Inflammatory Edema and Capillary Hemorrhage

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Many diversified human diseases carry an edematous component which is caused by inflammation or trauma. The edema itself is produced by a marked dilatatory state of the microcirculation, which causes increased venous pressure and increased capillary permeability. A most logical therapeutic approach is based upon the constriction (and, therefore, the correction) of these dilated vessels. The author has been able to obtain more than adequate therapeutic response with Kutapressin†, a satisfactory microcirculatory constrictor, which apparently adequately controls both capillary hemorrhage and inflammatory edema; these are closely related etiologically.

A NOVEL METHOD for teaching various aspects of clinical medicine might be through the use of riddles or conundrums. Here is an example: What do the allergies, acute prostatitic inflammations, infections, and other tissue inflammations have in common? The obvious answer is *tissue swelling*. All of these clinical entities show various grades of tissue swellings, which, in turn, are produced by tissue edemas. Inflammatory edema is a particular form which accompanies infection, trauma, or a combination of both etiologic factors.

One of the first observations a clinician witnesses when a patient has been traumatized by infection or physical force is the presence of tissue swelling. A blow to the eye region produces a pronounced puffiness of this facial area; the discoloration comes later. The first measure most persons take to reduce the swelling is to apply an ice bag; or they might treat the swelling by wrapping a raw steak around the involved area, having the misguided idea that the meat will draw out the swelling. The use of an ice bag possesses more merit because it, at least, is physiologically sound; the cold decongests the inflamed tissue by slowing down the increased blood supply to the injured area.

But what produces this tissue swelling primarily? Again, the involved area has experienced some form of trauma. The injury might have been caused by thermal agents, as those which are produced by a severe burn; or the trauma might have been caused by bacterial infection, which caused the inflammatory tissue response. Another common type of tissue swelling is caused by an insect sting (formic acid); or a patient could readily obtain an untoward tissue swelling response by sitting in a poison ivy patch—the television and radio reports as to the value of a current oral poison ivy preventive preparation notwithstanding! A friendly wifely swat to a husband's smirking visage can produce the telltale facial swelling which is subsequently reported to have been caused by a swinging door. The cold knife blade approach usually follows to reduce the evidence of such an untimely encounter.

Any form of trauma, as exemplified by such a

†Kutapressin® is manufactured by the Kremers-Urban Company, 141 West Vine Street, Milwaukee 1, Wis.

blow, can produce tissue swelling, but, unfortunately, it is not explained that easily; nor are all the scientific answers presently known to explain such a common episode. By the time all the smoke has cleared sufficiently, several important events have taken place in the traumatized area which are most worthy of further examination and explanation.

The traumatizing factor, be it a lowly bee sting or the intense heat from boiling water or oil, has, by its force, released certain pathologic chemicals in the injured tissue area. These substances produce a final marked dilatation of the microcirculatory blood supply to that area. The capillary permeability of the walls of these tiny vascular containers now allows the fluid contents to leave these vessels, the newly released fluid invades the adjacent tissue spaces, and tissue swelling takes place (1). Furthermore, venous pressure increases markedly, which event further increases the venous congestion in the involved area. This occurrence further tends to increase the presence and the scope of the tissue swelling. If on or near the surface of the body, this traumatized area can be seen to "puff up."

Now, let us examine these events as they occur in some of the common diseases, for these findings are observed daily in any physician's practice.

The Skin Allergies

It seems to me that lately many more patients exhibit various and more allergic disturbances than were discovered, say, 20 years ago. Patients now consult their physicians for reactions to the sulfa drugs, for procaine reactions, for reactions to tetanus antitoxin (horse serum), and for untoward penicillin reactions. The cause for such increase is that the patients are building up states of hypersensitivity to these foreign substances, perhaps because of their unlimited and untimely use for nonessential maladies, as for treatment of colds and the like.

