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Physiopathology of burns

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PHYSIOPATHOLOGY OF BURNS

**BY
W. MILLER DILBORTH**

SENIOR THESIS

**UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE
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INTRODUCTION

Divergent views are held as to the cause of the symptoms following extensive superficial burns, and as to the cause of death in the fatal cases. The clinical manifestations have been interpreted by some as indicating shock produced by extreme affection of the nervous system and by others as indicating profound toxemia. Some of the experimental works point to the existence of a toxin acting in the body after extensive burning of the skin, some to loss of function of erythrocytes and the production of thrombi as the essential factors in the causation of symptoms and death, while the work of others point to severe affection of the nervous system as the main factor.

Because of the divergent views, I am reviewing some of the more important literature and experimental studies on the physiology and pathology of burns. A review of the treatment per se will not be considered. I think that the solution to the proper treatment of burns lies in the more thorough understanding of the physiological and pathological changes that occur.

CLASSIFICATION OF BURNS

In tissues supplied freely with blood several grades of damage are noted, each dependent upon the severity of the burn; reddening, blister formation, and eschar or slough formation. These grades are commonly called by the name of degrees. The heat may act in two ways on vascular tissues, first, directly upon the exposed parts and secondly, upon the vessels either directly or indirectly. When the vessels are exposed their walls behave as do other tissues. The circulating blood suffers changes as soon as high enough temperatures are reached. Coagulation of the column of blood is produced with clotting of the plasma albumins at high temperatures.

The protective function of the vessels has been studied experimentally by several authors. On the ears of dogs Douglas, (1934) found that insignificant changes occurred when water at 50 to 56 degrees centigrade was applied for brief intervals and with five minute applications only mild inflammation was produced. Water heated to temperatures between 56 and 62.5 degrees centigrade on five minute applications

produced reddening and blisters of the epidermis with stasis in the venules and capillaries and a dry cutis after removal of the blisters. The effect of water at 87 degrees centigrade made the ear become dry and shriveled like parchment while the vessels became narrow and bloodless.

Douglas also demonstrated the fact that the blood flowing through the vessels is able to protect the tissue against the deeper effects of the heat by means of the following data: He repeated the above experiment on the ear, but first ligated the vessels at the base. He then exposed it to water at varying temperatures and immediately thereafter removing the ligature. Up to 49 degrees centigrade a dilatation of the vessels occurred on release of the ligature. This soon passed away. At 50 degrees centigrade partial necrosis developed while at temperatures above 53 degrees centigrade extensive necrosis followed. Since these temperatures are relatively much lower than those required to produce necrosis with the circulation intact, he concludes that the differences can only be explained on the basis of vascular effects.

First degree - This consists of a simple erythema with vascular reactions similar to that of any

simple inflammation due to the action of an irritant. Gunn (1935) states that it is essentially a reflex or exudative reaction. The reflex phase consists of contraction followed by dilation of the arterioles and venules, resulting in an increased flow of blood to the affected area and a local stagnation of the current. This naturally causes the redness and increased heat invariably associated with this type of burn. The exudative reaction is explained by an increased capillary permeability and consists of filtration of plasma into the tissue spaces, the migration of leukocytes, and the diapedesis of red blood cells. Within a few days the outer layer of the epidermis separates and peels off.

Fuerst (cited by Douglas) through many experiments on guinea pigs' ears, showed that the temperature limit up to which the heating without blister formation could be carried is between 49 and 51 degrees centigrade. The particularly interesting and important feature of this work is found in his demonstration of the effect of long continued heating on the skin. An exposure of the latter to water at 50 degrees centigrade daily resulted in "a gradually increasing hypertrophy and nuclear division of the epidermic cells

even to the formation of giant cells." With further exposure the formation of a fluid exudate in the deeper layers was noted. After thirty days he found that there would be no further important changes but at a slightly higher temperature (53° C.) a new increase in growth or hypertrophy which resulted finally in a thickening of the epidermis to six times the normal.

Second degree - This is essentially the degree of vesication. The epidermis undergoes true coagulation necrosis. By virtue of the increased capillary permeability there is an exudation of serous fluid and filtration of leukocytes from the tips of the papillae, resulting in the formation of blébs or bullae. In mild cases the exudation occurs within the epidermis and leaves the basal cell layer intact, thus forming the blab. In the more severe cases the fluid collects in large amounts beneath the full thickness of the epidermis, resulting in the larger and more serious bullae. In the very severe cases the fluid may even resemble plasma and in such cases organization of the fibrinous exudate is more likely to follow than absorption.

