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Use of anticoagulants in the treatment of frostbite

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THE USE OF ANTICOAGULANTS IN THE TREATMENT OF FROSTBITE

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Frostbite is by no means a rare condition. In any region or any occupation where sub-freezing temperatures are encountered, cases of frostbite will be seen. Winter warfare is a great producer of frostbite. This has been demonstrated time and time again with countless casualties occuring during winter campaigns, the latest being in Korea. Men on the ground are not the only ones suffering from the effects of excessive cold. High altitude aviation with its sub-zero temperatures and high velocity winds make even a few seconds of exposure sufficient to cause frostbite. Civilians too are at times subjected to conditions which can produce cold injury. The inadequately protected outdoor laborer, the snow storm marooned traveler and the collapsed drunk are but a few sources of frostbite cases. Whatever the cause, the lesions produced may result in serious injury to the individual. Loss of extremities or parts of extremities are common handicaps seen in those who have suffered severe frostbite. An adequate type of treatment could possibly have prevented some of these crippling losses. The search for that "adequate" form of treatment has as yet to produce it. During the past ten years, numerous methods have been proposed and used.

The methods of treatments of frostbite which have been and are being used are too numerous to mention in a paper of this type. Results reported by numerous men are conflicting in that

beneficial effects from almost any type of therapy are claimed. In some cases these methods may be diametrically opposed. For example, Greene (1942) recommended thawing of the frostbitten area at a temperature below normal body temperature and without any rubbing; whereas Brandstadt (1950) after a review of Russian papers, reported that warming and massaging the affected area was the treatment of choice. Another type of treatment which has been used quite extensively is that of sympathectomy. This is used to bring about dilitation of peripheral vessels. Grant (1942), Goadby (1942), Liebesny (1944) and Black (1943) among others, recommended this procedure as an adjunct in therapy. Chain and Jennings (1943) reported the use of novocain block and oil balsam bandages by the Russians who claimed very good results.

Thus, the list of different treatments becomes longer and longer. The use of anticoagulants is one of the latest additions to this list.

PHYSIOLOGY AND PATHOLOGY

The development of the fluorescein test by Lange and Boyd in 1942 helped a great deal in the study of the processes which occurred in a frostbitten area. This test consisted of the injection of small amounts of fluorescein into the blood stream near the frozen area and the following of its migration with the

blood stream and into the interstitial spaces under ultra violet light. In their experiments these investigators used rabbits which had depilated areas on their abdomens frozen by the use of a small glass filled with dry ice placed against the skin. The exposure varied from five to ninety minutes. For periods varying from thirty to one hundred and twenty minutes following such refrigeration no fluorescein appeared in the damaged areas indicating a severe spasm of the arterioles. After this a second stage was initiated during which all blood vessels reopened and fluorescein was seen throughout the exposed areas. The diffusion of fluorescein into the surrounding tissues in the second stage was many times greater than in the non-exposed skin, giving the picture of intense hyperfluorescence in the previously frozen areas. There was also marked swelling of the exposed areas at this time indicating the escape of fluids into the injured areas. Eight to fourteen hours after exposure a repeat fluorescein injection showed that the exposed parts were no longer fluorescent, indicating a pre-gangrenous state. This non-fluorescense increased in the next hours until finally the entire area was free of the chemical and was gangrenous. Biopsies taken at that time showed that there was clumping of the red cells in the smaller vessels which was probably due to loss of plasma through the highly permeable vascular walls. The red cells were stranded and silted the blood vessels forming sludge. They did not, however, represent true thrombi in the

beginning. A simple injection of saline enabled the investigators to work out the erythrocytes as individual cells. Only after about seventy-two hours did organization of these cells into thrombi occur. This thrombosis led to complete gangrene. It appeared that therapeutic attempts to avoid gangrene must be started before this stage of thrombosis.

Friedman, Lange and Weiner (1947) obtained similar results in their experiments with rabbits using heparin as a means of preventing vascular thrombosis and gangrene. They concluded that heparin prevented the formation of agglutinative erythrocytic thrombi and thus, gangrene. The same opinion was given by Laufmann, Martin and Tantiers (1948).

