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THE PATHOLOGY OF SECONDARY SHOCK*

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The term *secondary shock* is used here to imply a distinction from the uncomplicated effects of hemorrhage—*hemorrhagic shock*—and from *primary shock*. Hemorrhage is an obvious cause for low blood pressure and circulatory deficiency after injuries. Although the clinical signs are similar, the accompanying physiologic changes and the post-mortem findings after death from uncomplicated hemorrhage differ in several ways from those of secondary shock.[1]

Primary or "neurogenic shock" (Blalock [2]) is a neurovascular reaction like syncope or fainting. It may be excited by pain, emotional reactions, or perhaps by nerve impulses arising in damaged tissues (Phemister [3]). Primary shock develops promptly and usually is transient unless accompanied by extensive injury or hemorrhage; then it may merge into secondary shock with hemorrhage as a contributory factor. Combinations of neurogenic, hemorrhagic, and secondary shock in the same patient have caused confusion.[4] When the term shock is used without qualification in the succeeding pages, it will be understood to mean secondary shock, sometimes called collapse or peripheral circulatory failure.

DYNAMICS OF SHOCK: RESUMÉ

Shock from wounds was a major problem during World War I. An investigation by eminent physiologists, pharmacologists, internists, and surgeons compared observations on wounded men with data from experimental studies. The results were summarized [5] as follows:

"The theory of secondary shock which has the strongest support, both in clinical observations and in laboratory experiments, is that of a toxic factor, arising from damaged and dying tissue and operating to cause an increased permeability of the capillary walls and a consequent reduction of blood volume by escape of plasma into the lymph spaces. Thus the concentration of the corpuscles is also readily explained. It is recognized that after a sufficient time infection may occur and be

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of such character in itself as to induce a persistent low blood pressure. According to this theory there might be no essential difference between the effects of toxins given off by damaged tissue and of toxins resulting from activity of bacteria."

Later investigations by many workers indicated the importance of hemorrhage and loss of blood and fluid in traumatized regions. No evidence of toxic substances in the blood was found by the methods then in use. Many believed that all of the phenomena of shock could be explained by local loss of blood and fluid.

The first published report on the pathology of shock [6] indicated that hyperemia and edema of viscera, petechial hemorrhages, serous effusions, and acute degeneration of parenchymatous tissues are pathologic changes characteristic of this condition. These changes in visceral areas, remote from the region of trauma, indicated the effects of factors other than loss of blood and fluid. Our subsequent investigations indicated that the syndrome of shock occurs also after burns, poisoning, severe infections, and intestinal obstruction. The same pattern of visceral changes was seen in men and animals after death from these conditions.

The dynamics of shock was interpreted in accordance with the principles of capillary physiology (Krogh,[7] Landis,[8] Lewis [9]). Various agents and conditions injurious to endothelium produce atony and dilatation of capillaries and venules. This increases the volume capacity of the vascular bed. Endothelium, when affected by such agents, including anoxia, becomes abnormally pervious to colloids. This allows plasma to escape into the tissue spaces, causing edema and a tendency to hemoconcentration. The loss of plasma lowers the *total* blood volume, and the stagnation of blood in dilated vessels lowers the *effective* blood volume. This leads to a disparity between the volume of blood and volume capacity of the vascular bed, and diminishes the return flow of venous blood to the heart. These effects produce a circulatory deficiency characterized by decreased blood volume and volume-flow of blood, reducing the amount of oxygen delivered to the tissues. Tissue anoxia *per se* causes capillary permeability [8] and thus introduces a self-perpetuating factor which causes the circulatory deficiency to increase progressively. This vicious circle, unless interrupted, leads to an irreversible stage and to death. It appears that capillary permeability and anoxia have reciprocal effects; either of them presently brings the other into action. Abnormal permeability of endothelium deranges fluid balance. A tendency to visceral edema, hemoconcentration, and to stasis results.

Subsequent investigations indicated the presence of some substance, absorbed from areas of tissue injury, which produces vasodepressor

effects. Best and Solandt,[10] by an exchange transfusion of blood between traumatized and normal dogs, produced circulatory deficiency in the untraumatized animals. Kendrick, Essex, and Helmholz [11] reported similar results from transfusion by a different technic. Freeman, Cullen, and Schecter [12] produced shock by trauma to limbs which had been taped to prevent excessive loss of blood and fluid locally. They found evidence of a toxic factor absorbed from the traumatized region. Similar results were obtained by others when shock was induced by tourniquet and by freezing.

Blalock [13] produced massive pressure on the muscles of the limbs, simulating the "crush syndrome." Lymph from the thoracic duct, injected into other dogs, caused hemoconcentration and a decline in blood pressure. He believed toxic substances, arising in the injured extremity, had entered the lymph vessels. Experimental crush injury [14] caused hemoconcentration and a fall in blood pressure, accompanied, in some instances, by hematuria and retention of nitrogenous wastes in the blood. Katzenstein, Mylon, and Winternitz [15] found that lymph from the thoracic duct during tourniquet shock caused a protracted fall in blood pressure, often ending fatally, when injected intravenously into other dogs.

Aub and associates [16] showed that bacterial contamination of injured muscles produced toxic substances in the lymph collected from those muscles. Prinzmetal, Freed, and Kruger [17] induced shock by excising and grinding muscle tissue aseptically, then implanting this pulp into the bed from which the muscle was excised. This caused death usually within 24 hours. They believed that shock-producing substances, resulting largely from bacterial contamination, were absorbed from the crushed muscle. It is recalled that all open traumatic wounds are grossly contaminated, and that bacterial growth proceeds rapidly in crushed devitalized tissues.

Summarizing the problems of shock, Blalock [18] found general agreement that traumatic shock is due to regional loss of blood, toxemia, or nerve impulses, separately or in combination. He stated that the search for and identification of the toxic factor or factors is the problem of first importance. Among other problems in the pathogenesis of shock, he listed that of determining the rôle of infection superimposed upon injury.

Shorr, Zweifach, and Furchgott [19] made tests for vasodepressor and vaso-excitor substances in blood and fluids from injured and from anoxic tissues. Their results led to the conclusion that the development of shock is due to vascular atony resulting from a preponderance of vaso-

depressor effects, and that anoxia is a factor causing the circulatory deficiency to progress in a "morbid cycle" to an irreversible stage. Heilbrunn and co-workers [20] demonstrated that water extracts of muscle and of tissues from heat-killed animals contained some dialyzable toxic substances which caused death when injected into other animals. Before death these animals showed symptoms like those of heat-treated (scalded or burned) animals.

Recent contributions, as noted above, support the explanation of *traumatic toxemia,* but with important modifications and additions:

(1) It has been demonstrated that, in traumatic or surgical shock, local loss of blood and fluid plays a rôle not recognized formerly. The importance of this factor is in direct proportion to the volume of blood and/or fluid lost. In some instances this is so great as to make it the dominant factor. In other cases it may be minor.

(2) Anoxia is highly important in the vicious circle by which shock tends to progress to an irreversible stage. The anoxia may be *anoxic* as in asphyxia, or *anemic* as when the red corpuscles have been reduced below physiologic limits by hemorrhage or otherwise, or *stagnant* as by circulatory stasis, or *toxic* as from the effects of poisons upon the tissue cells (Blalock [2]). In any instance, anoxia tends to cause atony and permeability of capillary walls resulting in progressive circulatory deficiency and death. Anoxia is the factor which ultimately "stops the machine and wrecks the machinery."

(3) Comprehension of the mechanism of shock has led to the recognition of the same syndrome in conditions other than trauma, extensive surgery, and burns. Atchley [21] cited instances in patients with severe infection, diabetic acidosis, Addison's disease, bile peritonitis, vaccine reactions, heat prostration, and snake bites. These conditions led to stasis of blood in the capillaries, generalized anoxemia, capillary dilatation, and leakage of plasma into the tissues, operating in a vicious circle. Harkins [22] stated that shock may occur in association with a wide variety of conditions: hemorrhage; mechanical or operative trauma; burning; freezing; heat stroke; radiation burns; sunburn; asphyxia; vascular occlusion; intestinal strangulation; application of tourniquet; bile peritonitis; perforated gastric ulcer; pancreatitis; various poisons such as $HgCl_2$, arsenic, gold chloride, snake venoms; special capillary poisons such as products of tissue autolysis, histamine, peptone; medical conditions such as an anaphylaxis, diabetic coma, eclampsia; severe infections such as cholera, streptococcal and influenzal pneumonia, gas gangrene, diphtheria, peritonitis; and various anesthetic agents.

A condensed summary on the mechanism and associated features was issued by the Subcommittee on Shock [23] of the National Research Council. It set forth that the outstanding physiologic feature is peripheral circulatory failure caused by a discrepancy between the capacity of the vascular system and the volume of fluid which it contains. Shock was defined as the *clinical condition characterized by progressive reduction in circulating blood volume due to increased capillary permeability.* Any agency which affects the permeability of the vessels allowing the escape of plasma proteins, may lead to shock. This is accompanied by a progressive reduction of circulating blood volume due to the escape of plasma. Anoxia is a factor of prime importance causing capillary permeability and impaired circulation. This summary closed with a brief statement on associated tissue changes:

"The pathologic picture which is found when the tissues are examined after death from shock is that to be expected from peripheral circulatory failure. There is widespread congestion and engorgement of the capillaries and venules throughout the body . . . . This congestion is found throughout the viscera and in the lungs. There is edema in the tissue spaces and effusion in the serous cavities . . . . The impairment of circulation affects other organs as well. Necrosis of liver cells, liquefaction of the suprarenal medulla, and congestion of the pancreas are observed. The kidneys show evidence of parenchymatous degeneration. Patches of capillary hemorrhage occur in the medulla, and numerous red cells are found within the tubules in such regions. The pathologic picture thus confirms the clinical and experimental evidence on the significance of increased capillary permeability as the essential feature of shock."

The preceding data indicate that divergent views have been adjusted concerning the major factors in the dynamics of shock. Investigations on other features can now go forward relatively undisturbed by controversial discussions.

Material and Methods

The purpose of this survey is to secure information on the occurrence of shock from causes other than trauma, to collect additional data on associated pathologic changes, and to record evidence of physiologic disturbances, especially the renal effects.

The Director of the Army Institute of Pathology provided opportunity to study the material collected there. The clinical and postmortem records, histologic preparations, and the entire facilities of the Institute were made available for a survey on the pathology of shock as seen in the personnel of the U. S. Army. Thousands of records of death from all causes presented an abundance of material for study. To tabulate the data from all of these was an undertaking of staggering proportions, for which time was not available. Accordingly, the statistical approach was abandoned in favor of detailed studies of representative cases appropriately grouped. In every instance the

clinical and post-mortem data were taken directly from the records, but the microscopic studies were made by me.

