is treated initially with norepinephrine, but albumin is frequently also needed. Also included in this third group are the patients who initially require either albumin or norepinephrine on the basis of the clinical criteria, but who subsequently require the other agent for control of blood pressure. The last patients described are seriously ill patients with severe shock. Figure 2 depicts the course of such a patient.

These arbitrary rules for deciding initial treatment were followed to some extent in the treatment of patients shown in table 3. In order to obtain additional information about the effects of these agents, however, 1 patient with a low hematocrit "Tho" was purposely given albumin initially, and 1 patient with a high hematocrit "Joh" was given norepinephrine initially. Patient "Ham," though presenting with the same hematocrit level as "Joh," did, however, have warm dry skin and no increase in pulse rate at the time of shock and was started on norepinephrine. The complete course of this patient during shock is represented in figure 2. In addition, 1 patient, "Til," was studied before and after treatment with both albumin and norepinephrine, and this patient appears twice in table 3.

Mean arterial pressures were essentially the same for the 2 groups, but the average hematocrit was somewhat higher in the group receiving albumin. The increase in mean arterial pressure that occurred in the patients receiving albumin was mainly due to an increase in cardiac output in each patient; the peripheral resistance actually fell in 4 of the 5 patients. There was slowing of the pulse and a fall in hematocrit. The increase in mean arterial pressure following therapy with norepinephrine appears to be wholly due to a significant increase in peripheral resistance ($p = 0.02$). The cardiac output and hematocrit level remained unchanged.

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**Table 2.—Serial Observations in Patients with Hemorrhagic Fever**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Shock</th>
<th>Postfebrile</th>
<th>Hypertensive</th>
<th>Convalescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulr</td>
<td>0.96</td>
<td>20.2</td>
<td>4.78</td>
<td>56.5</td>
</tr>
<tr>
<td>Ham</td>
<td>2.17</td>
<td>33.9</td>
<td>6.37</td>
<td>48.3</td>
</tr>
<tr>
<td>Kim</td>
<td>1.79*</td>
<td>30.5</td>
<td>4.12</td>
<td>54.6</td>
</tr>
<tr>
<td>Til</td>
<td>1.40</td>
<td>27.6</td>
<td>3.40</td>
<td>37.9</td>
</tr>
<tr>
<td>Rom</td>
<td>1.14</td>
<td>17.8</td>
<td>3.55</td>
<td>36.6</td>
</tr>
<tr>
<td>Tho</td>
<td>1.86</td>
<td>24.9</td>
<td>3.39</td>
<td>33.5</td>
</tr>
<tr>
<td>And</td>
<td>2.37</td>
<td>31.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ger</td>
<td>2.27</td>
<td>34.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Por†</td>
<td>1.95</td>
<td>33.6</td>
<td>5.80</td>
<td>57.2</td>
</tr>
<tr>
<td>Ell†</td>
<td>1.92</td>
<td>34.3</td>
<td>4.05</td>
<td>44.6</td>
</tr>
<tr>
<td>Row</td>
<td></td>
<td></td>
<td>2.85</td>
<td>47.5</td>
</tr>
<tr>
<td>Gal</td>
<td></td>
<td></td>
<td>5.25</td>
<td>48.9</td>
</tr>
<tr>
<td>Gel</td>
<td></td>
<td></td>
<td>6.10</td>
<td>53.6</td>
</tr>
</tbody>
</table>

* After norepinephrine infusion. Preinfusion data inadequate. † Studies after 24 hours of treatment for shock (normotensive at time of study). ‡ Cardiac index (L./M'/.min.). § Plasma volume (ml./Kg.).
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Fig. 2. Shock in hemorrhagic fever. This 21-year-old soldier was admitted on the fifth day of hemorrhagic fever and later succumbed to his disease. Soon after admission he developed shock and was given norepinephrine; only slight hemoconcentration was present at this time. Note the alterations in skin temperature associated with a rising hematocrit and the response to intravenous albumin. Albumin was first given after hypotension and tachycardia occurred; the marked hypotension on the previous day was not attended by a rise in pulse rate. At each "arrow" 2 units of human serum albumin were given. The hemodynamic data represent values before and after the norepinephrine was started. LW—lukewarm; PR—peripheral resistance in units.