As the pathologic process progresses the clinical signs and symptoms accompanying the frostbite also change characteristically. Bigelow (1942) in a paper on treatment of frostbite adequately describes the clinical appearance of a frostbite lesion. This condition is a relatively rapid process. Following exposure to excess cold the skin becomes blanched. Subjectively there is tingling or stinging which in turn is followed by a sense of numbness and difficulty in walking, when the feet are involved. The extremity is white and firm with slight swelling and anesthesia. The apparent edema does not pit readily with pressure and the movements of extremities are slight or impossible.

The process of thawing or recovery of the frozen part, although varying with the intensity of exposure, goes through the stages of redness or apparent hyperemia and then swelling accompanied by the formation of blisters. In severe frostbite or in cases where additional trauma has occurred these blisters may be very large and filled with a straw colored or sometimes blood-tinged fluid. Pain may vary from dull numb aching to severe pain requiring sedation.

Some cases proceed to recovery from this point, but in the majority the skin over the greater part of the involved area and particularly the toes and pressure points becomes black, firm and dry. This produces the effect of complete gangrene involving the entire blackened area. Recovery may in some cases be complete or may be accompanied by residual neuralgic pains, joint pains, hypesthesias or sensitivity to cold, of which some cases, years later, show intermittant claudication as in peripheral arteriosclerosis. Gangrene is the most serious complication. It is usually of the dry type and results in loss of tissue varying from small superficial areas to entire extremities.

As in many other pathologic conditions, a method of grading lesions may be adopted in frostbite (Brownrigg 1943). This is practical since the type of treatment varies with the severity of the injury. In Brownrigg's classification, first

degree frostbite is that in which the patient complains of pain, but is still able to walk if the feet are involved. The extremities or other parts are swollen with some erythema present but with no other color changes. Movements are present and circulation is unaffected. In the second degree type the findings are the same as the first group but with the added feature of dry gangrene involving the distal portions of the involved areas. The third degree frostbite lesions are the worst, usually involving larger areas with the patient exhibiting signs of toxemia. Usually more extensive gangrene is present, being in many cases infective. The treatment of the first degree frostbite is simple, conservative methods being adequate since there is no serious tissue loss. The second and third degree types are much more serious in that they lead to more extensive loss of tissue and in many third degree cases may require radical amputations to effect a cure. Thus, adequate and rapidly instituted therapy is a must to prevent damaging tissue loss in these severe cases of frostbite. The methods of treatment are numerous, as has already been mentioned, and the treatment of choice is still debatable. Anticoagulant therapy is one of the newer methods which has been used limitedly in the treatment of acute frostbite.

MODE OF ACTION OF ANTICOAGULANTS

Previous to their use in frostbite therapy, the anticoagulants were used primarily to prevent clotting during

transfusion, prevent postoperative thrombi and to combat phlebitis, thrombophlebitis, pulmonary embolism and similar conditions which concerned the clotting of blood. The drugs used were heparin and dicoumarol. The actions of these drugs have been demonstrated to be quite different although the end results of their action are the same, that is, prolongation of the clotting time. Brinkhous (1940) demonstrated that heparin antagonized the activation of prothrombin to thrombin, the activity being proportional to the amount of the drug present in the circulating blood. It was further shown that the action of heparin in presence of blood on prothrombin was immediate and that such action ceased when enzymatic destruction of the heparin occurred. The production of prothrombin by the liver was shown to remain normal. Dicoumarol on the other hand affected the production of prothrombin by interfering with utilization of vitamin K by the liver (Quick 1944). This action took place only after a longer period of administration of the drug.

FIRST REPORTED USE OF ANTICOAGULANT THERAPY

In 1942 Bigelow suggested the possible use of heparin in the treatment of acute frostbite in an effort to combat thrombosis in peripheral vessels. Thrombosis had been shown to occur in experimental animals which were subjected to local freezing (Lange and Boyd 1942). Bigelow did not, however, put this theory to use and it was not until 1944 that Brambel and Loker had a case

of frostbite in which they attempted anticoagulant therapy with dicoumarin. In their studies of gangrene a case of bilateral gangrene of the feet following frostbite was encountered in a forty year old male who was working outdoors in wet boots. The patient was placed in bed and a heating cradle was placed over his legs. Oral dicoumarin and sulfathiazole were given. Two days later a lumbar sympathetic block was done. During the treatment hemorrhage from the injured areas became quite marked and transfusion was necessary. The hemorrhage was blamed on inexperience in disrupting the clotting mechanism. The patient recovered and was discharged from the hospital about two weeks after treatment was begun. On the basis of previous experience the authors believed that the gangrene would have led to amputation but in this case it was not necessary. Which phase of the treatment was the most important was, of course, debatable.

