A COMPARISON OF THE TREATMENT OF SKIN ULCERS OF
THE DIABETIC WITH TOPICAL INSULIN AND
THE LIGHT CRADLE

by

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ABSTRACT

A study was conducted to determine if insulin used topically was superior to the light cradle in treating skin ulcers of the diabetic.

Five diabetic patients with skin ulcers were treated. Treatment was assigned at random, each patient receiving both forms of treatment for seven days. The effect of treatment was monitored by measuring changes in the surface area of the skin ulcers daily. The topical insulin treatment was shown to be superior to the light cradle treatment.

Age, sex, age at onset of diabetes, the known length of time the patient had been a diabetic, the presence of neurological and vascular complications, the length of time the patient had the ulcer prior to treatment, control of the diabetes, zinc deficiency, concurrent diseases or problems, and drugs are all factors that may influence wound healing. Each of these factors were compared to the individual and group response to topical insulin therapy. No distinct relationship could be detected between the response to therapy and any of these factors. However, a larger sample may show that some relationship does exist between ulcer healing and the duration of the ulcer prior to treatment and between ulcer healing and control of the diabetes.
CHAPTER 1

INTRODUCTION

Diabetes Mellitus is a disease that often has complications. Retinopathy, nephropathy, hypercholesterolemia, neuropathy and peripheral vascular disease frequently plague the diabetic. As a result of these complications, the arterial blood supply and the nerve function are often reduced in the feet and legs of these patients. In turn, normal body response to trauma and infection are reduced. Occasionally, skin ulcers or wounds will develop at the site of stress, trauma or infection. Development of skin ulcers on the diabetic’s feet and legs can be quite serious and may heal very slowly, if at all. One of the greatest concerns is that gangrene may set in at these sites and amputation of the appendage may be necessary.

Skin ulcers in the diabetic have been treated by physicians in a variety of manners. Among these, a few physicians have reported to have successfully treated diabetic ulcers with insulin used topically. However, there has not been a systematic study in which the efficacy of topical insulin has been compared to another form of treatment. It may be shown that topical insulin promotes more rapid healing of diabetic ulcers than another form of treatment.
The light cradle has been used successfully in the treatment of diabetic skin ulcers. It represents an alternate form of treatment that will serve as a basis of comparison and as a control measure.

Because of the difficulties in healing diabetic skin ulcers, a more effective form of therapy is needed. Insulin used topically may be more effective than prior methods of therapy. The light cradle has been reported to have been used effectively in the treatment of diabetic skin ulcers and therefore could be used in a study comparing the two forms of treatment.

**Purpose**

This research compared the effect of insulin used topically on diabetic ulcers to the effect of the light cradle on diabetic ulcers. The initial hypotheses were:

1. There is no difference in the size of the skin ulcers of the diabetic as a result of the treatment where insulin is used topically.

2. There is no difference in the size of the skin ulcers of the diabetic as a result of the treatment where the light cradle is used.

The two forms of treatment were then compared to each other and the following major hypothesis was tested.

3. Treatment of the skin ulcers of the diabetic by insulin used topically will not produce any greater decrease in ulcer size than will treatment by light cradle.
Because there may be many variables involved in wound healing, patient factors which may inhibit or promote ulcer healing were evaluated. The following patient variables were compared to the results of the treatments.

1. The age of the patient.
2. The sex of the patient.
3. The age at which the patient became a diabetic.
4. The known length of time the patient had been a diabetic.
5. The presence and the extent of neurological and vascular complications.
6. The length of time the patient had the ulcer prior to treatment.
7. The control of the diabetes prior to and during treatment.
8. The presence and extent of zinc deficiency.
9. The presence and extent of concurrent diseases and problems.
10. The effect of drugs being taken by the patient.

Definitions

The Light Cradle

The light cradle consists of an aluminum frame with one or two 25 watt electric light bulbs and a bath thermometer. The light bulbs are enclosed by a wire mesh screen to prevent direct contact with the patient. The cradle is covered with a sheet or blanket to maintain a constant temperature. The light cradle represents a routine form of treatment of these wounds. The usual or routine treatment of diabetic ulcers varies with the physician and the institution. Methods of
treatment may include saline soaks, the use of a light cradle, local antibacterial preparations, local debridement, surgery, or simply regular cleaning with hydrogen peroxide. Because the light cradle has been used successfully, and is a relatively simple method of treatment of diabetic ulcers, it was used as a control measure.

**Diabetic Skin Ulcer**

A diabetic skin ulcer is a lesion that usually occurs on the lower legs or feet of diabetic patients. Frequently these patients have neuropathy and/or peripheral vascular disease. This lesion may be the result of some form of trauma to tissue that is already compromised by impaired circulation and nerve conduction. These ulcers are sometimes referred to as ischemic and neurotrophic or neuropathic ulcers. Bacterial infection may or may not be a complication.

**Limitations**

This study was limited to comparing the effect of treatment of diabetic ulcers with the light cradle and topical insulin. Only diabetics with leg or feet ulcers were included. While non-diabetics can develop a similar ulcer, these ulcers occur much more frequently among diabetics and appear to be a somewhat specific complication of that disease.
CHAPTER 2

REVIEW OF THE LITERATURE

Skin ulcers may occur in both diabetic and non-diabetic patients. In the diabetic, however, the result is usually more severe and more complications may be involved. One of the most feared complications is gangrene. Gangrene, which may be the result of peripheral vascular complications, occurs more frequently in the diabetic than in the non-diabetic. Fairbairn (1973) stated that in one series of diabetic patients, gangrene that necessitated amputation occurred 40 times more often in diabetic patients than in non-diabetic patients. According to Williams (1962), gangrene occurred from 53 to 156 times more frequently in the diabetic than in the non-diabetic, dependent upon the age of the patient.

If these wounds could be healed more rapidly and more effectively, amputation may be prevented and the length of hospitalization may be reduced. This could dramatically enhance the mental and physical welfare of the patient. Insulin has been used topically to promote healing of the skin ulcers of the diabetic.

Topical Insulin

Paul (1966) reported a diabetic patient that was under poor control and developed gangrene of the left fourth toe. The gangrene subsided with control of the diabetes. This patient exhibited signs of
peripheral arterial disease and neuropathy. There was diminution of sensation to pin-prick over the toes, vibration sense was absent over the shins, and ankle jerks were absent. Posterior tibial and dorsalis pedis pulses were not palpable on either side. Gangrene of the right great toe then developed. Below-knee amputation was performed and penicillin and streptomycin were administered. The stump became infected with Staphylococcus pyogenes and did not respond to treatment by irrigation or the use of erythromycin or cloxacillin orally. The antibiotics were discontinued and treatment with regular insulin was begun. A piece of gauze was soaked with 20 units of regular insulin which was applied to the wound and then covered with a bandage. This procedure was repeated twice daily. Paul (1966) reported that the infection cleared dramatically in three to four days. The treatments were continued for a short period of time and healing occurred.

Lopez and Mena (1968) cited success in treating two patients with topical insulin. The first patient was a 66-year-old diabetic male with an ulcer on the anterior aspect of the right leg. Posterior tibial and dorsalis pedis pulses were decreased bilaterally and there was diminution of sensation to pin-prick on both lower extremities. The ulcer was irrigated with a permanganate solution and parenteral procaine penicillin was administered to the patient with no apparent effect. The antibiotic was discontinued and 20 units of regular insulin was applied by compress twice daily. These physicians reported that the ulcer showed a striking tendency to heal. The other patient was a 20-year-old diabetic female that had a necrotic ulcer on her right foot. When benzylpenicillin and
local nitrofurazone failed to heal the wound, local insulin treatment was initiated. This ulcer also showed a striking tendency to heal and was almost completely healed in 13 days.