Marchand (cited by Douglas) pictures a second

degree burn as leading to a widespread necrosis of the deeper layers of the epidermis to which very soon is joined a sympathetic transudation out of the dilated vessels causing blister formation. He states that burns of so-called third degree lead to an even deeper necrosis of the cutis through a more intense action of the heat. The red color of the skin he attributes to blood pigments. Later this color changes to yellowish brown and after loss of the epidermis the skin due to a drying will take on a leathery consistency. In such cases the subcutaneous tissue is found edematous and more or less sanguine. He states that with the action of more intense heat two types of lesions are produced. First, by a short action of intense heat such as, for example, with molten metal, it is common to observe a necrosis hardly extending through the thickness of the true skin while the soft parts, the subcutaneous fat and muscle are toasted in situ; secondly, when the body is exposed to flame for a considerable length of time true charring occurs.

In second degree burns very soon after severe damage of the epidermis Marchand finds that the deeper parts will be drawn into sympathy. Transudation from

the vessels occurs even before other more marked changes develop. If complete necrosis develops in the upper part inflammatory infiltration is more marked in the portion beneath. In the zone of tissue becoming necrotic stasis is seen with true thrombosis here and there. Underhill et al. (1930) aptly termed the mass of tissue under a burned surface in which transudation and infiltration have occurred the "edema mass".

Third degree - In this case the epidermis is entirely destroyed as is part of the corium. Its distinguishing factor is that the interpapillary processes remain intact. The papillae appear as a reticular frame-work containing serum. The papillae show as red points on a white background. Two things should be noted about this type of burn. First, the exposed nerve-end in the interpapillary processes remain intact and as a consequence this is the burn accompanied by the most severe pain. Secondly, the sebaceous glands, the hair follicles and the sweat glands are intact and will regenerate new epithelium providing infection does not destroy their epithelial cell lining.

Fourth degree - In this there is destruction

of the entire thickness of the integument and complete disorganization of the skin involved. If the traumatizing factor is dry heat this area will vary from brown to black in color, be insensitive and leathery to touch. If, on the contrary, moist heat is the agent the affected area will be white, insensitive and finger pressure will not induce the usual color changes. Surrounding this zone will be areas of lesser degree burns, shading off from the third degree to the simple hyperemia of the first degree. An acute inflammatory process starts very early and the eschar retracts leaving a groove between the dead and living tissues. Sloughing of the dead tissue begins and is completed, normally within two weeks. At the same time proliferation occurs. Fibrinous exudation upon the surface exerts a chemotactic action upon the new tissue cells. The capillaries proliferate tufts of endothelial cells accompanied by new growth of fibroblasts, to grow along the fibrinous framework after the manner of healing by secondary intention. The endothelial cells grow out to form arches of new capillaries giving nourishment to the growing tissue. Scarring and contracture deformities result.

Fifth Degree - This type of burn varies only from the fourth degree in that the underlying muscles are involved. The resulting scar is, as a consequence, more deforming and may cause great functional impairment. The scar has a great tendency to break down and ulcerate.

Sixth degree - In this degree the tissues are carbonized and the heat may even fracture the underlying bone. It is usually seen in the very severe type of burn involving the digits and demands, invariably, amputation of the part.

Douglas (1934) is of the opinion from his works on the comparative rate of healing of experimental wounds produced by excision and by burning that healing in a burn is delayed by the process of sloughing, whereas in a wound made by the excision of tissue healing begins instantly and is only delayed if infection of the wound occurs.

SYSTEMIC REACTION

Almost immediately following extensive cutaneous burns the patient will suffer from an extreme grade of nervous shock which will be characterized by mental lethargy or unconsciousness, rapid feeble pulse, clammy skin and low blood pressure. This is usually attributed to over stimulation of peripheral injured nerves and even if promptly treated may lead to death from nervous exhaustion.

When a large burned area becomes infected, as so often happens in spite of all available precautions, the problem is then a difficult one because the infection ravages on already debilitated system. Many complications may occur. The commonest are pneumonia, nephritis, pyelitis, pyemia, decubitus ulcers, and septicemia.