EXPERIMENTAL WORK

In 1944 experiments in anticoagulant therapy of artificial frostbite were being carried out by various investigators. Loewe, Rosenblatt, Greene and Russel (1944) reported a practical demonstration of the therapeutic value of heparinization in the prevention of gangrene. This was made possible by the study of artificial frostbite in human volunteers. These volunteers were recruited from patients who were being treated for subacute

bacterial endocarditis at the Jewish Hospital of Brooklyn by the combination of penicillin and heparin. In one group the frostbite was accomplished by means of a porcelain crucible filled with dry ice and applied to the skin of the lateral aspect of upper arm without pressure for ten minutes. An area of about two square cm. came in contact with the skin and a temperature of about minus 22° C was achieved. Heparinization was begun immediately after exposure with one volunteer serving as a control. The other group was subjected to local refrigeration in the same manner but for two exposures of thirty minutes each. The initial or control exposure was allowed to develop for six days before the second frostbite was induced, immediately following which heparinization was begun. The clotting time in the treated cases was maintained at between 25 and 60 minutes. It was apparent from all observations on these human volunteers that all the adequately treated lesions escaped any deeper injury such as the superficial sloughing of skin in the controls. In all treated cases subcutaneous heparin in Pitkin menstrum (Loewe, Rosenblatt, Lederer 1942) was used. The menstrum contained gelatine, dextrose, glacial acetic acid and water. Using this material it was possible to achieve a consistent, retarded and equal release of the anticoagulant following subcutaneous injection.

Lange and Boyd (1945) used rabbits in a group of experiments which involved heparinization after artificial frostbite.

In one experiment ten rabbits were depilated on the abdomen and exposed to cold by applying the bottom of a small glass beaker filled with dry ice to the skin. Exposure varied from five to ninety minutes. After this exposure the skin froze solid and began to thaw after intervals varying from five to twenty-five minutes. Five of the animals were treated by heparinization, subcutaneously, within four hours after exposure. None of the heparinized animals developed gangrene while in the untreated controls all areas exposed for more than fifteen minutes became gangrenous. In another group of twenty-two rabbits, one hind leg was exposed to an alcohol dry ice bath of -12° to -20° C for a period of forty-five to ninety minutes with the leg protected by a thin boot of condom rubber. After exposure, eleven of the animals were heparinized while eleven remained untreated. Of the treated animals only two showed some slight surface lesions while the legs of the others remained completely intact with no gangrene. All controls lost their legs, bone and all, by complete gangrene.

Other experiments involving human beings were reported in 1947 by Lange, Weiner and Boyd. A group of four conscientious objectors was subjected to freezing of an area 3.5 cm. in diameter for thirty minutes by use of beakers filled with dry ice. Each received at least four exposures including an untreated control,

immediate subcutaneous heparinization for six days subsequent to exposure, heparinization for six days after an initial delay of twenty-four hours and heparinization for six days after an initial delay of twenty-four hours during which the exposed part was kept cool by means of an ice bag applied to the lesion without pressure. The latter was done in order to check on the validity of the concept that cooling subsequent to frostbite improves the course (Greene 1942).

The results were similar in all cases. The untreated exposure led to gangrene. Immediate heparinization lasting six days prevented gangrene. Heparinization after a twenty-four hour delay at room temperature gave almost as good a result as immediate heparinization. Cooling in the interim produced the poorest results. The blister content in all heparinized patients stayed liquid throughout. No clot formation was noticed. If the blister did not rupture in the intiial phase of marked tension its contents were slowly resorbed, a loose shriveled piece of skin remaining on the exposed spot. The experimentors believed that the fact that heparinization kept the interstitial fluids with all its constituents resorbable was of importance in the prevention of subsequent fibrosis and collagen replacement.

A similar study with a group of three conscientious objectors was done, but instead of cooling after exposure, warming

was carried out by use of a heating pad. The results were similar with the heating being of no value in the recovery, in fact, being detrimental to recovery.

