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# EARLY TREATMENT OF SEVERE BURNS*

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# EARLY TREATMENT OF SEVERE BURNS*

*Consulting Editor and Conference Chairman*
CHARLES L. FOX, JR.

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## Part II. Metabolism



## Part III. Metabolism, Heat Loss and Toxic Factors

## Part IV. Fluid Therapy



## Part V. Systemic and Local Infection and Immunity

# OPENING REMARKS

Charles L. Fox, Jr.
*Columbia University, College of Physicians and Surgeons and Bellevue Hospital, New York, N. Y.*

Members of the Conference, members of the Academy, and invited guests, it is a pleasure to welcome you to this conference. The importance of our subject is emphasized by the recent announcement of over 12,000 deaths from fire in the past year with over two million patients hospitalized with extensive burns. When this conference was in the talking stage, and those of us who thought that a gathering of investigators interested in the problem of thermal burns might be a valuable experience, many feared that only a small group would talk to one another and say the things they have been saying for years and that nothing new would result.

There seemed to be a way of avoiding this sterile exchange by inviting anyone and everyone to submit a paper and then to attempt to select what was new and well done and try to put the pieces together into a coherent program. As you can see by scanning the names on the program, there are many familiar names and there are many unfamiliar names, and I particularly would like to welcome the unfamiliar names to this conference. All of us who have been working in the field for some years are looking for new ideas, new thoughts, new approaches, and—most of all—new people who will go further than we have been able to go and, hopefully, solve some of the unsolved problems and accomplish some of the things that we have not been able to accomplish.

The premature death of Dr. Gunnar Thorsén of Stockholm, a pioneer in the use of dextran and a student of blood rheology, saddens all of us and deprives us of the presence of a valued friend and important participant.

In conclusion I would like to thank all of the participants for their efforts and talents in this enterprise, the New York Academy of Sciences for undertaking the sponsorship of the Conference, and all those organizations which have so generously contributed grants to help defray the Conference expenses.

## Part I. Pathophysiology of Thermal Burns

# MICROVASCULAR PATHOPHYSIOLOGY OF BURNED TISSUE*

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## Introduction

A correct and adequate treatment of diseased or traumatized tissues and organs must be based on a thorough knowledge and understanding of the pathophysiological mechanisms underlying the signs and symptoms of abnormality. This statement, which is in itself obvious, is especially valid for burned tissue and for the disturbances in body function induced by severe burns.

The survival and normal functioning of the cells of the body are dependent on the integrity of the circulatory system. This includes transportation of the blood, with its different constituents, via the heart and large vessels to and from the tissues. Equally important is the fact that the blood is then distributed to the various parts of the cells of the tissue, via the microvascular system, to establish and maintain environmental equilibrium, i.e., homeostasis.

Microvascular disturbances, involving structure and function, constitute one of the major mechanisms in the patho-physiology of burns. They are, to a large extent, responsible for local tissue derangement and destruction in burned areas. It is important to emphasize that they are also responsible for the systemic circulatory failure occurring in severe burns. Furthermore, microcirculatory pathology is involved in the functional failure of parenchymatous organs, such as the liver, brain and kidneys.

Against this background, I am now going to describe the structure and function of the microvascular system in tissue injury, as analyzed by different methodological approaches in animals and man. These approaches include vital microscopy,§ light microscopy, microangiography, electron microscopy, and infrared thermography. I shall discuss some of the observed phenomena in relation to diagnosis and treatment. A major part of the presentation will deal with local tissue changes, because they constitute a basic problem in therapeutic considerations, and in evaluation of the usefulness or risk involved in different kinds of treatment. Microvascular disturbances in nonburned tissues, accompanying thermal injury will, however, also be described and discussed.

### *Microcirculation and Tissue Injury*

The microvascular disturbances, which occur during and after tissue injury, have been studied in our laboratory in various animal tissues and also in man.

* The investigations reported here were supported by grants from the Swedish Medical Research Council, the National Institutes of Health – HE 5724, Swedish Association against Heart and Chest Diseases and the Swedish Cancer Society. Research assistance by Miss M. Dunér, Y. Winsnes, A. Hornö, A. Bengtsson and B. Häggfors is gratefully acknowledged.

† Bombay, India.

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§ The vital microscopic observations and registrations were performed in a modified Leitz intravital microscope.