TRAUMA

Under the heading of trauma are grouped those instances in which fatal circulatory deficiency resulted from traumatic or surgical injuries. The causative mechanism in such cases includes trauma, hemorrhage, infection (all battle wounds are grossly contaminated), and sometimes anesthesia, surgery, reaction to transfusions, renal complications and other contributory conditions. It is manifestly impossible to evaluate the relative weight of these several factors in any given case. The causation of shock in this group is more complex than in the succeeding groups.

Thirty cases of shock resulting from trauma and associated conditions were studied. They presented different degrees of severity as indicated by the interval between injury and death, ranging from a few hours to 6 days. These features are indicated briefly in the list which follows:

A.I.P. Accession Number	*Origin*
84837	Abdomen hit by the recoil of a 90 mm. gun. Death 8 hours later.
122323	Death during surgical operation for G.S.W.* received weeks before.
122486	Death during surgical operation for multiple G.S.W.
128121	S.F.W.* of thighs, compound fracture, transfusion reaction, anuria.
126488	G.S.W. of legs and feet, compound fracture. Death 24 hours later.
122293	G.S.W. of thigh, fractured femur. Death 24 hours later.
86750	G.S.W. of body, fractures. Death 24 hours later.
114945	G.S.W., multiple fractures. Death 30 hours later.
88192	Automobile accident, multiple fractures, gas gangrene. Death 34 hours later.
86134	Fall from fourth story window, compound fractures. Death 36 hours later.
97750	Automobile accident, fractures, internal injuries. Death 48 hours later.
118315	S.F.W. of thighs, pulmonary edema. Death 48 hours later.
118316	G.S.W. of leg and thigh, fractures. Death 48 hours later.
127136	S.F.W. of legs and feet, compound fracture, anuria. Death 48 hours later.
84641	Automobile accident, internal injuries, anuria, high nonprotein nitrogen. Death 53 hours later.
85677	Automobile accident, fractures of femurs, mandibles, ribs. Death 3 days later.
126438	G.S.W. of arm, fractures, gas gangrene, amputation. Death 3 days later.
127580	S.F.W. of buttocks, pulmonary edema, anuria. Death 3 days later.
102060	Resection of rectal carcinoma, oliguria, uremia. Death 4 days later.
119159	Automobile accident, compound fracture of pelvis. Death 4 days later.

* G.S.W. and S.F.W. indicate gunshot wounds and shell fragment wounds, respectively.

122144 S.F.W., comminuted fractures of legs and arms, gas gangrene, oliguria. Death 4 days later.
113425 Ileitis, surgical resection, anuria, high nonprotein nitrogen. Death 5 days later.
118404 S.F.W. of thighs and leg, compound fractures, anuria, high nonprotein nitrogen. Death 5 days later.
121439 G.S.W., transfusion reaction, anuria. Death 5 days later.
118313 G.S.W. of legs, transfusion (reaction?), high nonprotein nitrogen. Death 6 days later.
121411 S.F.W. of legs, comminuted fractures, shock developed 6 days later.
128117 S.F.W., multiple fractures, anuria, uremia. Death 6 days later.
126031 S.F.W., gas gangrene, amputation. Death 6 days after receipt of wound.
127269 G.S.W. of leg, ischemic gangrene. Death 6 days later.
118359 S.F.W. of buttocks and legs, fractures, gas gangrene, amputation. Death 10 days after receipt of wound.

Pathologic Conditions

Pulmonary hyperemia and edema were found regularly in all cases. In most instances these were marked; they were slight or moderate in only 6. Serous effusions were present in 21. Petechiae were noted at necropsy or found microscopically in 15. The development of pneumonia in shock with delayed death has been reported.[24] In 20 cases death occurred 48 hours or longer after the injury; terminal pneumonia was present in 12 of these, either incipient or well advanced (Figs. 1 and 10).

Some degree of atelectasis was present in 13 cases. In some this was noted grossly at necropsy; in others it was seen in varying degrees microscopically, as small scattered areas. This feature has not been reported hitherto as associated with shock. Its significance and mechanism of origin are not apparent.

Parenchymatous degeneration ranging to necrosis was a regular feature, especially in the kidneys, liver, and heart. In 20 cases, marked parenchymatous degeneration was present in the kidneys; in 12 of these, necrosis of tubular epithelium also was present; in 6 cases the degeneration was moderate or slight. In the remaining 2 instances, post-mortem changes made the recognition of degeneration uncertain. Casts were present in the tubular lumina in 19 instances; these were hyaline, granular, cellular, or mixed; in a few instances the casts contained brown pigment. In all instances the renal parenchyma was moderately or markedly hyperemic; minute hemorrhages were seen frequently, and red cells were often found in the tubular lumina (Figs. 4 and 5).

In 26 cases, parenchymatous degeneration of hepatic cells was marked; in 22 there was also necrosis. This varied from occasional scattered cells, focal necrosis, to extensive areas usually in the central

part of the lobules (Fig. 3). Degenerative changes of heart muscle fibers, ranging from slight to marked, were present in 21 instances. In a few cases foci of necrosis were present in lymphoid tissue and in the adrenals (Fig. 2). Splenic engorgement was noted in 13 instances.

In these cases, shock resulted not from a single causative agent but from a combination of causes: the delayed effects of tissue injury, hemorrhage, infection, and, in some instances, anesthesia, surgery, and unfavorable reaction to transfusion. The relative importance of these factors varied from case to case.

Hemorrhage and local loss of blood had occurred in many cases. That hemorrhage was not the sole factor was suggested by the facts: (1) that restoration of blood volume by fluids, plasma, and transfusion did not restore circulatory efficiency; (2) that in some instances a high red blood cell count indicated that some mechanism had disturbed fluid balance and had prevented the dilution of blood which normally follows hemorrhage; (3) that marked visceral congestion, edema, effusions, and petechiae indicated the effects of some other agency. These findings are not characteristic of death from uncomplicated hemorrhage.

In some instances infection was not apparent from the clinical or post-mortem data, while in battle wounds, some complicated by gas gangrene, infection was a prominent contributory factor. The visceral findings in these were like those seen throughout the group. There is evidence that products of bacterial growth may cause capillary permeability. Examinations of the blood, when recorded, showed varying degrees of hemodilution; in only 3 instances was there hemoconcentration. However, most cases had received fluid intravenously which would, of course, counteract hemoconcentration. In some, the large amounts of fluid given were more, perhaps, than a failing circulation could retain. Some degree of capillary permeability is a central feature in shock; such capillaries will allow saline fluids to escape rapidly, thus increasing the edema.

The circulatory disturbances which lead to shock may develop in varying degrees and with varying rapidity. Maximal degrees may cause death from failure of the circulation within 24 hours regardless of therapeutic measures. With lesser degrees the patient may respond favorably and recover; in others, a condition of sublethal shock persists for several days. In such cases, either renal insufficiency or terminal pneumonia may be expected to complicate the condition.

Oliguria or anuria is present early and continues as shock progresses (Atchley,[25] Freeman,[23] Blalock[2]). This often leads to uremia if the subject survives for a few days.[26] Renal deficiency and retention of nitrogenous wastes were present in 8 cases of this group and 3 of these followed transfusion reactions. A cause for renal insufficiency is suggested in the marked degeneration and necrosis of the tubular epithelium.

Transfusion reactions vary widely in degree. The severest reactions cause death from progressive circulatory collapse, sometimes resembling fatal anaphylactic shock (Best and Taylor,[27] Bordley,[28] Wiener[29]). Renal deficiency develops following severe nonfatal reactions and death may occur from uremia, as in cases 121439, 127136, and 128121. In these the visceral findings were the same as in delayed death after shock from other causes. Degenerative changes and necrosis of renal tubular epithelium were marked, as in other instances of uremia associated with shock.

Traumatic shock results from a combination of causes, the relative importance of which varies in different cases. The causative factors in subsequent groups do not include so many variables, hence an analysis of the mechanism will be less involved. Early death from traumatic shock results from circulatory failure. Death after 48 hours often is the result of a combination of circulatory deficiency with renal deficiency and terminal pneumonia.

Burns

Patients with extensive burns of the skin often present the complete picture of secondary shock. Harkins'[30] survey indicated that shock is the cause of death in 60 to 75 per cent of fatalities from burns. Examination of data from numerous cases indicated that they confirm what is already recorded in medical literature concerning the clinical course and the post-mortem findings after death from burns. Ten representative cases were studied for comparison with the findings in shock from other causes. Also 3 instances of burns made by phosphorus upon the skin or blown into the flesh were studied. In these, absorption introduced a possible factor of phosphorus poisoning.

A.I.P. Accession Number	*Conditions*
87628	Extensive 2nd and 3rd degree burns. Death 12 hours later.
122578	Extensive 2nd and 3rd degree burns, about 40 per cent of skin. Death 12 hours later.
125364	Extensive 2nd and 3rd degree burns. Death 15 hours later.

125903	Extensive 2nd and 3rd degree burns. Death 24 hours later.
107676	Extensive 3rd degree burns, high nonprotein nitrogen. Death 28 hours later.
86891	Fractures, 2nd and 3rd degree burns. Death 26 hours later.
127272	Extensive 2nd and 3rd degree burns. Death 48 hours later.
122679	Burns of entire body, anuria. Death 3 days later.
90393	Extensive severe burns, anuria. Death 4 days later.
118506	Extensive 2nd and 3rd degree burns, high nonprotein nitrogen. Death 8 days later.
114072	Phosphorus burns, 40 per cent of skin. Death 12 hours later.
93453	Phosphorus burns, 2nd and 3rd degree. Death 15 hours later.
106660	Phosphorus burns, 2nd and 3rd degree, anuria, high nonprotein nitrogen. Death 4 days later.

In every case the findings were like those of traumatic shock, but tended to be more severe. Pulmonary hyperemia and edema were marked (Fig. 6). Pleural effusions were noted in 7, and petechiae in 9 instances. Terminal pneumonia was present in the lungs of 3 men who lived longer than 2 days after burning. The degeneration and necrosis of renal tubular epithelium were marked; degeneration and necrosis of hepatic cells were extensive (Fig. 9). In 10 instances the adrenal cortices were degenerated and abnormally vacuolated. In a few instances, post-mortem changes made the recognition of degeneration uncertain. Myocardial degeneration was seen in 12 of the 13 cases. Casts were found in renal tubules in 7 instances. In one of these the casts contained quantities of brown pigment; no transfusion or sulfonamide therapy had been given in this case (Figs. 8 and 9).