Schumacker (1947) carried out further experiments which supported the favorable findings of the preceding investigators. He used rabbits in a manner similar to that of Lange and Boyd (1945) where the hind legs were exposed to cold and solidly frozen. Heparinization was sufficient to prolong the clotting time twenty to thirty minutes. His conclusions were that the milder the frostbite the more efficatious heparin therapy could be expected to be, and vice versa, and that the more prolonged the coagulation time the greater the efficacy of anticoagulant therapy in preventing gangrene. Also, such treatment may be futile unless it is begun promptly after freezing. Schumacker believed that he had demonstrated two facts rather conclusively. First, that heparin therapy was of some efficacy in preventing or limiting in extent and degree the gangrene of experimental frostbite and second, that this therapy was not as uniformly successful as had been reported by others.

Another favorable report of successful use of the anticoagulant therapy was made by Lempke and Schumacker (1949). The experiments used by these men utilized white mice whose tails were subjected to freezing. This was accomplished by use of an ether

bath cooled by dry ice. Various types of treatment were instituted including the use of heparinization. Various schedules of administering the drug were carried out; these being similar to other projects. The investigators concluded that heparin was quite valuable in preventing gangrene as a sequela to frostbite.

The first experimental evidence that did not support the favorable impressions held by the above workers was turned in by Quintanilla, Krusen and Essex (1947). Their experiments were carried out with the use of rabbits whose feet were frozen in a manner similar to that used by previous investigators. The temperatures for freezing varies from -15° to -47° C and the time from three minutes to ninety minutes. Heparinization was carried out at different times, before and immediately after exposure to cold, or continuously. In another group of animals an occlusive tourniquet was placed on the limb for three minutes. Heparinized animals fared no better than the non-heparinized ones. The frozen part of the extremity was completely lost. The conclusions drawn by the investigators were that heparin treatment used in the presence of severe tissue damage was ineffectual and that prolonged administration of heparin to rabbits whose extremities were frozen did not save the feet of the animals.

Fuhrman and Crimson (1948) reported that they too found heparinization ineffective in rabbits which were subjected to

artificial frostbite. They used methods similar to those of Lange and Boyd and Quintanilla et al but were unable to obtain the good results reported by the former group.

Similar results were reported by Pichotka and Lewis in 1949 following the same type of experiments on rabbits. An analysis of their results showed that tissue necrosis from frostbite was not significantly less in the heparin treated animals. This was true even in the least degree of cold injury that was followed by gangrene.

Somewhat better results were reported in 1950 by Finneran and Schumacker after they had experimented with white mice, albino rats, white rabbits and mongrel dogs. Their work was carried out under conditions similar to those used in earlier experiments. These investigators concluded that immediate heparinization of rats gave suggestive evidence of some efficacy in limiting the damage from frostbite of the tail and foot. The proportion of good and excellent results was not significantly increased. Heparin increased significantly the proportion of feet surviving without any loss of tissue but did not increase the proportion with gangrene limited to the toes. When heparin was withheld until three hours after freezing the results were no better than in untreated animals. Also, in their experiments with various types of frostbite treatment they concluded that heparinization was less effective than rapid thawing.

After the appearance of the above reports which indicated that heparinization as a treatment for artificially induced frostbite was of little value, Lange, Boyd and Weiner (1950) again undertook further experiments in an effort to substantiate their position on the subject. Their experiments again showed that with adequately heparinized animals the amount of severe damage resulting from artificial forstbite was markedly less than in untreated animals. They concluded that in order to arrive at accurate conclusions in such experiments the following factors should be considered:

1. The prevention of gangrene after frostbite requires a continuous uninterrupted prolongation of the coagulation time by heparin injections or infusions for at least five days after exposure.
2. Even brief interruptions of this prolongation led to a rapid increase in percentage of failures in this treatment.
3. Experiments in which such prolongation is not achieved continuously are of no value in judging the merits of the therapy.
4. The term "heparinization" should be reserved for such instances in which heparin injections are proved to have produced a continuously maintained elevation of coagulation time to the desired levels.

The author believed that those investigators who were not able to prevent gangrene after frostbite in rabbits failed to do so because their treatment lasted only a short time and was carried on without check on coagulation time in addition to the use of inadequate dosages.