Postfebrile (Oliguric-normotensive) Phase. Three patients were studied at the end of the febrile phase following recovery from hypotension or shock. Though oliguric, their average hemodynamic findings are similar to those noted in the control group. Hypertension developed in each of these patients 1 to 5 days after they were studied.

Hypertensive Phase. A total of 20 studies was made on the hypertensive patients, 13 of whom were oliguric at the time of study. As a group, the hypertensive patients showed a slight reduction of hematocrit (table 1). The cardiac index of the hypertensive oliguric patients was significantly elevated compared to the mean for the control patients ($p < 0.01$) and was also higher than the mean cardiac index of the hypertensive diuretic patients ($p < 0.05$).

Venous pressure was elevated in the hypertensive oliguric group, but normal in the group
TABLE 3.—Shock in Hemorrhagic Fever. Immediate Response to Early Therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>Mean Blood pressure (mm. Hg)</th>
<th>Hematocrit</th>
<th>Cardiac index ($L./M.2/min.$)</th>
<th>Peripheral resistance†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before*  After*</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Ulv</td>
<td>Albumin</td>
<td>63       72</td>
<td>63     58</td>
<td>0.96      1.37</td>
<td>56.1       38.5</td>
</tr>
<tr>
<td>Rom</td>
<td>Albumin</td>
<td>62       76</td>
<td>63     57</td>
<td>1.14      1.98</td>
<td>46.0       34.6</td>
</tr>
<tr>
<td>And</td>
<td>Albumin</td>
<td>75       90</td>
<td>58     52</td>
<td>2.37      2.54</td>
<td>28.4       31.8</td>
</tr>
<tr>
<td>Tho</td>
<td>Albumin</td>
<td>65       84</td>
<td>53     48</td>
<td>1.86      2.32</td>
<td>35.5       27.8</td>
</tr>
<tr>
<td>Til</td>
<td>Albumin</td>
<td>58       70</td>
<td>56     51</td>
<td>1.40      2.24</td>
<td>34.4       27.1</td>
</tr>
<tr>
<td>Til</td>
<td>Norepinephrine</td>
<td>70     94</td>
<td>51     51</td>
<td>2.24      2.06</td>
<td>27.1       41.5</td>
</tr>
<tr>
<td>Joh</td>
<td>Norepinephrine</td>
<td>70   99</td>
<td>56     57</td>
<td>1.40      1.68</td>
<td>45.0       54.8</td>
</tr>
<tr>
<td>Ger</td>
<td>Norepinephrine</td>
<td>66     73</td>
<td>51     53</td>
<td>2.27      1.96</td>
<td>26.5       34.1</td>
</tr>
<tr>
<td>Ham</td>
<td>Norepinephrine</td>
<td>52     75</td>
<td>56     59</td>
<td>2.17      2.24</td>
<td>19.5       28.6</td>
</tr>
<tr>
<td>Bas</td>
<td>Norepinephrine</td>
<td>62   88</td>
<td>51     52</td>
<td>1.96      1.90</td>
<td>27.8       40.7</td>
</tr>
</tbody>
</table>

* Data obtained just prior to and following therapy with either albumin or norepinephrine.

† Expressed in units (mean arterial pressure — venous pressure).

Cardiac index

whose diuresis had begun. The lack of a significant difference between the venous pressures of these 2 groups is probably due to the presence in the latter group of the only hypertensive patient who developed the “hyperdynamic syndrome” during the diuretic phase and whose venous pressure was 20 cm. of saline. The peripheral resistance of patients in diuresis was significantly elevated compared either to the normal subjects ($p < 0.01$) or the hypertensive-oliguric patients ($p < 0.02$).

Figure 3 relates the cardiac index during the hypertensive phase to the amount of albumin given during the prior shock phase. Four patients developed hypertension without having had shock. Their cardiac outputs were within the normal range. Six hypertensive patients had received 2 units of albumin during the shock phase, and they also showed no change in average cardiac output from normal. In those patients receiving over 2 units of albumin during shock, there was a definite increase in cardiac index during the hypertensive phase. Two of these patients with high cardiac output had pulmonary edema at the time of study. (One other patient also had pulmonary edema although he had received only 2 units of albumin for shock and had a normal cardiac output during the hypertensive phase.)

