A NOTE ON THE PROGRESS OF CICATRIZATION OF WAR WOUNDS.

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PLATE 6.

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The therapeutic effect of a physical or chemical agent on the cicatrization of wounds can be ascertained empirically from the rate of the process of cicatrization. To demonstrate this effect scientifically it is necessary first to determine exactly the normal evolution of a sterile wound,¹ that is the course of cicatrization in a given time; a unit of measure is thus obtained. When the normal progress of the cicatrization of a wound that is kept bacteriologically sterile is known, it becomes possible to study the changes taking place under physical or chemical influences.

This first question of a unit of measure was studied in Compiègne by du Noüy, under the direction of Dr. Carrel. We have worked according to du Noüy's formula, with the results here presented. All the work was done on wounded soldiers at Auxiliary Hospital 75.

To subject organic processes to a mathematical formula is always a hazardous procedure. However, we believe that by eliminating certain causes of error and adopting the controlled conditions of experimentation, results can be obtained which show the exact coincidence of mathematical forecasts with clinical evidence. This parallelism is constant and regular; if it becomes irregular, it is due to an error in therapeutic methods, thus furnishing a means of control of the care given to the patient.

The present work is the result of observations on twenty cases, in regard to the sterilization of the wounds as well as their rate of healing.

¹ By a sterile wound we mean bacterial or clinical sterilization; that is, with one or two cocci per field.
Cicatrization results from two processes, inodular contraction of connective tissue and epidermization. Contraction is in reality a mechanical action connected with the appearance of granulations on the surface of the wound.\textsuperscript{2} We know from the work of du Noüy that a sterile surface wound heals in a period of time which can almost invariably be predicted by the following simple calculation.\textsuperscript{3}

If $S_1$ and $S_t$ represent the surface area of a wound before and after $t$ days, then

$$S_t = S_1 [1 - i (t - \sqrt{T})]$$

$T$ representing the number of days elapsing since the first observation and $i$ a constant characterizing each wound. This constant $i$, or the index, can be determined by means of the first two observations made, for example, at 4 days' interval.

$i$ is expressed by the formula\textsuperscript{4}

$$i = \frac{S_1 - S_t}{t + \sqrt{T}}$$

or for $t = T = 4$,

$$i = \frac{S_1 - S_2}{6S_1}$$

Du Noüy has shown that the index is clearly connected with the age of the patient and the initial surface of the wound; from a considerable number of observations, a chart\textsuperscript{5} has been constructed which, on the assumption that the wound is sterile, makes it possible to determine the index \textit{i a priori}, after only one measurement of the surface, when the age of the patient is known. The index varies approximately between 0.02 and 0.08.

The circumference of the wound or the epithelial edge can easily be traced on a sheet of sterilized cellophane; the surface is then measured in square centimeters with an Amsler planimeter. It is interesting also to observe at the same time the surface of the cicatrix; it can be seen almost invariably, during the days immediately preced-

\begin{itemize}
  \item Text-fig. 1, du Noüy, \textit{J. Exp. Med.}, 1916, xxiv, 463.
\end{itemize}
ing recovery, that the surface of the cicatrix broadens as if the contraction of tissue, having become unnecessary, ceased to occur.\textsuperscript{2}

It is a simple matter to plot the calculated results or the direct observations in a curve with time as abscissæ and surface as ordinates. The curve resulting from the formula for $t = 4, T = 4, 8, 12, 16 \ldots$ shows the normal course which the healing of a wound should follow. The observed surfaces give a second curve which follows the first closely unless there are irregularities to be explained by faulty dressings, reinfection, or illness of the patient. In the present experiments the theoretical curve is drawn with a light line, the curve from direct observation with a heavy line for the epithelial edge, and with a broken line for the cicatrix.

From the fact that the theoretical curve of cicatrization can be drawn in advance, with two measurements of the surface at 4 days' interval, it is seen that the date when cicatrization will be complete can be predicted, often long in advance (Text-figs. 1 and 2).