One of the first symptoms such patients experience with these atopic reactions is generalized itching, perhaps because of the formation of a generalized dermal edema which irritates the skin nerve endings and thus produces itching, which is the precursor of pain stimulation. If the untoward allergic response progresses, the patient will note the rapid formation of skin wheals (hives) which itch intensely. If these are not adequately treated, an edema of the patient's glottis may occur, in which case, a pen-knife tracheostomy must be performed to enable the unfortunate patient to breathe.

This constitutes a striking example of tissue swelling (edema) produced by an atopic reaction (2).

The Hemorrhage Response

It might come as a shock to my readers to regard bleeding as being associated with those responses which accompany edema formation. But, considering that some of the events which produce edema are caused by fluid leaving the minute blood vessels in a traumatized area by means of diapedesis, then it can be seen that the relationship between fluid loss and its escape from the vessels is really a form of edema formation. With frank hemorrhage (rhexis) the continuity of these vessels' walls has been interrupted and the fluids escaping from these minute vessels invade the surrounding tissue because of the holes (large or small) in the vessel walls. What difference does it really make whether or not these vessels lose their blood because of rhexis or diapedesis? The results are the same, pathophysiologically speaking (3), and it would be well to bear this logic in mind, particularly when therapy is discussed.

The Diarrheal Response (Flux Formation)

It has been demonstrated repeatedly that inflammation of the gut walls takes place as a forerunner to the formation of diarrhea. In such an event, some alimentary toxin or toxins have produced gut inflammation, which is followed by a marked vascular dilatation of the vessels of the gut walls. The familiar edema-response is then set into motion, and the dilated gut vessels (intestinal microcirculation) spill their escaping fluid into the very thin gut walls. The close proximity of the alimentary lumen allows this vascular fluid to become siphoned out, and the fluid is forced into the intestinal lumen, thereby forming the diarrheal flux. Again, I ask that my readers bear these pathophysiologic events in mind when the newer therapy for diarrheal flux is discussed (4).

Fibroid and Keloid Formations

I have shown previously that edematous fluid invasion of normal tissue, if not removed presently, causes a chemotaxic response which produces an invasion with fibroblasts and a consequent piling up of such tissue. For example, when a wrestler or a pugilist suffers a severe blow to the parenchymatous tissue of his ears, an invasion of edematous fluid occurs in these damaged auricular tissues. If not removed reasonably soon, fibroblasts begin to invade this traumatized area, thus producing the well-known "cauliflower ears." During my college days, every participant in these sports was taken immediately to the University dispensary, where the edematous fluid was withdrawn with a needle and hypodermic syringe. This simple therapeutic procedure eliminated the later formation of the disfiguring aural lesions which are commonly known as "cauliflower ears." To my knowledge (I recently had the opportunity of discussing the above procedure with a university wrestling coach), cauliflower ears have never occurred in wrestlers who have submitted to this procedure.

Some years ago, I had many opportunities to test the aforementioned procedure in reverse; for I repeatedly injected certain circumscribed small thigh areas on myself with serum taken from myself and serum obtained from other patients. Control areas on the opposite thigh received normal saline solution. No growths occurred. But in those thigh areas which received the multiple blood serum injections, when these areas (plus the control areas) were extirpated by myself under local anesthesia, the tissue specimens showed definite early keloidal growths (5).

Injecting the uteri of virgin dogs with their blood serum, with the hope of producing uterine fibroids, was not successful. It was discovered later that dogs are not, as a rule, subject to fibroids. Lack of funds prevented my repeating the same procedure on virgin monkeys. When one recalls the crampings and squeezings which accompany all the menstrual cycles every female endures, it is no wonder that the trauma of birth might force some of the blood serum into the uterine walls and thus cause the subsequent growth of fibroids (6). It would be highly interesting if a research-minded surgical colleague would try the above experiments in suitable animals to try to produce uterine fibroids from inspissated blood serum.

