RELATIONSHIP OF BOWEL AND LIVER TO DRUG PROTECTION AGAINST SHOCK

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Recent studies related to shock mechanisms have implicated many seemingly unrelated factors as being critical in generating the irreversible phase of the syndrome. Reports bearing on the shock problem are confusing and present opinions and concepts which are quite unsettled. The available data, however, crystallize at least two basic considerations common to much of current shock research. One concerns the importance of the liver and intestine as principal sites of the derangement associated with irreversibility. The other is to emphasize the need for increased information on how and under what specific circumstances drugs of the chlorpromazine-dibenzylaline type induce such remarkable resistance to many forms of experimental shock.

Liver and bowel participation in the shock response is well documented. Baez has shown that protection against shock is afforded by arterIALIZATION of portal vein blood 1 and by intraportal injection of aureomycin. 2 Blockade of the reticulo-endothelial cells of the liver was shown by Zweifach 3 to predispose to shock and to be an effective method of eliminating pre-existing resistance to stress. Selkurt's 4 data postulates that the gut produces a toxic factor which predisposes to irreversibility in animals with impaired hepatic circulation. According to Fine's group 5 Eck-fistula dogs with blood outflow from the bowel diverted from the liver are more resistant to stress. Existing information on the characteristics of the protective effects of drugs broadly termed autonomic "blockers," although extensive, is still quite inadequate if only because these versatile drugs are so widely used, are such important research tools and potentially important therapeutic agents. While there is almost universal agreement that they are protective against many forms of experimental shock, there is little agreement on the specificity of the tissue systems they modify to produce protection. Their effectiveness can be manipulated and altered particularly in regard to the timing of their administration 6, 7, 8 in relation to the onset of the shock stimulus. This time factor alone raises the basic problem of whether these protective drugs operate to prevent the formation of toxic elements or whether they attenuate the deleterious effects of toxic materials already elaborated.

Because of the aforementioned considerations of the importance of the bowel and liver and the need for more precise documentation of the behavior of protective drugs these experiments were designed to combine the exploration of shock induced through injury to the bowel per se with protection directed primarily to the liver. Shock was produced by temporary ligation of the superior mesenteric artery and the protective drugs were injected into the portal vein.

MATERIALS AND METHODS

Wistar strain female rats (120-160 Gms.) were anesthetized with pentobarbital sodium, intramuscularly, 2.5 mg./100 Gm. body weight. Through a small, mid-line abdominal incision the bowel was reflected in situ and a silk ligature tied in place to include the superior mesenteric artery and a lubricated polyethylene splint of larger diameter than the artery. Immediately after placing the tie each rat received one of the following drugs via the portal vein, tail vein or carotid artery: (1) dibenzylamine, 0.01 mg./100 Gm. body weight, (2) GD-131, 0.05 mg./100 Gm. body weight, (3) chlorpromazine, 1.0 mg./100 Gm. body weight (GD-131 is a dibenzylamine derivative devoid of adrenergic blocking properties). Controls received saline in volume equal to drug solutions (0.2 ml). Surgical incisions were closed allowing the polyethylene splint to protrude from the abdomen. The splint was removed

Received from the Departments of Anesthesiology, New York University-Bellevue Medical Center and Beth Israel Hospital, New York, N. Y., and accepted for publication December 18, 1958.
seventy-five minutes after it was originally tied and the animals observed for forty-eight hours for survival. Gross autopsies were routinely performed. One group of rats was used as collateral controls to confirm the protective effect of these drugs in this particular form of experimental shock by administering the drugs in a more usual manner; namely, one to two hours before the onset of stress.

In selected experiments the blood pressure was monitored using a Statham gauge transducer and the hematocrit was serially determined by a micro method using the Adams mechanical hematocrit tube reader. The sequence of events in the vascular bed of the intestinal wall was also observed by direct microscopy and the diameters of blood vessels measured by means of an ocular micrometer. Selected typical blood vessels were photographed before, during and following the placement and release of the mesenteric arterial tie. This technique for direct visualization of the microcirculation of the bowel was developed in this laboratory and is described in detail elsewhere. 