Naji (1967) reported that he injected protamine zinc insulin (PZI) at the edges of a diabetic's wound when it was open, or in it and at its periphery when it was closed. He used six to twelve subcutaneous injections. This procedure was repeated every three to four days. During the treatment blood and urine glucose levels were checked for routine control of the diabetes. Thus, the control of diabetes may have been affected by the use of insulin at the site of the ulceration. It is assumed that subcutaneous injections would affect glucose levels in the diabetic patient, as this is the normal route of administration for insulin. It should also be kept in mind that the use of insulin topically could be absorbed sufficiently to affect blood glucose levels, although there were no reports in the literature of this occurring.

Csapo and Hodi (1966) also reported using local insulin in patients with diabetic gangrene with good results.

Regular insulin is an aqueous solution made from the antidiabetic principle of beef or pork pancreas or both. The principle is made from zinc-insulin crystals. Regular Insulin, USP is a solution made from zinc-insulin.

Topical zinc has not been proven to improve wound healing. Murray and Rosenthal (1968) applied zinc locally to various wounds, but they could find no difference in healing between the zinc treated wounds and the controls. Hubbard et al. (1969) used both oral and topical zinc
on corneal wounds, but they could find no improvement in healing.

Hallbook and Lanner (1972) gave oral zinc to two groups of patients. The first group represented patients that had serum-zinc levels below normal. The second group had normal serum-zinc levels. Leg ulcers were then treated in both groups with oral zinc. Wound healing was improved in the zinc-deficient group and no difference could be detected in the normal serum-zinc group. These studies suggest that any observed change in wound healing might be due to the effect of the insulin rather than the zinc.

There are many suggested mechanisms for the wound-healing effect of topically applied insulin. Paul (1966) felt that local insulin could help in the healing of a wound in a diabetic by promoting utilization of glucose at a cellular level. Lopez and Mena (1968) and Csapo and Hodin (1966) supported Paul's hypothesis. Lopez and Mena expanded Paul's hypothesis, however, by stating that it is possible to have a normal blood-sugar level while the sugar concentration in the affected tissues is elevated. This could cause cellular dehydration and could decrease local resistance to infection. Local application of insulin could enhance glucose transport within the cells and could improve wound healing. However, there is no proof for this hypothesis.

Mikkonen, Lampiaho and Kulonen (1966) studied the effect of local insulin on the biosynthesis of collagen in granulation tissue in the rat. The injection of Lente-insulin resulted in the stimulation of collagen synthesis. Tensile strength of the granulation tissue was also tested but no increase could be demonstrated.
Udupa and Chansouria (1971) demonstrated that PZI significantly increased the bursting strength of experimental abdominal wounds in rats. They also showed that PZI administered subcutaneously enhanced collagen synthesis. They reported that the collagen fibers appeared earlier, were more compact, more dense and better oriented than those in the control groups.

The Light Cradle

The light cradle has been reported to have been used successfully in the treatment of diabetic skin ulcers.

According to Goodman (1955) and Post et al. (1963), maximum vasodilatation is obtained by maintaining a constant temperature of 90 to 95 degrees Fahrenheit (32 to 35 degrees Centigrade) to the feet. This assures maximum blood flow to the extremities and promotes wound healing. The patient must remain under the light cradle continuously until healing occurs. Dressings and ointments are to be avoided during the treatment as the wound should stay dry and exposed to the air.

Goodman (1955) reported that the light cradle was effective in treating gangrene and impending gangrene in the diabetic patient. He cited two cases in which the light cradle was used successfully. The first patient was a 62-year-old male diabetic with ulcers on both feet. Oscillometry showed that peripheral circulation was reduced to approximately 33 percent of normal. The Achilles and patellar tendon reflexes were absent bilaterally. The diagnosis was perforating ulcers secondary to neuropathy. When the light cradle was used, healing began immediately and the ulcers were completely closed in eight months. Healing in this
patient was complicated by a burn to the feet due to a treatment error. The second case cited by Goodman was a 58-year-old female diabetic who had developed an ulcer on the plantar surface of the left great toe. In this patient peripheral circulation in the legs and feet was excellent but the Achilles reflexes were absent bilaterally. Healing began almost immediately after treatment with the light cradle was initiated. Complete healing occurred in six weeks.

Post et al. (1963) treated 30 diabetic patients who exhibited necrotic, ulcerative lesions in various locations. Every patient showed evidence of peripheral neuropathy and infection concomitantly. All patients were treated with a constant temperature light cradle and complete healing resulted in all cases.

These reports demonstrated that the light cradle has been used effectively to treat diabetic ulcers. However, on the basis of the literature, topical insulin appeared to promote healing of diabetic wounds more rapidly than the light cradle and did not confine the patient to the bed continuously. Use of the light cradle in a comparison study provided the patient with a safe form of treatment to be used as a control measure. Insulin used topically was then compared to the effect of the light cradle.

Wound Measurement

Recording changes in wound size appeared to be a practical method of detecting wound healing. When measured at selected intervals, increased healing should be reflected by a decrease in original wound size.
Myers and Cherry (1970) treated chronic leg ulcers with oral zinc. To record healing progress the following procedure was used. Once a week each ulcer was photographed on color film using a fixed light source and distance. A centimeter ruler placed in the plane of the ulcer was included in the photographs. The developed transparencies were projected onto a large sheet of drawing paper adjusting the distance of projector to paper until the image of the centimeter scale exactly coincided with the ruler used in the original photograph. The image size was thus 1:1 with that of the lesion. The borders were then traced and the areas of the ulcers measured with a compensating planimeter. The resulting values were plotted against time using both arithmetic and semilog graph paper. For any given segment of time, the healing rate in square centimeters per week was determined by subtracting the area at the end of the period from that at the beginning and dividing the resultant figure by the number of weeks. Healing ulcers thus received negative values; enlarging ulcers, positive values.

Pories et al. (1967) studied wound healing after oral zinc therapy. Wound size was measured on the basis of the volume of the wound. Wound volume was determined by taking impressions of each cavity at five-day intervals with a rapidly setting, innocuous, alginate hydrocolloid (Jeltrate). Wound volumes were then determined by the amount of water displaced by the cast.
CHAPTER 3

DESIGN OF STUDY

There are many variables within any one patient. When two patients are compared, the number of variables involved can increase dramatically. To conduct research on a group of patients requires that intersubject and intrasubject differences be reduced to as few variables as possible. With this criteria in mind, variation was reduced by several measures. One of the first and more important measures was to have each patient serve as his own control. This was accomplished by use of a randomized cross-over design. Patients were randomly assigned either the experimental (insulin) treatment as the first form of treatment; or the control (light cradle) treatment as the first form of treatment. The initial form of treatment was continued for seven days and then terminated. Then the second form of treatment, either insulin or light cradle, was applied for seven days and then terminated. This procedure was continued with treatment being assigned randomly to each new patient.

The surface area of the wounds was measured before treatment was started, each day of treatment and the day after the last treatment. The measurements were taken at the same time each day and were used to monitor any changes in wound size. With this information, the two forms of treatment were compared.
Photographs were taken of the wounds to document changes in wound size. A centimeter ruler (Appendix A) was placed on the patient adjacent to the wound to serve as a guide in determining wound size in the photographs (Appendix B).

To protect the patients and to reduce variability at the same time, certain complications of the disease state were avoided. Patients with purulent infection of the wound requiring local antibiotic therapy were not included in this study. This factor could increase intersubject variation and interruption of antibiotic therapy could interfere with the control of the infection.

