The concept of a toxic humoral substance produced within an animal during a stressful event such as circulatory shock represents an attractive mechanism to explain the pathophysiology of shock states. Indeed, toxic factors have been proposed as an explanation of the lethal effects of circulatory shock for some time. In 1943, two reports appeared (1, 2) indicating the presence of toxic substances in thoracic duct lymph during tourniquet shock. Lymph from normal dogs had no observable effect when it was injected into normal animals. The presence of toxic factors in lymph was subsequently confirmed in 1964 by Tice and Dumont (3), using shock induced by splanchnic artery occlusion. None of these studies clarified the nature of the toxic factor(s) present in the lymph of animals in shock. However, in 1970, Glenn and Lefer (4) showed that the thoracic duct lymph of cats in postoligemic shock contained cardiotoxic activity, and this activity was related to the presence of both lysosomal hydrolases and a myocardial depressant factor. These data help to clarify some of the earlier findings, since both of these substances are now recognized as toxic agents in shock.

Historically, other investigators have inferred the existence of toxic factors in shock but have not attempted to isolate or identify the toxic principle. Thus, Selkurt (5) postulated the presence of a vasoactive material in splanchnic artery occlusion shock, which originated in the ischemic intestine. Baez et al. (6) also found a substance(s) under similar conditions which exhibited vasoactive properties in isolated test systems, although no direct toxic effect was shown. In addition to these factors which were presumed to act on the peripheral vasculature, Gomez and Hamilton (7) postulated that a cardiotoxic material was released into the blood during hemorrhagic shock. This cardiodepressant substance was thought to contribute to the severe myocardial depression observed in the late stages of shock.

These studies called attention to the possibility that toxic factors may play a role in the pathogenesis of circulatory shock by acting on components of the cardiovascular system in a positive feedback fashion (i.e., impairment of the circulatory system results in the elaboration of humoral substances which further impair overall circulatory function, even though the humoral substance may correct one of the defects in circulatory function).

Many well-known substances, particularly the neurohumoral transmitters and the vasoactive substances (i.e., norepinephrine, acetylcholine, histamine, vasopressin, serotonin, ferritin, and angiotensin II), have been considered as mediators of shock (8-10). Recently, lactic acid (11) and bradykinin (12) also were suggested as toxic agents in circulatory shock. Although these substances increase transiently in the blood, they never achieve very high concentrations except perhaps in certain organs. Conceivably, this accumulation could prove to be toxic at some critical site, but no compelling evidence has been obtained to verify this assumption. More likely, the release of the neurohormors or the vasoactive agents is a compensatory response to the trauma of the shock-inducing event (e.g., hemorrhage, myocardial infarction, ischemia of tissues, etc.). From this viewpoint, the vasoactive agents can be considered substances which aid in the mobilization of the body’s defense mechanisms.
mechanisms to either maintain mean arterial blood pressure or preserve blood flow in face of a traumatic event, much like the release of corticosteroids is thought to mobilize substrates in metabolic terms. Thus far, no definitive toxic effect has been ascribed to these substances in concentrations which exist in plasma during shock. Although they may participate in the formation of other toxic factors, perhaps by inducing regional ischemia, these substances do not appear to be primary toxic factors themselves.

CRITERIA FOR SHOCK FACTORS

It is essential that a toxic factor satisfy specific criteria before it can be judged to be a true shock factor. Although every criterion may not be assigned equal weight, most investigators would probably agree with the following criteria.

A toxic factor in shock should not be present in animals that are not in shock at concentration levels which exert deleterious effects. A toxic factor could be a metabolite which accumulates to toxic concentrations, or it could be a substance which is formed only during shock (i.e., breakdown product of a cellular component). In the former case it probably would be present in small amounts of plasma from normal animals, whereas in the latter case it probably would not occur in normal animals.

A toxic factor in shock should also be produced in a variety of types of shock. This criterion is a test of the factor’s universality, and the criterion presupposes that a common pathophysiological mechanism exists for many forms of circulatory shock. Many investigators in the field contest this notion as being a simplistic view of the problem and claim that no single mechanism is prevalent in all forms of shock. However, there are many striking similarities among the various types of circulatory shock (e.g., hemorrhagic, endotoxic, splanchnic artery occlusion, cardiogenic, acute pancreatitis, and burn shock), although each form has its hemodynamic differences. One such common reaction to shock stimuli appears to be the activation of the sympathetic adrenergic system and the resultant peripheral vasoconstriction. Regardless of the hemodynamic response to shock, a single humoral factor could exist in these types of shock.