AUTOPSY FINDINGS

Bardeen (1897) studied material from five autopsies on cases in which death had occurred in from four to nine and one-half hours. The chief findings of interest were cloudy swelling of the liver and kidney and swelling of the lymph glands and gastro-intestinal lymph follicles with moderate hyperemia of the thoracic and abdominal organs. Microscopically he considered of chief importance the finding of parenchymatous degeneration in the liver, kidneys, and lymphatic organs. These findings, he felt would indicate that death was due to a severe acute toxemia such as that produced experimentally in animals by the injection of diphtheria toxin, abrin, ricin and other so-called toxalbumins. From the tissue examined he felt that neither destruction of red blood cells nor thrombosis played so prominent a part in producing death as did the poison in the blood plasma.

Weiskotten (1919) reports the necropsy findings in ten cases of superficial burns. Death occurred in these five hours to twenty days after injury. In all he found a definite pathological condition. The

lesions in the suprarenals and lymphatic tissue were very striking. In the latter he states that in early cases there was edema of the germinal centers with apparent necrosis of the cells evidenced by karyorrhexis. Endothelial leukocytes had accumulated in the centers of the nodules. Occasionally some of the endothelial leukocytes fused to form foreign body giant cells. In many instances he found that this process continued until the lymph nodule was represented by a large central area filled with phagocytic endothelial leukocytes surrounded by a narrow ring of lymphoid cells. These lesions were present in all cases under three days duration. In those over three days' duration he found evidences of repair. In the suprarenals the lesions in general were more or less comparable to the central necrosis occurring in the liver of the guinea pig in chloroform poisoning, except that in the suprarenals the process was diffuse. He quotes Kalorko as having described similar changes in the suprarenals in a number of cases of superficial burns.

Following even relatively small burns on experimental animals Hartman (1926) found definite evidence through the dilatation produced in the denervated iris of an increased epinephrin output which in some

animals persisted for hours. In such animals there was also depletion of epinephrine and lipoids in the adrenals.

In the heart muscle Weiskotten (1919) found evidence of an injury to the muscle fibers. In several this took the form of hyaline degeneration. In one there was necrosis of the fibers with an accumulation of polymorphonuclear and endothelial leukocytes. The kidneys showed fibrin thrombi in the glomerular tufts more or less completely occluding the vessels.

All of these lesions Weiskotten feels are similar to those which may be produced in the human by the toxin of diphtheria and certain other toxins and he concludes that they "indicate the presence in this class of a more or less specific poison in the circulating blood."

During the acute stage of illness from a burn ulcers may occur in any portion of the intestinal tract but are most common in the first portion of the duodenum and likewise occur more often in children than in adults. Such lesions resemble true peptic ulcers, and are called Curling's ulcers after one of the first men to describe them. Maes (1930) in an excellent paper giving a comprehensive review of the literature of

the subject, reports a fatal case and states that Curling's ulcer occurs in 6% or more of fatal cases of burns and is frequently overlooked. Novak (1925) states that ulcers nearly always are found in the first part of the duodenum; but in a certain number of cases other parts of the alimentary tract are involved. The mechanism of the production of these ulcers is shrouded in mystery.

Harris, (1930) reports a case of a child three and one half years of age which died on the third day following a superficial burn. The necropsy findings were as follows: "On the posterior surface of the duodenum 0.5 cm from the pylorus, there was a shallow ulcer measuring 1 x 0.5 cm. The left suprarenal was enormously distended with a blood clot which had completely disrupted the structure of the gland. The gland was one third the size of the kidney. Nothing remained of the gland structure save a thin margin of tissue surrounding the blood clot. The right suprarenal looked normal in gross but microscopically revealed hemorrhages involving the medulla and extending into the cortex close to the capsule."

The pathology of the internal organs is not by any means characteristic in burns. It has been noted

that the changes were similar to those found in the acute infectious diseases of the skin. At necropsy the following systemic changes have been noted. (Gunn, 1935)

Central Nervous System

Hyperemia of the brain and meninges with small minute hemorrhages into the brain substance and engorgement and thrombosis of the veins of the arachnoid.