The technique is as follows: The wound is made clinically sterile by Carrel's method. We have then in the center a granulating surface ($S$, Text-fig. 3) surrounded by an epithelial border ($L,L$); beyond, at the periphery of the surface of the new epithelium, is a line of union of the normal skin and new epithelium ($C,C$). The wound closes by two processes: (1) contraction of the granulating tissue (inodular contraction); (2) epidermization of the granulating surface. These two processes have a relative efficacy for cicatrization, differing according to the wound.

The course of cicatrization is most easily studied in a wound the site of which is not constantly in motion (as the bend of a joint), or one which is extendible and is well nourished, not a scalp wound or one due to loss of a large part of the skull.

The operator, having washed his hands with alcohol, applies to the wound, which has previously been dried with a sterile compress, a thin sheet of cellophane sterilized in the autoclave at 120°C. for 1 hour. In order to preserve the pliability of the cellophane during sterilization it is well to enclose it in a glass tube in the bottom of which is placed a tampon soaked in glycerol diluted one-fourth with water; the cellophane rests on a tampon of non-absorbent cotton, and another closes the tube.
Text-Fig. 1. Experiment 1. Age 28 years. Superficial wound cicatrizing without incident, according to the formula.
Then with a dermatograper's pencil, or, better, with pen and ink, as that allows a sharper and more exact line, a tracing is made of the

Curve corrected according to shape.

**Text-Fig. 2.** Experiment 2. Age 21 years. Long, narrow, superficial wound, cicatrizing without incident toward the date predicted. The corrected formula for this special kind of wound was employed in tracing the theoretical curve.⁶

**Text-Fig. 3.** Diagram of a wound, showing the granulating surface (S), surrounded by an epithelial border (L,L), and the line of union of the normal skin and new epithelium (C,C).

⁶ For wounds of this sort du Noüy's corrected formula should be used:

\[ S_n = S_{n-1} \left[ 1 - \left( t + \sqrt{\tau} \right) \right] - \frac{\sqrt{S_{n-1}}}{S_{n-1}} \]

See also du Noüy, *J. Exp. Med.*, 1917, xxv, 721.
epithelial edge and of the shape of the cicatrix. This is transferred to a sheet of ordinary paper, and on this are made the surface measurements with the planimeter.

**Surface Wounds.**

We have in this way studied a number of wounds treated with Dakin's solution by Carrel's method, keeping the bacterial flora regularly under observation both as to number and kind. Carrel's bacteriological curve was made for each wound.

Microscopic examinations, necessarily hasty, have no great value unless the results are positive, but the use of the curve sometimes points out a reinfection before it is observed, that is, before the microscope reveals it, as the observed curve deviates abruptly from the calculated curve,—which shows that cicatrization curves are not without value from the clinical point of view.

For wounds which are kept sterile the law holds, and cicatrization follows almost exactly the calculated curve (Text-figs. 1 and 2). If a wound previously sterile becomes accidentally infected and then becomes sterile again, the observed curve which separated from the calculated curve often rejoins it rapidly, and cicatrization is complete within a few days of the time predicted (Text-fig. 4). There seems to be a production of substances aiding cicatrization in the period preceding the infection. The substances are carried in the circulation but reinfection prevents their being used for epithelial cicatrization.

Cicatrization of certain wounds sometimes follows, at the beginning or later, a course more rapid than the calculated curve indicates. In such a case, if the wound is not a long, narrow one, secondary ulcerations, in which we have never found bacteria, occur and restore the surface of the wound to what it would have been theoretically (Text-figs. 5 and 6). If infection entirely destroys epidermization, it is restored much more rapidly than the calculated curve indicates (Text-figs. 5 and 6). In Text-fig. 6 the observed curve oscillates about the calculated curve. It is difficult in this case to find a satisfactory explanation of this phenomenon; it can only be said that secondary ulcerations are related to the presence of bacteria in the deeper
parts of the wound. It is necessary in all such cases to know whether the bacteria are not retarding cicatrization. Certain cocci commonly observed allow normal cicatrization, but we have never found bacilli that allowed the same evolution of cicatrization.

