

# Acceleration of Healing with Zinc Sulfate

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ZINC is a potent catalyst of wound healing and zinc deficiency may be a common cause of delayed tissue repair. It is curious that this element has been ignored for so long in studies of human nutrition. Physiologically, zinc is similar to iron in many respects and is present in nearly the same concentrations. It is more plentiful in the human body than other metals such as cobalt, iodine and fluorine and is intimately involved with such vital processes as protein synthesis and cellular respiration. To a great extent, knowledge has been limited by difficulties in analysis for only recently with the advent of sophisticated chemical techniques, could careful studies of zinc metabolism be made. As these investigations have progressed in the last few years, zinc has been identified as an important factor in repair of tissue.

The use of zinc to promote healing is not new. The ancient Egyptians used it topically in the form of calamine and since then zinc oxide, zinc sulfate and zinc stea-

rates in the form of powders, salves and ointments have continued to be used. It is likely that some of the element is absorbed through the skin, particularly through injured and granulating tissues.

Our interest in the systemic use of zinc began with a laboratory accident. During a series of wound healing studies in rats, a remarkable acceleration of healing was noted in a group fed a contaminated diet. After considerable searching, zinc was finally identified as the beneficial impurity and further experiments in rats confirmed that zinc was a potent factor in healing.<sup>5</sup> Subsequent observations in patients suggested that zinc also played a role in human healing. The purpose of this report is to present the results of a carefully controlled study which suggests that dietary zinc supplements can accelerate the rate of healing in man.

## Materials and Methods

Extension of zinc therapy from animal studies<sup>5</sup> was a problem until it was found that the wound formed by excising pilonidal sinuses in young airmen was very satisfactory for healing studies. These wounds should reflect the behavior of normal granulating tissues as the excisions were carried into normal tissues on all sides and as the lesions were left open to heal by second intention. The excision sites were dressed daily with Balsam of Peru and the volumes were measured by taking impressions of

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each cavity at approximately 5-day intervals with a rapidly setting, innocuous alginate hydrocolloid, Jeltrate, as previously described,<sup>4</sup> and as shown in Figure 1. After 25 days, many volumes were less than 1 ml. and accurate measurement of volume by this method was no longer possible.

The second method of quantifying the rate of wound healing was the determination of the number of days required for complete healing. Healing was considered complete when the entire surface was covered with epithelium and no further scab formation took place which proved to be a remarkably clear end point.

Twenty patients were studied. These airmen were young and healthy and continued their usual diets during the study. They were randomly divided into treatment groups on the basis of serial numbers, with odd numbers assigned to control and even numbers to zinc therapy. Ten patients became controls and were maintained on their usual diets *ad lib* without medication during the period of healing. The remaining ten formed the therapy group and were given daily dosages of zinc sulfate in addition to their usual diets *ad lib*. The medicated patients were supplemented with capsules containing 220 mg. of zinc sulfate USP ( $ZnSO_4 \cdot 7H_2O$ ) at a dosage of one capsule three times a day in order to supply the equivalent of an additional 150 mg. of elemental zinc per day.\* This dosage was well tolerated by all patients. The capsules were taken either with milk or after a meal to avoid possible gastro-intestinal irritation by zinc sulfate; the salt has an emetic dose of 2 Gm. All patients were maintained on regular house diets until three days after operation, when they were returned to full duty and resumed their usual dietary habits. All patients healed without difficulty and, to date, there have been no recurrences.

\* Supplied by Smith, Kline & French Laboratories, Philadelphia, Pa.