Kidneys

Marked changes are found in the kidneys. Acute glomerulitis is an early finding with cloudy swelling and fatty degeneration appearing later in the proximal convoluted tubules. Thrombi have been noted in the vessels, particularly in the glomerular tufts. Necrotic areas are found in the more severe degrees of burns and hemoglobin occurs throughout the renal cortex to give the kidney the brownish-red color seen almost invariably in fatal burns. According to Mallory (1914) this type of lesion "can be produced experimentally in animals by the injection of diphtheria toxin."

Suprarenal Glands

The pathologic findings in these organs are most interesting because attempts have been made to ascribe the fatal effects of burns to disturbance of their function. The normal weight of the suprarenal glands is from 4 - 7 grams and in the severely burned cases it

often weighs from 20-25 grams. Experimentally within 24 hours there is marked hyperemia and occasional hemorrhages noted in the glands. The perirenal fat is markedly edematous. Later the glandular cells are swollen, hydropic and frequently show necrosis.

Spleen

The spleen is enlarged and shows focal necrosis in the germinal centers of the lymph nodules. The endothelial cells proliferate rapidly to occupy the germinal centers and may fuse to form giant cells. Later hyaline degenerative of the lymph nodules may be seen.

Heart

This organ in the late severe cases shows hyaline and fatty degeneration with necrosis of the muscle fibers.

Liver

Parenchymatous degeneration with focal necrosis and hyperemia is usually seen in this organ.

Lungs

In fatal cases of burns the lungs are found congested with thrombi in the smaller branches of the pulmonary artery. Focal pneumonia is usually present.

Lymph Nodes

The usual lesion seen in the lymph node is

central necrosis of the follicles with endothelial proliferation.

Gastro-intestinal Tract

Hyperemia is noted throughout the gastro-intestinal tract with petechial hemorrhages into the mucosa. Ulcerations may occur anywhere along the tract but are found most frequently in the duodenum.

SYSTEMIC CHANGES IN METABOLISM

The alterations in the chemical and physical characteristics of the circulating blood following severe burns have been made the subject of study of many authors.

Locke, 1902, gave a good general summary of the blood findings in severe burns. He gave credit to Cumin and Glasgow for having first called attention to "congestion of the internal organs" and "high arterial action," and to Baraduc who as early as 1862 stated "the thrombosis so generally found in such cases are due to the thickening of the blood, with slowing of the current in consequence of the withdrawing from the blood of the serum found in the blisters." This change in character he considered brought about a sufficient alteration in function of the blood to be the chief cause of death in fatal cases, a view held by Blalock from experimental work. Klebs, 1877, (quoted by Locke) emphasized the effects of burns on the circulation, stating his findings of marked stasis in the large blood vessels and an enormous crowding together of red blood cells.

Tappenier, (1881, quoted by Locke) made a careful

study of four cases of fatal burns and felt that the cause of death was due to many factors but chief among them the loss of blood plasma through transudation. His findings of marked increases in red blood cells are significant. In addition Silverman (quoted by Locke) showed the red blood cells to be much less resistant to thermic, chemical, and mechanical influences in burns than under normal conditions.

Locke made a careful study of the blood in ten cases of burns. His chief findings were: sluggish flow and dark purplish appearance of blood; an immediate increase of from 1 to 14 million red blood cells; a rapidly increasing leukocytosis to between 30 and 50 thousand; a considerable destruction of leukocytes; the presence of myelocytes in severe cases; a marked increase in the number of blood platelets.

Underhill, 1923, and his coworkers found the blood concentration greatly increased in a large number of cases of human burns as evidenced by marked increase in the percentage of hemoglobin. They pointed out that the low blood pressure, high temperature and symptoms of circulatory failure in burns are probably due in large measure to the high blood concentration, and that the latter is roughly proportional to the extent of the area burned. They showed that introduction of

large quantities of fluid into the system reduced this concentration with improvement of symptoms.

Experimentally Willis (1925) showed that following severe burns the blood concentration became high as evidenced by an increase in the number of red corpuscles and the hemoglobin percentage. He demonstrated that debridement of the burned area would prevent the development of a high blood concentration.