While most of the authors cited indicated successful use of topical insulin in infected tissue, it was felt that a more homogenous sample could be obtained for comparison by avoiding greatly complicated conditions. Patients with fulminant gangrene requiring surgery were not included. To attempt this treatment on patients with this advanced stage of disease could endanger their lives and therefore was avoided. Patients taking steroids or immunosuppressive agents were not included in this study. According to Goodman and Gilman (1970), both of these agents can inhibit wound healing. Also avoided were conditions that could severely limit wound healing or increase intersubject variation.

According to Peacock and Van Winkle (1970), ascorbic acid deficiency resulted in the failure of fibroblasts to produce collagen and therefore inhibited wound healing. Goodman and Gilman (1970) stated that a plasma level of 1-2 milligram percent of ascorbic acid will saturate the storage sites and maintain an adequate body concentration.
To achieve this plasma level in an adult, the recommended daily dietary allowance is approximately 55 to 60 milligrams. It was not known if any of the patients were deficient in ascorbic acid. It was felt that blood ascorbic acid tolerance determinations were an additional demand on the patient that could be precluded by simply administering a small amount of oral ascorbic acid each day. Therefore, 100 milligrams of ascorbic acid was given to each patient each day. This dose was large enough to prevent deficiency and yet small enough to not be a significant factor in wound healing.

There are a large number of variables within any single patient. In the diabetic, there are many complications of that disease as well as many other factors which can affect the patient. Therefore, before treatment was initiated, each patient was assessed.

The first priority in the treatment of any diabetic complication is good control of the diabetes (Menendez 1967). Therefore, blood and urine were monitored for glucose and ketones. Past and immediate histories were reviewed. A determination was made as to whether the patient was a mature-onset or a juvenile-onset diabetic. Mature-onset diabetics are less frequently insulin dependent and suffer from vascular complications more frequently and sooner than the juvenile-onset diabetics (Waife 1969). Many mature-onset diabetics may be stabilized on diet alone and may need no medication to maintain control. Oral hypoglycemic agents or insulin may be required in other patients.

Of concern also was the presence of other diseases which may or may not be related to the diabetes. Hypertension, urinary tract
infections or other problems could have had an effect on wound healing in any one patient. A complete list of each patient's problems was made. Drugs for the control of other diseases could have affected the patient's response to therapy. The patients were therefore interviewed carefully to determine all of the drugs being taken.

According to Fairbairn (1973) and Ellenberg (1973), neuropathy and peripheral vascular disease (especially arteriosclerosis obliterans) may be a primary cause of peripheral ulcers in the diabetic. Therefore, an assessment was made of peripheral circulation and the presence and extent of peripheral neuropathy.

Peripheral circulation was evaluated by use of an oscillometer and by palpation of the popliteal, posterior tibial and dorsalis pedis arteries. This information was used to determine the presence or extent of occlusion. Neuropathy was evaluated by testing for deep tendon and ankle jerk reflexes and for pin-prick and vibratory sense.

Another factor that could have an effect on treatment was the length of time that the patient had the wound. Long-standing ulcers in a patient under poor diabetic control could theoretically be larger and more resistant to treatment.

The age of the patient could have been a significant factor, particularly as age relates to the length of time the patient has been a diabetic. According to Steinke and Thorn (1970) and Waife (1969), duration of diabetes is related to the onset and severity of its complications.
In the studies done by Hallbook and Lanner (1972), it was suggested that wound healing was impaired by subnormal serum-zinc levels. To insure that the patients in this study were not zinc deficient, serum-zinc levels were determined.

From this discussion it can be seen that there are many variables involved in the treatment of diabetic ulcers. In designing this study, an attempt was made to reduce the number of variables to as few as possible. Every effort was made to secure a homogenous sample. The effect of individual differences were reduced where possible by using each patient as his own control. In this manner, the effect of the two forms of treatment were compared first within the subject and secondly between the subjects. It was hoped that by minimizing the number of variables, any changes in wound size might be attributable to the form of treatment involved. Because there are so many factors involved that affect the disease state, control in a study of this type was very difficult. For example, a blinded treatment sequence would have offered certain statistical advantages in this study; however, such a procedure was virtually impossible because of the obvious physical differences in treatments. Therefore, an effort was made to maintain constants through comparison of specific characteristics of the disease state that were shared by all subjects. These characteristics, already discussed, included age and time factors, sex, extent and complications of disease, and control of the diabetes. At the same time, other factors that were subject to manipulation were held constant. These included such things as serum-zinc and ascorbic acid levels and drugs being taken for other
than the control of diabetes. Utilizing these methods, a relatively homogenous sample was obtained.

**Methodology**

All diabetic patients presenting with ulcers on their legs or feet were considered for inclusion in the study. These patients were then evaluated on the basis of medical history, presenting symptoms and physical examination. Patients with ischemic or neurotrophic types of ulcers and without the complications already discussed were admitted to the study.

Upon admission to the study, the patient was re-evaluated. Blood was drawn and checked for glucose and ketones. A Serum Multiple Analysis-12 was done on each patient, both as a routine in-patient hospital policy and to get a better over-all evaluation of the patient. Urine glucose was monitored four times a day throughout the study with Clinitest tablets. Acetone was also monitored using Acetest tablets.

The degree of arterial blood flow to the lower extremities was assessed by use of a Collen's Sphygmo-Oscillometer. This instrument consists of a pressure cuff and meter. The cuff was wrapped around the patient's leg and inflated (just as a blood pressure cuff). The cuff was inflated to approximately 50 millimeters of mercury above the patient's systolic blood pressure of the arm. The cuff was then deflated very slowly and the maximum excursion of the needle on the meter was recorded. This procedure was used to evaluate arterial blood flow at mid-thigh (femoral artery), below the knee (popliteal artery) and above the ankle (tibial arteries). Patients with values significantly below
normal were suspect of occlusive complications. Arterial blood supply was further assessed by palpation of the posterior tibial, dorsalis pedis and popliteal pulses.

The patients were then examined for signs and symptoms of neuropathy in the lower limbs. They were tested for deep tendon (hamstring) reflex; ankle jerk (Achilles) reflex; pin-prick to toes and feet and vibratory sense (pallesthesia) over the ankles and shins.

The ulcers were measured by placing an acetate sheet over them and carefully tracing the edge of the wounds with a finely sharpened wax pencil. This system of measurement offered several advantages. There was no discomfort to the patient. The flexibility of the thin acetate sheet made it easy to fit the contours of the area of the limb bearing the wound. Because the acetate was transparent it was easy to compare changes in the shape and size of the wound on successive tracings.

The acetate tracings were then placed over a grid bearing one millimeter squares. The surface area of the wound was determined by counting the number of squares. Measurements were made before treatment was started, each day of treatment and the day after the last treatment.

To further document wound size and the effects of therapy, photographs were taken at selected intervals. Photographs were taken before treatment was started, whenever it was felt that there was a significant visual change in the appearance of the ulcer and the day after the last treatment.
All wounds were cleaned before the first form of therapy was initiated. Three percent hydrogen peroxide was used to remove excess purulent matter.

Treatment sequence was assigned by the investigator by use of a table of random digits. In this manner, either the light cradle or topical insulin was randomly assigned as the first form of treatment to each successive patient.

**Light Cradle Treatment**

The limb bearing the ulcer was placed under the aluminum frame of the light cradle. A sheet was then placed over the frame. The light bulb on the frame was turned on and the temperature within the cradle was maintained at a constant 90-95 degrees Fahrenheit (32-35 degrees Centigrade). No ointments, dressings, or coverings were used on the wounds. Except for bathroom privileges, the patients remained under the light cradle day and night for seven days of therapy.