![Text-Fig. 4. Experiment 3. Surface wound of the right knee. The wound healed according to the law. Two infections in the course of cicatrization did not prevent the wound from healing in the calculated time.](image)

![Text-Fig. 5. Experiment 4. Age 30 years. Superficial wound of the abdomen, in the iliac region. The wound was aseptic during the entire period of cicatrization. It healed at first more rapidly than the theoretical curve indicated, but more slowly than the curve from the corrected formula for long, narrow wounds. From information subsequently received from the patient himself it was learned that the wound reopened and finally healed on July 19, as the curve had indicated. Certain infective processes produce ossifying myositis or hospital gangrene, the first with an extension of the wound, which spreads out as a flower opens, the second with induration of tissue which will...](image)
Text-Fig. 6. Experiment 5. Age 31 years. Surface wound of the right leg. The observed curve oscillates about the calculated curve. When the real surface is smaller than the calculated surface, secondary ulcerations, in which no bacteria have been found, bring the observed surface back to a size very near the theoretical one. Hitherto no satisfactory explanation has been found for this phenomenon. See also Experiment 4.
Text Fig. 7, a and b. Experiment 6. Age 21 years. Two parallel wounds in the back, (a) upper wound, (b) lower wound. The wounds were sterile during the period of cicatization. The curves show the effect produced by contraction of tissue; each wound alone would have cicatized according to the calculated curve, taking for the index the figures furnished by the chart, for 50.35 and 36.85 sq. cm., and 21 years. The index calculated from the first two surface measurements gave a second theoretical curve, drawn with a dotted line. The real curve of cicatization remains almost entirely between the two calculated curves, especially for the lower wound. From the time when contraction no longer occurred (the broken line toward the 46th day), cicatization took place rapidly, overtaking the calculated curve.
not contract. Thus it is clinically demonstrated that the nature of
the infecting organism can influence the rapidity of cicatrization.

We have observed that if the mechanical contraction of tissue is
hindered, by adhesions for instance, cicatrization occurs more slowly
than is indicated by the calculated curve. Thus, cicatrization of two
wounds near each other can be restricted by contraction in opposite
directions. An example of this is Experiment 6 (Fig. 1, Text-fig. 7,
a and b), two long parallel wounds in the dorsal region, generally
sterile, restricting each other. Examination of the curves shows that
the cicatrization of each wound if it had been alone would have fol-
lowed the light line (index determined by the chart); in reality it
more nearly followed the dotted line (index determined from two
actual measurements), at a slower rate. But in the last days before
healing was complete, contraction of the tissues ceased (see the
broken line), cicatrization went on much more rapidly, and the ob-
served curve caught up with and even passed the calculated curve.

This experiment is related to a second theoretical cicatrization
curve which we have frequently worked out. A continually infected
wound can cicatrize according to the law provided, first, that the in-
fection is within certain limits, that is that the number of bacteria
is at most 14 to 15 per field; and second, that the infection is from
cocci or diplococci, and that streptococci or bacilli are found only ex-
ceptionally. A theoretical cicatrization curve can be drawn from an
index obtained from the two surfaces first measured. The observed
curve will follow the calculated curve, and one should keep as close
as possible to this.

Furthermore, a second theoretical curve may be made with the
index determined by the chart, from the initial surface of the wound
and the age of the patient. This, which would be the cicatrization
curve if the wound were sterile, is the normal curve, and we should
try to follow it in treating the wound. The observed curve will lie
practically between the two calculated curves (Text-fig. 8, a).

It seemed possible that the two curves could be of use when it is
understood that the calculated index is not equal to the index deter-
mimed by the chart, the two curves thus drawn constituting two limits
between which the observed curve should continually remain.
Deep Wounds.

By an analogous procedure we have tried to follow the cicatrization of deep wounds. We first undertook to measure the volume of the wound by filling it with the fluid used for treating it, by means of a graduated pipette which could easily be sterilized. But the practical difficulty of placing the patient in a position in which the wound could be easily and thoroughly filled was so great, and the volume of the wound, which was often a cavity, was so variable, according to the patient's position, that we abandoned this procedure.