CLINICAL REPORTS

Heparinization as a treatment of frostbite in human beings has had trial in only a relatively few reported cases. However, in a vast majority of the patients there were very gratifying results following such therapy.

Brambel and Loker reported a case in 1944 which was covered earlier in this paper. They experienced some difficulty when the patient began to hemorrhage from his lesions but this was controlled and the final result was much better than had been expected. judging from the severity of the frostbite.

Loewe, Rosenblatt, Greene and Russel reported a case in 1944 which had been treated at the Research Unit of the New York Medical College. A man was sent in following exposure to temperature of 18° to 20° F for at least 14 hours while lying in the street. His hands were completely unprotected and his feet were protected only by thin socks and low shoes. His lower extremities were ice

cold from the feet to the knees and remained so for five hours after admission. He was heparinized by the intravenous route for five days. This consisted of the administration of 300 mg. of heparin in 2000 c.c. of physiologic saline solution for each twenty-four hours. The solution was given at a rate of approximately twenty to twenty-five drops per minute. The clotting time was maintained between thirty and sixty minutes (Lee and White method) and was checked every twelve hours. During the treatment the patient developed considerable blistering, especially on the hands, but completely escaped any permanent tissue loss. From experience with similar lesions and periods of exposure, it was thought that this man, without heparinization, would probably have had more or less extensive loss of the extremities.

Thies, O'Connor and Wahl (1951) reported the largest group of patients ever treated for frostbite by anticoagulant therapy. At Cook County Hospital in Chicago during the winters of 1949 and 1950 thirty patients suffering from frostbite were admitted. Fourteen of these had acute frostbite and were treated with effective anticoagulant therapy. In the remainder of the cases the exposure to cold had taken place days or weeks before admission and since gangrene or necrosis was already present it was decided that anticoagulant therapy should not be attempted because it would probably be useless. At the time of exposure the temperature had varied from 5° to 20° F. However, the severity

of the frostbite was also dependent upon other factors such as wind velocity, humidity, and general condition and age of the patient The duration of the exposure was difficult to determine since some of the patients had been found lying on the sidewalk,, frequently in an alcoholic stupor and unable to recall the immediate past events. One of the patients had been shoveling coal without gloves for seven hours. All the patients were men and the average age was fifty-four years, ages varying from thirty-five to eighty. The extremities were affected to the greatest extent. All four extremities were involved severely in two of the cases, the patients being admitted to the hospital in shock with no obtainable blood pressure or pulse. Paralysis or paresis was noted in two cases and three others complained of paresthesias and hypesthesias.

The routine treatments which had been employed previously were continued in this series of cases so that beneficial effects of the anticoagulant therapy might be permitted. This included bilateral lumbar paravertebral blocks on four patients early in the series. This was discontinued later because of the danger of hemorrhage from deep needle puncture in the presence of anticoagulant therapy. One patient received tetraethylammonium chloride as a vasodilator. Blood and plasma transfusions were necessary in four patients to combat shock. Local treatment of the affected areas consisted of gentle cleansing with soap and water and alcohol,

and the application of sterile dry or petrolatum gauze pressure dressings. Penicillin was given all patients to combat infections. The extremities were thawed at room temperature with no external heat or cold being applied.

Anticoagulant therapy was begun as soon as possible after admittance of the patients. This consisted of the intravenous administration of 50 mg. of heparin sodium at three hour intervals until adequate prothrombin deficiency was established by the use of bishydroxycoumarin therapy. This was begun as soon as the patients were able to swallow and a blood prothrombin level had been obtained. The initial dose of the bishydroxycoumarin was 300 mg. and subsequent daily doses were determined after obtaining prothrombin levels. The effective level was determined to be at between ten and twenty percent of normal. This therapy was continued for eight days during which time the patients were not allowed to walk or traumatize their feet in any other way.

As compared to previous years, this type of treatment resulted in far more satisfactory recovery. Only one patient required amputation of a finger although considerable loss of tissue had been expected. This patient was one of the two who had all extremities involved. One patient died as a result of massive retroperitoneal hemorrhage following repeated lumbar blocks (O'Connor, Preston, Thies 1950). This patient was an eighty year

old man who had received seven daily bilateral lumbar paravertebral blocks and had died on the eleventh day of his hospitilization. The autopsy revealed a large retroperitoneal hemorrhage from the psoas muscle which had been penetrated many times by the blocking needle. Other than this, no other major difficulties were noted. The average period of hospitilization was forty-two days, the longest being 270 days.