**Topical Insulin Treatment**

Because the possibility existed that insulin used topically could be absorbed sufficiently to affect blood glucose levels, some additional monitoring was felt to be necessary. In addition to the initial blood glucose determinations, blood glucose was determined four hours after the first application of insulin. If this determination indicated that there was a marked decrease in the blood glucose level, the test would be repeated until it was assured that the patient would not become hypoglycemic. If there was no change, urine glucose would continue to be monitored and the patients were followed closely.
Twenty units of U-40 Regular Insulin (Iletin, Insulin Injection, Lilly) was drawn into a one milliliter tuberculin syringe. The insulin was diluted to one milliliter of solution, in the same syringe, with Sterile Water for Injection. The syringe was rotated back and forth a few times to mix the solution and then a few drops of the solution were dropped directly into the ulcer. Just enough solution was placed into the crater of the ulcer to insure that all of the ulcer had been put into contact with the insulin solution. A two by two inch piece of sterile gauze was dampened with three milliliters of normal saline. The insulin solution remaining in the syringe was dripped onto the damp gauze. It was felt that it was necessary to dampen the gauze slightly so that all of the insulin would not be absorbed into the gauze. The gauze was then placed onto the wound and was left there for 30 minutes. This procedure was repeated three times each day for seven days. The wounds were not washed out between treatments and no other therapy was administered to the ulcers. Sterile technique was employed throughout the procedure.

Throughout both procedures, measurements were taken at the same time each day on any single patient. At the end of two weeks, the size of the ulcers under the two treatment systems were compared.

After both forms of treatment were finished for the trial period, the patients were evaluated for need of further treatment. If a patient's ulcer appeared to be healing satisfactorily and the insulin treatment was helping, the patient was instructed in the application of the insulin and discharged. If healing was not satisfactory, the patient was either continued on with the treatment or some other form of treatment was initiated.
CHAPTER 4

DISCUSSION OF RESULTS

The incidence of diabetic ulcers among the general population is small. During the period in which this study was conducted, approximately 3000 patients were screened in three hospitals and 14 nursing homes. Out of all of these patients, only five were found to meet all of the requirements for inclusion in this study. As a result, this study was limited to these five patients.

Nine diabetic patients with leg or foot ulcers were interviewed and evaluated for inclusion in the study. Three of the patients had developed gangrene to the extent that surgery was required. Another patient was not a good candidate for the study because of age and numerous other complications. The remaining five patients met the basic criteria and were treated according to the protocol of the study. The data were analyzed to determine if either method of treatment resulted in tissue healing.

Two patients included in this study did not receive both forms of treatment. Patient #2 was started on the light cradle first. She responded very well exhibiting a 25 percent decrease in wound size in the first seven days of treatment. Because the ulcer was healing satisfactorily and her other problems had been resolved, she was discharged as there was an acute need for her bed in the hospital. Patient #4 had
a very large neuropathic ulcer on her left shin. She was started on topical insulin initially. The ulcer responded slightly by decreasing approximately ten percent in size in the seven days of treatment. Because the ulcer was so large and the healing was slow, it was feared that the exposed subcutaneous tissue would become infected. To preclude this and the ultimate possibility of amputation, a skin-graft was done. Despite these complications, both of these patients were treated in the same manner as the other patients in the study. Therefore, the data obtained were felt to be significant and were included in the study.

Any change in ulcer size was determined by measuring the surface area of the wound each day. During the seven days of each treatment, the change in wound size was determined by subtracting the surface area at the end of treatment from the surface area before treatment began. Where healing occurred, the surface area of the wound decreased. If the ulcer did not heal, the surface area of the wound increased or stayed the same. The net change in ulcer size was stated as a percentage of original wound size. This was calculated by dividing the net change in the surface area of the ulcer by the initial size of the ulcer prior to the treatment involved. Thus:

\[
\frac{\text{Net change in } \text{mm}^2}{\text{Initial ulcer size}} = \text{Percent change}
\]

Where the ulcers became smaller, the decreasing wound size resulted in a negative percentage. Where the ulcers became larger, the increasing wound size resulted in a positive percentage. The greater the change in wound size, the greater the percentage of change. The sign of the percent change reflected only the increase or decrease in ulcer size.
Analysis of Measurement Error

Before the data could be analyzed, it was necessary to evaluate the measurement procedure. It was important to establish that any change in ulcer size was due to treatment rather than measurement error.

A test was devised to evaluate the reliability of the investigator to measure consistently. To conduct this test, it was necessary to secure the cooperation of an investigator not involved in this study. With the help of an independent investigator a blinded test of measurement error was conducted. The independent investigator took the original tracings of the ulcer outlines that had been made on a daily basis and made several xerox copies of them. Using a table of random digits, he assigned numbers to the ulcer outlines. He continued this procedure until 48 ulcer outlines had been chosen at random. The ulcer outlines were then placed in manila envelopes. Each envelope contained approximately six to ten ulcer outlines of varying sizes. The envelopes were then given to the primary investigator for remeasurement.

The same procedure that was used for the initial measurement of the surface area of the ulcers was also used for the remeasurement. One envelope at a time was opened, the surface area of the ulcer outlines was determined and the results were written on a separate sheet of paper. The outlines were then returned to the envelope and the envelope was then closed. Then the next envelope was opened and the procedure repeated. This procedure was repeated until all ulcer outlines had been remeasured twice. All measurements were done independently. The results were then submitted to the independent investigator. He pooled all
measurements done on each ulcer and statistically evaluated the variation due to measurement error.

Ulcer measurements were broken down into two groups. One group represented the percent change in ulcer size as a result of topical insulin treatment. The other group represented the percent change in ulcer size as a result of the light cradle treatment. The variation due to measurement error was seven percent for the percent change in the topical insulin treatment group and 16 percent for the percent change in the light cradle treatment group.

Changes in ulcer size were then evaluated in relation to the standard measurement error. It was found that individually, the changes in ulcer size were always larger than two standard measurement errors. This eliminated measurement error as a source of bias in interpreting the results of the individual treatments and the comparison of the two forms of treatment.

**Analysis of Treatment Results**

Once the extent of measurement error was established, the results of the treatments were analyzed. These results are presented in Table 1.

Listed in Table 2 is a summary of the experimental results. The numbers represent the percent change in ulcer size plus or minus one standard measurement error. Percent changes and mean are shown for both the topical insulin and the light cradle groups. The mean is expressed as a mean percent change in ulcer size plus or minus one standard error. The standard error includes both between patient variation and within patient measurement error.
Table 1. Size and Change in Size of Ulcers at the Beginning and End of Topical Insulin and Light Cradle Treatments. -- Ulcer size is stated in square millimeters.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Topical Insulin Treatment</th>
<th>Light Cradle Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start</td>
<td>Finish</td>
</tr>
<tr>
<td>#1</td>
<td>100*</td>
<td>62</td>
</tr>
<tr>
<td>#2</td>
<td>(No Treatment)</td>
<td>40*</td>
</tr>
<tr>
<td>#3</td>
<td>50*</td>
<td>32</td>
</tr>
<tr>
<td>#4</td>
<td>3746*</td>
<td>3372</td>
</tr>
<tr>
<td>#5</td>
<td>287</td>
<td>201</td>
</tr>
</tbody>
</table>

* Represents the size of the ulcer upon admission, prior to any treatment.
Table 2. Percent Change in Ulcer Size, Plus or Minus One Standard Measurement Error for Topical Insulin and Light Cradle Treatments.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Topical Insulin</th>
<th>Light Cradle</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>-38 ± 0.8</td>
<td>+20 ± 2.5</td>
</tr>
<tr>
<td>#2</td>
<td>No Treatment</td>
<td>-26 ± 2.5</td>
</tr>
<tr>
<td>#3</td>
<td>-36 ± 3.5</td>
<td>+59 ± 3.0</td>
</tr>
<tr>
<td>#4</td>
<td>-10 ± 1.1</td>
<td>No treatment</td>
</tr>
<tr>
<td>#5</td>
<td>-30 ± 2.0</td>
<td>+5 ± 1.5</td>
</tr>
<tr>
<td>Group Mean</td>
<td>-29 ± 13.0</td>
<td>+15 ± 35</td>
</tr>
</tbody>
</table>

The first and second null hypotheses were tested by paired t-tests at the five percent level. The results, as shown in Table 3, permitted rejection of the first hypothesis that there is no difference in the size of the skin ulcers of the diabetic as a result of the treatment where insulin is used topically. In the topical insulin group, $t$ was equal to 4.46. With three degrees of freedom, the hypothesis would have been rejected at any value of $t$ greater than 3.182. As a group, the ulcers treated with topical insulin decreased in size significantly.

