RATIONALE FOR VASOCONSTRICTIVE THERAPY OF INFLAMMATORY EDEMA*

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THE PERSUAL of current dermatologic literature for specific information as to the role of edema in various dermatologic disorders reveals a paucity of information on edema which is applicable for the busy physician. Edema is a commonly concomitant finding which accompanies many diseases, both of the skin and of other tissues and organs.

Edema causes the omnipresent swelling in parenchymatous tissue which is produced by the process of inflammation. Edema (1) is defined as an "excessive accumulation of fluid in the tissue spaces; due to disturbances in the mechanisms of fluid exchange. There may be a decrease in osmotic pressure of the plasma from reduction in protein concentration, increased hydrostatic pressure in the capillaries due to cardiac failure, increased permeability of the capillary walls from injury or inflammation, or there may be obstruction of the lymph channels."

The significance of edema in disease has been of prime importance to most inquisitive physicians since the first description of Celsus.

Edema is only one manifestation for the presence of inflammation. Hence, one cannot exclude the fundamental condition of inflammation when the highly important subject of edema is to be considered. Dible(2) recorded that "the reaction of living tissues to injury is known as inflammation." Christopher(3) wrote that inflammation is the most fundamental of all pathologic processes. He noted that "not only is the surgeon concerned with removing irritants and aiding the tissues to resist their action, but he produces some degree of inflammation with every stroke of the knife. Moreover, inflammation blends so imperceptibly with the process of repair that it is impossible to say in any given case where one ceases and the other begins."

Wounds are characterized by the cardinal signs of inflammation which are rubor (redness) turgor (edema or swelling), calor (heat), dolor (pain or itching) and functio laesa (loss of function). Some pathologists include only those aspects of local change which are exudative in nature when considering the process of inflammation(4).

In spite of being obviously important, the subject of tissue edema has not received much enlightening information in the literature as to its exact role in disease.

The authors questioned some colleagues about their thoughts as to the significance of edema. Few of these doctors placed much stress on its presence. The mutual thought on this topic was that something should be done to relieve its pressure if it produced discomfort to the patient or if it interfered with normal function.

This reaction reminded the authors of the profession's attitude to the presence of pus many years ago. Pus was laudable at that time. However, the passing years have changed the profession's attitude to "laudable pus" when its real significance became both known and understood.

Karsner(5) wrote: "The inflammatory reaction is principally on the part of the mesoblastic tissue. Included are (a) changes in the blood vessels and blood within them, and (b) proliferation of cells of the supporting connective tissue. These are concerned with all kinds of exudative inflammation. Parenchymal cells are involved in what is called alternative inflammation, but that involves degeneration and necrosis rather than proliferation. The blood vascular reaction begins almost immediately after injury. The reaction in the connective tissue is delayed for a short time but may be observed in less than a half hour. The vascular alterations lead to exudation. Cells of the exudate and some of those of the fixed tissues remove debris and bacteria; they cleanse the region."

However, this cleansing action through exudation, if it reaches uncontrollable proportions, can create a most serious situation by this outpouring of blood serum, as in the case with extensive burns. Hence, such an untoward and unbridled exudative situation can very well lead to a very serious and severe state of hypoproteinemia(6).

One of us demonstrated the pathologic action

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which trauma is quite capable of exerting on parenchymatous tissue. The mere presence of "locked-in" blood serum might be capable of releasing leukotaxin (Menkin) which is capable of attracting a definite fibroblastic response(7). Such a bodily reaction is connected definitely with the early phase of tissue healing. However, if such a response becomes marked it can initiate a piling-up of fibroblasts. Keloids or hypertrophic scars may well be the end result.

In order to treat such unwarranted tissue response, Gathings(8) employed hyaluronidase and Kutapressin. This investigator reported that "this is probably the best method for treating keloids and hypertrophic scars with the aim of causing softening and resolution."

Recently, it has been demonstrated that hyaluronidase is biologically antagonistic to the bioflavinoids, such as hesperidin(9) and quite possibly the concomitant use of vitamin C, which definitely exerts a synergistic action with these bioflavinoids.

The exudative phase, connected with the highly important phenomenon of inflammation, is enhanced definitely through vasodilatation. The blood vessels in the affected area become dilated and hyperemia is produced. Along with vasodilatation goes increased capillary permeability and a disturbed osmotic pressure of the walls in the vascular tree. Hence, an outpouring of fluid results in the parenchymatous tissue. This is known as edema.