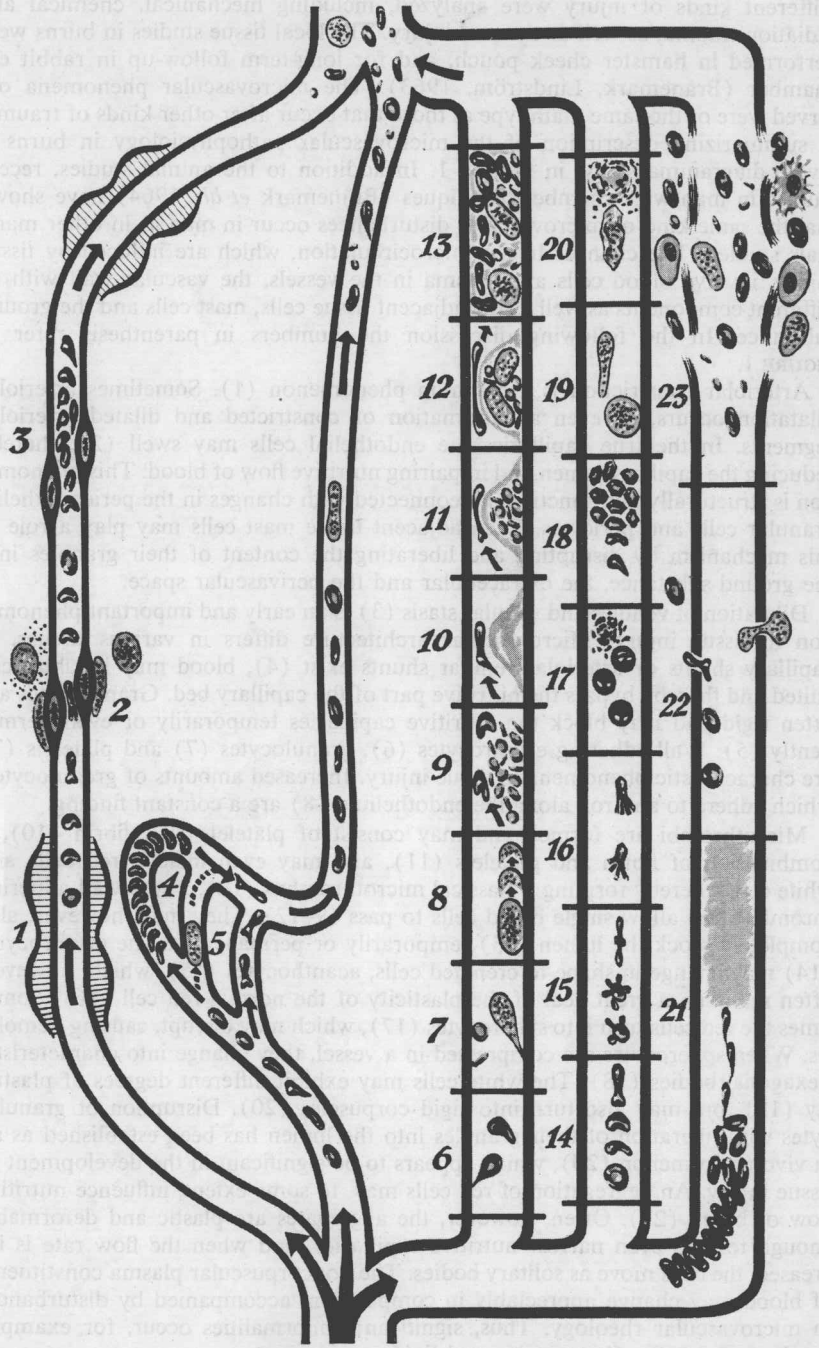


FIGURE 1. Diagrammatic representation of microvascular patho-physiology in tissue injury, including intravascular, endothelial and perivascular changes. For detailed description see text.

Different kinds of injury were analyzed, including mechanical, chemical and radiation trauma, as well as thermal injury. The local tissue studies in burns were performed in hamster cheek pouch, and for long-term follow-up in rabbit ear chamber (Brånemark, Lindström, 1963). The microvascular phenomena observed were of the same main type as those that occur after other kinds of trauma. A summarizing description of the microvascular pathophysiology in burns is given, diagrammatically, in FIGURE 1. In addition to the animal studies, recent studies in man with chamber techniques (Brånemark *et al.*, 1964) have shown that the same kind of microvascular disturbances occur in man as in other mammals studied. The changes in the microcirculation, which are induced by tissue injury, involve blood cells and plasma in the vessels, the vascular wall with its different components as well as the adjacent tissue cells, mast cells and the ground substance. In the following discussion the numbers in parenthesis refer to FIGURE 1.

Arteriolar constriction is a common phenomenon (1). Sometimes arteriolar dilatation occurs, or even an alternation of constricted and dilated arteriolar segments. In the true capillaries the endothelial cells may swell (2), thereby reducing the capillary lumen and impairing nutritive flow of blood. This phenomenon is structurally and functionally connected with changes in the periendothelial granular cells and pericytes. Even adjacent tissue mast cells may play a role in this mechanism by disrupting and liberating the content of their granules into the ground substance, the extracellular and the perivascular space.

Dilatation of venules and venular stasis (3) is an early and important phenomenon in tissue injury. Microvascular architecture differs in various tissues. If capillary shunts or arteriolar-venular shunts exist (4), blood may be short-circuited and thereby bypass the nutritive part of the capillary bed. Granulocytes are often rigid and may block the nutritive capillaries temporarily or even permanently (5). Wall-adhering erythrocytes (6), granulocytes (7) and platelets (7) are characteristic phenomena in tissue injury. Increased amounts of granulocytes, which adhere to and roll along the endothelium (8) are a constant finding.