Pulmonary Fibrosis and Retrolental Fibroplasia

Let us now give some consideration to two lesser known diseases which may well exhibit similar pathophysiologic aspects. Interstitial pulmonary fibrosis perhaps contains a tissue allergy background. One of the first tissue responses to injury in this disease is the exudation of serous fluid, which invades the lung. One of the main causes for this marked serous exudation (edema) is the presence of the markedly dilated capillaries. The inspissated serum, as was the case with early keloidal growth, cannot escape, and it exerts a chemotaxic response which attracts fibroblastic infiltration, which attacks the alveolar walls, and deposits collagen and reticulin.

To summarize: an allergenic response produces capillary dilatation; the blood serum leaves the capillary vessels and invades the alveolar walls, and a fibroblastic invasion follows. So we can note the marked similarity which exists between each of these separate diseases. The basic pathophysiologic similarity is the insult to viable tissues, which is followed by capillary dilatation and invasion of the edematous transudate, which, in turn, sets off a fibroblastic tissue invasion and the subsequent replacement of normal, functioning tissue with fibrous tissue (7).

Retrolental fibroplasia is an involvement of the retinal blood vessels which later become detached, causing subsequent loss of vision. This disease is thought to be produced by high oxygen concentrations. Later, the retinal vessels become markedly dilated, and a serous exudation (edema) is produced, which process is followed by a retinal fibroplasia and loss of vision. Here again is met the aforementioned cycle; namely, tissue injury (caused, in this case, by excessively high oxygen concentrations), which produces retinal vessel dilatation, then excessive edema formation, and then the influx of fibroblasts (8).

Acute Benign Prostatic Hypertrophy

The last disease entity which will be examined, but by no means the only other comparable patho-

which remove much of the thick, nonpharmacologically active substances. Among the toxic ingredients removed are the materials which both increase and decrease systemic blood pressure; so the purified product (Kutapressin®) exerts no known ill effects upon the systemic blood pressure. The final product is non-allergenic, and it shows practically no minimal lethal dosage of clinical importance; as a matter of fact, an entire ampule (10 cc.) of Kutapressin® can be administered subcutaneously at one time without any known danger, since it has no known contraindications.

The usual dose is two cubic centimeters, given subcutaneously in an uninvolved arm area. If a patient has a marked or a generalized or a particularly large edematous area, five cubic centimeters can be administered initially with comfort to the recipient. This dose can be repeated as indicated or desired, since it absorbs readily and it is not painful upon administration.

A few clinical examples may help my readers to better understand the use of this medication. A three-year-old boy, weighing only 20 pounds, was brought to the office. Malnutrition was obviously present, with the usual accompanying rachitic signs. This child had passed 12 blood stools that day, and he was markedly dehydrated. But what brought this child to us was the rectal prolapse; the rectum protruded about six inches. The child had just been released from an osteopathic hospital, where the physician had manually replaced the rectal prolapse every time it herniated.

The child was immediately given two cubic centimeters of Kutapressin® subcutaneously, and the diarrhea, which was rapidly causing the marked dehydration, stopped completely upon administration of this injection. The child was hospitalized promptly, and subcutaneous fluids were administered. He received what most physicians would consider a massive dose of Vitamin D—10,000 units per day. Within a week's time, the child had gained eight pounds, his bowel movements became normal, and the erstwhile rectal prolapse reduced itself. The boy has continued to gain weight and remained well.

Since he was seen, I had a similar case in which the rectal prolapse again corrected itself with the strengthening of the child's rectal musculature. As with the first child, the diarrheal flux was terminated immediately by the use of Kutapressin®, because the markedly dilated gut microcirculation became vasoconstricted, thus preventing further exudative responses and, therefore, preventing further diarrheal flux.

A few days before this writing, an adult male patient reported stacking a hay bundle which contained poison ivy. When I saw him, his penis and its foreskin exhibited a marked phimosis and paraphimosis. Because of the action of the highly toxic urushiol which the poison ivy contained, the microcirculatory vessels of the involved penile areas had become noticeably dilated, and edematous involvement ensued, producing phimosis and paraphimosis with marked weeping.