Some writers disregard the systemic effects of burns and attribute depleted blood volume and hemoconcentration to local loss of fluid in and about the burned areas. The importance of such loss is unquestionable; its effects are proportional to the amount of fluid lost. But loss of fluid locally does not account for the intense hyperemia, edema, acute degeneration and necrosis occurring in visceral areas remote from the burn. These indicate widespread and serious *systemic* effects. No treatise on burns will be complete unless it provides an acceptable explanation for the systemic as well as the local effects.

It has been suggested that degeneration and necrosis may result from the absorption of tannic acid, sulfonamides, or other drugs applied to the burns. It should be remembered that visceral hyperemia, edema, and degeneration and necrosis of hepatic and renal cells were set forth as characteristic features long before such local treatments were practiced (Bardeen,[31] Pack [32]). Significant evidence has accumulated indicating the systemic effects of toxic products absorbed from the burned tissue itself, and no evidence incompatible with this interpretation has been shown.

Poisoning

It has been observed that acute poisoning often is accompanied by signs of shock. These include weakness, perspiration, vomiting, rapid pulse, low blood pressure, and oliguria. Hemoconcentration usually accompanies this syndrome.[83] Often the visceral changes, including hyperemia, parenchymatous degeneration, edema, and petechial hemorrhages, are like those already described. These effects result from various poisons, hence they are not the specific effect of some particular drug or chemical. It is of interest to compare the changes seen in the viscera after death by poisoning with those seen after shock from trauma and from burns. Data and post-mortem evidence from 20 cases of poisoning were studied.

A.I.P. Accession Number	*Conditions*
89731	Shock reaction, delayed 3 days after neoarsphenamine. Death 24 hours later.
111925	Immediate reaction to mapharsen, oliguria, high nonprotein nitrogen, hemoconcentration, uremia. Death 7 days later.
120574	Arsenic poisoning, oliguria, high nonprotein nitrogen, hemoconcentration. Death 36 hours later.
128449	Suicide by arsenic, shock. Death same day.
129165	Suicide by arsenic, shock, hemoconcentration. Death 28 hours later.
60482	Mercuric poisoning, anuria, hemoconcentration. Death 2 days later.
66984	Suicidal mercuric poisoning, anuria, high nonprotein nitrogen. Death 8 days later.
98365	Mercuric poisoning, shock, hemoconcentration. Death 24 hours later.
72500	Suicide, rat poison (phosphorus). Death 7 days later.
85342	Suicide, rat poison (phosphorus). Death 9 hours later.
98461	Suicide, rat poison (phosphorus), shock. Death 5 days later.
103527	Overdose of barbiturate. Death 24 hours later.
106299	Found dead, barbiturate poisoning.
106544	Seconal poisoning, shock, found unconscious.
108088	Found dead, barbiturate poisoning.
116989	Suicide by barbiturate. Death 2 days later.
113935	Alcoholism and barbiturate poisoning. Death 48 hours later.
128452	Suicide by barbiturate poisoning, shown by chemical analysis.
128656	Barbiturate poisoning, shown by chemical analysis.
128611	Protracted drinking bout, acute alcoholism.

Pulmonary hyperemia and edema were present in marked degree in 13; in 6 they were slight or moderate; and in one, suicide by arsenic, they were absent. Atelectasis was seen in 4 instances. Terminal pneumonia was found in 4 of the 7 men who lived 48 hours or longer. Petechial hemorrhages were recorded in 12, serous effusions in only 4. Degeneration and necrosis of renal tubular epithelium were found regularly, regardless of the type of poisoning. Necrosis was more marked after poisoning with arsenicals, mercury, and phosphorus than

after barbiturate poisoning; also, fewer casts were found in the tubules in the latter. Likewise degeneration and necrosis of hepatic cells were regularly present, but were less marked after barbiturate poisoning. Myocardial degeneration was seen in 13 cases; in 7 cases no histologic section of heart muscle was saved. Splenic engorgement was present in 13 cases.

Traumatic shock results from the combined effects of several causative and contributory conditions, hence the difficulty of accurate analysis, but shock from the effect of poisons is less complicated since the contributory factors are few. There is no possibility of nerve impulses from wounded tissues, of hemorrhage or leakage of plasma locally, of infection, anesthesia, or reaction to transfusion of blood or plasma. These indeterminate variables have been eliminated from the equation, making analysis relatively simple.

Students of capillary reactions [7, 9, 34] have shown that various drugs and chemicals, sometimes called "capillary poisons," may cause atony, dilatation, and increased permeability of capillary endothelium. Any kind of injury to capillaries increases the permeability of their walls.[9] These considerations indicate that various poisons may produce shock by their direct effects upon capillary endothelium. This interpretation is supported by the visceral findings; the capillovenous hyperemia, edema, serous effusions, and petechiae indicate atony, dilatation, and abnormal permeability of the walls of the minute vessels. Such changes did not vary in kind or degree with the various types of poison. The renal effects of poisons, especially mercurials and arsenicals, are well known. These are considered in a later section.

Infections

Internists have observed that severe fulminating infection may cause progressive circulatory failure like that of shock from other causes. This effect does not depend upon the bacterial species, but upon the virulence in the individual case. Ten cases of severe infection, as listed below, were studied.

A.I.P. Accession Number	*Conditions*
118865	Fulminating meningitis. Death 12 hours later.
93449	Fulminating meningitis. Death 12 hours later.
106479	Fulminating meningitis. Death 24 hours later.
128538	Fulminating meningitis. Death 24 hours later.
108004	Mixed streptococcal and staphylococcal meningitis.
101617	Septicemia (organism not stated). Death 6 hours later.
108955	Streptococcal septicemia. Death 7.5 hours later.

102147	Influenza. Death 48 hours later.
111409	Severe infection (tularemia?), anuria, high nonprotein nitrogen, "uremic frost." Death 12 days later.
125907	Falciparum malaria, anuria, high nonprotein nitrogen. Death 9 days later.

The pathologic findings in each of these cases presented the same degeneration ranging to necrosis, as seen in shock from trauma, burns, and from poisons. Pulmonary hyperemia and edema were intense in 9 cases, moderate in one (93449). Petechiae were present in 9 and absent in one (111409). Hepatic, renal, and cardiac degeneration and necrosis were marked in all cases. Two of the 4 cases of fulminant meningitis—Waterhouse-Friderichsen syndrome—had extensive adrenal hemorrhages. In one case these were absent and in one no observations on the adrenals were recorded and sections of them were lacking.

Two patients, cases 125907 and 111409, died of uremia on the 9th and 12th days, respectively. In one, terminal pneumonia also was present. Each showed extensive degeneration and necrosis of renal tubular epithelium, casts, and débris in the tubular lumina. Similar renal findings were present in the patient with influenza dying in 48 hours.

The occurrence of circulatory collapse is not unusual in diphtheria, septicemia, meningitis, gas gangrene, cholera, plague, yellow fever, malaria, and in other acute infections. Its occurrence seems to depend on the severity or virulence of the infection. Dale [35] stated that the action of bacterial ferments upon proteins may give rise to cleavage products which will cause secondary shock. Atchley [21] believed that this results from paralysis of the capillaries by bacterial toxins. He cited an instance of pneumococcal vaccine given intravenously, resulting in shock. Brodie [36] found that small amounts of diphtheria toxin caused an immediate fall in blood pressure when given intravenously to animals. MacCallum [37] made similar observations. Harding [38] surveyed 800 cases of diphtheria and noted that circulatory failure, with hemoconcentration like that of wound shock, occurred in the toxemic stage. Influenza of fulminating severity produces progressive circulatory deficiency ending in death. Other instances might be cited.

Shock in severe infections, like that resulting from poisons, is relatively simple in its origin; trauma, hemorrhage, anesthesia, local loss of fluid and other complicating factors are not involved. Many believe that bacterial toxins, or products of bacterial metabolism in the tissues, affect endothelium like histamine or other capillary poisons. This

interpretation is supported by necropsy findings in such cases. These are not different in kind from those seen in shock from other causes.

It is recognized by internists that severe infections often cause deficient renal function. This occurrence is not limited to yellow fever and falciparum malaria but is seen with other infections. Two of the cases studied showed this feature. The gross and microscopic changes in the kidneys were like those accompanying renal failure in the other groups.

Anoxia

The importance of *anoxia* in the mechanism of secondary shock has been emphasized by many authors. It is believed to be a major factor in the vicious circle by which shock progresses to an irreversible stage. For this reason, findings after death from simple lack of oxygen, or from asphyxia, are of interest. A group of 15 such cases was studied.

A.I.P. Accession Number	*Conditions*
83172	Removed O_2 mask in low pressure chamber, equivalent altitude 36,500 ft.
108338	Removed O_2 mask in flight at 23,000 ft.
111237	O_2 line disconnected in flight at 27,000 ft.
114331	O_2 line disconnected in flight at 30,000 ft.
114333	O_2 line frozen in flight at 30,000 ft.
114342	O_2 line disconnected at 31,500 ft.
114334	O_2 line disconnected at 30,000 ft.
114356	O_2 tank empty at 26,000 ft.
114357	O_2 line frozen at 26,000 ft.
100788	Asphyxiated by CO.
128137	Asphyxiated by CO.
128450	Asphyxiated by CO.
129055	Asphyxiated by CO.
127170	Suffocation by fumes in burning building.
128153	Death by drowning.

Ten additional records of death by anoxia in aviation were reviewed. In these the necropsies were done 24 to 48 hours after death, hence observations on parenchymatous changes were unsatisfactory. The circulatory changes in these 10 were exactly like those given below, but figures from these are not included in the findings.

The visceral changes were like those in the preceding groups except that hyperemia was more intense and necrosis and edema were less marked. In each case there was intense hyperemia of the lungs, liver, and kidneys. Petechial hemorrhages were noted in the post-mortem records in each instance. Edema of the lungs was marked in 3, moderate in 8, and absent in 4 cases; serous effusions were not recorded in any instance. Parenchymatous degeneration of the liver and kidneys was marked in 8 cases, slight in one; in 6 instances, post-mortem

changes made the recognition uncertain. Myocardial degeneration was seen in only 7 instances. Some degree of necrosis of both hepatic and renal tubular cells was seen in 8 cases.

The time interval between the beginning of anoxia and the cessation of circulation is not known; however, it probably was short, perhaps 15 to 30 minutes. Perhaps this was insufficient time for the development of edema and effusions. The presence of severe parenchymatous degeneration and of beginning necrosis deserves comment. Since they developed in so short a time, it appears that renal and hepatic epithelium is delicately susceptible to anoxia, even of short duration. It is significant also that petechial hemorrhages were seen in every case.

