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Crush syndrome

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The syndrome of lower nephron nephrosis occurs under a variety of conditions among which are included severe or prolonged shock or trauma, massive intravenous hemolysis of donor erythrocytes, intravenous hemolysis of patient's erythrocytes after intravenous administration of sterile water, sulfa drug reactions, hyperthermia, periarteritis nodosa, blackwater fever, thermal burns, and paroxysmal and nocturnal hemoblobinuria.[4] The one thing peculiar to all of these conditions is the development of acute renal failure. However, the lower nephron nephrosis following severe crushing injury resembles the other conditions only in the clinical picture and differs in history, pathogenesis, pathology and the nature of the pigment deposited in the kidney tubules. The scope of this paper will be restricted to these considerations and to the general subject of therapy for lower nephron nephrosis.

Historically, the lower nephron nephrosis following severe crushing injuries was first mentioned during the 1914-1918 period by German authors, the renal changes were described by Hackradt in 1917 and the clinical picture was later described by Kayser in 1922[7]. Bywaters in reviewing the literature found that following 1918 there was minimal reference to it, in spite of the pro-

bable occurence of the syndrome in occupations such as mining. In 1941, attention was again called to the condition during the air raids on London during which many persons were pinned beneath falling debris and remained so for varying lengths of time until rescue attempts were successful.

The incidence of occurence of the syndrome in air raid casualties was shown by Bywaters to be about one percent while the incidence amongst battlefield casualties ran about 18.6%[12]. The reason for the great degree of variation probably lies in the speed with which the crushed members were released from pressure, since the incidence of occurence varies directly with the duration of the imprisonment of the extremities.

In the typical case there is a history of a crushing injury to an extremity. This finding was characteristic of the four cases which were reported by Beall and Bywaters in 1941, and upon the release of the crushed member, it was seen in all of the cases to be swollen hard, the skin showed small petechiae, there were erythematous wheals and large blisters over the surface. Generally, on admission to the hospital, there was a hemoglobin concentration and within a few hours the blood pressure fell only to rise progressively until death which usually fol-

lowed in about a week. There was usually an oliguria of a severe nature which set in about the second day after the injury and became worse, as in one case reported by Bywaters in which the urinary output dropped from 650 cc on the second day to 205 cc by catheter on the third day. There were pigmented casts in the urine obtained. From the first day there was severe vomiting which persisted to the end accompanied by severe thirst. Chemically, the venous blood showed progressive rises in the blood urea besides a steady lowering of the carbon dioxide combining power. Towards the end the patient showed a slight mental depression, he became apprehensive and anxious, rales developed in the chest, he became alarmed, there was a weakened pulse, there was profuse generalized sweating, the systolic pressure fell from 155 to 30, the pulse became irregular and the patient died in a few seconds.[7] Chemical studies of the blood of these patients reveals a hyperphosphatemia, a depression of the blood chlorides and an elevation of the serum potassium, as well as the other changes noted above. This is fairly typical of the usual clinical course of these patients in the fatal cases, and also of those patients developing lower nephron nephrosis due to other causes.

In those cases which recover, the critical point in the course of the illness seems to be the seventh day,[25] after which the clinical improvement is accompanied by parallel changes in the blood chemistry. The urea clearance increases, the albumin and casts disappear from the urine and the serum potassium falls steadily to normal. In a case of recovery reported by Blackburn (1941), the urea clearance rose from 9.3% of normal on the ninth day to 57% of normal one week later, the blood pressure fell from 195/95 on the seventh day to 135/80 on the fifteenth day, and the serum potassium fell steadily from 25 mg% to subnormal and then recovered. Maitland (1941) reports a similar case of recovery. In comparing these cases with those of Bywaters it is seen that the urea nitrogen in the former cases did not rise to the height that it did in the latter where it rose to a maximum of 640 mg%. Also, the serum potassium in the cases of Bywaters rose to a maximum of 34 mg% whereas, in Blackburn's single case, it rose only to 25 mg%. This seems to indicate one criterion by which the prognosis of a given case can be determined. Other criteria include: the extent of the injury to the extremity or extremities (less renal damage occurs in the case of crushing injury to the upper extremities),

the degree of hemoconcentration, and the severity of the oliguria (Bywaters, 1942). Similarly, a quantitative estimation of the creatine and myohemoglobin gives a basis for the calculation of the extent of renal impairment; and it may also be determined on the basis of local plasma loss which is derived from a consideration of the degree of hemoconcentration, Crooke and Morris' figures for dye distribution and degree of limb swelling.[9]

As would be expected, the most of the pathology is found in the kidneys, but Bywaters describes three grades of severity of the lesions seen in the crushed muscles. In some instances, the muscles appeared grossly normal with only a patchy necrosis of fibers associated with arterial spasm; in other instances all of the muscle fibers were necrotic; and in still others there was necrosis of the muscle tissue only in the areas subjected to the direct pressure which caused ischemia. The identification of the pigment found in the kidney tubules as myohemoglobin was an important step because it identified the crushed muscles as the source, and the above findings serve to confirm this.