Blalack, 1921, made the important observation from experimental animals that the increase in weight of a burned extremity on a dog over a normal unburned one would average as much as 3.34% of that of the body after time intervals of six to twenty-six hours. This he calculates would constitute about 57% of the total plasma. From these facts he concludes that the outpouring of this fluid plays an important role in the reduction of blood volume and pressure. He also showed that the fluid which collected in the subcutaneous tissues has as high a protein content as does plasma. He thinks that such a change over an extensive area would provide an adequate explanation of the high degree of blood concentration and of circulatory shock produced.

Underhill et al, 1930, first showed that the

sodium chloride content of the blood is greatly reduced during the stage of blood concentration in burns. They felt that "in the rapid interchange of fluid during the inflammatory stage of burns, sodium chloride functions prominently." Davidson, 1926, found low sodium chloride values in 24 humans severely burned. These values persisted until the sloughs separated and then rose to normal with a corresponding increase in urinary chlorides. His observations suggest the administration of sodium chloride to correct the deficiency.

Bigger (1926) stresses the significance of the finding of the high blood concentration and low blood volume and reports good results in restoring the blood volume in one patient critically burned by using hypertonic sodium chloride solution intravenously.

Willis (1924) found a definite increase in the non-protein nitrogen following severe burns in experimental animals. While Underhill (1930) found this same increase in clinical cases, he felt that his results might be in error due to the existence of a high blood concentration at the time of his determinations.

Davidson, 1926, found low non-protein nitrogen values for the blood of burned patients treated with tannic acid.

Underhill and his co-workers, 1930, demonstrated

that a superficial burn involving one-sixth of the total surface area of rabbits induced within a period of six hours a significant loss of fluid from the blood in the form of subcutaneous edema. The fluid reaches its maximum accumulation in the first 24 to 36 hours after which there is a tendency for it to diminish probably due to re-establishment of the process of reabsorption.

Considerable literature has recently accumulated to show that the adrenal glands are severely involved following extensive burns and that through this involvement the adrenalin content of the blood and consequently the blood sugar is affected. The pathological changes described by Bardeen and Weiskotten have already been stated. Olbrycht described marked changes in these glands both clinically and experimentally and noted that they were similar to those in peptone poisoning or anaphylactic shock. He stated that the epiniphrine content was lowered in such cases.

Grunwald and Eliasberg, 1926, reported two fatally burned human cases in which marked hypoglycemia was present. Their experimental studies led them to conclude that soon after burns there is marked hyperactivity of the suprarenal glands. This results in a

release of adrenalin which in turn leads to a marked hyperglycemia. This effect they felt was due to the shock of the burn acting on the sympathetic nervous system producing changes in the innervation of the suprarenals resulting in an outpouring of epinephrine into the circulation. Death occurred early in these cases.

In cases in which death occurred later than 24 hours the authors found marked degenerative changes in the suprarenals with low blood sugar levels. Degeneration of these glands was followed by regenerative changes in the cases which recovered. They found that during the degenerative stage a decreased amount of adrenalin is thrown into the blood stream thus inhibiting the liver in its normal glycogenolytic function. They conclude that these changes are not sufficient alone to cause death but that other changes in parenchymatous organs occur. They conclude also that adrenalin administration is to be limited to the secondary stage or that of suprarenal exhaustion and is contraindicated in the primary stage.

Slocum and Lightbody, 1931, made studies of the concentration of sugar and lactic acid in the blood of rabbits, burned with the suprarenal glands intact, and

after the removal of the glands. The concentration of both sugar and lactic acid were found to be increased. The increases of lactic acid were small and do not appear to account for the high sugar values. Twenty-four hours after burning, animals with the intact glands were found to have maintained the increased blood sugar while the lactic acid concentrations were reduced below the initial values. The studies indicate that increased activity of the suprarenals do not account for the increased blood sugar through lactic acid as an intermediate, or by a decreased rate of oxidation of the sugar. Weiner, Rowlette, and Elman, 1935, from their study of burned patients showed that the albumen-globulin ratios was high, i.e., between 2.9 to 3.2 indicating a loss of relatively more globulin than albumen. As the patients recovered the value returned to normal. They showed that in most of the serious burns there was a failure of the kidneys to put out more than 10 to 20% of the amount of fluid administered. They concluded from their studies that the loss of serum protein is a serious result of extensive burns and that the store of body protein is not sufficient to restore rapidly this loss when only water, glucose, and electrolyte

are administered. The injection of blood plasma is apparently more efficacious than whole blood because of the excessive concentration of red blood cells already present.