Edema is the principal cause for tissue swelling. Boyd(10) stated that "the exudate which collects at the site of irritation is partly derived from the blood (hematogenous), partly from the tissues (histogenous). The various forms of leucocytes of the blood migrate through the vessel walls; the blood plasma also passes out, and gives rise to the formation of fibrin; the wandering cells of the tissues accumulate at the site of irritation. These three constitute the inflammatory exudate." Boyd states also that "the amount of the exudate varies greatly, depending on two main factors, the irritant and the site. (1) The bite of a mosquito and the sting of a nettle are examples of irritants which cause a marked outpouring of fluid. In a blister the exudate is almost serous . . . (2) The more open the tissue, the greater will be the exudate. It is most marked in serous sacs (pleurisy, peritonitis). In loose cellular tissues the fluid may be abundant . . . In such dense structures as bone the amount is negligible"(11).

Boyd gave a poignant relationship of inflammatory changes to the well-known cardinal signs of inflammation(12). He related that "the heat is due to the increased amount of blood flowing through the part. The redness is also caused by the local hyperemia. The swelling is to be attributed in part to the vascular dilatation, but much more to the accumulation of exudate in the tissues. The chief constituent of the exudate responsible for the swelling is the lymph, the accumulation of which leads to inflammatory edema . . . The pain is caused by pressure on the nerve endings . . . Loss of function, varying in degree is partly due to pain, partly due to destruction of tissue," and possibly, we might add, because of the infiltration of tissue by the edema which invades the injured areas.

According to Moore(13) the causes for shock are due to capillary injury and increased capillary and cellular permeability, which produce marked changes in fluid and electrolytic economies of the body. Moore(14), in discussing the pathologic alterations in effective filtering pressure, states that "normally the outflow and the inflow from the vessels are delicately balanced, but under pathological conditions the outflow may greatly exceed the inflow, and fluid may accumulate in the tissues — a condition designated as 'edema'. Thus if the gradient of pressure is shifted toward the venous side by arteriolar dilatation, as in local or general increase of temperature and inflammation, greater amount of fluid will promote the movement of fluid from blood to tissue. Generalized edema or an anasarca is usually more conspicuous in the lower extremities, where the hydrostatic pressure of the long column of blood is effective."

It appears obvious that the production of tissue swelling is the result of edema formation. Edema is but a part of any viable tissue's reaction to injury. If this formation becomes excessive, many substances wholly important to the body's economy can become lost. Vital protein substances and electrolytes are excreted in the bandages which cover such wounds. Any clinician has only to remember such marked losses which arise in connection with extensive burns. If allowed to persist for some time, and if these precious substances and fluids are not

replaced rapidly, shock can be expected. Hence, transfusions are employed to replace such losses. Pressure bandages are used to stop or at least control the loss of these life-sustaining materials.

Therefore, it is mandatory that each clinician employ every therapeutic means to conserve those important elements which are found in the exudative outpouring as the result of burns, disease, or other aspects due to trauma.

This subject is too comprehensive to review all the conditions where such massive loss of tissue fluids exist.

This subject of edema formation and its extravasation from the body's economy has been a problem which has intrigued the writers for many years. Perhaps this conservation of edematous exudate with vasoconstrictive means is the reason why Sano and Smith(15) studied the effect of lowered temperature upon fibroblasts which were grown in vitro. These investigators found that temperatures between 5 and 10 degrees Centigrade were bacteriostatic. Furthermore, these observers discovered that temperature of 20 to 25 degrees Centigrade were adequate for wound healing in the deeper tissues where connective tissue repair was taking place. It has been known generally for many years that cold causes a narrowing of the apertures in blood vessels. Vasoconstriction, through the application of cold as with the use of ice packs slows the circulation around a healing wound. Thus, the products of metabolism remain in close contact with the cells for a longer time than they could if the blood stream became accelerated.

It is known that the use of a firm compression bandage produces some vasoconstriction. This same vasoconstriction effect can be produced at least partially through the use of tension sutures which compress the gauze dressing of wounds. We have had plenty of opportunities to test this belief, and we have observed both the better conservation of tissue fluid coupled with a more rapid healing rate of such surgical wounds. Furthermore, the chance for the formation of hypertrophic scars and keloids appears to be lessened markedly if the above measures are employed.