Figure 4 shows the variations of plasma and blood volume during the hypertensive phase according to the amount of albumin given during the prior shock phase. This table suggests a progressive increase in mean blood and plasma volumes during the hypertensive phase correlated with the quantity of albumin given.
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During the shock phase. All values for blood and plasma volumes in this figure are within the range found in normal patients, however.

Phlebotomy (400 to 500 ml.) was performed in 3 hypertensive patients on whom hemodynamic studies were done. The series was small because of reluctance to perform phlebotomy on patients with anemia (low hematocrit), and without specific indications for phlebotomy. Two phlebotomy patients were in pulmonary edema and had normal blood volumes and high cardiac indices. The venous pressure of each of these patients was elevated. They responded well to phlebotomy with fall in venous pressure, decrease in intensity of the second pulmonic sound, and disappearance of gallop rhythm and abnormal breath sounds. The postphlebotomy cardiac index was reduced 16 per cent in one, but only 7 per cent in the other patient. Phlebotomy has been recommended for treatment of patients who have convulsions during the hypertensive phase, and the effects of phlebotomy were determined in another hypertensive patient, not in pulmonary edema. His cardiac index was normal and blood volume low. No clinical change was noted following phlebotomy, and the cardiac index was reduced only 7 per cent. These changes are similar to those previously reported.

Normotensive Diuretic Phase. Five patients in this stage were studied. Two patients could be considered convalescent though still having polyuria from impaired renal function; otherwise they felt subjectively well and their hemodynamic findings were normal. The 3 remaining patients in this group were still on bed rest and were weak and malnourished; 2 had low cardiac indices (2.04 and 1.55 L./M2/min.) and their blood pressures were normal. Anemia, commonly seen at this phase, was present in some, but the average red cell mass was normal. Plasma and blood volumes were normal. Increased peripheral resistance persisted into this stage in some patients.

DISCUSSION

Fever Phase. The febrile phase of hemorrhagic fever lasts from 4 to 6 days and late in this phase there is usually a progressive increase in the venous hematocrit. This increase is believed to be due to leakage of plasma from the intravascular compartment. Only 1 of the patients studied during this phase showed hemoconcentration. The majority of patients with marked hemoconcentration develop manifestations of shock during defervescence.

Shock Phase. The most consistent and impressive finding in all patients with shock is reduced cardiac output. The cause of this reduced output is probably multiple. Reduced circulating blood volume owing to extravascular plasma leakage and pooling in capillaries is a most likely major cause. Inadequate vasoconstriction in the face of hypotension and the myocardial damage often seen at postmortem examination are considered to be the other chief causes of shock in hemorrhagic fever. Although adrenal medullary hemorrhage and cortical damage can occur, adrenal insufficiency.
does not seem to be a contributing cause of shock in most instances of this disease.²

Late in shock, whether it is untreated or treated with albumin, norepinephrine, or both, almost all patients demonstrate cool, if not moist skin, and cannot be divided clinically or hemodynamically into the 2 groups mentioned earlier. Two patients were studied 24 and 42 hours after the onset of shock. Both patients had been treated with albumin and were relatively normotensive (although still on shock blocks) at the time of study. In both cases the peripheral resistance was significantly elevated.

Many of these patients develop hypotension or shock with warm dry extremities, and the clinical impression of “insufficient peripheral vasoconstriction” is supported by the findings of normal or only slightly elevated calculated peripheral resistance in patients with low blood pressure and reduced cardiac output (table 3).

The choice of initial treatment in shock on the basis of clinical criteria of pulse rate, hematocrit, and skin temperature seems justified by the hemodynamic data gathered in this study. In addition, for patients studied early in shock, those with the highest hematocrit levels had the lowest cardiac indices \( r = -0.70 \), and the highest calculated peripheral resistances \( r = +0.73 \). The course of a patient in shock, “Ham,” where indications for treatment changed from an initial choice of norepinephrine to a later choice of albumin is shown in figure 2.

The charts of patients who developed shock during the fall epidemic of hemorrhagic fever (1953) were reviewed to see if the immediate response to therapy could be correlated with pulse rate or hematocrit at the time of therapy. Approximately 35 charts were reviewed. The immediate response to albumin was equally good in patients with tachycardia or relative bradycardia. In general, the response to albumin therapy was much better in those patients with the highest hematocrit values. A rise in mean arterial pressure was obtained from small doses of norepinephrine in practically all cases, irrespective of pulse rate or hematocrit (although no cases were started on norepinephrine with a hematocrit of 60 or more).