Microthrombi are formed and may consist of platelets (9), fibrin (10), a combination of fibrin and platelets (11), and may even include red cells and white cells, thereby forming a classical microthrombus (12). These wall-adhering thrombi often allow single blood cells to pass (9–12). They may, however, also completely block the lumen (13) temporarily or permanently. The erythrocytes (14) may change in shape to crenated cells, acanthocytes (15), which, however, often maintain a great deal of the plasticity of the normal red cell (16). Sometimes the red cells turn into spherocytes (17), which may disrupt, causing hemolysis. When spherocytes are compressed in a vessel, they change into characteristic hexagonal bodies (18). The white cells may exhibit different degrees of plasticity (19), but may also turn into rigid corpuscles (20). Disruption of granulocytes with liberation of their granules into the lumen has been established as an in vivo phenomenon (20), which appears to be significant in the development of tissue injury. An aggregation of red cells may, to some extent, influence nutritive flow of blood (21). Often, however, the aggregates are plastic and deformable enough to pass even narrow nutritive capillaries, and when the flow rate is increased, the cells move as solitary bodies. The noncorpuscular plasma constituents of blood may change appreciably in composition, accompanied by disturbances in microvascular rheology. Thus, significant abnormalities occur, for example, in plasma proteins, lipoproteins and lipids.

The endothelial wall disrupts functionally with leakage of plasma, resulting in

FIGURE 2. Vital microphotogram showing severe endothelial damage in arteriole and venule with blockage of venule and leakage of blood cells into the perivascular space. Observe erythrocyte in arteriolar wall (at arrow). (Orig. mag. × 800)

edema and the passage of single blood cells (22), or structurally, resulting in bleeding into the tissue and more or less complete breakdown of the microcirculation (23). This is then followed by derangement and necrosis of the tissue. (See FIGURE 2).

The importance of simultaneous analysis of structure and function for the understanding of these pathophysiological mechanisms in animal and in man is illustrated in FIGURE 3, which shows the dynamics of a platelet-fibrin microthrombus.* Therefore, the microcirculation should be analyzed, not only with respect to linear dimensions, but also with respect to time.

A new methodological approach, which has recently been successfully applied for this kind of investigation in our laboratory, is illustrated in FIGURE 4. The

* This is characterized by a turn-over phenomenon, which means that some platelets leave and others join the thrombus. Erythrocytes and granulocytes show similar dynamic features.

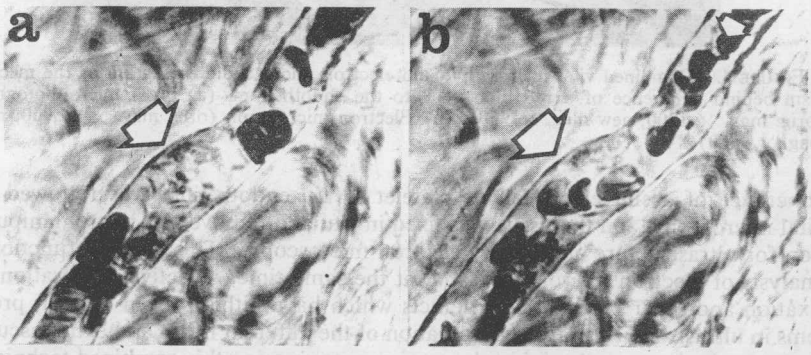


FIGURE 3. (a) Microthrombus consisting of platelets and fibrin in a venule. There was complete blockage of flow for a few seconds, but then the thrombus was penetrated by red blood cells as shown in (b). (Orig. mag. × 1100; new mag. × 880) (b) The dynamics of microthrombi should be considered when the degree and duration of thrombotic blockage and its effects on the peripheral circulation are evaluated.