It seemed better to follow the indirect method of tracing on sterilized cellophane the successive outlines of the wound, as if we were dealing with a surface wound, and then to measure these areas. By means of calculations identical with those which served for surface wounds, we have determined a theoretical cicatrization curve with an index calculated from the first two observed surfaces, or with an index determined from the chart. We have thus been able to show that a deep wound properly treated and sterilized, the edges of which are gradually drawn together at the proper time by adhesive plaster, with elastic strapping, should cicatrize at least equally and often even more rapidly than a surface wound of the same contour (Text-figs. 9, a and b and 10, a and b). We have also observed that the gradual drawing together by means of the elastic traction is superior to the partial closure by suture intervening in the course of cicatrization (Text-fig. 8, b).

On October 13 the wound had been sterilized and the edges drawn together by an elastic traction; from that day cicatrization continued normally and steadily, and the observed curve lay between the two calculated curves (light line and dotted line). On November 7 the wound was partially sutured and decreased from 50 to 45 sq. cm., but presumably, from the general aspect of the curves, normal cicatrization would have decreased it to 35 or 36 sq. cm. After the operation the wound was reinfected and the surface extended to 52.75 sq. cm., decreasing again immediately, but at a much slower rate than was indi-

Without the bandage a deep wound, at least one of small dimensions, seems to cicatrize according to a law analogous to that of the cicatrization of surface wounds, but more slowly.
TEXT-Fig. 8, a and b. Experiment 7. (a) Small wound. Example of cica
tization of a wound slightly but constantly infected. (b) Large deep wound. Example of a sterile wound whose edges have been drawn together by an elastic traction. An attempt at a partial suture was made, the action of which seems to have been injurious, if one considers that the observed curve deviates from the calculated curve. A new elastic traction placed December 9 hastened cica
tization; the observed curve tended to rejoin the calculated curve.
Calculated curve for superficial wound.

Text-Fig. 9, a and b. Experiment 8. Age 25 years. Deep hip wounds. The observed curves show the effect of the elastic traction on cicatrization, which took place rapidly in spite of the frequent presence of bacteria.
TEXT-FIG. 10, a and b. Experiment 9. Age 21 years. (a) Deep bullet wound in the lumbar region, treated with an elastic traction and cicatrizing more rapidly than a surface wound of the same contour. The smaller curve (b) was drawn after December 2, when the wound had become entirely superficial.
cated by the calculated curves, until the application of a second elastic traction again hastened the healing process. No conclusion can be drawn from this experiment, but it shows that in certain conditions in longitudinal wounds simply drawing the edges together gives rapid results.

SUMMARY.

Some hypothetical conclusions bearing on the evolution of cicatricial tissue can be suggested. The arterial circulation deposits in the wound chemical substances necessary for contraction of the wound and for epithelial proliferation. When the biologic process is not hindered by any special or severe bacterial infection this deposit is as regular as the circulation itself, and enables us to determine in advance the date of cicatrization. It even seems as though when the epidermization process is retarded by a slight infection the substances necessary for epidermization are stored up in the wound, and when the delay due to infection is removed the epithelium finds an accumulation of nutritive substances, and, so to speak, makes up the lost time.

Moreover, when an infection entirely or partially stops epidermization, we have observed (Experiments 3, 4, and 5) that after the infection has disappeared the progress of new epidermization is much more rapid than normally; it even passes the calculated curve. The infection apparently destroyed only the epithelium and left in the wound the chemical substances which activate epidermization.

The existence of these physical or chemical activating agents has been indicated again by two anatomical clinical facts. In treating a scalp wound in which there had been practically no epidermization for many months, we applied over the entire surface of the sterile wound dermo-epidermic grafts of fetal skin. After apparently taking, the grafts were absorbed and disappeared, but epidermization of the periphery of the wound, which hitherto had not progressed, took place abundantly, almost a hundred times as much as before.

We believe that by mathematical measurements we can solve the problem of the action of various organic fluids on the cicatrization of wounds.
Fig. 1. Experiment 6. Age 21 years. Two parallel wounds in the back. Appearance of the wounds on October 6, 1916.
FIG. 1.

(Tuffier and Desmarres: Cicatization of war wounds.)