As a group, the ulcers treated with the light cradle did not change in size significantly. Therefore the second hypothesis was not rejected. For the light cradle group, $t$ was equal to 0.86 (Table 3).
Table 3. Results of the Paired t-Tests.

<table>
<thead>
<tr>
<th></th>
<th>Topical Insulin</th>
<th>Light Cradle</th>
</tr>
</thead>
<tbody>
<tr>
<td>t</td>
<td>4.46</td>
<td>0.86</td>
</tr>
<tr>
<td>Degrees of Freedom</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>p</td>
<td>0.025</td>
<td>0.4-0.5</td>
</tr>
</tbody>
</table>

With three degrees of freedom, a t value greater than 3.182 would be needed to permit rejection of the hypothesis at the five percent level.

The third hypothesis stated that treatment of the skin ulcers of the diabetic by insulin used topically will not produce any greater decrease in ulcer size than will treatment by light cradle was tested with an unpaired t-test. The results, shown in Table 4, permit rejection of the hypothesis at the five percent level. For the two treatments, t was equal to 2.36. With six degrees of freedom, a t of greater than 1.943 in a directional test was significant. The two forms of treatment were significantly different. Use of insulin topically resulted in a significant reduction of ulcer size. Use of the light cradle resulted in no change in ulcer size. The topical insulin treatment was superior to the light cradle treatment. The same analysis using the arcsine transformation of the percent changes yielded identical results.

The ulcers were photographed before, during and after treatment. The photographs depicting changes in physical appearance and size of the ulcers are presented in Appendix B.
Table 4. Results of the Unpaired t-Test, Topical Insulin versus the Light Cradle.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>t</strong></td>
<td>2.36</td>
</tr>
<tr>
<td>Degrees of Freedom</td>
<td>6</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>0.05</td>
</tr>
</tbody>
</table>
CHAPTER 5

PATIENT VARIABLES AND ULCER HEALING

The effect of the patient variables on wound healing was also analyzed. None of the variables lent themselves readily to statistical analysis. Comparisons were made on what was known about the progression of the disease process.

Because of the major differences in onset and progression of mature and juvenile onset diabetes, analysis of patient variables would have more meaning if each disease entity were considered separately. Therefore, correlations among variables of the mature onset group were considered first. The single juvenile onset is discussed individually and then he is compared to the mature onset diabetics.

The mature onset diabetics ranged in age from 48 to 83 years (Table 5). The mean age was 68. All four patients were female with the mean age of onset of diabetes being 59. The mean length of time the patients had been known diabetics was nine years. All patients had been known diabetics for at least five years. These patient statistics paralleled the general population of diabetics. Newill (1964) stated that the greatest prevalence of diabetes is found in the 65-74 age group. Eighty percent of all diabetics are 40 or older and forty percent are 65 or older. Additionally he stated that, among the older diabetics, there is a higher incidence of the disease in women.
Table 5. Patient Variables: Age, Sex, Onset of Diabetes, Age at Onset, and Known Length of Time Patient was a Diabetic. -- Age and time specified in years.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Onset of Diabetes</th>
<th>Approximate Age at Onset</th>
<th>Known Length of Time a Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>69</td>
<td>Female</td>
<td>Mature</td>
<td>58</td>
<td>11</td>
</tr>
<tr>
<td>#2</td>
<td>73</td>
<td>Female</td>
<td>Mature</td>
<td>65</td>
<td>8</td>
</tr>
<tr>
<td>#3</td>
<td>83</td>
<td>Female</td>
<td>Mature</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>#4</td>
<td>48</td>
<td>Female</td>
<td>Mature</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>#5</td>
<td>30</td>
<td>Male</td>
<td>Juvenile</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>
Table 6 shows the results of arterial and neurological evaluation. All four mature onset diabetic patients exhibited some circulatory impairment. Patient #1 appeared to have the greatest involvement. All oscillometric readings were below normal and dorsalis pedis and posterior tibial pulses were not palpable bilaterally. This may be explained by the fact that one of her problems was arteriosclerosis. In contrast, she did not exhibit signs of neuropathy when she was evaluated. Patients #2 and #3 were the oldest. Oscillometric readings were the highest on these two patients indicating adequate circulation. However, there was some arterial involvement because the popliteal pulse was reduced in both patients and the dorsalis pedis pulse in Patient #2 and the posterior tibial pulse in Patient #3 were not palpable. Patient #2 did not exhibit signs of neuropathy. Patient #3 showed some signs of somatic involvement. In this patient, the ankle jerk reflex was diminished and the hamstring reflex and vibration sense were absent. All pulses were palpable in Patient #4, but oscillometric readings indicated significantly reduced or impaired circulation. This patient also exhibited a diminished ankle jerk reflex and diminished vibration sense.

Patients #3 and #4 exhibited symptoms of neuropathy. According to Skillman (1967), skin ulcers, localized gangrene and peripheral neuropathy are the result of peripheral vascular disease. The primary lesion in this disease may be atherosclerosis, medial arteriosclerosis, nonatheromatous intimal proliferation, or capillary basement membrane thickening. All but the last lesion may affect both diabetics and non-diabetics. However, in the diabetic the lesions develop earlier, progress
Table 6. Patient Variables: Arterial Assessment and Neurological Evaluation.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Arterial Assessment</th>
<th>Neurological Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oscillometer Pulses</td>
<td>Hamstring Reflex</td>
</tr>
<tr>
<td></td>
<td>MT*     BK  AA  PO  DP  PT</td>
<td>Ankle Reflex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pinprick Response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vibration Sense</td>
</tr>
<tr>
<td>#1</td>
<td>1 2 1 D*** - -</td>
<td>+** + + + +</td>
</tr>
<tr>
<td>#2</td>
<td>11 10 4 D  -  +</td>
<td>+  +  +  +</td>
</tr>
<tr>
<td>#3</td>
<td>10 11 3 D  +  -</td>
<td>-  D  +  -</td>
</tr>
<tr>
<td>#4</td>
<td>4 3.5 1.5 +  +  +</td>
<td>+  D  +  D</td>
</tr>
<tr>
<td>#5</td>
<td>12 10 5 D  L+R- L+R-</td>
<td>+  D  -  D</td>
</tr>
</tbody>
</table>

NOTE: All values are bilateral except in Patient #5 for Dorsalis Pedis and Posterior Tibial Pulses. Normal Values for Oscillometer: MT = 8-15, BK = 4-10, AA = 1-5.

* MT = Mid-Thigh; BK = Below Knee; AA = Above Ankle; PO = Popliteal Artery; DP = Dorsalis Pedis Artery; PT = Posterior Tibial Artery.

** + = positive; - = not detectable.

*** D = diminished.
more rapidly and produce greater disability. This correlated with the clinical findings in this study. Patients #1 and #2 presented with the concurrent problems of arteriosclerosis and atherosclerotic heart disease, respectively. Patients #3 and #4 exhibited signs of somatic neuropathy which was consistent with the findings in their medical histories.