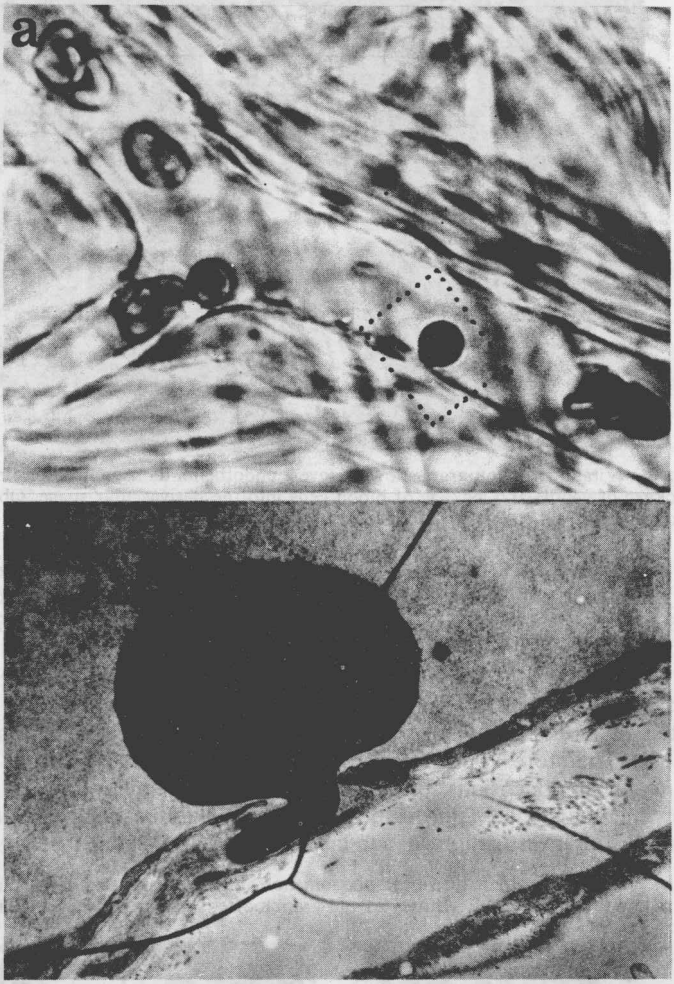


FIGURE 4. Combined vital microscopic and electron microscopic evaluation of the mechanism behind adherence of a red blood cell to the endothelium. (a) Vital microphotogram (orig. mag. × 1200; new mag. × 960). (b) Electron micrograph (orig. mag. × 12,000; new mag. × 9600).

adherence of a single red cell or platelet to the endothelium was followed by vital microscopy, and the tissue was fixed in situ and removed by micromanipulation for ultrastructure analysis by electron microscopy.* This enabled functional analysis of electron micrograms, and, at the same time, objective registration of fixation and other preparation artefacts which have hitherto been difficult problems in ultrastructure analysis. Evaluation of the different intra- and extravascular patterns of microvascular injury is now in progress using this combined technique of vital and electron microscopy. (Brånemark and Ekholm 1966e)

* Performed by R. Ekholm.

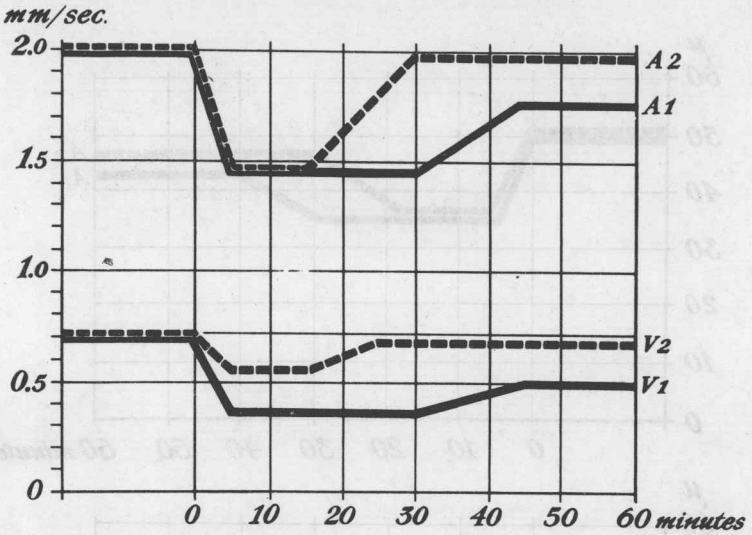


FIGURE 5. Corpuscular flow velocities in arterioles and venules in hamster cheek pouch after severe burn, not affecting the pouch. A1 and V1 without treatment, A2 and V2 after premedication with an anti-inflammatory drug.

So far, local tissue microcirculation after thermal injury has been discussed. The effect of severe local burns on the peripheral circulation in nonburned areas has also been analyzed in preliminary studies. In a series of hamsters the cheek-pouch was everted and exposed and the microcirculation studied by vital microscopy, before and after a severe burn. This was produced by applying a metal plate at 100° C for 15 sec to the lower legs and back of the animal. In these anesthetized animals, five to seven min after the burn, a reduction in corpuscular flow velocities in arterioles and venules occurred, indicating an early traumatic shock. (FIGURE 5) There was also a concomitant reduction in vascular lumen (FIGURE 6).

In order to determine if it is possible, by premedication of anti-inflammatory drugs, to reduce the general microcirculatory disturbances that occur after severe burns, the same experiment was performed on animals which had been given 3,5,6, tribensylethyl-D-glucofuranovit* two hr before injury. FIGURES 5 and 6 show that a certain favorable effect was obtained.

In preliminary experiments, attempts have also been made to improve the microcirculatory conditions in the border zone between permanently damaged and normal tissue. (FIGURE 7) Accordingly, local circumscript burns were produced in rabbit ears. Some of the animals were given the anti-inflammatory drug before the trauma, others were nontreated controls. The burned area and the neighboring tissue were observed by transillumination for about a week. The microvascular system was then outlined by microangiography.† In some of the animals a difference in microcirculatory architecture, and a pattern between the two groups was noted, as shown in FIGURE 8.

* Obtained from Ciba.
† Performed by J. Lundskog.