-THEORIES

The various phenomena associated with burns have long engaged the attention of investigators in the fields of physiology, pathology, and clinical medicine. While as yet there has been presented no single theory which satisfactorily explains all of the observed changes following the primary burn, several more or less plausible theories have been advanced. Of these four may be discussed briefly.

The reaction of the body to a burn strongly resembles the clinical state described by the term "toxemia" which implies the presence in the circulation of some toxic agent. The more serious cases usually present early in the course a clinical picture commonly described by such terms as shock or exhaustion. There is a profound disturbance of the circulatory and of the heat regulating mechanism and in all probability equally serious interference with many other functions of the body. MacLeod (1919) states that the extent of the burned area is of more importance than the depth. He further writes as regards prognosis that a burn of even mild degree may cause a fatal issue and that this is almost inevitable in an adult if the area affected

is more than one third of the total body surface. Authentic cases in children are recorded of burns of apparently slight severity, which have been followed by death. On the other hand, patients with much more severe burns are known to have recovered and to have shown but a mild general reaction. There seems to be something especially harmful in a superficial burn.

The theories which have been evolved to explain these phenomena may be arranged roughly into the following groups: (1) Those in which interference with the normal function of the skin is considered to be the essential factor in the causation of phenomena; (2) Those in which the effects observed are attributed to changes in the blood resulting in altered function; ³ those in which the picture is explained on the basis of absorption of a toxic substance in the blood stream; and (4) those in which a bacterial toxin is responsible for the systemic manifestations of burns.

I. Theories of Interference with Normal Function of the Skin

A disturbance of one or another of the various functions of the skin, namely, respiration, excretion, temperature regulation, and sensation has been made

the basis of theories explaining the clinical course which follows extensive burns. The data that have been presented in support of the theory that failure of the respiratory function of skin in mammals results in overwork of the viscera is entirely unconvincing. The theory of retention of normal excretory products of skin was shown to be improbable by demonstrating that the ill effects of girding experimental animals is due to the abnormal biological conditions produced in the skin rather than to the retention of excretory products. It has been shown that girding destroys the vitality of the area covered and that the microscopic picture is not unlike that seen in first degree burns. (Davidson, 1926) The theory of failure of the heat regulating mechanism has been disproved by showing that animals die in spite of adequate protection against such heat dissipation. German workers discredited the theory based on the sensory function of the skin by demonstrating that interference with the nerve supply to a burned part in a rabbit's ear had no effect on the constitutional reaction, while division of the blood supply prevented it fairly effectively. This conclusion was further supported by the division of the nerves, to the burned extremity in a guinea pig which did not diminish the severity of the toxemia.

II. Theories Based on Alteration of the Blood

It has been established that after burns concentration of blood takes place (Locke, 1902) (Ravogli, 1915) and the erythrocytes undergo certain morphological changes, there is some loss of function of the red blood cells and thrombosis frequently takes place. Robertson and Boyd (1923) emphasize the fact that there is a greater increase of urea nitrogen than of total non-protein nitrogen. Underhill (1930) believes that the increase of non-protein nitrogen and urea nitrogen is best explained on the basis of blood concentration.

Harkins (1935) from experimental studies concluded that the local loss of fluid from the blood vessels into the burned tissues is a factor in the production of shock and that the type is secondary. The concentration of the blood as shown by increase in the percentage of hemoglobin and in the hematocrit reading was roughly proportionate to the loss of fluid, but the blood pressure remained near normal until death approached, and then it fell rapidly. The accumulation of fluid in the burned tissues begins in many cases before the burning is completed, and the rapidity of this accumulation may account

for many of the cases that have been mislabeled primary neurogenic shock.

From experimental work Osterberg, 1933, reached the conclusion that with the concentration of the blood following burns there is a failure of circulation and resultant oxygen starvation of the tissues. He observed that concentration of the blood to 140% of the normal value is in a short time incompatible with life, and concentration of 125% of the normal value results in a precarious condition.