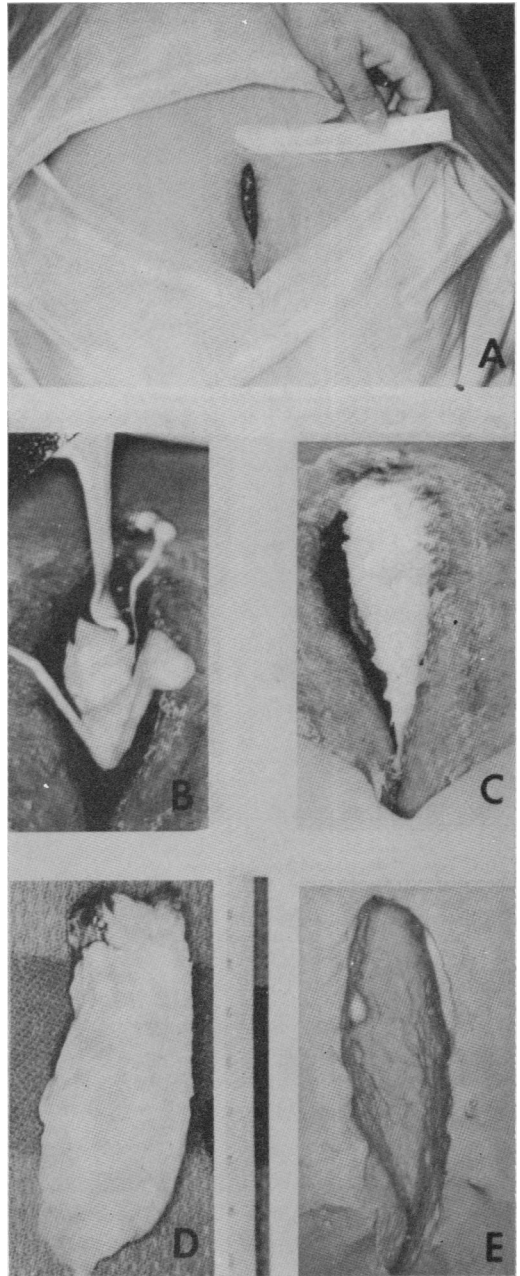


FIG. 1. The measurement of human healing: The granulating wound (A) is filled with Jeltrate (B). The alginate sets rapidly (C) and can be removed easily as an impression (D). The volume of the wound can be measured by immersing the impression in a graduated cylinder of water and recording the volume displaced. The impression can also be used to make a permanent cast of the wound (E) for later comparisons.

TABLE 1. *Wound Healing in Controls and Airmen Medicated with Zinc Sulfate USP*

Patient	Age	Wound Volume (ml.)	Days for Complete Healing	Healing Rate (ml./day)
Controls				
1	27	10	40	0.25
2	21	2.5	46	0.05
3	40	40	48	0.83
4	23	47	53	0.89
5	23	28	63	0.44
6	24	52	71	0.73
7	23	42	85	0.50
8	24	7.5	93	0.08
9	23	45	121	0.37
10	22	49	181	0.27
MEAN ± SE	25.0	32.3	80.1 ± 13.7	0.44 ± 0.09
Zinc Sulfate USP, 220 mg. t.i.d.				
1	19	100	33	3.03
2	24	28	34	0.82
3	22	30	43	0.70
4	18	44	44	1.00
5	28	35	46	0.76
6	40	140	46	3.04
7	28	30	48	0.63
8	23	50	51	0.98
9	22	49	52	0.94
10	22	39	61	0.64
MEAN ± SE	24.6	54.5	45.8 ± 2.6	1.25 ± 0.30
Significance			$p < 0.02$	$p < 0.01$

### Results

The significant acceleration of wound healing produced by zinc therapy is emphasized by the data in mean healing values summarized in Table 1. In the control group, wounds healed in  $80.1 \pm SE 13.7$  days.\* In the zinc-medicated patients, wounds healed in  $45.8 \pm SE 2.6$  days ( $p < 0.02$ ). Thus wounds of patients receiving 150 mg. of metallic zinc daily were healed 34.3 days earlier than the controls even though their initial wounds were almost twice as large (54.5 ml. vs. 32.3 ml.). Acceleration is also shown in the rate of wound closure. The control wounds closed at the rate of 0.44 ml./day, whereas those of patients medicated with 150 mg. of zinc closed at the rate of 1.25 ml./day, or almost three times faster ( $p < 0.01$ ).

\* Standard error.

There was a considerable difference in the appearance of the wounds between the two groups. The wounds of the airmen on zinc sulfate therapy demonstrated cleaner, pinker and *healthier* granulations with considerably less purulent exudate.

Although the medicated group healed more rapidly throughout the course of the experiment, the differences were small during the first 15 days. As shown in Figure 2, the effect of zinc sulfate therapy is greatest during the second half of the healing period in the epithelization phase. Acceleration of epithelization in the terminal stages of healing is similar to the pattern observed in our earlier animal studies.<sup>5</sup>

### Discussion

It is not surprising that zinc should play an important role in human wound healing. Considerable experimental evidence has

been available that this element is essential for wound repair. Zinc-deficient cattle, poultry, sheep and swine spontaneously develop ulcerating lesions, especially of their legs, which heal only if adequate dietary zinc is supplied. Miller *et al.*,<sup>2</sup> noted the dependency of healing on adequate zinc stores, and suggested that poor healing in cattle can be used as a sign of zinc deficiency.

Zinc probably acts primarily at the wound site where it is incorporated into enzyme systems. Savlov *et al.*<sup>5</sup> demonstrated that radiozinc is preferentially concentrated in healing tissues with a peak of activity during the first 7 days after injury, followed by a gradual decrease. The migration of zinc into the wound appears to be temporary since at the time of complete scarring, 100 days after injury, these investigators found no evidence of zinc-65 in the scar although the radioisotope was still detectable in most tissues.