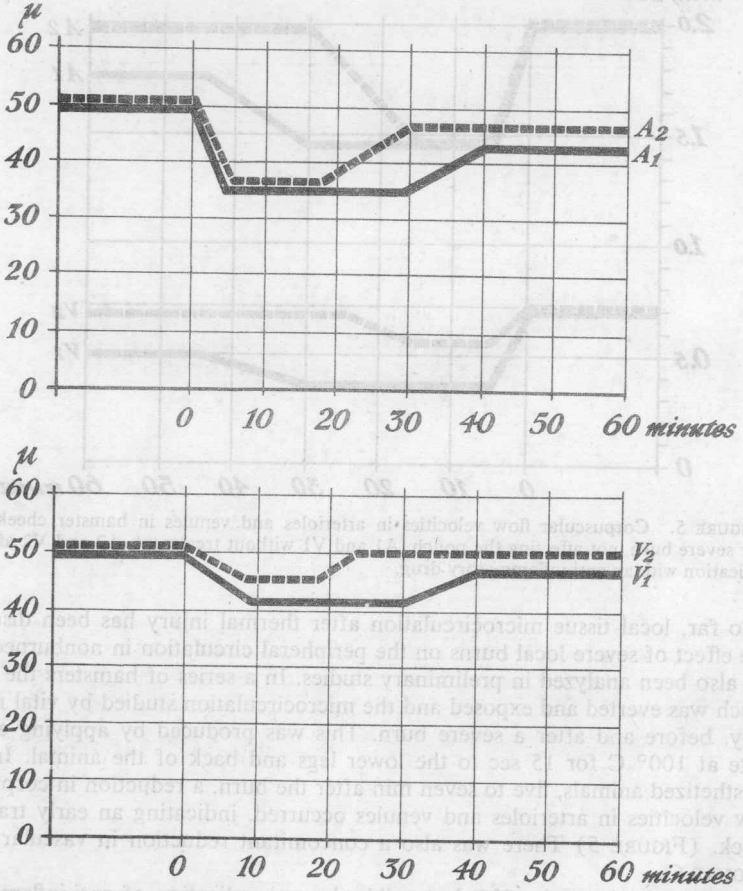


FIGURE 6. Arteriolar (top) and venular (bottom) diameters in the same experiment as in FIGURE 5.

In another series of local tissue injury in rabbit ear chamber and also in rabbit mesentery, studied by vital microscopy, it was found that it was possible, even with existing systemic circulatory disfunction, to improve markedly the microcirculatory conditions in the injured tissue by i.v. administration of isoxysuprenaline.* These results encourage further experimentation with this or similar drugs for the purpose of improving and maintaining the microvascular vitality of the border zone. In this connection, it is also of interest to compare these results with the increase in local tissue circulation, after isoxysuprenaline, occurring in rheumatoid arthritis, which we were able to register in the granulation tissue. (Brånemark *et al.*, 1966d)

In order to tie together the local and general circulatory changes occurring after thermal injury, a hypothesis is presented in FIGURE 9, illustrating the possible connections between local tissue injury in the burned area and microcirculatory disturbances in the intestine, and in all tissues of the body. Liberation of endo-

* Duvadilan® supplied by AB Ferrosan, Malmö, Sweden.

toxins from the intestine, and the interaction between this mechanism and microvascular pathology establish a vicious circle, which results in burn shock.

In order to illustrate and emphasize the magnitude and importance of the problem of microvascular disturbances in burns, with respect to their relation to systemic circulatory effects and traumatic shock, FIGURE 10 shows, diagrammatically, the various zones of tissue injury occurring after thermal injury. The first zone consists of completely and permanently dead tissue (3); the second zone of more or less temporarily damaged tissue, but with severe manifestations of microcirculatory failure (2); and the third zone shows slight abnormalities in micro-