Among these four mature onset diabetic patients, Patients #1 and #3 responded significantly to topical insulin therapy. Patient #2 was the only patient in the study to respond to the light cradle. Patient #4 responded slightly to topical insulin therapy but required skin grafting. Patient #2 did not exhibit signs of neuropathy and exhibited the least amount of arterial impairment. This may be related to the fact that she was the only patient to respond to the light cradle. Patients #1 and #3 suffered from arterial occlusion and somatic neuropathy respectively but both responded to topical insulin. All three of these patients (#1, #2, and #3) were of advanced age and had been known diabetics in excess of seven years. There did not appear to be any correlation between the age of the patient, the approximate age of the onset of the diabetes, the known length of time the patient had been a diabetic and healing in this group of patients.

Patient #4 had the largest ulcer, was the youngest mature-onset diabetic, had been a known diabetic for the least amount of time and responded the least to therapy among all patients who received topical insulin therapy. This may have been related to the fact that this patient appeared to have the greatest amount of both vascular and
neurological impairment. This could have also been related to the extremely large size of her ulcer upon admission. On the basis of the data from this study, however, there did not appear to be any correlation between initial ulcer size and the extent of wound healing.

Patient #5 was the only juvenile onset diabetic in this study. He was 30 years old and had been a diabetic for 20 years. As indicated in Table 6, his ankle-jerk reflex and vibration sense were diminished and he had lost all sensation to pin-prick. Upon palpation he exhibited an unusual response in that dorsalis pedis and posterior tibial pulses were not symmetrically palpable. Dorsalis pedis pulse was not palpable and posterior tibial pulse was diminished in the right leg. Both of these pulses were readily palpable on the left leg. This was unusual in that most diabetics exhibit symmetrical involvement.

Consistent with the right sided vascular involvement, Patient #5's ulcer was on the right foot. It was located at the base of the large toe and could have been the result of pressure at that point on his foot. Coincidentally, he had an abscess on the arch of the right foot. He was treated with the light cradle initially, however, his ulcer got larger rather than smaller. He responded significantly to the topical insulin treatment with a 30 percent decrease in wound size at the end of one week's therapy. Patient #5 had been a known diabetic longer than any of the other patients. He also suffered more from the complications of diabetes than did the other patients. He required insulin to maintain control of his diabetes, whereas the mature onset diabetics maintained control through sulfonylurea agents or diet.
There was very little difference in the response to topical insulin
treatment between him and Patients #1 and #3. In comparing his response
to topical insulin therapy to that of Patients #1 and #3, there did not
appear to be a correlation between age, sex, known length of time the
patient had been a diabetic, or neurological or vascular complications
and the extent of wound healing. All three patients responded approxi­
mately equally, while the other parameters discussed varied.

Control of the diabetes is a primary factor in preventing or
treating complications of that disease. To compare the effect of control
of the diabetes on wound healing, the data in Tables 1 and 7 was carefully
analyzed. From Table 7 it can be seen that all patients, except Patient
#2, appeared to come under progressively better control during the course
of therapy. All patients exhibited hyperglycemia upon admission. All
patients, except Patient #2, exhibited decreasing Fasting Blood Glucose
levels after one week of therapy. It is probably safe to assume that
most diabetic patients would exhibit decreasing blood glucose levels
simply by virtue of being hospitalized. Most diabetic patients would
probably not maintain as good care at home as they would in the clinical
environment. Hyperglycemia in Patients #1, #3, #4, and #5 appeared to
decrease as a result of hospitalization. Ulcer healing did not appear
to correspond, however. Patients #1, #3 and #4 received the topical
insulin therapy during the first week of hospitalization. Patients #1
and #3 responded significantly to that therapy. Patient #4 did not
respond sufficiently. Patient #2 responded to the light cradle therapy
during the first week of therapy. However, this patient became more
hyperglycemic during this first week of hospitalization.
Table 7. Patient Variables: Duration of Ulcer Prior to Treatment, Fasting Blood Sugar, and Presence of Serum Zinc Deficiency.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of Ulcer</th>
<th>Fasting Blood Sugar</th>
<th>Serum Zinc Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Upon Admission</td>
<td>After One Week</td>
</tr>
<tr>
<td>#1</td>
<td>8 Weeks</td>
<td>225*</td>
<td>176</td>
</tr>
<tr>
<td>#2</td>
<td>1 Week</td>
<td>159</td>
<td>172</td>
</tr>
<tr>
<td>#3</td>
<td>4 Weeks</td>
<td>140</td>
<td>89</td>
</tr>
<tr>
<td>#4</td>
<td>8 Weeks</td>
<td>140</td>
<td>130</td>
</tr>
<tr>
<td>#5</td>
<td>12 Weeks</td>
<td>476</td>
<td>335</td>
</tr>
</tbody>
</table>

* Fasting blood sugar values are stated in milligrams per 100 milliliters of blood.
Patient #5, the single juvenile onset diabetic, admitted he had been out of control for more than one month prior to admission. Upon admission he had a fasting blood glucose level of 476 milligram percent. Even after one week of clinical therapy, he still had a fasting blood glucose level of 335 milligram percent. It was not until the second week of diet and large doses of insulin at regular intervals that this patient's blood glucose levels approached normal. Table 1 shows this patient's ulcer became larger during that first week while on the light cradle therapy. During the second week, while on topical insulin therapy, his ulcer healed significantly. Thus Patient #5 progressively came under better control over the two-week period. There may have been a relationship between the response to topical insulin therapy and the extent of control in this patient. It was not known, however, how he would have responded if topical insulin therapy had been administered during that first week of hospitalization.

As shown in Table 7, all patients had their ulcers for varying lengths of time prior to admission. Duration of ulcers prior to treatment ranged from one week to three months. The average duration was 6.6 weeks. When the results of treatment (Table 1) were compared to duration of ulcers prior to treatment, there was little apparent relationship. Patients #1, #3, #4, and #5 all had ulcers for at least one month prior to treatment. However, their response to treatment differed. Only in Patient #2 did there appear to be a possible relationship between duration of wound and healing. Patient #2 responded rapidly to treatment with the light cradle. However, her initial ulcer size was smaller than
any of the other patients (Table 1). This may have been the result of
the short duration between onset of the wound and treatment and may
explain why she was the only patient to respond to the light cradle.
Patient #3 had endured her wound for one month. She had an ulcer that
measured 50 square millimeters, only 10 square millimeters larger than
Patient #2. She responded rapidly to topical insulin therapy. On the
basis of relatively shorter duration, relatively smaller wound size and
relatively rapid response to therapy, Patient #3 paralleled Patient #2.
However, Patient #3 did not respond to the light cradle therapy.

Because previous studies have suggested that zinc deficiency may
inhibit wound healing, serum zinc levels were determined on all five
patients. All patients had normal serum zinc levels and no patient was
deficient (Table 7). This factor was a constant in this group of patients.