The cause of death in this group was simple. Neither nerve impulses from traumatized tissues, hemorrhages, local loss of fluid, poisonous substances, bacterial toxins, nor products of tissue autolysis were possible factors. Yet the visceral changes were of the same pattern as when one or more of the factors just mentioned were operative. Anoxia appears to be the one common factor in the mechanism of secondary shock from diverse causes. Perhaps it is the most important cause for petechial hemorrhages and for the parenchymatous changes found after death by shock.

When men succumbed to lack of oxygen in high altitude flight, the additional factor of low atmospheric pressure was introduced. The intense hyperemia, extreme dilatation of capillaries and venules, and the occurrence of numerous petechiae may be due in part to decreased extravascular (atmospheric) pressure. This would tend also to cause edema. Hyperemia, edema, and petechiae can be produced locally by applying a vacuum cup to a normal skin surface.

In the instances of death by drowning, nitrous oxide anesthesia, suffocation, and asphyxia by carbon monoxide, the anoxia was not accompanied by low atmospheric pressure. The same pattern of changes was present in these cases although the congestion and edema were less intense than when anoxia was combined with low atmospheric pressure.

Low Atmospheric Pressure

Aviation at high altitude often causes collapse resembling surgical shock even though abundant oxygen is supplied. "The most dangerous aspects of severe reactions resulting from exposure to lowered barometric pressure are the latent period of from 1 to 6 hours which frequently precede the manifest appearance of clinical shock; and the consequent resistance to treatment of what may be, at this point, a full-blown vicious circle of peripheral circulatory insufficiency, tissue anoxia, and marked hemocentration." [39] Chambers from which the air was ex-

hausted, to simulate atmospheric conditions at various altitudes, were used to test the ability of aviators to withstand the effects of low pressure; oxygen was supplied as in actual high altitude flight. Fatalities occasionally resulted even under most careful supervision of such tests. I had opportunity to study the data and to determine the pathologic findings in 5 such cases for comparison with those of shock from other causes.

A.I.P. Accession Number	*Conditions*
95412	72 minutes at 38,000 ft. Death 10 hours later.
100822	One hour at 30,000 ft. Death 24 hours later.
100893	Discomfort and pain at 38,000 ft. Death 47 hours later.
103767	Discomfort and pain at 38,000 ft. Death 17 hours later.
127451	20 minutes at 30,000 ft. Death 55 hours later.

Since little is known of the mechanism causing shock from low atmospheric pressure, such cases are of special interest. Accordingly, condensed clinical and pathologic data from 2 representative cases are given.

Case 100822

After 1 hour at 30,000 ft. and while ascending to 38,000 ft., the subject gave up the test because of severe "bends" and "chokes." When taken out of the chamber he was very weak and sweating profusely. He was given oxygen by inhalation, and was placed under observation. The blood pressure was 140/104 mm. Hg; pulse, 90; red blood cells, 5,400,000; leukocytes, 23,000; hematocrit, 60. Roentgenograms of the chest showed pulmonary edema, recorded as moderately severe. Four hours later he was restless and vomited twice. The pulse was 140; the blood pressure, 120/80, later declining to 90/0. Plasma given intravenously caused no increase in the blood pressure; oxygen was continued. The next day he was weaker, restless, and cyanotic. Death occurred about 24 hours after the test.

At post-mortem examination, 750 cc. of serous fluid was found in each pleural cavity. The lungs, weighing 850 and 742 gm., were congested and markedly edematous. The heart weighed 410 gm. and showed no visible abnormalities. The spleen weighed 220 gm. and the liver, 2395 gm., with no abnormal features. Petechial hemorrhages were seen in the gastric mucosa and marked hemorrhages in the lining of the jejunum and ileum. There was congestion of the meninges. The kidneys, weighing 200 and 180 gm., were congested.

Microscopic Examination. The lungs showed intense capillovenous hyperemia and edema. The myocardium was edematous and the fibers showed parenchymatous changes. The spleen was ischemic. The liver showed degeneration, marked fatty changes, and central necrosis. There was intense hyperemia of the gastrointestinal mucosa. The cortical cells of the adrenals were vacuolated. The brain and meninges were hyperemic and edematous. The renal cortex and the medulla were moderately hyperemic. The tubular epithelium showed degenerative

changes which seemed more advanced in the upper than in the lower segments.

Case 100893

At a relative altitude of 38,000 ft., the subject became pale, the respirations were increased, and he complained of muscular pain and weakness. The altitude was reduced gradually and the test was discontinued. The pulse was 60; the blood pressure, 100/60 mm. Hg. The heart sounds were normal, the breath sounds were decreased, and the skin moist. He seemed drowsy and unable to talk coherently.

When placed in the hospital, the pulse was 80; the blood pressure, 110/80. Four hours later he seemed worse, irrational, and was thrashing about. Plasma, saline solution, and oxygen were given, and his general condition improved. The hematocrit at this time was 56.1; the white cells, 20,000. Three hours later his condition became grave, the hematocrit was 64.9, no pulse could be obtained; he was sweating and apparently in profound shock. The extremities were cold but the rectal temperature was 107.6°F.; on recheck 10 minutes later, this was 108.4° F. He was packed in ice and given plasma and saline solution. On the following day the general condition seemed improved but still critical. He was restless and the breathing was labored. The blood pressure was 122/80; hematocrit, 55. He was given plasma and saline solution continuously. On x-ray examination the cardiac shadow was not enlarged, but the pulmonary markings were increased and interpreted as vascular stasis. On the next day the respirations were easier, the blood pressure more nearly normal, and the temperature lower. The hematocrit was 50; white cells, 13,500. The urine showed a specific gravity of 1.017; albumin, 4 plus. He was seized with convulsions, the circulation failed, and death occurred 45 hours after admission to the hospital.

Post-mortem examination revealed marked hyperemia and edema of the lungs. These were described as solid in the posterior portions. The liver and brain were congested. No other gross abnormalities were recorded.

Microscopic Examination. The lungs were intensely hyperemic and edematous. There were areas of atelectasis and capillary hemorrhages (Fig. 16). The myocardium was edematous and degenerated. The splenic pulp was deficient in red blood cells. The liver was hyperemic; the cells showed advanced parenchymatous degeneration ranging to necrosis (Fig. 17). The adrenal cortex was hyperemic; the cortical cells were vacuolated. The brain showed widespread autolysis and a few perivascular hemorrhages. The renal parenchyma was hyperemic. The tubular epithelium was flat and the lumina were wide. Albuminous material was present in the glomerular spaces. The collecting tubules contained *dark, pigmented casts,* granular casts, and erythrocytes. The stroma was edematous (Figs. 18 and 19).

In each of the 5 cases, the gross and microscopic findings were essentially the same as in these 2. Shock from low atmospheric pressure presents some features not seen in shock from other causes: The body temperature was excessively high; there were convulsions and other signs of neurologic disturbances; extensive degeneration was found in

various parts of the central nervous system. In these particulars the syndrome resembles that of heat stroke, as will appear in the succeeding group. Several items were especially noteworthy in these cases: The concentration of the blood was high; in one case the hematocrit reading was 64.9. Other clinical signs of circulatory failure were marked. It is significant that the visceral findings were of the same pattern as in the other groups. The development of renal failure, with progressive retention of nitrogenous wastes, was rapid in case 100893. Pigmented casts and other changes in the kidneys were like those seen in the "crush syndrome" [40] although no transfusions nor sulfonamide therapy had been employed.

Several items are suggested as possible factors in the mechanism of shock from low atmospheric pressure. Low external pressure would contribute mechanically to the dilatation of minute vessels and to the leakage of fluid through their walls. This might derange fluid balance as seriously as would toxic or anoxic injury to endothelium; hence the hemoconcentration and circulatory deficiency. It has been suggested that low barometric pressure interferes directly with internal respiration even though abundant oxygen is supplied for breathing. Neither oxygen nor other gases under low pressure are absorbed readily by fluids. The hemoglobin of the erythrocytes is essentially a fluid; it may not absorb physiologic amounts of oxygen if the gaseous pressure is greatly decreased. Low external pressure may be directly injurious to the central nervous system. Extensive neurologic damage was found histologically in various parts of the brain. It is known that trauma, embolism, infection, or hemorrhage in some areas of the brain may produce the clinical syndrome of shock accompanied by hemoconcentration and characteristic visceral changes. The exact mechanism of these phenomena has not been shown and should be a fruitful subject for investigation by neurophysiologists.

Once the circulation and fluid balance are deranged, by any one of these mechanisms or by their combined effects, the resulting anoxia in the tissues will perpetuate the vicious cycle of secondary shock with its characteristic visceral and renal effects.

Heat Stroke

Features of resemblance between heat stroke and secondary shock have been reported.[26] Drinker [41] noted sudden collapse and coma accompanied by vomiting and high fever, rapid pulse, and low blood pressure as the usual signs. He stated that the condition resembles surgical shock except for the elevation of temperature. Hill [42] ob-

served that at necropsy "the organs . . . . show capillary congestion, as in wound-shock."

Several authors [21, 22, 41, 43] include heat stroke among the conditions which may cause shock. Hartman [44, 45] observed manifestations of shock in cases of therapeutic hyperthermia resulting fatally. In one, the blood pressure sank to 68/20 at the end of the treatment; death came 20 hours later. He stated that the pathologic changes, both in human cases and in experimental animals, were typical of anoxia produced in other ways.

Twelve representative cases of heat stroke were selected in which death occurred after intervals varying from 25 minutes to 6 days; one case following therapeutic hyperthermia is included. Shock had been noted clinically in most cases.

A.I.P. Accession Number	*Conditions*
84012	Fell unconscious during drill. Death 25 minutes later.
97543	Fell unconscious during hike. Death 3 hours later.
96187	Collapsed, comatose, after 25 mile hike. Death 6 hours later.
112746	Severe sunstroke while on duty. Death 6.5 hours later.
85876	Collapsed during "K.P." duty. Death 12 hours later.
102099	Fell unconscious while marching. Death 24 hours later.
97148	Collapsed during heat; shock, high temperature. Death 25 hours later.
97556	Collapsed during long distance run; oliguria. Death 34 hours later.
113428	Collapsed during heavy work in heat; oliguria, high blood nonprotein nitrogen. Death 36 hours later.
96554	Comatose after exposure to heat; oliguria, high nonprotein nitrogen. Death 3 days later.
102705	Heat exhaustion; oliguria, albuminuria, high nonprotein nitrogen. Death 6 days later.
89594	Collapse after therapeutic hyperthermia; anuria, high nonprotein nitrogen. Death 6 days later.