It should be possible to isolate a toxic factor in a partially purified form from animals in shock. No factor has been completely purified, identified, and synthesized. These steps would be the ultimate validation of a shock factor. However, a goal that can be more readily achieved is the isolation and partial purification of a factor from the plasma of animals in shock.

The toxic factor should exert a severe pathophysiological effect on some vital organ or essential metabolic pathway. Several substances have been proposed as shock factors, but not all are associated with a deleterious effect on an essential system in the body. It is not sufficient to demonstrate the action of a substance on an isolated tissue or organ; one must show that the action compromises the animal’s chances of survival. Thus, an important test of a shock factor would be to inject it in the amounts present in plasma from animals in shock into test animals not in shock and to demonstrate the production of shock or at least of a severe impairment of an important organ or system.

Finally, a toxic factor in shock should be present in man as well as in experimental animals during shock. If one is to ascribe clinical significance to a toxic factor, it must be found in patients during clinical shock. The problems of species variability and of idiosyncratic reactions in certain species have been intensively discussed among investigators in the field of shock. Nevertheless, shock represents a common defect in all species, namely a critical reduction in blood flow to the systemic organs. Therefore, it would not be completely surprising if, despite differences in the precise homeostatic adjustments to the shock stimulus, some mechanism was common to most mammalian species including man.

GENERAL CHARACTERISTICS OF SHOCK FACTORS

A summary of the known characteristics, properties, and actions of proposed toxic factors in shock is presented in Table 1. The factors are quite diverse in their chemical properties. They range from simple small molecules with molecular weights less than 1,000 to complex molecules with molecular weights of 1,000,000 or more. Some of the factors are partially characterized chemically (e.g., hemochromogen, some of the lysosomal hydrolases, and to some degree myocardial depressant factor [MDF] and reticuloendothelial depressant substance [RDS]), whereas the others are not. However, none of the toxic factors is completely characterized in specific molecular terms. Knowledge of the chemical structure could lead to information about the metabolism and the clearance of a
HUMORAL FACTORS IN CIRCULATORY SHOCK

by guest on November 12, 2017

Circulation Research, Vol. XXXII, February 1973

131

HUMORAL FACTORS IN CIRCULATORY SHOCK

toxic factor and ultimately to the synthesis of molecular analogues which could be useful in the treatment of circulatory shock. Despite the lack of complete information about the toxic factors, one can attempt to evaluate each factor in terms of its fulfillment of the criteria and thus determine its significance in the pathophysiology of shock.

The first criterion for a shock factor (i.e., that the factor not be present in high amounts in control animals) is essentially satisfied by all of the factors in Table 1. Any factor that failed to satisfy this elementary requirement could not be seriously considered further.

The finding that certain factors occur in so many types of shock having diverse etiologies is striking. Moreover, of all the investigators who have studied a specific toxic factor in shock, none have reported a type of shock in which they failed to find that factor.

At present, the factors reported by Fukuda (58, 59), Thal and co-workers (60, 61), and Clowes and colleagues (62-64) as well as by others (19, 65) have not been isolated in sufficient purity to warrant further consideration of their chemical nature. However, those factors which have been partially purified (i.e., lysosomal hydrolases, RDS, and MDF) and those about which chemical properties are known (i.e., hemochromogen and endotoxin) can be said to have partially satisfied the third criterion.