Complications, concurrent diseases, and problems are listed in
Table 8. Some of the diabetic complications have already been discussed
in relationship to the findings of neuropathy and arterial problems. In
the general population of mature onset diabetics, complications may occur
at any time but generally increase with the age of the diabetic and the
duration of the disease. Skillman and Tzagourais (1973) pointed out that
retinopathy occurs approximately 20 years after the onset of diabetes.
He also stated that nephropathy usually occurs at least 15 years after
the onset of the disease. Leopold (1964) stated that retinopathy usually
occurs 17 to 18 years after onset for those under 50 years of age and
sooner for those diabetics greater than 50 years old. He also pointed
out that this occurs more frequently in female than in male diabetics.
Table 8. Patient Variables: Complications, Concurrent Diseases, and Problems.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Complication, Concurrent Disease or Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Arteriosclerosis</td>
</tr>
<tr>
<td></td>
<td>Chronic Urinary Tract Infections</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Peripheral Vascular Disease</td>
</tr>
<tr>
<td>#2</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Atherosclerotic Heart Disease</td>
</tr>
<tr>
<td></td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td>#3</td>
<td>Cerebral Vascular Accident with Left Hemiplegia</td>
</tr>
<tr>
<td></td>
<td>Chronic Urinary Tract Infections</td>
</tr>
<tr>
<td></td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td></td>
<td>Monilial Mouth Infection</td>
</tr>
<tr>
<td></td>
<td>Neuropathy (Somatic)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td>#4</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Neuropathy (Somatic)</td>
</tr>
<tr>
<td>#5</td>
<td>Abscess on the Arch of the Right Foot</td>
</tr>
<tr>
<td></td>
<td>Chronic Urinary Tract Infection</td>
</tr>
<tr>
<td></td>
<td>Kimmelstiel-Wilson's Disease</td>
</tr>
<tr>
<td></td>
<td>Retinopathy</td>
</tr>
<tr>
<td></td>
<td>Neuropathy (Somatic and Visceral)</td>
</tr>
</tbody>
</table>
Waife (1969) stated that nephropathy usually occurs 10 to 15 years after the onset of diabetes. According to Prockop (1971), the average onset of neuropathy occurred in diabetics greater than 50 years old. Additionally, he stated that the average duration of the disease prior to the onset of neuropathy is greater than five years.

None of the mature onset diabetics suffered from retinopathy. Patient #1 exhibited some signs of nephropathy and Patients #3 and #4 exhibited symptoms of neuropathy. All of these patients were close to 50 years old or older and all had endured the disease at least five years. This corresponded with prior findings. Patients #1, #2, and #3 all had several complications or additional problems and yet all responded to treatment. Patient #4 had few apparent complications or concurrent problems and was the youngest, but did not respond to treatment. Again, in Patient #4 the large size of her ulcer may have had a more significant effect on healing than other variables. There did not appear to be any significant relationship between the response to therapy and concurrent diseases or problems. However, Patients #1 and #3 did respond to topical insulin therapy in the presence of their many problems.

According to Williams (1962), greater than 90 percent of all juvenile onset diabetics developed one or more complications in 20 years. Waife (1969) stated that approximately 70 to 80 percent of all juvenile onset diabetics develop neurological and vascular complications within 20 years. Moss (1972) stated that juvenile onset diabetics usually develop retinopathy 10 to 15 years after the onset of the disease. Patient #5 had been a known diabetic for 20 years and suffered symptoms
of neuropathy, nephropathy and retinopathy. This corresponded to previous findings in the general population of these diabetics. Additionally, Patient #5 was being treated for an abcess on the same foot as the neuropathic ulcer. The abcess responded to treatment during the two weeks of therapy, while the neuropathic ulcer responded only during the second week while being treated with topical insulin. It was very difficult to assess the relationship between the apparent lack of control of diabetes, the multiple complications, the response of the abcess and the different response to both the light cradle and topical insulin therapy. Patient #5 did respond to topical insulin therapy in the presence of all the other factors.

Table 9 lists the drugs being taken by the patients during therapy. Patients #1, #2, and #3 had multiple problems and were taking several medications accordingly. Patient #1 was taking acetohexamide to control her diabetes. Upon admission, it was suspected that the hydrochlorothiazide she was also taking may have been contributing to her hyperglycemia. Because it was felt that this latter drug was necessary to control her hypertension, the dose of the acetohexamide was increased rather than the hydrochlorothiazide withdrawn. She responded favorably. It was necessary to maintain Patient #2 on both chlorpropamide and phenformin to retain control. This patient was also placed on a 1200 calorie diet because she was overweight. Control of diabetes was maintained in Patients #3 and #4 by diet alone. Patient #5, as the single juvenile onset diabetic, was on large doses of insulin to control his diabetes. He was also on antibiotics to control his abcess and urinary
Table 9. Patient Variables: Drugs Taken During Treatment.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Acetohexamide</td>
</tr>
<tr>
<td></td>
<td>Chloral Hydrate</td>
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<td>Hydrochlorothiazide</td>
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<td>Triamterene</td>
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<td>Sodium Levo Thyroxine</td>
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<td>#3</td>
<td>Cephalothin</td>
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<td>Furosemide</td>
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<td>Nystatin oral suspension</td>
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<td>Potassium Chloride</td>
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<td>Propoxyphene Hydrochloride</td>
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<td>Sulfisoxazole</td>
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<td>#4</td>
<td>(Diet Only)</td>
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<td>#5</td>
<td>Cephalothin</td>
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<td>Lente Insulin</td>
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<td>Nafcillin</td>
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tract infection. Patient #3 was on antibiotics to control her pneumonia and urinary tract infection. Patients #3 and #5 responded to topical insulin therapy and did not respond to light cradle therapy. Patient #3 received topical insulin as the first form of therapy and Patient #5 received topical insulin as the second form of treatment. In four out of the five patients, drugs were used to control one problem or another. The only relationship that may have been involved in this group of patients was between drugs used for the control of the diabetes and wound healing. Even under conditions that represented control, Patients #1 and #3 did not respond to the light cradle. Patient #4 was not on any drugs and did not respond to therapy. In general, no relationship was detected between wound healing and what was known about drug therapy in this group of patients except for the possible relationship of the drug control of the diabetes.
Complications of diabetes mellitus may include microangiopathy, visceral and somatic neuropathy and occlusive vascular disease. These complications may result in the development of skin ulcers on the feet and legs of diabetic patients. Skin ulcers may develop at the site of stress or trauma and may heal only very slowly, if at all. Ulceration of the skin of the diabetic may enhance the onset of gangrene which often results in amputation of the affected limb.

Skin ulcers of the diabetic have been treated in a variety of ways. Among these, a few physicians have reported using insulin topically. These researchers have claimed success in individual patients. But, because these reports have been sporadic and inconclusive, it was felt that this form of treatment should be evaluated in a controlled study.

Summary

To evaluate the effect of insulin used topically on diabetic skin ulcers, a clinical test was devised in which the insulin therapy could be compared to another form of treatment. The light cradle was chosen as the control form of treatment because of its simplicity and prior use in treating diabetic ulcers.

To reduce variability between patients and within individual patient response, a randomized cross-over design was employed.
forms of therapy, topical insulin and light cradle, were applied to each patient. To minimize hospital stay and yet provide sufficient time to record response to therapy, each form of treatment was limited to seven days. As each patient met the criteria for inclusion in the study, the treatment to be used first was randomly assigned. Each patient was treated with either the light cradle or topical insulin for seven days and then treated another seven days with the remaining form of treatment.

After criteria for inclusion in the study were established, approximately 3000 patients in three hospitals and 14 nursing homes were screened. Of these, nine patients were suggested to meet these criteria. Three of these patients had already developed gangrene and required surgery. One of these patients was too old and had too many complications for inclusion in the study. The remaining five patients met the basic criteria for inclusion and were accepted into the study.

Prior to treatment each patient was given a physical examination and was interviewed and evaluated. Fasting blood sugar was determined and neurological and vascular assessment was made. Age, sex, and factors relating to the duration and extent of diabetes mellitus were determined. Serum zinc levels were determined, concurrent problems and current drugs were recorded.

The topical insulin therapy consisted of applying 20 units of U-40 Regular Insulin directly to the ulcer three times a day. No other ointments, dressings or coverings were used. Possible adverse patient response in the form of hypoglycemia was monitored through blood and urine glucose determinations.
Patient response to therapy was evaluated by determining changes in surface area of the skin ulcers. Before treatment, during each day of treatment and after the last treatment, the ulcers were measured. A clear acetate sheet was placed over the wounds and the edges of the ulcers were carefully traced with a wax pencil. The outlines of the ulcers were then placed over a grid containing one square millimeter. The surface area was then recorded in square millimeters.