The gross and microscopic changes found after death from heat stroke, therapeutic hyperthermia, and heat exhaustion were of the same types as described in the previous groups. Petechial hemorrhages were found in every case. The lungs were intensely hyperemic in 11, moderately hyperemic in one. Pulmonary edema was present in 9, atelectasis in 6, incipient pneumonia in 2. The spleen was engorged in 6. The kidneys were hyperemic in every instance. The myocardium was hyperemic in 7, edematous in 8, and showed degeneration in every case.

Parenchymatous degeneration and necrosis of the liver, kidneys, and heart were present regularly and were more extreme in degree than those seen in any other group of cases. It is known that postmortem changes develop most rapidly after death from heat stroke; perhaps this is due to the high body temperature which regularly pre-

ceded death. In 5 instances necropsies were performed in 1 to 3 hours after death; the changes mentioned were equally intense in these cases.

It is noteworthy that signs of renal disturbance occur incident to heat stroke. Albuminuria was noted in 4, oliguria in 4, and retention of nitrogenous wastes in 6. In many instances no laboratory studies on the urine and blood had been made. On microscopic examination, casts were found in the renal tubules in 6 of these cases (Figs. 25 and 26).

Subsequent to these studies, an extended survey on the pathology of heat stroke has been published by Malamud, Haymaker, and Custer [46] based upon material from 125 cases in the Army Institute of Pathology. Hyperthermia was a clinical feature in all but 2 of these. Clinical signs of shock were prominent; the ultimate outcome usually depended upon the degree of shock sustained. Pathologic changes in the central nervous system were conspicuous: progressive degeneration of neurons, congestion, edema, and petechial hemorrhages. The degeneration was attributed to excessive heat, the other changes to shock. "Evidences of acute circulatory failure, such as hemorrhage, edema, and vascular engorgement, were observed in virtually all cases regardless of the duration of illness." Serous effusions were recorded in 33 cases. "In virtually all cases there was intense vascular [pulmonary] congestion." This regularly was accompanied by edema; in no case was the weight of the lungs within normal limits. Some degree of pneumonia was found in 31 cases. Myocardial degeneration was frequent, ranging from irregular patches to large foci of necrosis. The kidneys regularly were hyperemic and above normal weight. The degree of parenchymatous change was less in cases of short duration. "Lower nephron nephrosis" was observed in 19 cases; this was severe in those who lived 35 hours or longer. The livers were congested and above normal weight; central lobular necrosis was seen in 12 of the cases which survived 31 hours or longer.

The recorded data support the belief that secondary shock is an important factor in death from heat stroke. Thermic deaths are accompanied by acute neurologic lesions. The mechanism by which such lesions cause shock has not been shown, but the presence of shock in such cases seems clearly established. The associated anoxia probably causes the parenchymatous degeneration and necrosis seen in the kidneys, liver, and heart. The clinical evidence of cerebral damage, the accompanying high fever, and the pathologic conditions found in the brain and in the viscera indicate that deaths from low atmospheric pressure and from heat stroke have certain features in common.

Abdominal Emergencies

It has been observed that serious abdominal conditions may present the syndrome of shock. Instances are seen in perforations of the viscera, acute pancreatitis, intestinal obstruction as by volvulus or strangulated hernia, mesenteric thrombosis, and others. In several of these, such as acute hemorrhagic pancreatitis, perforation of the gall-bladder or of an ulcer, the onset of shock is immediate. In others, such as intestinal obstruction or peritonitis, the circulatory failure may be delayed somewhat. Ten such cases were surveyed:

A.I.P. Accession Number	*Conditions*
101591	Intestinal infarction, shock, anuria. Death 2.5 hours later.
106742	Intestinal obstruction, resection of gangrenous bowel. Death 24 hours later.
108433	Intestinal obstruction, operation for volvulus, anuria, albuminuria.
114688	Intestinal obstruction, operation. Collapse and death on 5th post-operative day.
116017	Intestinal obstruction, colostomy, followed by shock.
117545	Intestinal obstruction, operation. Death 2 days later.
123485	Intussusception, operation, anuria and albuminuria. Death 7 days later.
111691	Acute pancreatitis, oliguria, albuminuria. Collapse and death.
130718	Acute pancreatic necrosis of 2 days' duration, anuria, albuminuria, death.
133910	Acute pancreatitis, high nonprotein nitrogen, hemoconcentration. Death 5 days later.

The findings in these cases were of exactly the same character as in shock from trauma and from other causes. The lungs were intensely congested and edematous in 7, moderately so in 3. Serous effusions were recorded in 7, petechiae in 6. The kidneys were markedly hyperemic in 3, moderately so in 7. The spleen was hyperemic in only 4. Parenchymatous degeneration ranging to necrosis was present in the liver and in the renal tubules in 6; post-mortem changes in 4 made the presence of these changes uncertain. The myocardium showed degenerative changes present in 7, absent in one; in 2 cases sections of heart were lacking.

In 6 cases, surgical relief had been attempted. These might have been included appropriately in the first group. They represent shock resulting from a combination of factors, including anesthesia, surgical trauma, local loss of blood and fluid, and the grave condition of disease which made operation necessary. In the remaining 4 instances, the disease itself led to circulatory failure and death. It is significant that evidences of renal disturbance were seen clinically in several cases; in others no laboratory tests were recorded.

Miscellaneous

Under the heading of miscellaneous are included deaths from various causes including anaphylaxis, allergic reactions, and sudden death from unexplained causes. Sometimes acute infection or poison was shown as the cause of death by post-mortem examinations; such cases are not included in this group. Ten representative instances of sudden or unexplained death were studied.

A.I.P. Accession Number	*Conditions*
86556	Child died in bed; no previous illness, lymphoid hyperplasia found.
104029	Shock reaction after injection of nupercaine. Death 1 hour later.
105156	Received typhoid and cholera vaccine, collapse. Death 20 minutes later.
109249	Sudden death, cause undetermined.
116783	Typhoid vaccine intravenously, treatment for arthritis. Death 23 hours later.
116840	Received typhus vaccine, no immediate reaction. Died during night.
121120	Shock reaction to diphtheria antitoxin. Death 14 hours later.
128537	Sudden death, cause undetermined.
131480	Sudden death, cause undetermined.
145523	Sudden death, cause undetermined.

In each instance, pulmonary hyperemia and edema were marked; petechiae were present in 9; serous effusions were found in 2. The kidneys were hyperemic in 9, the liver in 7, the spleen in 5. The liver and kidneys showed marked degeneration, ranging to necrosis in 7 cases; post-mortem changes in 3 made degeneration uncertain.

It is known that the visceral findings after anaphylactic death in man and in some animals often are identical with those of secondary shock. Those dying of trivial or insufficient causes often are shown to have a subnormal amount of adrenal cortical tissue. This has been suggested as an explanation for status lymphaticus. The adrenals were hypoplastic in cases 86556, 105156, 109249, and 145523; in 2 other cases no sections of the adrenals were available. Since the adrenal cortical hormone is an important factor in the "alarm reaction" (Selye [47]), deficiency of it may be a factor in deaths without apparent adequate cause.

Renal Pathology

It has been observed by many authors that shock from diverse causes was accompanied by an increase in the nonprotein nitrogen of the blood. This was thought by Whipple, Smith, and Belt [48] to arise from two sources: disintegration of the body's own protein, and deficient elimination of nitrogenous wastes by the kidneys.

Evidence of renal effects accumulated as the phenomena of shock

were studied, until by 1941 their importance appeared so paramount that they were included among characteristic functional disturbances in a definition of shock.[26] That evidence is too extensive for detailed review here. It included Bell's [49] report on "clinical acute nephritis" as distinct from glomerulonephritis, the contributions of Bordley [28] and Daniels, Leonard, and Holtzman [50] on renal effects of transfusions, Lambret and Driessens' [51] studies on physiologic disturbances accompanying surgical shock, Helwig and Schutz' [52] and Boyce and McFetridge's [53] reports on uremia associated with so-called "liver death," Christophe's [54] observations on "acute nephritis" as a regular feature of burns, both clinical and experimental, Bywaters' [40] observation on uremia from compression of limbs, and the review of Jeghers and Bakst [55] on extrarenal uremia.

The reported conditions under which acute uremia developed, independent of glomerulonephritis, included intestinal obstruction, toxic jaundice, "hepatorenal syndrome," extensive surgery, intestinal perforation, poisoning with phenobarbital, cincophen and other drugs, streptococcal cellulitis and other severe infections, diabetic coma and other metabolic intoxications, anaphylactic reactions, transfusion with incompatible blood, acute pancreatitis, cerebral lesions such as abscess or hemorrhage, sublethal shock from trauma as in the "crush syndrome," and burns. In many instances it was recognized that the renal deficiency was associated with shock. Some found hemoconcentration of value in differentiating this type of uremia from other types.

In the cases summarized here, renal deficiency was prominent when a state of sublethal shock had persisted for 2 days or longer. Instances of this were seen after accidental trauma; gunshot wounds; extensive surgical operations; transfusion reactions; burns; poisoning with arsenicals, mercury, barbiturates and with phosphorus; tularemia, malaria, and other infections; shock from low atmospheric pressure, therapeutic hyperthermia, and from heat stroke, intestinal obstruction, and after miscellaneous causes. In many of these instances, neither transfusion of blood nor chemotherapy, as with sulfonamide drugs, had been employed.

The pathologic features set forth in previous reports do not differ in essential particulars from those described in the groups of cases summarized here. Grossly, the kidneys may be of normal size or moderately enlarged; usually they are soft, indicating edema. The capsule often strips with unusual ease; the stellate veins in the cortical surfaces are engorged. The color varies, depending upon relative degree of congestion and of parenchymatous changes. When congestion pre-

dominates, the color is deep red; degenerative changes produce varying degrees of pallor; cloudy swelling usually is mentioned. Red streaks are seen in the medulla and the cortical markings frequently are obscured. Sometimes petechiae are described in the parenchyma or in the pelvic lining.

The microscopic picture shows varying degrees of changes within a regular pattern. Usually hyperemia of the glomerular tufts and of the intertubular capillaries and venules is conspicuous. Sometimes capillary hemorrhages are seen. Red streaks in the medulla result from patchy dilatation of groups of venules which parallel the straight tubules. The epithelium of the convoluted tubules shows varying degrees of acute degeneration. The cytoplasm is granular; more marked degeneration is indicated by vacuolation of the cytoplasm or disintegration of the cells. The nuclei may be hyperchromic, hypochromic, or karyolytic.