All of the factors listed induce shock or at least exert severe disturbances in the normal functioning of the cardiorespiratory or the reticuloendothelial system when injected into normal animals. Thal and co-workers (60, 61) have not injected their factor into intact normal animals, but they have perfused the lungs of the shock animal, thereby partially fulfilling this requirement. Although all the factors are capable of exerting a biological effect that can be considered detrimental to survival, the degree of toxicity of the factors is variable. Thus, hemochromogen, endotoxin, and, to some extent, lysosomal enzymes appear to exert part or all of their detrimental effects indirectly by releasing other agents, which act as toxic factors, and thus in a sense are secondary toxic factors. These factors also have high molecular weights and thus may be degraded further to produce a toxic factor. The other factors either depress the heart directly (28, 42, 44, 45, 62), induce hypotension (56, 58), which may be a cardiac or a peripheral vascular effect, or impair phagocytosis (38-42). Some of the factors also exert effects on other organs or loci in addition to the ones cited above (i.e., MDF also constricts the splanchnic vasculature [58], Thal's factor stimulates vascular smooth muscle [61], etc.). However, these actions probably are not of primary importance in the direct actions of the factors, although they may play some role in their overall effectiveness.

Regarding the final criterion, namely the presence of the factors in plasma from human subjects in shock, only MDF (57) and endotoxin (66) have been identified in the plasma of patients having a variety of forms of shock, although Thal's factor (61) and hemochromogen (27) have each been found in one shock patient.

CRITIQUE OF SHOCK FACTORS IN GENERAL

One type of criticism is often proposed against toxic factors in general, and that is the question of how the homeostatic balance is so overwhelmed in shock that it produces a substance which is lethal to itself. There are two kinds of answer to this question. (1) The priorities that are designated in the homeostatic regulation of the circulatory system sometimes conflict with one another. For example, vasodilation of the cutaneous vessels (i.e., to effect heat loss) appears to have priority over vasomotor regulation of systemic mean arterial blood pressure, so that sometimes in heat stress syncope results. This condition, of course, is usually a temporary situation, which can be brought into balance by an alteration in position or temperature of the body. In the case of shock (e.g., brought about by severe hemorrhage), the coronary and the cerebral circulations invoke a higher priority than do the splanchnic, renal, and cutaneous vasculatures for blood flow. The significance of this priority system is obvious as a short-term adjustment (i.e., protection of the heart and brain). However, if the situation is prolonged and not alleviated, the resultant splanchnic ischemia will induce irreversible autolytic changes in the cells of the splanchnic organs (e.g., activation of lysosomal and zymogenic enzymes) which can lead to destruction of these organs. Richards (67) has eloquently discussed and classified these errors in homeostasis and has cited numerous examples of inappropriate or excessive responses to a change in an organism's status quo.

(2) The second answer is that homeostasis is not omnipotent. It works within finite limits, and these limits can be reached under prolonged adverse conditions. Thus, there are homeostatic mechanisms
<table>
<thead>
<tr>
<th>Name of factor</th>
<th>Species</th>
<th>Forms of shock</th>
<th>Chemical properties</th>
<th>Type of molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysosomal hydrolases</td>
<td>Dog</td>
<td>SAO (13, 14)</td>
<td>M.W. 25,000-200,000</td>
<td>Proteins</td>
</tr>
<tr>
<td></td>
<td>Cat</td>
<td>Hemorrhagic (15)</td>
<td>Water soluble</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endotoxic (16)</td>
<td>Heat labile</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiogenic (17)</td>
<td>Nondialyzable</td>
<td></td>
</tr>
<tr>
<td>Hemochromogen</td>
<td>Dog</td>
<td>SAO (24, 25)</td>
<td>M.W. 68,000</td>
<td>Hemoglobin derivat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute pancreatitis (24)</td>
<td>Nondialyzable</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemorrhagic (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endotoxin</td>
<td>Rabbit</td>
<td>Endotoxic</td>
<td>M.W. 200,000-2,000,000</td>
<td>Lipopolysaccharide</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>Hemorrhagic (29, 30)</td>
<td>Nondialyzable</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAO (31, 32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Catecholamine (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reticuloendothelial depressant</td>
<td>Dog</td>
<td>Hemorrhagic (36, 37)</td>
<td>M.W. 10,000</td>
<td>Unknown</td>
</tr>
<tr>
<td>substance (RDS)</td>
<td>Cat</td>
<td>SAO (38)</td>
<td>Dialyzable (39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Can be frozen (39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Soluble in methylene chloride (39)</td>
<td></td>
</tr>
<tr>
<td>Myocardial depressant factor (MDF)</td>
<td>Cat</td>
<td>Hemorrhagic (44–46)</td>
<td>M.W. 500–1,000 (52, 53)</td>
<td>Peptide, glycopeptide</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>Endotoxic (18)</td>
<td>Dialyzable (25)</td>
<td>(27, 45, 52, 53)</td>
</tr>
<tr>
<td></td>
<td>Baboon</td>
<td>SAO (14, 47–49)</td>
<td>Can be frozen (28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Man</td>
<td>Cardiogenic (17)</td>
<td>H₂O soluble (28, 45)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatitis (50)</td>
<td>Not soluble in methylene chloride (27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burn (51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fukuda's factor</td>
<td>Dog</td>
<td>Hemorrhagic (58)</td>
<td>H₂O soluble (59)</td>
<td>Appears to be protein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endotoxic (59)</td>
<td>Heat labile (58)</td>
<td>(58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Precipitated by ammonium sulfate (58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Probably large M.W.</td>
<td></td>
</tr>
<tr>
<td>Thal's factor</td>
<td>Dog</td>
<td>SAO (60, 61)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Clawson's factor</td>
<td>Dog</td>
<td>Septic (62, 63)</td>
<td>M.W. 1,000–3,000</td>
<td>Possibly peptide</td>
</tr>
</tbody>
</table>