Ulcer response to treatment was documented with photographs taken before treatment, whenever there was an apparent visual change in the wounds and at the end of therapy.

To determine if insulin used topically had an effect on skin ulcers of the diabetic, the following hypothesis was tested: there is no difference in the size of the skin ulcers of the diabetic as a result of the treatment where insulin is used topically. This hypothesis was rejected at the five percent level. As a group, the ulcers treated with topical insulin decreased in size significantly.

To determine if the light cradle had an effect on skin ulcers of the diabetic, the following hypothesis was tested: there is no difference in the size of the skin ulcers of the diabetic as a result of the treatment where the light cradle is used. This hypothesis could not be rejected at the five percent level. As a group the ulcers treated with the light cradle did not change in size significantly.

The two forms of treatment were then compared and the following major hypothesis was tested: treatment of the skin ulcers of the diabetic by insulin used topically will not produce any greater decrease
in ulcer size than will treatment by light cradle. This hypothesis was rejected at the five percent level. Topical insulin treatment resulted in a significant decrease in ulcer size, while light cradle therapy resulted in no change in ulcer size.

There are many factors which may affect wound healing. These factors represent variables that affect the patient and may enhance, have no effect or decrease wound healing. Several patient variables were evaluated to determine if there was any relationship between the variable and the results obtained in this study.

Variables such as sex, age, age at onset of the diabetes, and the known length of time the patient had been a diabetic were correlated with the results of therapy in this sample of patients. It was found that the patient sample in this study paralleled the general population of diabetics in the incidence and manner in which these factors affected them. However, there did not appear to be any relationship between these factors and the observed patient response to therapy.

Neurological and vascular complications, the length of time the patient had endured the ulcer prior to treatment, the size of the ulcer prior to treatment, control of the diabetes prior to treatment, and serum zinc deficiency were also compared to healing in this group of patients.

All patients suffered either neuropathy or arterial insufficiency or both. It was felt that based on prior research and the findings in this study, the presence of these complications was related to the presence of the ulcer. However, there did not appear to be any
correlation between the extent of neurological or vascular complications and the extent of wound healing in these patients.

Only in one patient did there appear to be any correlation between size and duration of the ulcer prior to treatment and wound healing. This one patient had a small ulcer of short duration and responded rapidly to the light cradle therapy. This was the only patient that responded favorably to the light cradle therapy.

Prior research has established that control of the diabetes is essential to management of any complications of that disease. During hospitalization, four of the patients indicated improved control through decreasing fasting blood sugars. However, ulcer size decreased when these patients were treated with topical insulin and did not decrease when treated with the light cradle.

None of the patients were zinc deficient and therefore this did not appear to be a factor in this study.

Complications, concurrent diseases and problems were considered as possible inhibitors of wound healing. All patients suffered from a variety of problems. All patients, except one, responded to therapy. The one patient that did not respond to therapy suffered the least amount of concurrent problems.

Drugs taken during therapy may enhance, inhibit or have no effect on wound healing. All drugs being taken by the patients in this study were carefully reviewed for possible correlations with wound healing. It was felt that there was a possible relationship between drugs used to maintain control of the diabetes and the observed response to
therapy, but not enough was known about that relationship to determine its exact nature.

Conclusions

The diabetic patients involved in this study appeared to parallel the general population of diabetics in incidence, extent and duration of disease, sex, age and extent of complications. This supports the assumption that this small sample was representative of the general population of the diabetic patients.

The biggest limitation in assessing the use of insulin topically on diabetic ulcers on the basis of this study was the limited number of patients available for inclusion into this study. In spite of this problem, the major hypothesis which stated that treatment of the skin ulcers of the diabetic by insulin used topically will not produce any greater decrease in ulcer size than will treatment by light cradle, was rejected at the five percent level. As a group, the ulcers treated with topical insulin did respond significantly. This was also supported by the statistical outcome of the test of the first hypothesis. The first hypothesis stated that there is no difference in the size of the skin ulcers of the diabetic as a result of the treatment where insulin is used topically. This hypothesis was rejected at the five percent level.

The second hypothesis stated that there is no difference in the size of the skin ulcers of the diabetic as a result of the treatment where the light cradle is used. This hypothesis was tested at the five percent level and was retained. Therefore, in this group of patients
the topical insulin treatment was superior to the light cradle treatment in treating diabetic skin ulcers.

An attempt was made to evaluate the other factors involved in wound healing. There was no apparent correlation between the amount of ulcer healing and such factors as sex, age, duration of diabetes and the age at onset of the disease.

No distinct relationship between neurological and vascular complications and the extent of wound healing could be detected in this group of patients. There was no distinct relationship detectable between ulcer healing and the duration of the ulcer prior to treatment or the control of the diabetes in this group of patients. It was suspected, however, that some relationship between neurological and vascular complications, duration of the ulcer prior to treatment, control of the diabetes and ulcer healing does exist, but that a larger sample would have been required to establish this.

If a serum zinc deficiency does inhibit wound healing, it could not be detected in this group of patients. No patients were zinc deficient.

Finally, concurrent diseases and problems and drugs were compared to ulcer healing. Again, no distinct relationship was found.

Insulin used topically has been demonstrated to successfully treat diabetic skin ulcers in this group of patients. The limitations and varied conditions under which this treatment may or may not work has yet to be explored. More patients for longer periods of time should be treated and evaluated. While the topical insulin treatment was not
entirely successful in all patients treated, it was superior to the light cradle treatment and may offer a great advantage to many diabetic patients with skin ulcers.
APPENDIX A

ADHESIVE CENTIMETER RULER FOR MEASURING WOUNDS
APPENDIX B

PHOTOGRAPHIC RECORD OF PATIENT RESPONSE

The following photographs document patient response to therapy. The photographs were taken at selected intervals whenever there appeared to be a visual change in ulcer appearance. The size of the ulcers is stated in square millimeters and is listed at the beginning and end of each type of therapy. The wounds have been enlarged for better visualization and are about 1.6 times life size. The actual size of the scale shown in the photographs can be seen in Appendix A.
Before Treatment, (100 mm$^2$).

After Three Days of Topical Insulin Therapy, (81 mm$^2$).

Finish Topical Insulin (62 mm$^2$), Begin Light Cradle Therapy.

End of Light Cradle Therapy and All Treatment, (77 mm$^2$).

Figure 1. Patient #1, Response of Ulcer to Treatment.
Before Treatment, (40 mm²).

End of Light Cradle Therapy, (30 mm²).

Figure 2. Patient #2, Response of Ulcer to Treatment.
Before Treatment, (50 mm$^2$).

After Three Days of Topical Insulin Therapy, (42 mm$^2$).

Finish Topical Insulin (32 mm$^2$), Begin Light Cradle Therapy.

End of Light Cradle Therapy and All Treatment, (51 mm$^2$).

Figure 3. Patient #3, Response of Ulcer to Treatment.
Before Treatment, (3746 mm²).

After Three Days of Topical Insulin Therapy, (3577 mm²).

After Five Days of Topical Insulin Therapy, (3440 mm²).

End of Topical Insulin Therapy, (3372 mm²).

Figure 4. Patient #4, Response of Ulcer to Treatment.
Before Treatment, \((272 \text{ mm}^2)\).

Finish Light Cradle \((286 \text{ mm}^2)\), Begin Topical Insulin Therapy.

After Three Days of Topical Insulin Therapy, \((261 \text{ mm}^2)\).

End of Topical Insulin Therapy and All Treatment, \((201 \text{ mm}^2)\).

Figure 5. Patient #5, Response of Ulcer to Treatment.
REFERENCES