Hyaline droplets in the cytoplasm are seen often when degeneration is marked; the lumina may contain globules or masses of this deeply acidophilic material when the cells containing it have disintegrated. Because of their dense staining, these may be mistaken for red blood cells or their pigment. Sometimes these changes are more marked in the upper segment, sometimes in the lower, but usually all portions of the convoluted tubules are affected. Plugs of débris often occur in the lumina of the lower segments as such débris, originating in the upper portion of the nephron, collects in the narrow lumina of the lower portion. Hyaline, granular, and sometimes pigmented casts, débris, erythrocytes, and the nuclei of the degenerated epithelial cells are usually found in the collecting tubules. Edema is a varying feature usually more marked in the medullary than in the cortical zones.

Two recent reports have dealt with renal changes associated with shock. Herbut [56] confirmed the syndrome of uremia noted by others, consisting of oliguria, albuminuria, casts, erythrocytes and débris in the urine, and progressive azotemia. These features developed incident to acute or to sublethal shock from diverse causes. Cases were described resulting from transfusion reactions, bile peritonitis, ulcerative enteritis, abscess, burns, extensive necrosis of neoplasm, obstructive jaundice, sulfonamide therapy, mercuric and arsenical poisoning. The gross features of the kidneys were as described above. The microscopic characteristics were hyperemia and edema of the glomeruli and interstitial tissue; severe degeneration ranging to necrosis of the tubular epithelium, most marked in *proximal* portions; granular eosino-

philic material in the lumina of both proximal and distal portions; and various types of casts in the distal and collecting tubules.

Lucké [57] reported on "lower nephron nephrosis," based upon records and material from numerous cases in the Army Institute of Pathology. These represented battle wounds, crushing injuries, abdominal operations, burns, transfusion reactions, sulfonamide intoxication (combined with infections, trauma, etc.), heat stroke, malaria, various poisons, hemolytic anemia, and miscellaneous conditions such as eclampsia, pancreatitis, and shock from various causes. Shock and vomiting were the two conditions most commonly associated. The clinical manifestations were oliguria, dark or bloody urine containing heme pigment, albumin and casts, progressive azotemia, hypertension, edema, and uremia. The gross features of the kidneys were essentially as given above. Microscopically, acute degeneration ranging to necrosis was found regularly. This involved chiefly the *lower* segments of the convoluted tubules. Protein material was present in the capsular spaces. The tubular lumina contained pigmented and nonpigmented casts and cellular débris.

These changes were as observed by others except for one particular: Lucké [57] found degeneration and necrosis sharply limited to the lower portion of the nephron. Others have described such changes in similar cases as involving all parts of the convoluted tubules. My own observations coincide with the latter findings (Figs. 4, 7, 18, 20, 24, and 25).

Summary

In the cases studied, the pattern of visceral changes characteristic of secondary shock was found after death from various forms of acute disease. These included the combined effects of trauma, hemorrhages, infection, anesthesia, transfusion, and surgery; burns, poisoning with various drugs and chemicals, severe infections, anoxia from sundry causes, low atmospheric pressure, heat stroke, abdominal emergencies such as intestinal obstruction and pancreatitis, and sudden death from anaphylaxis and other causes.

The pattern of changes indicative of endothelial damage included dilatation and engorgement of capillaries and venules in the thoracic, abdominal, and cranial viscera, petechiae in serous and mucous surfaces and within parenchymatous tissues, and edema of soft viscera. Two modes of origin are suggested for the acute degeneration ranging to necrosis which was seen in the kidneys, liver, and myocardium: (1) The same injurious agents which damage endothelium and cause

capillary dilatation and permeability likewise may cause parenchymatous degeneration and necrosis; this is seen in the effects of various poisons and bacterial products. (2) The same effects resulted from uncomplicated anoxia, indicating that endothelial, renal, hepatic, and myocardial cells are delicately susceptible to lack of oxygen. It seems probable that the parenchymatous changes, found after death from shock, result from a combination of these two mechanisms.

Pulmonary hyperemia and edema occurred in a high percentage of cases. When death was delayed 48 hours or longer, the development of secondary or terminal pneumonia often occurred. Lungs in which the circulation is impaired and the spaces filled with albuminous fluid will almost certainly develop secondary pneumonia if neither death nor recovery occurs soon.[24] This was exemplified in numerous instances when shock persisted for several days in a sublethal degree.

Some degree of atelectasis was found in almost one-half of the cases. No previous comment has been made on this feature; its origin and relationship to the mechanism of shock are not apparent. Hemorrhagic infarcts, suggesting embolism, were found in several cases.

Renal functional deficiency was a prominent feature of sublethal shock lasting several days. This was manifested clinically by oliguria, albuminuria, hematuria, and by progressive retention of nitrogenous wastes sometimes terminating in uremia. The pathologic renal features included hyperemia and edema; parenchymatous degeneration and necrosis of tubular epithelium, with desquamation into the lumina; débris; hyaline, granular, and sometimes pigmented casts. These features correspond to the picture of *acute tubular* or *parenchymatous* nephritis described by internists and pathologists of the preceding generation.

Hepatic degeneration and necrosis were regular features, but their degree and distribution were inconstant. Degeneration tended to be diffuse and the degree varied from granular cytoplasm and vesicular nuclei to necrosis. Absence of nuclei, pyknosis, and disintegrating cells were the criteria for necrosis. Frequently this involved only scattered groups of cells; when the groups were larger, focal necrosis was seen. Occasionally, as after burns, heat stroke, or death from low atmospheric pressure, extensive necrosis involved the centers of the lobules and resembled that produced by poisons.

Degeneration of the myocardium was less constant than that of the kidneys and liver; its degree varied. Often the cross striations were obliterated, the substance of the fibers was granular or lumpy rather than of uniform density, and the nuclei were swollen or distorted.

Apparent liquefaction of the fibers, basophilic staining reaction, or marked transverse fragmentation indicated severe degeneration.

Splenic changes were not consistent; in some instances the spleen was enlarged and engorged, in others it was flabby, contracted, and ischemic. In a number of sections it was noted that the lymphoid follicles were small, inconspicuous, and contained few lymphoid cells. This apparently did not pertain to any one type of causative condition; it was observed in several of the groups. There was no evidence to indicate whether its origin is related to shock. The histologic preparations did not always include lymph nodes; when present they were regularly edematous and occasionally hyperemic.

Hyperemia, edema, and petechiae often were found in the mucosa of the stomach and small bowel. This feature was not regular. Petechial hemorrhages in mucous and serous surfaces and in the substance of organs were present in the majority of cases. Their highest frequency was after poisoning, burns, anoxia, and after heat stroke. This indicates that lack of oxygen is an important factor in endothelial damage.

Sections of adrenal were available in about one-half of the cases. In the majority of these the cells of the zona fasciculata appeared abnormally vacuolated. In some, the cells were disintegrated and in a few instances there was focal necrosis. These observations are in accord with those of Selye [47] who emphasized depletion of the adrenal cortical cells as a feature of shock. In a few cases of fulminating meningoccal meningitis, the adrenals were diffusely hemorrhagic and almost totally necrotic. This was not seen in any instance of shock from other causes.

Other ductless glands were not regularly included among the sections available. In several instances the pituitary body was markedly hyperemic and the cells of the anterior lobe appeared degenerated. Occasionally the thyroid and thymus were hyperemic.

This study corroborates the occurrence of secondary shock in other conditions than severe trauma, burns, and after extensive surgery. It develops in sundry conditions which may cause either capillary atony or anoxia. The resulting circulatory effects in the viscera indicate widespread capillary damage. The changes varied somewhat in degree but the pattern was consistent.

The parenchymatous effects may be ascribed in part to the injurious agent itself, in part to anoxia. The severe effects seen regularly in the renal tubular epithelium probably are related to the anuria and other evidences of renal functional deficiency which accompany shock.

It appears that secondary shock, like other conditions of disease, is accompanied by distinctive morphologic changes which are related to its mechanism of origin and to the associated functional disturbances.

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DESCRIPTION OF PLATES

PLATE 52

FIG. 1. Army Institute of Pathology accession no. 114945, multiple gunshot wounds. Lung showing intense capillovenous hyperemia, edema, capillary hemorrhages, and slight leukocytic infiltration. × 160. (A.I.P. negative no. 86843.)

FIG. 2. From the same case as Figure 1. Adrenal cortex showing focal necrosis. × 145. (Neg. 89858.)

FIG. 3. A.I.P. acc. 102060, shock following surgery, death after 4 days. Liver showing acute degeneration and necrosis. × 220. (Neg. 89849.)

FIG. 4. From the same case as Figure 3. Renal cortex showing albuminous matter in the capsular space, degeneration and necrosis of tubular epithelium affecting both upper and lower segments, and débris in the lumina. × 250. (Neg. 86826.)

FIG. 5. Renal medulla from the same section as Figure 4. Of note are masses of desquamated renal epithelium filling the lumina of the collecting tubules. Many contain erythrocytes. × 160. (Neg. 86836.)

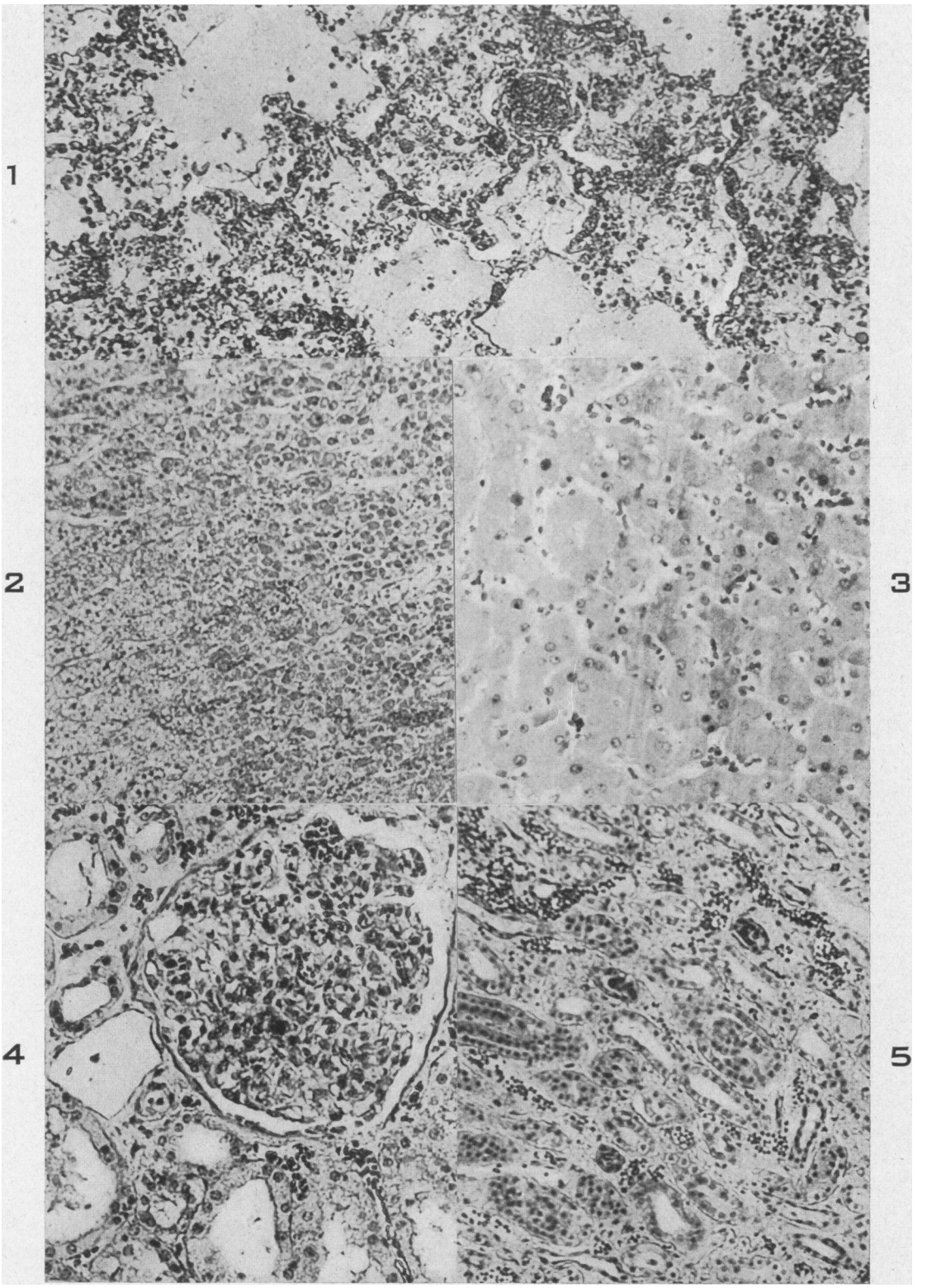
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PLATE 53