SAO = splanchnic artery occlusion, M.W. = molecular weight, MDF = myocardial depressant factor, and RE = reticuloendothelia.

available to protect against these enzymes and other substances which induce cellular autolysis, but this second line of defense can also be overwhelmed in untreated shock. These protective mechanisms include the compartmentalization of the enzymes within subcellular particles (e.g., lysosomes and zymogen granules), the presence of local inhibitors and enzymes which degrade these enzymes (e.g., pancreatic trypsin inhibitors and certain proteases), and the occurrence of unfavorable conditions which prevent the optimal activation of these enzymes (e.g., neutral or basic pH). However, cell damage, binding of inhibitors, and the acidosis of shock act to override these protective mechanisms.

Another general criticism that can be applied to the toxic factors is that to date none have been identified and synthesized. This deficiency is undoubtedly due to the difficulty of such a task and does not necessarily detract from the validity of toxic factors. Of course, identification and synthesis of any of these factors will enable a much more rigorous testing of its role in shock, as mentioned previously.
HUMORAL FACTORS IN CIRCULATORY SHOCK

<table>
<thead>
<tr>
<th>Origin in body</th>
<th>Biological actions</th>
<th>Prevention of formation of factor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ischemic splanchnic region (18-20)</td>
<td>Sensitize heart to other toxic factors (18)</td>
<td>Pharmacological doses of glucocorticoids (14)</td>
<td>Found in lymph in shock (4)</td>
</tr>
<tr>
<td>pancreas (14, 15)</td>
<td>Cause hypotension (14, 18)</td>
<td>Slight hemodynamic effect in presence of intact RE system (18)</td>
<td></td>
</tr>
<tr>
<td>spleen (18)</td>
<td>Constrict pancreatic vessels (23)</td>
<td>Action not blocked by glucocorticoids (15)</td>
<td></td>
</tr>
<tr>
<td>intestine (13, 21)</td>
<td>Participate in the formation of MDF (15, 17, 18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kidney (22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood absorbed by damaged intestinal mucosa (26)</td>
<td>Unclear whether there are direct effects Hypotension</td>
<td>Unknown</td>
<td>Occurs in patients (27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Does not depress myocardium (28)</td>
</tr>
<tr>
<td>Schematic intestine absorbed through damaged intestinal mucosa (31, 32)</td>
<td>Unclear, may release vasoactive agents</td>
<td>Nonabsorbable antibiotics (32) (challenged by others [33-35])</td>
<td>Does not depress myocardium (16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Germ-free animals not protected in shock (34)</td>
</tr>
<tr>
<td>schematic splanchnic region (possibly intestine [36, 40])</td>
<td>Depresses phagocytosis by fixed macrophages (37, 40, 41) May depress heart (42) Impairs survival (43)</td>
<td>Unknown</td>
<td>Passively transferred to another animal (36, 41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Formed despite absence of intestinal flora (38)</td>
</tr>
<tr>
<td>schematic splanchnic region (52) pancreas is major source (15, 23, 47)</td>
<td>Negative inotropic effect (44, 45, 54, 55) Constricts splanchnic resistance vessels (56) May depress RE system (42)</td>
<td>Pharmacological doses of glucocorticoids (52) Trasylol (53) Lymph diversion (4)</td>
<td>Found in lymph (4) and in pancreatic autolysates in shock (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Occurs in plasma of patients in shock (57)</td>
</tr>
<tr>
<td>schematic splanchnic region (particularly liver)</td>
<td>Hypotension (59)</td>
<td>Pharmacological doses of glucocorticoids (59)</td>
<td>Passively transferred to another animal (57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not blocked by glucocorticoids (59)</td>
</tr>
<tr>
<td>ischemic splanchnic region (60, 61)</td>
<td>Induces lesion in lung (59) Stimulates vascular smooth muscle (61)</td>
<td>Phenoxylbenzamine (60)</td>
<td>May not be one factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probably splanchnic region (64)</td>
<td>Increases pulmonary vascular resistance Induces focal alveolar collapse and right heart failure (63, 64)</td>
<td>Glucocorticoids Trasylol (partially effective) (63)</td>
<td>Activity is free of endotoxin (63)</td>
</tr>
</tbody>
</table>