Five cubic centimeters of Kutapressin® were administered subcutaneously in the arm, whereupon the severely involved areas began to lose their edematous infiltrations. The patient was hospitalized and two hours later received a repeat dose of Kutapressin® (5 cc.). Within six hours after I first saw this patient, his penile areas were normal, and he was discharged from the hospital on the day after his admission. Kutapressin® had been employed to constrict the dilated penile microcirculation, which was the source of the edematous invasion in the involved areas.

The rationale behind this new therapy is simple to understand, when one has the facts concerned with these disorders.

The described therapeutic procedure should be confined to patients who have edemas of inflammatory origin. Kutapressin® will not be effective in patients who have edemas of heart, kidney, or other areas if inflammation is not the essential factor.

It has been previously mentioned that this preparation has been used adequately to stop capillary types of hemorrhage, particularly in patients who have had tonsillectomy.

Another male patient, 63 years of age, complained of bleeding from his penile orifice. I received the following report from his Board urologist:

Mr. X has had a prostatic resection and has quite a tendency to bleed from inflammatory polypi, which developed in and around the prostatic bed. In March, 1958 he was brought to me as an emergency with a bladder full of blood clots. I then cleared the bladder clots and electrocoagulated the bleeding areas. He got along very well all summer, but was

physiologically produced disease with a comparable etiology, is the acute form of benign prostatic hypertrophy. Numerous other diseases show similar disease cycles which can be triggered by a dilated microcirculation; however, this prostatic type of disease is described here because it lies in an entirely different part of the human body.

It has been demonstrated repeatedly that bacterial infections and other forms of trauma produce a markedly dilated microcirculation in patients with the acute form of benign prostatism. This marked dilatation of these prostatic vessels allows the blood serum to escape and invade the glandular parenchyma; hence, the acute forms of this disease always contain an edematous component. If left undisturbed and untreated, a marked fibroblastic influx follows, which tends to replace the edema with fibroblastic overgrowth; thus, this pathophysiologic cycle has many points of similarity with keloidal growth elsewhere in the body (9).

The chronic forms of prostatitis have lost the edematous component, and these glands have become fibrosed markedly.

All the various diseases which we have discussed, plus many, many more diseases which we have not mentioned, exhibit diseased microcirculations, exemplified by the presence of marked dilatation of the tissues' microcirculation. Edema is formed because of the subsequent escape of the blood fluid which invades the adjacent tissues. Unless the clinician removes the inspissated edematous fluid, a fibroblastic invasion ensues, which invades the erstwhile normally functioning tissues, causing scar tissue or even a piling up, due to the formation of excessive fibrous tissue infiltrations.

The clinician will do well to remember always the adverse role which can be played by the presence of edema formation produced because of microcirculatory dilatation (10). Therefore, whenever the question arises as to whether or not to rid the involved area of the invading edema, the answer invariably must be a resounding YES, and the sooner the better.

Specific Therapy for the Removal of Tissue Edema

The hypothesis presented did not evolve overnight, but came as a result of more than 20 years of hard work, and it appears that it will take another 20 years to persuade my medical confreres to drop their current views on edema formation in favor of this new approach.

The data were unfolded as I began treating successfully with a single medication patients with acne vulgaris, then keloids, and finally numerous other disorders. Many colleagues inquired how one medication could give adequate therapeutic results in so many diversified cases. The answer becomes quite understandable when one recalls that all these diseases exhibit microcirculatory dilatations, a marked edematous component, and fibrosis if the patient is not adequately treated. A successful medication must exert its pharmacologic effect upon one or another of the pathologic dilated vascular components, which is exactly what the medicament used does. It constricts the dilated microcirculatory vessels and thus prevents further edema formation and eventual fibrous tissue invasion. We have plenty of drugs which constrict the dilated systemic vessels, but to my knowledge, no other material is now known which is limited to a specific microcirculatory constricting action. This knowledge is of recent origin and is the result of many clinical studies which were performed by myself and my various research colleagues.