In addition to the changes in the crushed muscles, Navasquez described very fully the changes seen in the

kidneys.[24] The kidneys are not, as a rule, greatly swollen; in one case the right one weighed 180 grams and the left weighed 240 grams. Microscopically, the changes are more remarkable. In the glomeruli the capillary tufts show no changes but the capsular space is filled with a granular, eosinophilic debris in the form of lightly stained spherical masses. This suggests an increased glomerular permeability. These changes appear the second day and are still present on the fourth day. The lining cells of the capsule show proliferative changes which are more marked adjacent to the exit of the tubule, as if the tubule had grown and extended into the capsule producing a funnel-like opening. This appearance is similar to the endocrine effect described by Selye (1939) and Crabtree (1941).

There is an intense catarrh in the proximal convoluted tubules and they are filled with what appears to be necrosed epithelial cells. This change continues through the descending tubule and the loop of Henle. The most severe damage is seen in the ascending limb and the loop of Henle. Here, there is complete necrosis in small areas which is often perivascular with the formation of thrombi in the vessels and in places, rupture of

the tubule may occur. The casts in the ascending limb are hyaline and solid-looking. Around the focal areas of necrosis there is edema and a well-marked histiocytic reaction, and later, in these areas, proliferation of the interstitial tissue may replace them so that a patchy fibrosis develops giving the renal cortex a distinct pattern under low magnification.

The pigmented casts appear first in the distal convoluted tubules, are later found throughout the rest of the nephron and are especially prominent in the collecting tubules. These casts give a positive benzidine reaction. It is suggested that the casts are formed as a result of condensation and loss of water, from the looser debris seen higher up in the nephron and the absorption, by this necrotic material, of myohemoglobin from the glomerular filtrate. In the collecting tubules, the condensation of the pigmented material appears to proceed a step further, so that in transverse sections of the papillae many tubules are filled with dense brown masses. All stages of cell desquammation and degeneration are seen and the transition from nucleated unpigmented cells which have just become desquammated, to granular blocks of pigmented amorphous material may be easily followed. These casts are thought to be formed, at least in part, from

desquammated epithelium. A further change seen in those who have lived a week is a polymorphonuclear leucocytic infiltration of certain cast-containing tubules, as a rule, most marked in the medulla.

In addition to the changes described above, Goormaghtigh reports an increased size of the juxta-glomerular apparatus and the appearance of granules in its cells. This, he theorized, possibly causes a liberation of vasopressor substance in the crush syndrome with arteriolar spasm at the vascular pole of the glomerular tuft.[17]

The reason for the development of the acute renal failure following severe crushing injuries and the serious prognosis is the aspect of the problem which is the most baffling and concerning which numerous theories exist. At the beginning of Bywaters' investigation of the problem, he reached the conclusion that one of the basic mechanisms involved was that of a fall in blood pressure which came about when the process of vasoconstriction was unable further to compensate for the decrease of blood volume due to the loss of blood into the injured tissues. This would explain the pathogenesis of the shock seen in these patients. Not so simple was the explanation of the source of the pigment and its nature, seen in the distal

convoluted tubules of the kidney and its role in the production of the syndrome. It was at first thought that the pigment was hemoglobin, but this was eliminated because cases had been reported to develop the syndrome without transfusion, there were no clinical symptoms of transfusion reaction and only cases with crushing injuries developed the condition. By means of the Hartridge reversion spectroscope the pigment was finally identified as myohemoglobin, but the reason for its presence in the tubules was still unexplained since the size of the molecule is only one-fourth that of the hemoglobin molecule and it should pass readily through the glomerular filter, and so on out the tubules. (Lucke, 1946)[19] Several theories have been advanced to explain this phenomenon. Baker and Dodds[24] state that when the pigment reaches the lower tubules, the acid pH causes hematin to precipitate and that this process is accelerated when the concentration of sodium chloride reaches one percent. In direct opposition to this theory is that of Barnes, Kondi and Navasquez who maintain that the pigment is more readily precipitated in alkaline solutions. In support of the former theory is the experimental work of Bywaters who reproduced the kidney lesions of the crush syndrome by the