CRITIQUE OF THE INDIVIDUAL SHOCK FACTORS

Lysosomal hydrolases appear to be involved in the pathogenesis of circulatory shock indirectly by

One hazard of a lack of knowledge of the precise molecular structure of each factor is that investigators may separately discover the same factor. For example, Fukuda’s factor (58, 59) and one which has been described only on a preliminary basis (19) appear to be similar to lysosomal hydrolases. They appear to be proteins which are released from either the ischemic or the damaged liver, but this release can be prevented by large doses of glucocorticoids (59), drugs which are known to stabilize splanchnic lysosomes (14). In another instance RDS was compared with MDF (42), and each purified plasma extract contained high activity of both factors. Of course, both factors could have been present together in the same plasma extract rather than being a single entity. Nevertheless, the chemical properties of RDS and MDF are strikingly similar except for their apparent difference regarding their solubility in methylene chloride (42). Further work is necessary to clarify whether any two or more of these factors are truly identical or whether they represent separate but similar substances.
sensitizing the heart (18) and perhaps other target organs to the effects of other toxic factors and by aiding in the formation of at least one toxic factor (15, 18). However, lysosomal hydrolases exert little hemodynamic effect acutely in an animal with a normal reticuloendothelial system (18, 22), partially because of the rapid clearance of the enzymes by this system (18). Specific inhibitors of lysosomal enzymes would be useful agents to clarify the role of these enzymes in shock and to determine whether they have a direct toxic action.

Hemochromogen is formed as a consequence of denaturation of hemoglobin liberated during the hemolysis that frequently occurs in shock (26). This abnormal pigment is presumably absorbed across the necrotic mucosal surface of the intestine during shock (26). This hemorrhagic necrosis is a phenomenon that is not generally considered to occur in all species and appears to be a peculiarity of the dog. The one shock patient in which hemochromogen was found had intestinal bleeding from multiple foci (27) so that intestinal absorption of hemochromogen was facilitated and hence resulted in increased concentrations of this substance. It should be determined whether hemochromogen can be absorbed in the cat or the primate when frank intestinal necrosis does not occur during shock or in clinical shock when the complications of intestinal bleeding do not occur. Furthermore, although injection of a large amount of hemochromogen can cause hypotension (24), it is not clear how this dose (i.e., 0.015 mM/kg body weight) relates to the amount actually present in the plasma of animals in shock. Moreover, the directness of this effect and its actual toxic mechanism are completely unknown.