RESULTS

Figure 1 presents a graphic protocol of a typical control experiment in the rat. During the period of mesenteric arterial occlusion the blood pressure is relatively unchanged except for a transient increase following the onset of the occlusion. With the release of the tie there is an abrupt significant fall in blood pressure, some rebound which is brief and not sustained, followed by a progressive unremitting drop in blood pressure to extreme hypotensive levels over the ensuing two hours. The hematocrit typically increases during the arterial occlusion but the rate of increase in hematocrit is approximately twofold greater following the release of the tie reaching ap-
TABLE 1
PROTECTION BY PRETREATMENT WITH VARIOUS DRUGS IN SHOCK PRODUCED BY TEMPORARY LIGATION OF SUPERIOR MESENTERIC ARTERY IN RATS

<table>
<thead>
<tr>
<th>Dose (mg./100 Gm. body weight)</th>
<th>Number Animals Survivors/Total Number</th>
<th>Per Cent Survivors at 48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (saline 0.2 ml.)</td>
<td>8/27</td>
<td>30</td>
</tr>
<tr>
<td>Dibenzyline (1) (0.02 mg.)</td>
<td>13/22</td>
<td>55</td>
</tr>
<tr>
<td>GD-131 (2) (0.05 mg.)</td>
<td>16/23</td>
<td>70</td>
</tr>
<tr>
<td>Chlorpromazine (3) (2.5 mg.)</td>
<td>17/22</td>
<td>77</td>
</tr>
</tbody>
</table>

(1) Intravenous injection 60 minutes before arterial occlusion. (2) Intravenous injection 120 minutes before arterial occlusion. (3) Subcutaneous injection 60 minutes before arterial occlusion.

proximately thirty per cent higher than the control value.

Blood vessels of the intestinal wall show a cessation of blood flow during the occlusion. With the release of the tie there is a resumption of blood flow approaching the control level. This situation is only briefly sustained to be followed by slowed flow with ultimate stagnation occurring usually within two to three hours. The submucous arteries and arterioles constrict during the period of ischemia, dilate somewhat with the resumption of blood flow but then constrict progressively and remain narrowed for as many hours as they were observed (up to 8 hours). Submucous veins and venules are also somewhat constricting during the ischemic interval. With the release of the arterial ligature they revert to normal caliber briefly, then constrict markedly at about the time that the arteries and arterioles begin to constrict. Shortly after the over-all blood flow is slowed the venous vessels dilate quite rapidly and progressively until it becomes obvious that considerable blood is being sequestered in these widely dilated venous vessels. Extensive petechial formation occurs during this phase of venous dilatation. Autopsy routinely reveals typical splanchnic congestion most marked in the liver and ileum with focal hemorrhages in the ileum.

In protected surviving animals the sequence of events is not significantly different from those seen in unprotected controls until after the release of the mesenteric artery tie. Following this release the blood pressure does not fall to the same low levels, is sustained at moderately hypotensive values for a variable period and ultimately increases to reach control levels after several hours. Hematocrit increases to the same extent as in unprotected controls except in the chlorpromazine treated group in which the increase averages only eight per cent of initial values. With the removal of the tie the overall blood flow is only somewhat slowed, remains well distributed and unidirectional and gradually returns to normal after several hours. The arteries and arterioles do not show the intense protracted constricted state noted in unprotected animals and gradually revert to control diameters. Veins and venules, after an initial period of more moderate constriction, gradually return to normal caliber and do not show the extreme dilation and sequestration of blood noted in animals which ultimately die. Very few petechiae are seen. At autopsy, protected survivors grossly show a somewhat pale but essentially normal liver and ileum.

Table 1 indicates the survival rates in the collateral control experiments in which the protective drugs dibenzyline, GD-131 and chlorpromazine are given as pretreatment one to two hours before the onset of arterial ligation. The significantly higher survival rates, from 55 to 77 per cent, of the pretreated rats over the 30 per cent survival rate of controls indicates that these drugs are as effective in this form of experimental shock produced by temporary occlusion of the superior mesenteric artery in rats.