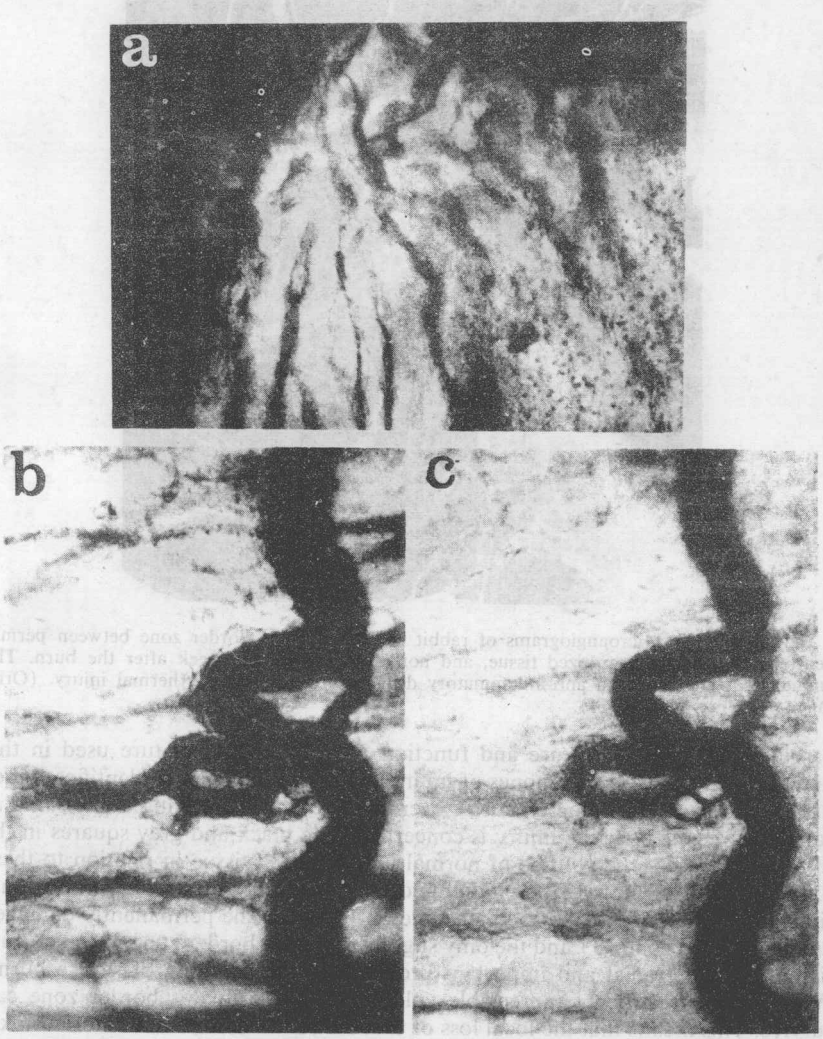


FIGURE 7. Vital microphotograms illustrating tissue and microvascular pathology in burn. (a) Completely and permanently damaged tissue. (b) Border zone with damaged, but still functioning venule and a few capillaries. (c) Additional injury has been induced, resulting in permanent damage to most parts of this border zone. (Orig. mag. × 100; new mag. × 90).

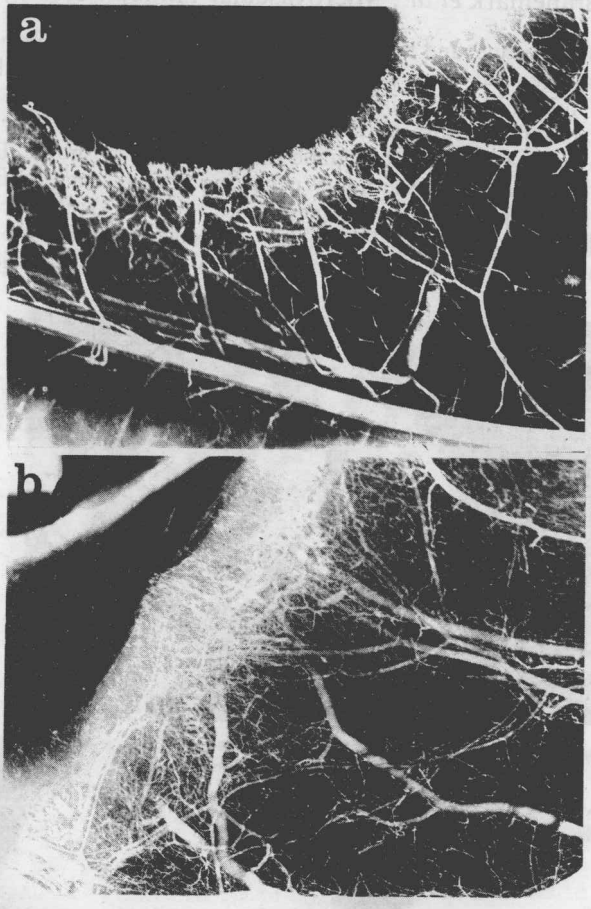


FIGURE 8. (a) Microangiograms of rabbit ear showing the border zone between permanently damaged and necrotized tissue, and noninjured tissue one week after the burn. The animal in (b) received an anti-inflammatory drug before exposure to thermal injury. (Orig. mag. × 20; new mag. × 14).

vascular and tissue structure and function (1). The nomenclature used in this diagram relates to different zones of injury and not to the clinical identification of first, second and third degree burns, even if the biologic meaning is the same as far as the degree of tissue injury is concerned. The black and grey squares in the diagram represent the volume of normal and damaged tissue in relation to these different zones of injury. The vitality and the possibilities of structural and functional restitution in the intermediate zone (2) between the permanently damaged and devitalized zone (3) and the only slightly damaged border zone to the normal tissue (1) are crucial and important problems in the handling of severe burns. With correct treatment, appreciable volumes of tissue in this border zone can survive. This means that the local loss of tissue is reduced, and that different toxic products from this zone, which influence the general condition of the body, are reduced in number and quantity.