Endotoxin has been proposed by Fine and co-workers (29-32) as the primary shock factor in several types of shock. These workers have presented considerable data to show that there is absorption of live gram-negative bacteria or their endotoxin or both via the intestine during shock and that endotoxin induces toxic effects in animals in shock. One of the problems with verifying this hypothesis has been the detection of endotoxin in the plasma of animals in shock. Recently, Fine and co-workers (32) have demonstrated endotoxin-positive material in the plasma of animals in shock induced by splanchnic artery occlusion and in man with a variety of septic and nonseptic disorders (66). However, others have not been able to find endotoxin in the blood of animals in shock (68). Moreover, no data are presently available showing actual endotoxin titers in normal control nonseptic patients. The concentration of endotoxin detected in peripheral plasma by the assay technique must eventually be related to the concentration required to produce shock in animals before this work can be evaluated. Furthermore, the endotoxin hypothesis has been challenged on a number of other points: (a) the finding that chronic administration of nonabsorbable antibiotics, which should eliminate the organisms that produce endotoxin, either failed to stop a bacteremia (33) or did not prevent the ultimate lethality of shock (34, 38), (b) animals rendered "bacteria-free" developed shock similar to that in ordinary animals (34), (c) no endotoxin was found in hepatic portal venous blood of animals in lethal shock induced by splanchnic artery occlusion, although a toxic factor was present in the blood (68), (d) endotoxemia per se did not necessarily sensitize animals to other forms of shock (35), and (e) extracts of spleen from normal animals, which are supposed to detoxify circulating endotoxin in animals in shock (69), actually were toxic themselves due to their high endogenous lysosomal enzyme content (18). Endotoxin does not appear to exert a direct toxic action on the circulatory system but may release vasoactive agents which alter circulatory function. Finally, the mechanism of absorption of endotoxin from the damaged intestine to the peritoneal space and then to the blood (70) is not completely clear at present. Until all these questions are satisfactorily answered, there will be reservations about endotoxin as a primary toxic factor in shock.

RDS is another toxic factor in shock which is identifiable with a serious deleterious effect. The depression of the reticuloendothelial system is well documented in a variety of forms of shock (37, 71), and this event represents a serious challenge to the survival of the animal. Although the exact chemical structure of RDS is unknown, it is a small molecule and therefore is less likely to release other factors or be hydrolyzed into smaller active agents in the blood than are the larger toxic factors. The major problem with evaluating the role of RDS is the differentiation of other conditions which may depress the reticuloendothelial system in shock (e.g., depletion of plasma opsonins and ischemia of the liver) from the RDS effect. In this regard, Saba (72) and Schildt and Bouveng (73) have called attention to plasma proteins and other substances which promote phagocytosis, and they claim that the opsonins decrease during shock. These workers...
suggest that this decrease may mislead one to presume the presence of RDS. However, these studies were done only on rats and mice, and RDS may still be important in higher mammals. Also, the possibility exists that RDS may actually act to deplete the opsonins in the blood. Clarification of these points would enable a more direct evaluation of the significance of RDS in shock.

MDF has been found in a variety of shock states by various groups including those of Lefer and Glenn (14-18, 28, 44, 45, 47, 50, 52-56), Ledingham (46), Shires (51), and Williams (48, 49). A large body of information concerning its chemical properties, mechanism of formation, origin in the body, biological actions, and methods of prevention has been collected. MDF appears to be a small peptide (47, 52, 53) which originates in the ischemic pancreas (15, 23, 47) largely due to the hydrolytic actions of lysosomal (14, 15, 18, 50) and perhaps zymogenic proteases (50). It exerts a prominent negative inotropic effect in isolated heart tissue (43, 54, 55) and in the whole animal (15). In addition, it constricts the resistance vessels of the splanchnic region (56) and perhaps depresses the reticuloendothelial system (42). These latter two effects would tend to set up positive feedback loops by further enhancing MDF production (i.e., splanchnic vasoconstriction) and preventing the clearance of MDF from the plasma (i.e., reticuloendothelial depression).

MDF cannot explain the entire picture observed in shock and is not the only shock factor; however, it appears to have considerable merit as a toxic substance. One question which arises regarding MDF is whether cardiac depression occurs in the absence of MDF due to direct ischemia of the myocardium or to other cardiotoxic substances. Although the data are by no means complete, it appears that the coronary circulation usually exhibits adequate autoregulation during shock to protect the heart from direct ischemic damage except at extremely low blood pressures. The fact that cardiac lysosomes are relatively well preserved in the late stages of hemorrhagic shock is consistent with this concept (15). Moreover, no other agent that acts as a potent cardiodepressant appears in the plasma of animals in shock.