TABLE 2
EFFECT OF PORTAL VEIN ADMINISTRATION OF DRUGS IN SHOCK PRODUCED BY TEMPORARY LIGATION OF SUPERIOR MESENTERIC ARTERY IN RATS

<table>
<thead>
<tr>
<th>Dose (mg./100 Gm. body weight)</th>
<th>Number Animals Survivors/Total Number</th>
<th>Per Cent Survivors at 48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (saline 0.2 ml.)</td>
<td>5/16</td>
<td>31</td>
</tr>
<tr>
<td>Dibenzyline (0.01 mg.)</td>
<td>13/18</td>
<td>72</td>
</tr>
<tr>
<td>GD-131 (0.05 mg.)</td>
<td>7/14</td>
<td>50</td>
</tr>
<tr>
<td>Chlorpromazine (1.0 mg.)</td>
<td>17/20</td>
<td>85</td>
</tr>
</tbody>
</table>
artery as they have been previously demonstrated to be for other forms of experimental shock.

When these drugs are injected into the portal vein, immediately after the onset of intestinal ischemia, table 2, survival rates of from 50 to 85 per cent are seen in the drug-treated rats as compared with a 31 per cent survival rate in the controls. Significant protection was achieved by rapid exposure of the liver to dibenzylone, CD-131 and chlorpromazine without the usual interval of pretreatment.

The significance of injection into the portal vein in relation to time of administration of these drugs is apparent when compared with other routes as shown in experiments in which dibenzylone, CD-131 and chlorpromazine, tables 3 and 4, are also injected after the placement of the arterial ligature but via the tail vein and carotid artery. In the absence of the usual period of pretreatment, dibenzylone and chlorpromazine are no longer effective protective agents since animals receiving these drugs do not show survival rates significantly different from the controls.

**Discussion**

This group of experiments utilizing a preparation in which shock is induced by temporary ischemia of the bowel and protective agents are given by portal vein, has a bearing on several significant aspects of the characteristics and possible pathways of effect of the dibenzylone-chlorpromazine group of protective drugs. One such aspect is the time factor as related to the interval between the administration of the drug and the onset of stress. With few exceptions almost every modality of experimental protection, including these drugs, required “pretreatment” to produce increased survival. While the term “pretreatment” is subject to varied interpretation, it has usually indicated either a period of days for conditioning with antibiotics,10 endotoxins,11 physical training associated with tumbling trauma12 or of hours for administration of autonomic blocking agents13 prior to the onset of stress. Only a few reports6,7 on the use of these drugs indicate effective protection after the onset of stress in comparable experimental circumstances. The increased survival rates observed in this study can reasonably be interpreted as being related to the intraportal injection of drugs since similar small doses given by other routes do not provide protection. Injection of the portal vein was selected because it rapidly exposes the liver to a relatively high concentration of the drugs.

It is of further interest that the portal route is effective where very little if any of the drugs is present in the ischemic bowel during the period of stress. If the deleterious substances leading to irreversibility arise in the wall or lumen of the ischemic bowel, as predicated by Fine and his co-workers14 and others,6 the elaboration of these factors is not aborted in these experiments. Toxic substances of intestinal origin are therefore subsequently liberated into the systemic circulation, but they first pass through the liver as an experimental circumstance in these studies. The liver, in the presence of the protective drug is apparently more capable of attenuating the deleterious effects of such toxic materials. This consideration would also be valid if disturbed liver function per se is the basis for irreversibil-

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**TABLE 4**

**Effect of Intracarotid Administration of Drugs in Shock Produced by Temporary Ligation of Superior Mesenteric Artery in Rats**

<table>
<thead>
<tr>
<th>Dose (mg./100 Gm. body weight)</th>
<th>Number Animals Survivors/ Total Number</th>
<th>Per Cent Survivors at 48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (saline 0.2 ml.)</td>
<td>6/12</td>
<td>50</td>
</tr>
<tr>
<td>Dibenzylone (0.01 mg.)</td>
<td>7/12</td>
<td>58</td>
</tr>
<tr>
<td>GD-131 (0.05 mg.)</td>
<td>8/12</td>
<td>66</td>
</tr>
<tr>
<td>Chlorpromazine (1.0 mg.)</td>
<td>1/12</td>
<td>8</td>
</tr>
</tbody>
</table>

**TABLE 3**

**Effect of Tail Vein Administration of Drugs in Shock Produced by Temporary Ligation of Superior Mesenteric Artery in Rats**