Hemoconcentration in shock of other infections has been noted, but mostly this is mild and does not reach the severe degree seen in patients with hemorrhagic fever. The hemoconcentration and reduced blood volume together are probably the cause of the precarious clinical state of these patients. Shock in patients with severe burns is similar, in that hemoconcentration and low plasma volume occur. A few patients with “burn shock” have had cardiac output studies.³ These patients show consistently low cardiac output and usually a very high peripheral resistance.

Cardiac output determinations were recently reported for 5 patients in shock due to bacterial infection.⁹ These patients showed normal or slightly reduced cardiac outputs and low peripheral resistance. The response to norepinephrine and albumin in these patients was reported to be similar to the response seen in hemorrhagic fever. Norepinephrine caused a rise in total peripheral resistance in all 4 patients, and a slight reduction in cardiac output occurred in 3 patients. One patient was given a small amount of albumin intravenously, and this was followed by an increase in cardiac output.

The effect of changes in viscosity on hemodynamics in dogs with and without reduction in blood volume has been studied extensively by Seligman, Frank, and Fine.¹⁰ With blood volume remaining constant, slight increases in hematocrit are associated with a fall in peripheral resistance and with a rise in relative viscosity; the mean arterial pressure and cardiac output remain normal. Further increases in hematocrit and apparent relative viscosity are associated with a rise in peripheral resistance, a fall in cardiac output, with the mean arterial pressure remaining unchanged. When hemoconcentration is produced in dogs with reduced blood volume, they become quite sensitive to further reduction in blood volume. Cardiac output reaches a critically low limit at higher mean pressures than would be the case were the blood viscosity not elevated. This level of blood pressure may produce a deceptively favorable impression of the state of the circulation. Indeed, such dogs may have irreversible shock at relatively high blood pressures, 80 mm. Hg and higher.¹⁰
**Hypertensive Phase.** Hypertension occurs in approximately one fourth of patients with hemorrhagic fever and may be quite labile. It usually lasts about 5 days and may be severe and associated with convulsions and pulmonary edema. Only 15 of the 20 patients studied had mean arterial pressures over 100 mm. Hg, although all were in the hypertensive phase by sphygmanometric readings at the time. Of the 15 patients with mean arterial pressures over 100 mm. Hg, 8 had elevated cardiac indices with normal peripheral resistance, 2 had elevated peripheral resistance with normal cardiac indices, and 5 showed both elevated cardiac indices and elevated peripheral resistance. When divided into 2 groups on the presence or absence of diuresis, significant differences are noted with higher cardiac index, venous pressure, and pulse rate in the oliguric patients, although there is no significant difference in mean arterial pressures between the 2 groups ($p = 0.2$).

During the hypertensive phase, some of the patients present the clinical syndrome of full veins, bounding pulse, unusual finger and toe pulses, exaggerated apical thrust, wide pulse pressure, and hypertension. This has been termed “relative hypervolemia” by Earle. Perhaps a more descriptive term is “hyperdynamic state.” Seven of the patients studied during the hypertensive phase presented these findings. Six were oliguric or anuric and 1 was in the second day of the diuretic phase. Generally, the cardiac index was high, peripheral resistance and hematocrit low. These findings are correlated with high foot and toe peripheral blood flow determinations done in 4 of these patients. The course of a patient “Ham” demonstrating these findings is shown in figure 5.

![Figure 5](image-url)

**Fig. 5.** Hemorrhagic fever, fatal case. This figure represents the complete hospital course of the patient whose shock phase is shown in figure 2. In addition to norepinephrine 4 units of albumin were given. On the eighth hospital day pulmonary edema developed with a high cardiac output and an elevated venous pressure. Following phlebotomy (500 ml.) the venous pressure fell to normal and signs of pulmonary edema cleared. The cardiac index after phlebotomy was 5.3 L./M./min. He remained febrile throughout the hospital course and died on the tenth day, again in shock, unresponsive to norepinephrine, transfusion, cortisone, and aqueous adrenal extract. Autopsy revealed bronchopneumonia, minimal pulmonary congestion, and the usual pathologic changes noted at this stage of the disease.
ENTWISLE AND HALE