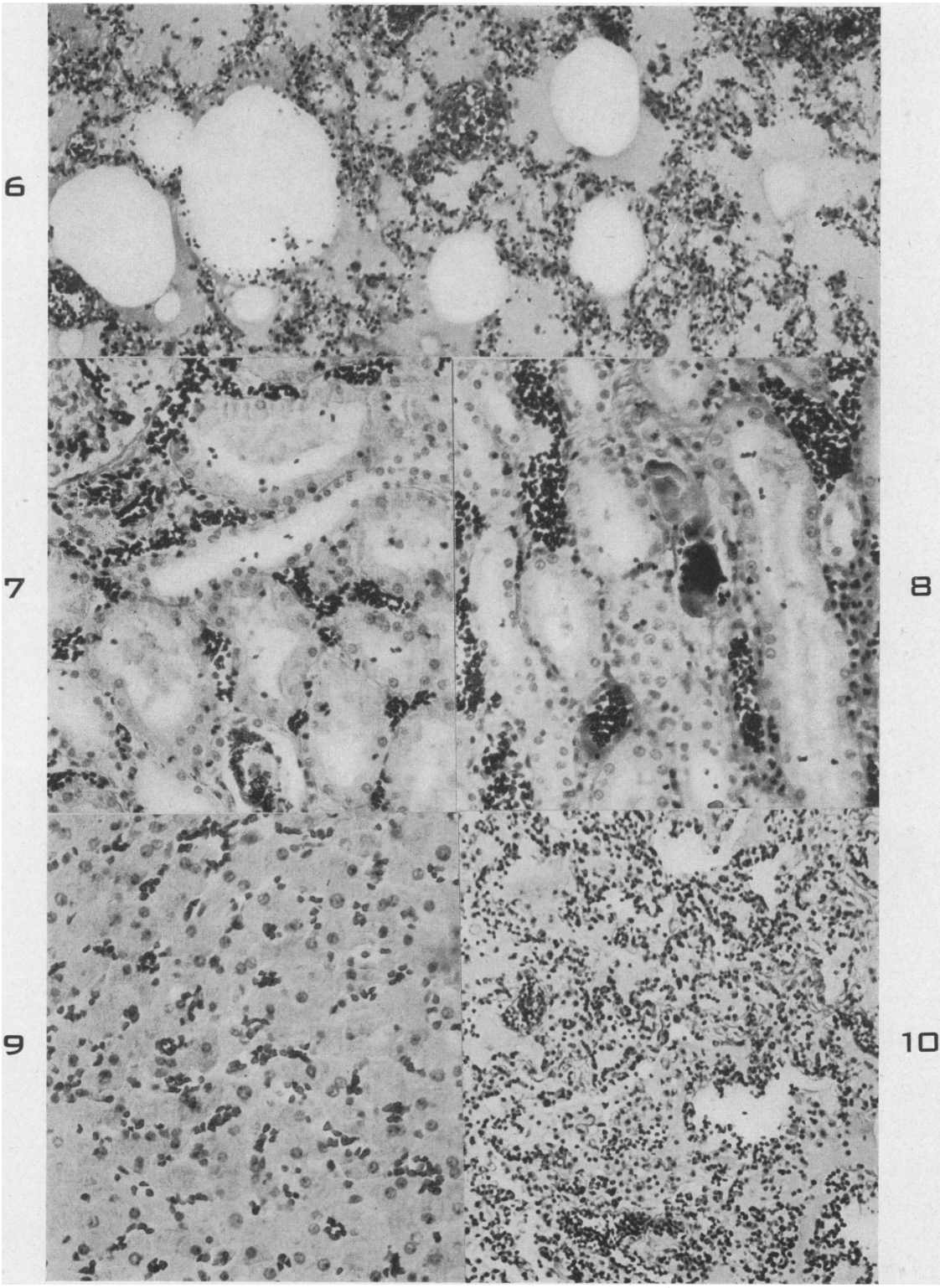
FIG. 6. A.I.P. acc. 114072, death 8 hours after burns of the skin. Lung showing intense hyperemia, edema, and capillary hemorrhages. × 145. (Neg. 68819.)

FIG. 7. A.I.P. acc. 118506, death 8 days after burns, post-mortem interval of 1 hour. Renal cortex showing acute degeneration, necrosis of individual cells, casts and débris in lumina, and albuminous matter in capsular space. × 230. (Neg. 86813.)

FIG. 8. Renal medulla from the same section as Figure 2. Of note are hyperemia, casts, and débris in the lumina. × 230. (Neg. 86821.)

FIG. 9. Liver from the same case as Figure 8. Marked acute degeneration and necrosis. × 280. (Neg. 89850.)

FIG. 10. From the same case as Figures 3 to 5. Lung showing hyperemia, edema, and beginning pneumonia. × 160. (Neg. 86824.)



Moon Pathology of Secondary Shock

PLATE 54

FIG. 11. A.I.P. acc. 111925, shock reaction to mapharsen. Lung showing hyperemia, edema, and early pneumonia. × 130. (Neg. 89855.)

FIG. 12. From the same case as Figure 11. Renal cortex, showing degeneration and necrosis of the tubular epithelium, casts, hyperemia, and edema. × 145. (Neg. 89856.)

FIG. 13. From the same case as Figures 11 and 12. Renal medulla, showing granular and pigmented casts and erythrocytes in the lumina. Edema and hyperemia are seen also. × 175. (Neg. 86829.)

FIG. 14. A.I.P. acc. 116989, poisoning with phenobarbital. Myocardium showing degeneration and fragmentation. × 160. (Neg. 89864.)

FIG. 15. A.I.P. acc. 118865, fulminating meningitis. Lung showing hyperemia, edema, and slight atelectasis. × 120. (Neg. 89863.)

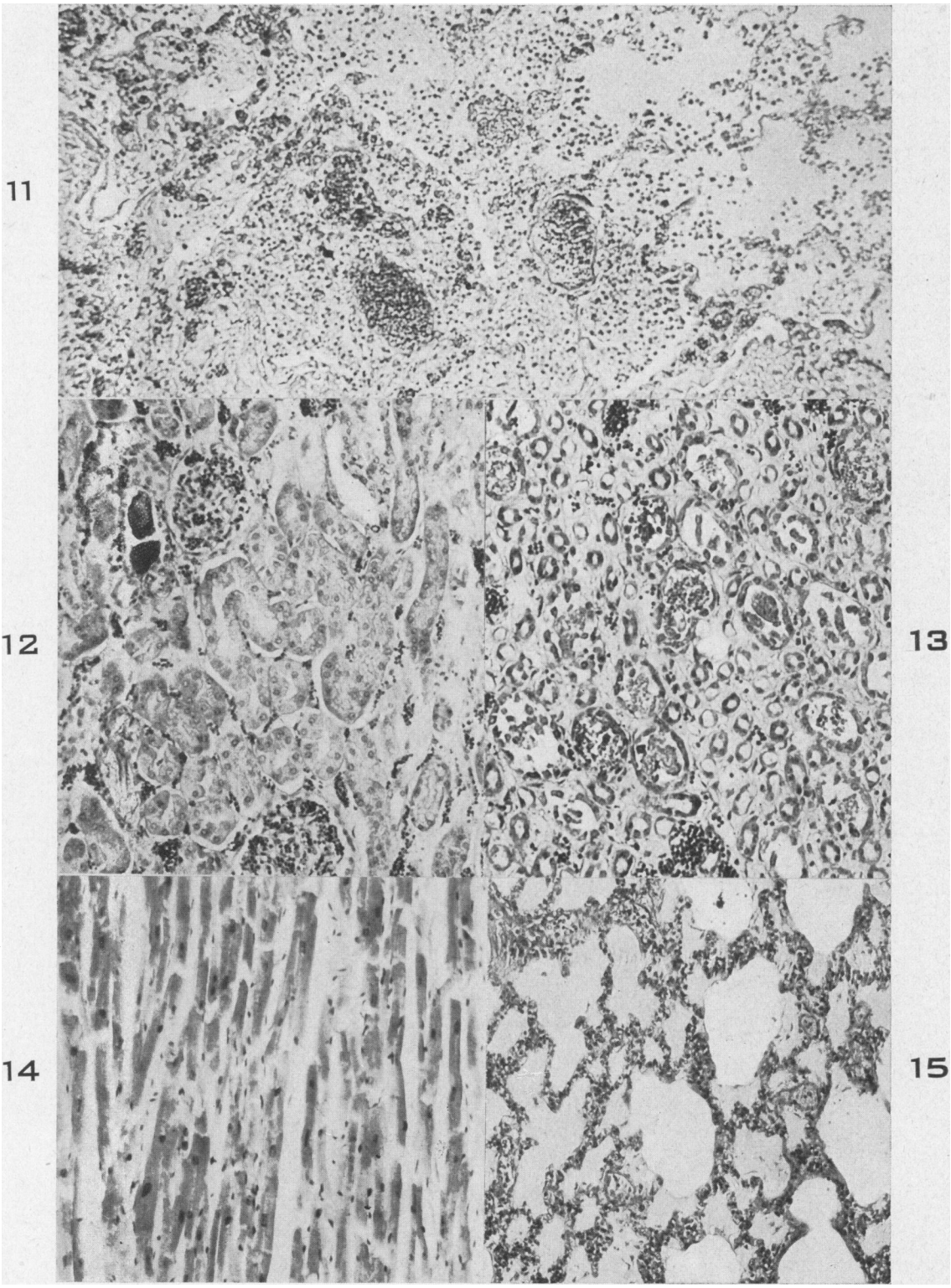

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PLATE 55

FIG. 16. A.I.P. acc. 100893, shock from low atmospheric pressure in experimental test. Intense hyperemia, edema, and slight leukocytic infiltration are shown in this lung. × 145. (Neg. 86838.)