This is illustrated in part B of FIGURE 10. Thus, if additional trauma is added

to the original burn, the zone of permanently damaged tissue will proceed further down into the tissue, thereby increasing the volume of destroyed and lost tissue, and converting second degree burns to third degree burns. This three-dimensional analysis of burns is important, because a supplemental injury may, in severe burns, affect the survival prognosis and, certainly, the healing process by significant increase in damaged tissue. As previously mentioned, this also implies possibilities of liberating more toxic products from the burned tissue into the circulation.

### *Wound Disinfectants*

There are certainly many ways in which such an additional trauma can be produced. We have studied the local tissue effects of various kinds of wound disinfectants with respect to microcirculatory structure and function. We were able to show (Brånemark, 1965, 1967) that almost all of the most commonly used wound disinfectants contribute additional trauma, some of them seriously impairing the vitality of the tissue, and thereby delaying wound healing. It was, however, also shown that with slight modifications in vehicle or concentration, the local tissue damage could be appreciably reduced. (FIGURE 11)

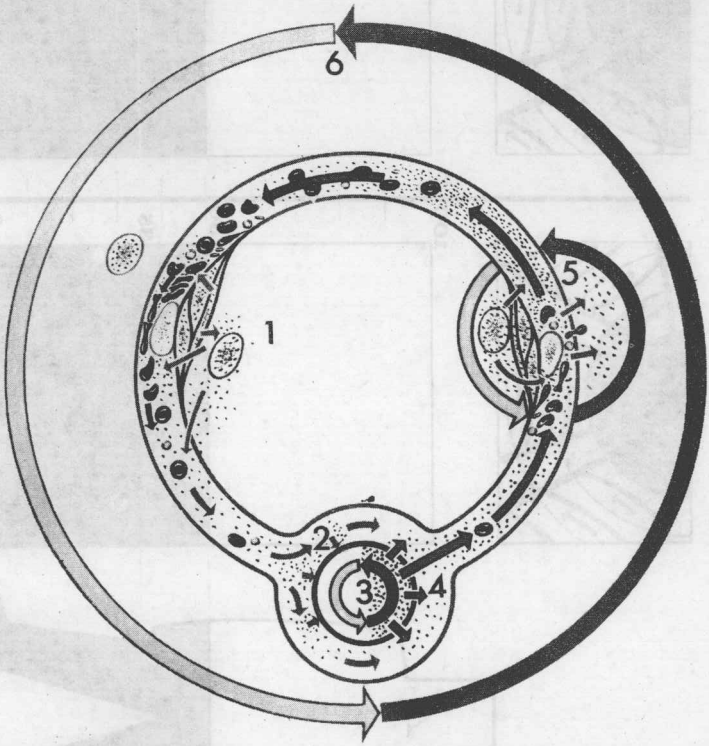


FIGURE 9. Diagram illustrating working hypothesis for the possible interaction between microvascular patho-physiology at the local site of burn (1), subsequent increased permeability of capillaries in intestine (2 and 3), accompanied by absorption of endotoxin into the circulation (4), resulting in systemic microvascular disturbances (5) and further injury in the burned area (1). This mechanism thus establishes a vicious circle (6). (From Brånemark & Urbaschek, Angiology **18**: 667, 1967).