The blood volume of these hyperdynamic patients was over 72 ml./Kg. with 1 exception. The blood volume in the hypertensive nonhyperdynamic patients was below 72 ml./Kg. with 2 exceptions. From these findings there appears to be a close correspondence between the clinical picture of the hyperdynamic state and calculated blood volume. However, as noted in table 1, the average and standard deviation of blood volumes in both hypertensive groups are the same as in the normal group and because of these essential findings the condition was specifically labeled as "relative hypervolemia" by Karle.2

Accurate calculations of "central hypervolemia" were not obtained. In the absence of these determinations, other indirect evidence on the subject has been gathered. There is a positive relationship between the amount of albumin given in the treatment of shock and the cardiac index of the hypertensive phase (fig. 3). This is also true of the blood and plasma volumes after albumin (fig. 4). The possibility that this relationship is due to over-all severity of the disease has, however, not been completely ruled out.

Pulmonary edema occurred in 3 of 10 patients who had received 2 to 4 units of albumin, whereas it did not occur in 4 patients who did not receive albumin nor in 4 patients who received 6 to 9 units of albumin. This observation suggests that albumin therapy may lead to pulmonary edema, but perhaps only in the presence of other factors not illuminated by this study.

Since the hyperdynamic state occurs during the stage of renal insufficiency of hemorrhagic fever, it is logical to consider what part, if any, the manifestations of renal insufficiency may play in producing this condition. As already mentioned, high cardiac outputs are usually noted in the patients before diuresis has begun. Although many of these hypertensive patients were mildly anemic (low hemoglobin in this group was 9.3 Gm.), anemia was not considered to be a factor in the increases in cardiac output. Analysis of chemical changes in the blood revealed no consistent relation between the level of blood urea nitrogen and cardiac output, although high cardiac outputs were noted more frequently when the blood urea nitrogen was rising or at its peak. However, consistent differences could not be demonstrated between the average blood urea nitrogen for the group of patients with high cardiac outputs and the group with low cardiac outputs. The potassium levels were normal in all these patients and the sodium and chloride levels were normal to low in both groups, and changes in electrolytes bore no relation to changes in cardiac output.

On the positive side, there was a relation between acidosis and cardiac output. High cardiac outputs were most commonly seen with mild (carbon dioxide content of 15 to 20 mEq. per L.) to moderate acidosis (carbon dioxide content of 10 to 12 mEq. per L.) On the other hand, normal cardiac outputs were seen in the absence of, or with only mild, acidosis. Although the argument for relative hypervolemia is fairly cogent, it is suggested that oliguria and acidosis, particularly in combination, may play a significant role in the production of the hyperdynamic state. This conclusion is supported by experimental evidence in dogs that metabolic acidosis was associated with increased cardiac output.12

Pulmonary edema is an uncommon but frequently fatal complication of hemorrhagic fever. It has been suggested that internal shifts of fluid, perhaps the result of re-absorption of the retroperitoneal edema fluid, may overload the vascular compartment. As a group, patients who developed pulmonary edema during the epidemic of 1952 did not show enlargement of heart by x-ray, elevated venous pressure, or response to the usual therapy for acute left ventricular failure. This group of patients was not divided according to the presence or absence of hypertension at the time of this complication.

During the epidemic of 1953, it was noted that patients who developed pulmonary edema with normal or low blood pressure had a high mortality and uniformly showed hemorrhagic pulmonary edema at autopsy. The 2 patients with this complication studied in this report, however, developed signs and symptoms of pulmonary edema with hypertension and responded to phlebotomy, with clearing of their symptoms and fall in elevated venous pressure.
X-ray films of the chest were not taken to determine heart size. It appears then that some patients with hemorrhagic fever in pulmonary edema will respond with complete clearing of this complication by phlebotomy. Observations of other patients with pulmonary edema during 1953, who were not included in this hemodynamic study, suggest that some improvement to complete clearing of pulmonary edema occurs in patients who are hypertensive while in pulmonary edema, but pulmonary edema in patients with normal blood pressure or hypotension is almost uniformly fatal.