injection of metmyoglobin into an acidified rabbit but Bing, (1943) was unsuccessful in reproducing the lesions using a dog. However, by the use of methemoglobin, he was able to reproduce the lesions. Fay, Altman, Barnes and Kondi have later stated that the pigment precipitation is related to the destruction of the tubular epithelium which occurs, while other authors relate its presence to an inadequate flushing of the tubules following the development of oliguria.[19] Another theory, according to Lucké, is that the proteins reach their isoelectric point in the distal tubules and with the presence of a so-called "X" factor, they precipitate. However much truth there may be to any or all of these theories, it is fairly well agreed by most of the authors that the mechanical blockage of the tubules is not the cause of the renal shutdown; for, as Bywaters and Dible point out, if it were due to mechanical blockage, then what urine is excreted by the kidneys would be of normal composition since it would come from normal nephrons, and this is not the case; for the urine is poorly concentrated and there has been little resorption of chlorides. Therefore, there must be some other mechanism involved.

Many of the workers on the problem maintain that the renal shutdown is explainable on the basis of the destruc-

tion of the tubular epithelium, and that the precipitation of the pigment is secondary to this.[22] The production of the tubular necrosis may be due to successive periods of prolonged hypotension and early shock due to bleeding which results in a progressive renal vasoconstriction,[19] and thus in an ischemia which leads to a destruction of the tubular epithelium. (Fine,1946) He demonstrated by the use of tourniquets applied to dogs' legs that renal blood flow was reduced to 50% of normal within a few minutes, and after one hour was down to about 20% of normal. Using the same technique on rats, whose muscles contain little myoglobin, he concluded that renal failure in the crush syndrome was due to the coincidence of renal vasoconstrictive ischemia and myoglobinuria.[19] The effects of ischemia on the kidney tubules can be divided into three phases; the first being reduced kidney function without the production of damage to the nephrons, the second being the production of reversible damage to the nephrons, and the third being the production of irreversible damage.[19]

The production of the renal ischemia is said by Goormaghtigh to be the result of release by the kidney of a vasopressor substance which results in arteriolar spasm at the vascular pole of the glomerular tuft, and tubular necrosis due to anoxia results. He identifies the juxta-

glomerular apparatus as the source of the vasopressor substance and has described an increase in the size of this structure and the appearance of granules in its cells. (1945) Scheinman (1949) concurs with this opinion and uses it as the basis of therapy for the condition. Fine, Frank and Seligman, however, maintain that there is a vasoconstrictor substance liberated during the period of early shock, but that its source is the damaged muscle, and that the reason for the damage being found only in the distal tubules is the patchy distribution of the renal ischemia. Mallory (1947) maintains that renal ischemia produces necrosis only in the proximal tubules, but it is his contention that the cause of the renal failure in the crush syndrome is a synergistic phenomenon of shock and metamyoglobinemia, which is, in part, in agreement with the opinion of Fine.

In 1946, J. Trueta published a preliminary report on his work on the problem of the relation of the renal circulation to the development of the lower nephron nephrosis of the crush syndrome. It was his investigation of this problem which led to his discovery of an alternative circulation through the cortex and the medulla of the kidney respectively. He has shown that the shunting of the blood flow from the renal cortex to the

medulla is a neurovascular mechanism which can come about as the result of peripheral or central stimulation, and that this phenomenon can be prevented by the use of splanchnic nerve blocks. He theorized that this is a protective mechanism employed by the body in an attempt to protect the vital cortex from the effect of toxins carried in the blood stream, and that when this protective mechanism was operative over too long a time, permanent damage to the renal cortex results. Peters (1947), on the other hand, states that the ischemia results as a consequence of elevated intra-renal pressure which follows swelling and edema of the kidney. This theory, however, fails to explain why diuresis in those who recover, occurs on the eleventh or twelfth day when congestion and swelling are at their peak.[18] Bywaters in 1942, agreed that an elevated renal pressure was possible as the result of partial kidney blockage by myoglobin pigments.