As has been stated heretofore, severe burns are notorious for producing marked losses of precious tissue fluids through overproduction and loss of edematous fluids. To put our hypothesis to a test, and in order to determine if vasoconstriction of a burned area can enhance the healing process, we compared vasoconstricted burns with those cases who were not given vasoconstrictive measures(16). It was found that the excessive formation of tissue edema distinguished second degree from first degree burns. We thought that second degree burns could be converted into first degree burns by inhibiting this serous exudate. And so a small series of cases with second degree burns were treated with a sulfathazole-allantoin ointment with compression bandages. The average healing time was 34 days per case. Then a similar series of cases with second degree burns were treated in like fashion. However, beforehand, each case was given a non-toxic injectable material* subcutataneously to vasoconstrict the burned areas. It was found that when vasoconstriction, ointment, and compression bandaging were employed, these burns healed nearly five times as fast as when this vasoconstricting agent was not used. Therefore, it seemed possible to convert second degree burns into first degree burns and thus lessen the average healing time for these burned areas.

We felt that the trauma connected with child birth produces marked edema in the post-gravid uterus. Hence, post-partum lochia could be considered as a special form of exudation. It was our desire to determine if vasoconstrictive measures in these post-partum patients would control the lochial discharge(17). It was found that Kutapressin, a new non-toxic selective vasoconstrictor, was successfully used in 68 consecutive post-partum cases to suppress lochial discharges. By the sixth post-partum day, the lochial discharges were eliminated. Furthermore, uterine involution appeared to keep pace with lochial control under this therapy, while those patients in the control group, and who had not received Kutapressin (vasoconstrictive) therapy, showed no similar findings.

Edema production is marked in cases with poison ivy dermatitis. Local measures, such as moist compresses with Burow's solution, are used routinely to relieve the intense itching caused by the excessive formation of tissue edema in the integument. It has been found

*Kutapressin, a non-toxic vasoconstricting aqueous solution which is prepared from liver by a series of fractionations. This material is manufactured by the Kremers-Urban Company of Milwaukee. It has been demonstrated definitely that Kutapressin will not affect systemic blood pressure.

that the signs and symptoms produced by contact with poison ivy in susceptible patients can be relieved rather dramatically by producing vasoconstriction in these edematous skin areas with the use of Kutapressin(18).

Unpublished observations by the authors have been obtained in other cases where the presence of edema is an important factor. Cases with angioneurotic edema, Quincke's disease, and pruritus ani have responded adequately to therapy with the non-toxic vasoconstricting injections. Although our experiences with cases of hydrocele, hydrothorax, and ascites, due to hypoproteinemia are not extensive, the therapeutic results have borne out the contention that vasoconstrictive measures, as with the use of Kutapressin, bring highly acceptable results wherever the presence of edema happens to occur, and if other concomitant serious pathologic lesions, such as malignancies and cardiac decompensation, are not present.

It is not the intent of the authors to give anyone the idea that the use of this vasoconstriction procedure produces a completely specific result. But as far as we are aware, this procedure appears to be the best which happens to be available at this time.

We feel sure some colleague will desire to mention the use of the steroids for the treatment of such edematous conditions as have been mentioned in the course of this paper. Allow us to quote the experience of Professor Cleveland J. White, of Chicago, who, while discussing the problem of chronic urticaria(19), had the following to state: "I might mention at this time that Kutapressin used symptomatically in my hands over the past seven months, has given brilliant results. This preparation is a vasoconstrictor put out by the Kremers-Urban people in Milwaukee . . . It is amazing the number of cases I have had which did not respond to the steroids, but did respond to Kutapressin in symptomatic relief; and sometimes resulted in a definite cure while we were attempting to uncover the etiologic factors."

CONCLUSIONS

The exudative aspects of edema probably exert a cleansing action in traumatized tissue. If the exudate becomes inspissated, fibromatous changes may occur, as exemplified by hypertrophic scars and keloid formations. The treatment of edematous states, as in burns, the postpartum uterine lochias, and exudative lesions, as seen in poison ivy cases, show more marked and more rapid healing when such areas are vasoconstricted. It is the opinion of the authors that edema does not serve a very useful purpose. Its suppression brings about better healing in those varied diseases which have been treated by the authors with vasoconstrictive measures.

Recently, Overman(20) wrote: ". . . Some attempts should be made to reduce edema whenever and wherever it forms . . ." This constitutes important advice to the clinician whenever this aspect of inflammation is discovered.

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