The development of edema is due to increased permeability of the capillaries, particularly those in the periphery of the burned area. This results in the loss of fluids, the composition of which is similar to that of plasma, from the blood stream to the tissues. Absorption from the burned area is exceedingly slow indicating that the increased permeability is in only one direction. The loss of water from the blood stream may, under certain conditions, be as high as 70% of the total blood volume. McClure, 1936, showed that whatever water and protein are lost from circulation appear to remain largely within the body.

III. The Toxemia Theory

There is certain convincing evidence that suggests the formation at the site of the burn of a toxic substance, the absorption of which is responsible for the constitutional reaction. The first reported autopsies were those of William Cummin, published in 1813. (cited by Davidson, 1926) In cases of early death the chief lesion found was hyperemia of the thoracic and abdominal organs, while in instances in which death was delayed several days, there was observed a well marked inflammatory reaction. Bardeen (1897) in a very admirable study of five fatal cases in children who ranged in age from sixteen months to eight years, and who died from four to nine hours after being burned, observed degenerative changes in the liver, spleen, kidney, and bone marrow. He further noted a general edema of all lymphoid tissue, which was most marked at the germinal centers. The alterations observed were nearly identical to those found in lymph glands of children who die of an acute infection, like diphtheria in which it is known that a toxin is present in the circulating blood. He concluded that the changes were of sufficient extent

to make it unnecessary to assume a nervous factor as the cause of death and that the phenomena observed were best explained on the basis of an acute toxemia.

A substance has been isolated from the urine of burned patients, which is toxic for animals, which has many of the properties of pyridine (Reiss, 1904) The finding of toxic agents in the urine has been confirmed by numerous investigators but there is no agreement as to the identity of the toxic substance present.

Voccarezza (1922) observed that when parabiosis was established between two animals and one was burned, the other animal showed evidence of toxemia. The symptoms in the burned animal were observed to be less severe under such circumstances than when it was alone. It was further demonstrated that toxic symptoms did not develop in the unburned animal when it was separated from the burned animal within the first 12 hours, but both animals finally died of toxemia when left united.

Pfeiffer (1914) isolated cleavage products of protein decomposition from burned skin which were found to be neurotoxic and necrototoxic. These he

described as being soluble in water, alcohol and glycerol, and insoluble in chloroform and ether. Robertson and Boyd (1923) have also demonstrated the toxicity of the products of protein autolysis in burned tissue. They concluded that the toxic material was composed of two elements; one which is thermolabile, non-diffusible and necrotoxic; the other thermostable, diffusible and neurotoxic. They further showed that the toxin circulated in blood either in or was absorbed by the erythrocytes because whole blood was found to carry the toxic principle, while blood serum was found poisonous only in enormous doses when given intraperitoneally to guinea pigs.

Wilson and his coworkers (1937) are of the opinion that edema fluid which accumulates in a burned area gradually acquires toxic properties; when collected at 48 hours after burning it is frequently lethal to healthy animals of the same species. They showed that the actions of toxic edema fluid suggests the presence of more than one toxic component, and that the proportions of the components vary in different samples. The effects produced include toxic action on the nervous system,

circulatory depression and degeneration of liver cells. They think the toxic principles are associated mainly with the globulin fraction. Their evidence indicates that the more active principles are higher protein derivatives.

Histamine was shown to rise in the blood at about the time when secondary shock is liable to develop. Barsoum and Gaddum (1936) showed that after large burns the histamine-equivalent rose to at least four times its normal level, and was maintained at high values for many days. Smaller burns caused smaller effects, and there appeared to be a direct relation between the area of the burn and the magnitude and duration of the rise in histamine equivalent.

Rosenthal (1937) showed that in the blood of burned shoats, adult pigs, guinea pigs, and humans there was a substance that caused contraction of the virgin guinea pig's uterus. This substance was at first linked with the red blood corpuscles, but was later found in the serum. The substance differs from histamine in that it is heat labile and it does not act upon the virgin guinea pig's uterus under certain conditions when histamine does.

IV. Bacterial Toxin Theory

The very latest of the theories concerning the deleterious effects of thermal burns is reported by Aldrich (1933) who generously ascribes the idea and the resulting proof. While discounting the tissue toxin theory entirely and admitting the probability of Underhill's blood concentration theory, this investigator believes that a bacterial toxin is responsible for a good proportion of the systemic manifestations of burns. He cites in the stage of secondary shock that burned patients succumb during this period even when the concentration of the blood has been restored to within normal limits.

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