The presence of the myoglobin pigment in the tubules led to the question of whether or not this pigment was nephrotoxic. Pure solutions of hemoglobin and myohemoglobin are not nephrotoxic, but hematin, a normal degradation product, is toxic and causes an intense renal vasoconstriction and tubular damage. These, however, are

not the sole agents of tubular damage, for their role in the genesis of the lesions is still not completely explained. Adenosine pyrophosphate is nephrotoxic and is liberated from the crushed muscle tissue. In addition, various catabolic products of muscle function have been proved capable of producing kidney damage. For instance; Navasquez states that the distal convoluted tubule damage of the crush syndrome resembles that produced in animals by the injection of uric acid and acid sodium phosphate, and Dunn states that lithium monourate produces the same damage with the exception that there are none of the tubulo-venous lesions seen in crush syndrome pathology. In addition to this, Dunn was able to extract a nephrotoxic substance from damaged muscle which he states is unstable, non-dialyzable and formed only under anaerobic conditions.

Just as there are many theories as to the pathogenesis of the lesions of the crush syndrome, so there are many as to the proper therapy for the condition. In general, the recommendations for therapy have followed a course of development parallel to that of the theories of pathogenesis. At first, when the precipitated pigment was thought to be the cause of the renal failure and its precipitation the result of a combination of aciduria and

myoglobinuria; the major premise governing therapy was that the urine should be made alkaline in reaction to prevent precipitation of the pigment.[7] This theory has been more or less abandoned since, in some cases, the urine was shown to be alkaline all during the course of the illness, and also to the fact that some workers have failed to reproduce the lesions by the use of injection of metmyoglobin in the acidified dog.[2] In addition, the precipitation is now assumed to be secondary to the tubular necrosis which occurs and so it would seem that attempts at therapy should be directed towards the prevention of this development. This would mean that the cases would have to be subjected to vigorous therapy within the first three days.[27]

The course of therapy, therefore, would depend upon which of the theories for the development of the tubular necrosis is accepted. Renal ischemia has been suggested as the basic mechanism and this may be the result of shock, the presence of a vasoconstrictor substance in the blood stream, or the elevation of intra-renal pressure. For the first of these, the treatment is obvious and consists of the restoration of the normal circulating blood volume with the hope that the destruction of the kidney substance has not progressed too far. Pyrogens have been

suggested as a means of combatting the generalized vasoconstriction to prevent renal ischemia,[2] while Peters has suggested the use of decapsulation to relieve intrarenal pressure and thus bring about the same result.

Since it has also been claimed that the renal damage may be the result of the presence in the blood of a nephrotoxic substance which originates in the crushed muscle, it would seem logical that some means of preventing this material from reaching the kidneys should be adopted. This gave rise to the plan of applying alternate positive pressure bandaging to the crushed extremity or the use of freezing of the member. However, it remained for Trueta to point out that there existed a normal mechanism in the kidney to prevent damage to the vital cortical tissue by blood-borne toxins.[28] He points out, however, that the over-working of this protective mechanism is probably responsible for the damage to the kidney, and so this should be avoided. Therefore, it would seem that a combination of two plans would be the logical procedure so that too much of the toxin could not get into the bloodstream in the first place and when the operation of the normal neuro-vascular mechanism for the protection of the renal cortex begins, the nerves for its control could be blocked to prevent prolonged ischemia of the cortical tissue. Thus, the use of pressure bandaging of the ex-

tremities and splanchnic nerve blocks is suggested.

In those cases where renal insufficiency has supervened, the problem assumes grave proportions and would seem to consist of maintenance therapy until the tubular epithelium has a chance to regenerate, so that the kidney can take up its normal function. It is in these cases that the use of continuous peritoneal lavage and the artificial kidney has been considered the only course.

It would seem, therefore, that a logical course of therapy in cases of lower nephron nephrosis would be, first; the problem of combatting shock, second; the prevention of the failure of the kidney by the use of the pressure bandage or freezing techniques on the extremity, and failing in the last; the use of the artificial kidney or peritoneal lavage to tide the patient over the period of oliguria which seems to last for about 11-12 days. From here on, the therapy would be that of a normal convalescence.

In summary, the following considerations seem to be of outstanding importance in the syndrome of lower nephron nephrosis following crushing injuries:

1. Common to all cases is a crushing injury to muscle tissue with necrosis of the muscles involved.
2. There is destruction of the epithelium of the distal convoluted tubules resulting from overwork of

the normal neurovascular protective mechanism of the renal cortex, followed by the precipitation of myoglobin in the tubules and acute renal failure.

3. Therapy in these cases falls into three categories:

   (1) Emergency treatment of shock.

   (2) Maintenance during the phase of oliguria and anuria.

   (3) Reparative therapy during the early phase of diuresis followed by therapy of the convalescent.

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