FIG. 17. From the same case as Figure 16. Liver showing acute degeneration, necrosis of individual cells, and edema. × 230. (Neg. 86834.)

FIG. 18. From the same case as Figures 16 and 17. Renal cortex showing low cuboidal epithelium, débris and casts in wide lumina, degeneration and necrosis of epithelium, and albuminous matter in capsular space. × 250. (Neg. 86835.)

FIG. 19. From the same case as Figures 16 to 18. Renal medulla, same section as Figure 18. Of note are the granular, amorphous, pigmented, and epithelial casts. No transfusion of blood and no drug therapy had been given. × 250. (Neg. 86817.)

FIG. 20. A.I.P. acc. 127451, shock from high-altitude aviation. Renal cortex showing marked degeneration and necrosis, desquamation, débris in lumina, and in the capsular space. × 280. (Neg. 86812.)

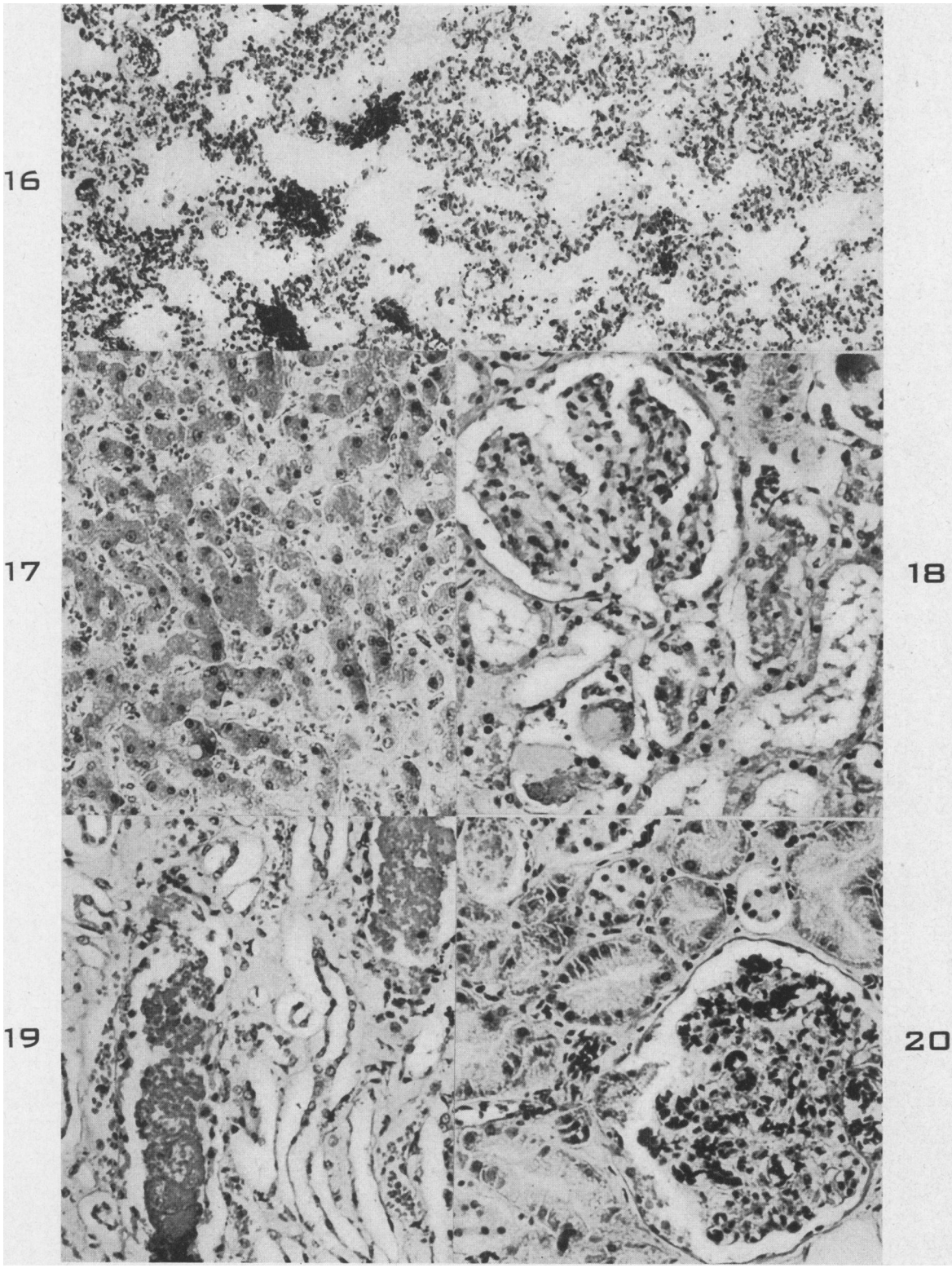
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PLATE 56

FIG. 21. A.I.P. acc. 128485, intestinal obstruction and surgery. Lung showing hyperemia and edema. × 175. (Neg. 86840.)

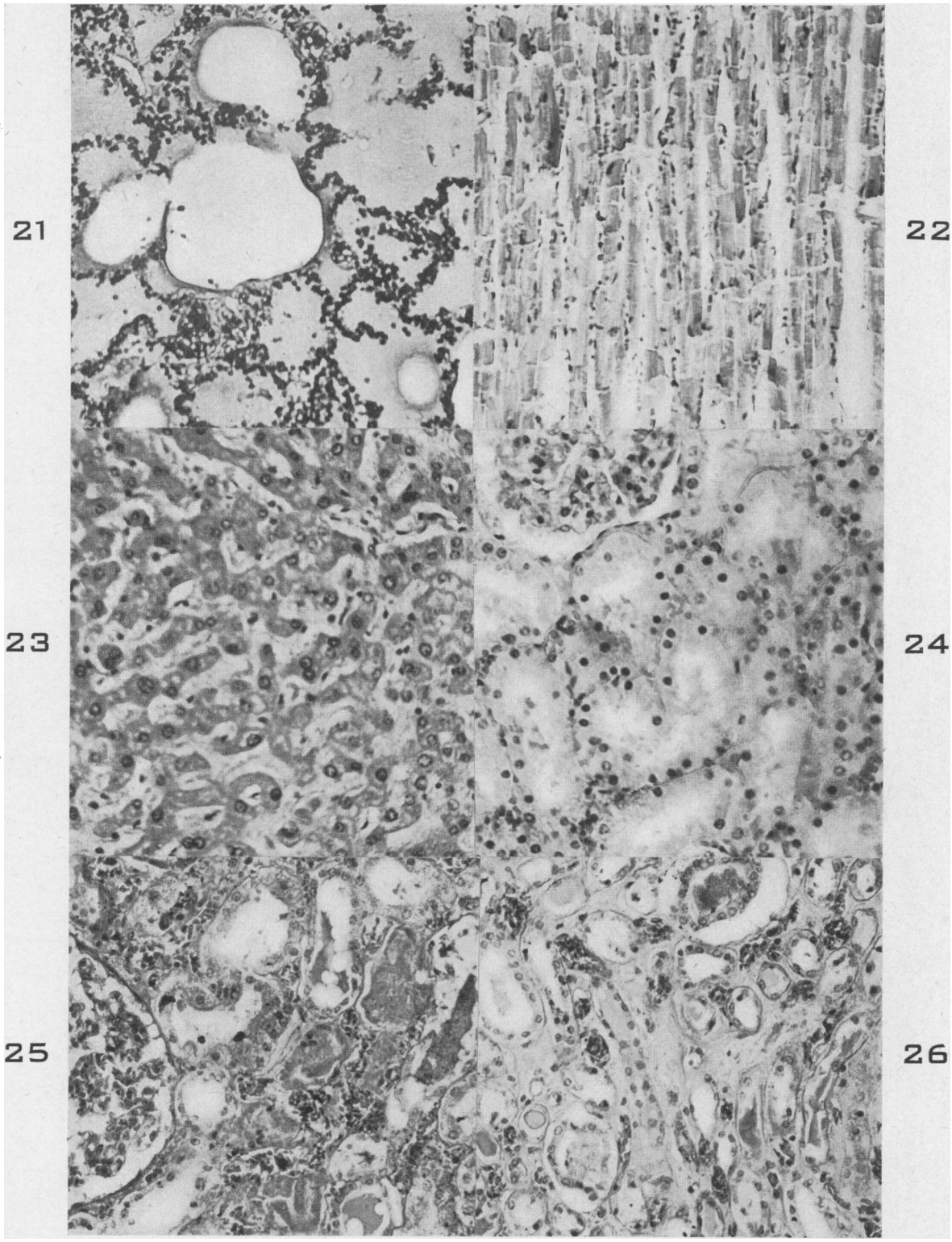
FIG. 22. A.I.P. acc. 128537, sudden death, cause undetermined. Myocardium showing marked degeneration, fragmentation, necrosis, and slight edema. × 180. (Neg. 86833.)

FIG. 23. A.I.P. acc. 83172, death from lack of oxygen. Liver showing acute degeneration, early necrosis, and marked edema. × 230. (Neg. 86810.)

FIG. 24. A.I.P. acc. 111237, lack of oxygen in high-altitude aviation. Renal cortex showing acute degeneration of epithelium, many pyknotic nuclei, and albuminous matter in the capsular space. × 300. (Neg. 86831.)

FIG. 25. A.I.P. acc. 113428, heat stroke fatal in 36 hours. Renal cortex showing extensive necrosis, casts, and débris in the lumina. × 230. (Neg. 86825.)

FIG. 26. Same section as Figure 25. Renal medulla. Of note are the granular, hyaline, amorphous, and pigmented casts. This patient had received no transfusion of blood nor drug therapy. × 230. (Neg. 86822.)



Moon

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