Urschel et al. (74) failed to find a myocardial depressant factor in the plasma of dogs in hemorrhagic shock, but they may not have waited long enough, since their dogs had not developed any significant myocardial depression. A similar situation recently occurred in endotoxic shock. Thus, Hinshaw and co-workers (75) reported that there was no evidence of cardiac depression 3 hours after endotoxic shock in dogs. However, these workers (76) found marked evidence of cardiac impairment and even cardiac failure 6-9 hours after administration of endotoxin. This latter time is consistent with the work of Wangensteen et al. (16), who reported the appearance of a plasma myocardial depressant factor 7 hours after the onset of endotoxic shock. Therefore, it appears that in the early stages of shock cardiac performance is relatively stable and that plasma MDF has not yet accumulated to high levels. However, as shock progresses, MDF accumulates and cardiac impairment ensues. The concept of a gradual cardiac impairment becoming important in the late stages of shock has been well documented by Crowell and Guyton (77) and by Gomez and Hamilton (7).

Not enough information is presently available on the factors of Fukuda (58, 59), Thal (60, 61), or Clowes (62-64) to accurately assess their overall significance in shock or to determine whether any of these factors are identical with any of the more well-established factors. Nevertheless, the fact that two of these factors adversely affect the lung is of great significance, since recent developments indicate that pulmonary damage may be important in shock (75).

There are many interesting similarities among the various shock factors. Figure 1 summarizes the origin, the route of transport, and the sites of action of the shock factors discussed in this review. All of the shock factors listed appear to originate in the splanchnic region: endotoxin, hemochromogen, and RDS from the intestine, MDF from the pancreas, Fukuda's factor from the liver, lysosomal enzymes from throughout the splanchnic region but primarily from the liver and the pancreas, and Clowe's and Thal's factors from somewhere in the splanchnic region.

Several of the shock factors are transported to the systemic circulation from their site of origin primarily through the lymphatic system, particularly the high molecular weight factors (i.e., endotoxin and lysosomal enzymes). In addition, MDF appears to be in part transported via the lymphatics, which may indicate that at some stage in its formation it is bound to a larger molecule. The other low molecular weight factors (i.e., RDS and Clowe's factor) are probably directly taken up by the microcirculation in the region in which they are formed.
In the cases of hemochromogen and Fukuda's factor, the routes of transport are not clear, although some of the hemochromogen is absorbed via the damaged intestinal mucosa or via mucosal capillaries into the systemic circulation.

Once transported to the systemic circulation, either directly or via the lymphatic system, the factors are then rapidly and easily delivered to virtually all the peripheral tissues. However, it is not known to what extent any of these factors can penetrate the blood-brain barrier. Figure 1 also shows that, despite the similar origin of the shock factors, there is a diversity in the target organs on which the shock factors exert deleterious effects. Thus, MDF and to a lesser degree lysosomal enzymes have a cardiodepressant action, ThaTs and Clowes's factors primarily exert a damaging effect on the lungs, RDS acts on the fixed macrophages of the reticuloendothelial system (i.e., in the liver and perhaps in the spleen), and lysosomal hydrolases (and perhaps endotoxin) appear to exert a damaging effect on the splanchnic vasculature. However, the precise target organs of Fukuda's factor and to some extent endotoxin are not clearly established at the present time.

The target organs which are known to be adversely affected by shock factors are clearly among the more vital organs (i.e., heart, lungs, peripheral vasculature, and reticuloendothelial system) and are obviously necessary for the continuing functioning of the organism. Perhaps the brain may be spared because of its unique situation (i.e., the blood-brain barrier), although there is no evidence that the brain is in fact free of humorally induced effects.
HUMORAL FACTORS IN CIRCULATORY SHOCK

It appears that an appropriate therapeutic management of circulatory shock should involve prevention of the splanchnic ischemia which engenders toxic factors as well as the specific antagonism of the pathological actions of these humoral factors. A comprehensive regimen such as this has not been adequately tested, and thus an important application of basic laboratory knowledge to an important clinical problem remains to be achieved.

References


50. LEFER, A.M., AND GLENN, T.M.: Role of the pancreas in the pathogenesis of circulatory shock. In Fundamen-