Zinc is the metal moiety in a number of essential enzyme systems.<sup>8</sup> Metalloenzymes known to contain zinc include alkaline phosphatase, carbonic anhydrase, carboxypeptidase and the following dehydrogenases: alcohol, glutamic acid and lactic acid. In addition, zinc acts as a cofactor to a number of enzymes including arginase, carnosinase, dehydropeptidase, glycyglycine dipeptidase, histidine deaminase and tripeptidase, as well as oxaloacetic carboxylase and some of the lecithinases and enolases. Evidence accumulated from studies in microorganisms also supports the thesis that the action of zinc is in the area of protein and nucleic acid synthesis. Zinc deficiency in *Mycobacterium smegmatis*, for example, interferes with the synthesis of RNA and thus secondarily inhibits the synthesis of DNA and other proteins. Whether similar pathways are affected in humans remains to be shown.

It is desirable to offer readily available zinc to the organism during periods of

wound healing as zinc appears to be essential to protein synthesis. Studies on rats first demonstrated that such an approach was sound. The addition of extra zinc to a commercial rat feed accelerated the healing rate of wounds and burns in these animals by 30 per cent.<sup>7</sup> The present studies on young airmen on normal diets suggest that zinc salts are also beneficial during tissue repair in humans. The healing of standard granulating wounds was accelerated by 34.3 days, or 43 per cent, over that in controls (80.1 + SE 13.7 days vs. 45.8 + SE 2.6 days). Most of this acceleration occurred during the stage of epithelization. Perhaps this is related to the fact that 20 per cent of the body's zinc stores is in the skin, concentrated in the epithelium and epithelial structures.<sup>8</sup>

It is becoming apparent that zinc deficiency may be a common problem in our

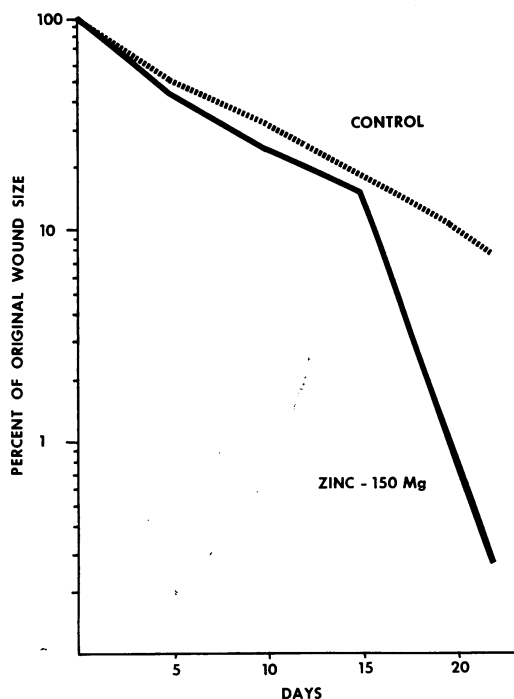


FIG. 2. The effect of zinc on wound healing in man. Almost all of the acceleration occurs after the second week of healing, during the stage of epithelization. Almost 20% of the body's zinc stores are in the epithelium.

patient population. Studies in 47 patients with severe burns have shown a marked zinc deficit beginning shortly after the burn and lasting as long as 2 to 3 months after injury.<sup>3</sup> More recent observations in post-operative patients have shown a marked zincuria with a fall in zinc stores during the early postoperative period.<sup>1</sup>

Zinc is obtained only in a limited number of foods and in these the zinc content is often variable; the element is primarily absorbed and excreted by the small intestine. In the chronically malnourished patient such as the aged, the obese, the faddist or those with serious debilitating illnesses severe zinc deficits due to the negative zinc balance can and probably do easily develop. This may account for wound dehiscences, poor healing and frequent hypoproteinemia so often seen in this group. Since zinc medication was so beneficial in young, healthy airmen with relatively minor wounds, it is likely to be even more so in seriously ill patients with severe nutritional problems. Further studies of these groups of patients are now underway.

Fortunately, zinc sulfate is an extremely safe compound for oral use and toxicity levels are about 30 times the dosages used in these studies. It is well tolerated and offers a safe and effective method of promoting healing, especially in the marginally nourished patient with deficient zinc stores.

### Summary

Zinc is intimately involved in healing. Zinc-deficient animals heal poorly, zinc-65

localizes preferentially in healing tissues and the addition of extra readily available zinc salts accelerates healing in rats.

Zinc also appears to play an important role in human healing. Patients with severe burns develop significant zinc deficits and it is likely that patients with other healing problems also have zinc stores inadequate to meet the demands of healing tissues.

Oral medication with 220 mg. of zinc sulfate USP three times a day, resulted in the acceleration of healing by 43 per cent in a well controlled study of young men with granulating wounds. Zinc therapy deserves a trial as an adjunct in the treatment of patients with healing problems.

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