The use of anticoagulant therapy for acute frostbite has not been given a trial by the armed services where in winter warfare a large number of cases are encountered. Edwards (1951) stated that such treatment was not practical under combat conditions. Even if an anticoagulant were given soon after excessive exposure to cold there would still be danger of promoting hemorrhage from a previous wound. Also, the heparinized soldier would be in great danger if he were wounded since hemorrhage then could be uncontrollable. Similarly, these drugs could not be used as a preventative measure.

Wright (1951) was of the same opinion although he went so far as to theorize that such therapy might be possible if the patients could be evacuated rapidly to a hospital capable of administering heparin. However, too frequently the position of the soldier who was subjected to frostbite would be such that many hours or even days might pass before he could receive adequate therapy.

SUMMARY

The major objective of this paper is to evaluate the use of anticoagulants in the treatment of acute frostbite. A brief introduction to the subject includes references to the importance of frostbite both in the military services and in civilian life. This is followed by a discussion of the physiology and pathology encountered in the lesions of frostbite. Since this is not the major theme of this paper, the physiopathologic discussion is limited to a few of the more recent studies which give the generally accepted views of most investigators. A description of the development of a moderately severe frostbite lesion is included along with a method of classification of lesions which differ according to degree of exposure of the affected part of the patient.

A few of the countless methods of treatment of frostbite are mentioned in an effort to inform the reader of the conflicting ideas concerning the proper types of treatment. The idea of the use of anticoagulants as a means of therapy in acute frostbite is introduced. There is included a short discussion of the mode of action of the anticoagulants, heparin and dicoumarol.

The experimental work is presented next. This includes experiments which were carried out with the use of animals and with human volunteers. The evidence supporting the efficacy of anticoagulant therapy in acute frostbite is presented first. This is

followed by other evidence which fails to support this method of treatment. A description of the method used in each experiment is given unless it is similar to the procedure used by other men and has been mentioned earlier in this paper.

The clinical use of anticoagulant therapy is then considered. The single cases of two groups of practitioners are considered first along with data concerning the conditions under which the patient was exposed to cold.

The methods by which anticoagulants were administered are discussed. Results of these early attempts at such therapy are recorded. A report of a relatively large group of patients (14) treated by anticoagulant therapy after exposure to cold is discussed. This is the only series of more than two patients reported to date. The patients were suffering from second and third degree frostbite after variable lengths of time of exposure. The methods by which the patients were treated are given in some detail with specific mention of the initiation and continuance of anticoagulant therapy. The results which, on the whole, were very satisfactory are discussed. One case of this group died from massive retroperitoneal hemorrhage following multiple lumbar paravertebral blocks which were instituted as a means of producing peripheral vascular dilitation. This is reported separately.

CONCLUSIONS

Anticoagulant therapy in cases of acute frostbite has been shown to be very effective in preventing gangrene and extensive tissue loss. This has been demonstrated in experimental work with human beings and animals. A minority of investigators have reported results which are contrary to these favorable findings and all of these have been in laboratory experiments with animals. Clinical use of this method of treatment has been reported in only a relatively few cases but results have, for the most part, been very gratifying. Incidence of gangrene and tissue loss has been reduced markedly.

Treatment must be instituted as soon as possible after exposure to cold, preferably within the first sixteen or twenty hours. The progress of the therapy should be followed closely with daily prothrombin times which should be kept around ten to twenty percent of normal.

The use of the therapy is limited to those cases which can be put under treatment in a hospital with good laboratory facilities and a well trained staff. Patients with open wounds such as would be seen in a military combat zone, could not be treated by this means because of the danger of uncontrollable hemorrhage brought about by a markedly decreased prothrombin time.

Also, those patients who were put under anticoagulant therapy in a combat area would be in danger of trauma which might result in great blood loss. Thus, they too should not be treated in this manner.

The good results obtained by the use of this type of treatment suggest that is is valuable and practical in selected cases and that it deserves further trial wherever possible.

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