Normotensive Diuretic Phase. The low cardiac indices occasionally seen in this phase (2 of 5 studies) may well account for the occasional patient who has late shock and may contribute to the precarious fluid balance noted in some patients at this time. In the 2 cases observed, the peripheral resistance was high and the blood pressure was normal. Lyons has reported that the peripheral blood flow at this stage (15 to 20 days) was low normal. The cause of the low cardiac output is likely dehydration, sodium depletion, or reduced venous return resulting from poor skeletal muscle and venous tone. One patient was studied who had been moderately ill with scrub typhus and in bed for 12 days. His hemodynamic findings were very similar to those of the normotensive patients in the diuretic phase of hemorrhagic fever. It seems probable that these same findings are present in the early recovery phase of other infectious illnesses.

SUMMARY

A hemodynamic study was done on 34 patients during the various stages of hemorrhagic fever. In the initial febrile phase some increase in cardiac output was noted, especially in patients with high fever. During the subsequent shock or hypotensive phase, striking reductions in cardiac output were associated in most patients with warm, dry extremities and mild hemoconcentration. A minority of patients presented low cardiac outputs associated with a high peripheral resistance and moderate to marked hemoconcentration. The latter group responded well to treatment with intravenous human serum albumin and showed a rise in cardiac output. The former group was treated with norepinephrine and the resulting rise in mean arterial pressure was due to increased peripheral resistance.

Twenty studies were performed during the hypertensive phase of hemorrhagic fever. Patients were divided into 2 groups according to the presence or absence of diuresis. When a hypertensive patient was also oliguric, high cardiac output was frequently found that was associated with a normal or slightly elevated peripheral resistance. Hypertensive patients who had begun a diuresis had normal cardiac outputs and significantly elevated peripheral resistance.

Some of the patients during the hypertensive phase presented the clinical syndrome of "relative-hypervolemia" described by Earle. As a group, these patients were oliguric, had high cardiac outputs with normal to low peripheral resistance, and had higher blood volumes than the hypertensive patients not presenting this syndrome. Metabolic acidosis was common in this group.

Pulmonary edema, an infrequent but usually fatal complication of hemorrhagic fever, responded to therapy if the patient was also hypertensive at the time of pulmonary edema, but this complication was uniformly fatal in normotensive or hypotensive patients.

SUMMARIO IN INTERLINGUA

Esseva executate un studio hemodynamic in 34 patientes durante le varie stadios de febque hemorrhagique. Durante le prime phase febril, un certe grado de augmento del rendimento cardiac esseva notate, specialmente in patientes con alte nivellos de febrilitate. Durante le subsequent phase de choc (o phase hypotensive), frappante reductiones del rendimento cardiac esseva associate in le majoritade del patientes con calide extremitates sie e leve grados de hemoconcentration. Un minoritade del patientes presentava basse rendimentos cardiac, associate con alte resistentia peripherie e grados moderate usque a marcate de hemoconcentration. Iste secunde grupo respondeva ben al tractamento con injectiones intravenose de human albumina sereal e manifestava un augmento del rendimento cardiac. Le prime del
duo gruppox esseva tractate con nor-epinephrina, e le resultante augmento del pression arterial medie esseva le effecto de elevationes del resistentia peripheric.

Vinti studios esseva executate durante le phase hypertensive del febre hemorrhagic. Le patientes esseva dividite in 2 gruppox secundo que illes habeva o non habeva diurese. Quando un patiente hypertensive esseva etiam oliguric, un constatation frequente esseva un alte rendimento cardiac associate con normal o levemente augmentate resistentia peripheric. Patientes hypertensive qui habeva commenceat lor diurese monstrava normal rendimentos cardiac e elevationes significative del resistentia peripheric.

Durante le phase hypertensive, certe patientes presentava le syndrome clinic de “hypervolemia relative” describite per Earle. Iste grupo de patientes esseva oliguric, habeva alte rendimentos cardiac con normal o basse resistentia peripheric, e monstrava plus alte volumines de sanguine que le patientes hypertensive qui non presentava iste syndrome. Acidosis metabolic esseva commun in iste grupo.

Edema pulmonar, un infrequentemente sed generalmente letal complication de febre hemorrhagic, respondeva al terapia si le patiente esseva etiam hypertensive al tempore del declaration del edema pulmonar, sed iste complication esseva uniformemente mortal in patientes normo- o hypotensive.

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Hemodynamic Alterations in Hemorrhagic Fever
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