<table>
<thead>
<tr>
<th>Dose (mg./100 Gm. body weight)</th>
<th>Number Animals Survivors/ Total Number</th>
<th>Per Cent Survivors at 48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (saline 0.2 ml.)</td>
<td>5/11</td>
<td>45</td>
</tr>
<tr>
<td>Dibenzylone (0.01 mg.)</td>
<td>5/10</td>
<td>50</td>
</tr>
<tr>
<td>GD-131 (0.05 mg.)</td>
<td>7/12</td>
<td>58</td>
</tr>
<tr>
<td>Chlorpromazine (1.0 mg.)</td>
<td>6/12</td>
<td>50</td>
</tr>
</tbody>
</table>
ity without regard to toxic materials or abnormal cellular function arising elsewhere. The experimental findings confirm and more clearly delineate the role of the liver in conditioning the character of response to shock.

In regard to the hemodynamic component of the shock syndrome attention has recently been directed to the circulatory derangement in localized vascular beds. Studies of the circulation in so-called critical tissues represent an attempt at establishing a more precise relationship between localized vascular decompensation and other parameters characteristic of the response to shock. Relatively few reports on the status of the circulation in the intestinal wall in shock are available. The data from these studies represent relatively indirect vascular measurements based on observations derived from the larger intestinal vessels providing for inflow and outflow. Direct observation of the important vascular connections between these larger vessels in shock has not been previously reported and was made possible because of the technique developed by Baez. The intestinal mural bed has several structural and functional characteristics which differ from those described in other tissues. These special features are probably important in the local regulation of blood flow and distribution to the various layers of the intestinal wall.

The adjustments to stress of the vascular bed of the intestine in animals in shock is generally similar to that reported in the omentum and mesoappendix. A favorable overall adjustment is in the direction of a sustained, unidirectional, restricted blood flow and the absence of stagnation, overfilling of capillaries and dilatation. Several details of the course of events apparently peculiar to the intestinal vasculature are of particular interest since they have not been previously noted in the vessels of the omentum, mesoappendix or other visceral vascular beds. For instance, the submucous arteries and arterioles do not dilate with the onset of the decompensatory phase in animals not surviving. Rather these vessels constrict further and remain constricted until the animal dies. Another feature regularly observed was the intense venous segmental constriction in the submucous plexus. In rats irreversibly shocked, the caliper of the veins was reduced to less than that of their accompanying arteries. This was most evident at the mesenteric border of the bowel. As a consistent observation it is suggestive of mechanical impedance to venous outflow from the intestinal bed and points to a possible mechanism for the sequestration of blood in the wall of the gut with consequent formation of petechiae and loss of blood into the intestinal lumen. It is also of significance that a specific vascular site of visceral pooling of blood in shock is also identified by this method of direct visualization. There is no readily apparent explanation for this unusual pattern of vascular behaviour in the intestine. It may, however, be related to the local vasactive effects of hormonal mediators, such as serotonin which is present in high concentration in intestinal tissue.

The observations and data made during these studies are of course inconclusive in terms of identifying basic mechanisms involved in the production of shock. They do not warrant development of far-reaching implications or conclusions to be added to the already confused situation. As a method of study this method of producing shock in either the rat or the dog offers an experimental approach that could yield significant direct and critical information about the pathogenesis of the syndrome.

**Summary and Conclusions**

Shock was induced in rats by temporary ligation of the superior mesenteric artery using a method which permitted continuous, direct microscopic observation of the intestinal vascular bed. Dibenzyline, GD-131 or chlorpromazine was injected into the portal vein immediately following the onset of bowel ischemia and the resulting survival rates were compared with those following the administration of these shock protective drugs by other routes. The portal vein route which rapidly exposed the liver to a relatively high concentration of these drugs, increased survival rates over those noted when the drugs were given by other routes. Surviving, protected animals also showed more favorable blood pressure responses and the absence of typical visceral congestion at autopsy. The over-all pattern of behavior of the intestinal mural circulation was more favorable in survivors than in fatalities and was an
accurate index of eventual irreversibility. Several features of the vascular responses in the bowel were different from those reported in other visceral pools of blood in the submucous veins was identified and a possible mechanical component for this sequestration was observed. The data emphasize the importance of the liver and bowel in the shock response and provide further information on the properties of protective drugs.

This research was supported in part by grants from the U. S. Public Health Service (H-2743) and the Levy Foundation for Medical Research, New York.

REFERENCES