By correcting the omnipresent microcirculatory dilatation which allows the formation of transudatory edema of inflammatory nature, we prevent its occurrence. In so doing, we prevent, furthermore, the resulting sequelae, such as the edematous exudates which follow gall bladder surgery, the lochias which follow the trauma connected with childbirth, and even the hematogenous exudates which produce epitaxic episodes, as well as a host of other exudatory phenomena. Since prevention is the best form of therapy, by vasoconstricting the microcirculatory components of inflamed tissues, we thus prevent these various and lesser understood exudatory signs which can accompany many diseases (11).

Kutapressin,® the Microcirculatory Constrictor

The substance is derived from crude liver by a series of selective extractions and concentrations,

in the office in November, 1958 and stated that he had again some hematuria. At the time of the office examination the urine was free of blood but showed considerable pus and I prescribed Terramycin®. If the bleeding is not profuse, treatment of the infection might suffice. If it is profuse an indwelling catheter for a few days should prove beneficial. He does not have cancer.

I did not employ a catheter, although the patient continued to bleed profusely; but he was given the above antibiotic, which rapidly cleared the urinary infection. He also received daily Kutapressin® injections in an arm area (2 cc.), and within 24 hours, the hemorrhage stopped. He went for three days without further therapy, then he began again to hemorrhage from the penile orifice. He again was given a Kutapressin® injection, and within 12 hours the bleeding stopped. Now, whenever he notices the onset of bleeding, he reports for therapy, and the Kutapressin® injection controls the bleeding from three to eight days. He has been able to build up and maintain his blood count adequately, and he has not missed a day's work since receiving the Kutapressin® control for his bleeding inflammatory polypi.

What has this form of therapy done to control such hemorrhage? We succeed, apparently, in vasoconstricting the markedly dilated microcirculatory components of these polypi with Kutapressin®. I believe that properly constricted capillary vessels will not hemorrhage (via diapedesis, which is strikingly similar to the pathogenesis of an inflammatory edematous transudate). There is no reason to hemorrhage, because the *capillary permeability* of these vessels is *not increased, nor is venous pressure increased.* On the other hand, when these same blood vessels become dilated, then both the capillary permeability and venous pressure become greatly increased, thus inviting diapedesis to recur.

Recently, a lad of five was run down by an automobile. The only pathologic finding noted upon examination (followed by extensive x-ray studies) was a hemorrhage from the right ear canal. This area continued to bleed until 15 minutes after the administration of two cubic centimeters of Kutapressin®. The hemorrhage has never recurred. The bleeding seemed to be a capillary type of oozing, similar to the oozing which is noted upon surgery of the abdomen. Apparently, the vasoconstricting effect from this preparation adequately stopped the further oozing of blood from the ear canal.

Whenever a capillary form of oozing of blood occurs anywhere in the body, it has been our practice for several years to administer immediately Kutapressin® therapy to control hemorrhage. Naturally, if a sizable blood vessel is cut, it must be tied and transfixed immediately; but the capillary type of bleeding usually responds rapidly and adequately to vasoconstriction with the use of Kutapressin®.

Another youngster, age nine, was struck by a car, and the only pathologic finding was blood, which was found upon repeated spinal taps. The patient received Kutapressin® in two cubic centimeter doses every four hours. The bloody spinal fluid cleared, and the child made an uneventful recovery within a week after injury.

No hypothesis is worth its salt if its therapeutic applications do not give the clinician and his patients adequate therapeutic results. Although I could continue extolling the value of this new therapy, few colleagues would be impressed; for the best method of allowing oneself to become "sold" on a new idea or procedure is to try it, not just on one patient, but on at least a half dozen or more suitable patients. After doing so, if you do not obtain suitable results, then write and inform me that a terrible mistake has been made; but at least try my suggestions. After all, you might be pleasantly surprised; for, as the old adage has it:

The proof of the pudding is in the eating thereof!

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