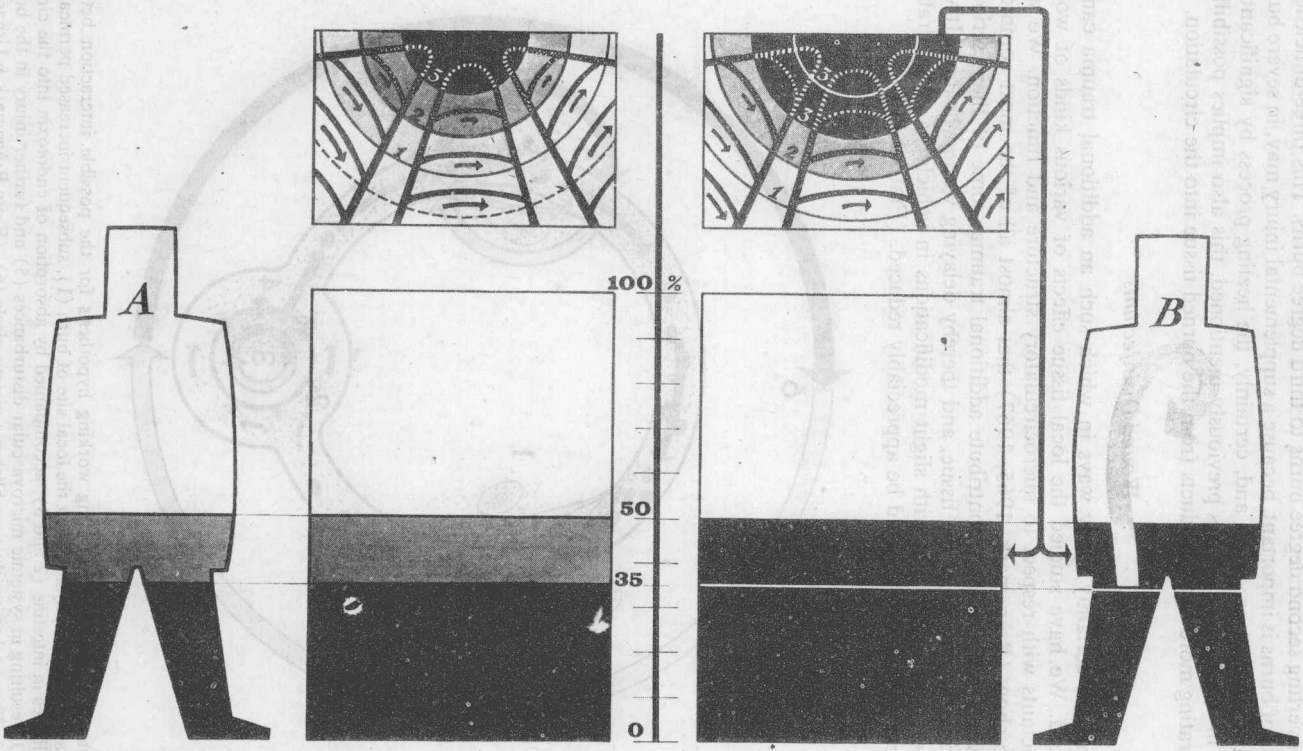


FIGURE 10. Diagrammatic representation of prognostic problems of the border zone between completely damaged and noninjured tissue in burns. Additional injury to the border zone results in an increase in the volume of lost tissue and in the output of toxic material as shown in the right half of the the diagram, which may result in aggravation of the prognosis. For further explanation, see text.

As another example concerning the same problem, we have recently analyzed the effect of sodium hypochlorite on damaged tissue. A series of hamsters were anesthetized with intramuscular barbiturates, the cheek pouch was everted and a microdefect was prepared by removing the epithelium, thereby exposing the ground substance and the connective tissue vessels. The drug was then applied onto the wound. In another series the drug was injected into the tissue without removing the epithelium. This procedure was used in order to ensure penetration of the drug into the tissue. In both series three different concentrations of hypochlorite were tested: 0.05, 0.1 and 0.2%.

It was found that the same kind of microvascular disturbances were produced by these concentrations: including intravascular hemolysis: large numbers of microthrombi and moderate numbers of wall-adhering granulocytes; and blockage of capillaries and venules. The changes were, however, more severe in the higher concentrations, as manifested by the time span of complete blockage after a single application. Thus, after 0.05% the microcirculation was almost completely restituted after 15 min. The corresponding blockage time for 0.1% was 20 min and for 0.2% 25 min. But with these concentrations many vessels did not regain normal flow conditions. When the hypochlorite was applied to a tissue defect, and attempts were made to restore function by irrigating with Tyrode's solution, only a few vessels regained flow. The mast cells were found to be disrupted when analyzed by in vivo staining with toluidine blue.

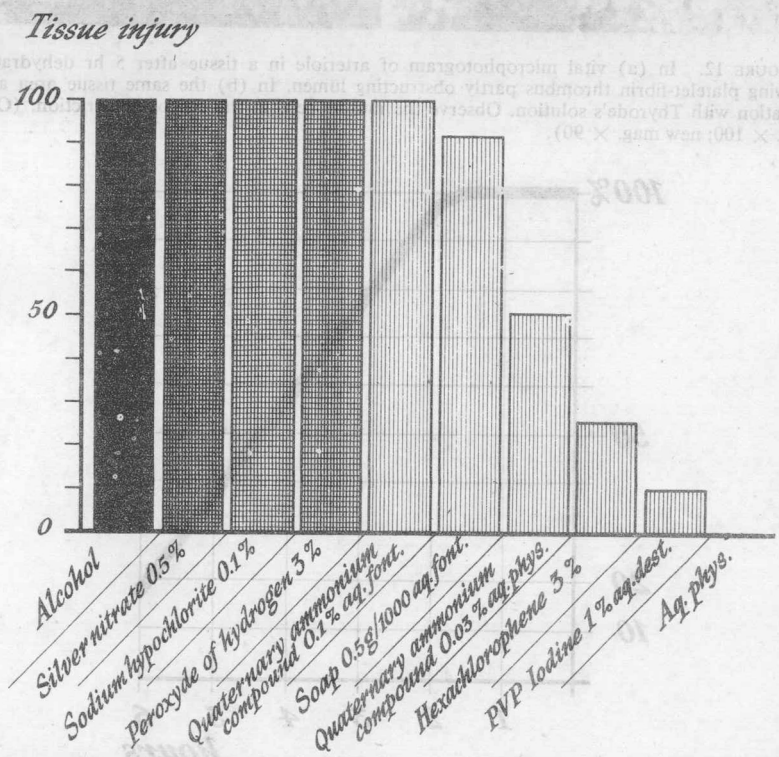


FIGURE 11. Microvascular disturbances induced by different kinds of wound disinfectants. The diagram is based on the acute effects as well as on the effects on wound healing.