CICATRIZATION OF WOUNDS.

II. Mathematical Expression of the Curve Representing Cicatrization.

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In order to study the process of cicatrization, a technique for measuring accurately the area of wounds was developed. Sterilized cellophane was applied to the wound and the edge was outlined with a wax pencil. This drawing was transferred in ink to an ordinary sheet of paper. Afterwards the area was measured by means of a planimeter, either the Amsler system or some other. A curve was obtained by carrying the area, in square centimeters, in ordinates, and the time, in days, in abscissæ.

In many experiments made by Dr. Carrel the curve representing the cicatrization of aseptic wounds was of regular and geometric appearance. These curves were expressed by a mathematical equation in function of time and area.

After a large number of slightly infected wounds had been studied, a simple extrapolation formula was obtained. Marked deviation from the calculated curve showed generally that infection had set in. By means of the formula the area of the wound after a given time can be foreseen. The formula may be expressed in two equations.

$$(1) \quad \frac{\frac{S - S'}{S}}{t + \sqrt{T}} = i$$

$$(2) \quad S'' = S' [1 - i (t' + \sqrt{T + t'})]$$

S represents the area of the wound at the beginning of the experiment.

S' represents the area of the wound t days later, at the time of the second observation. (We may say 4 days, in order that the area cicatrized, $S-S'$, may be of sufficient size.)

t represents the time elapsed between the first two observations, S and S', in days.

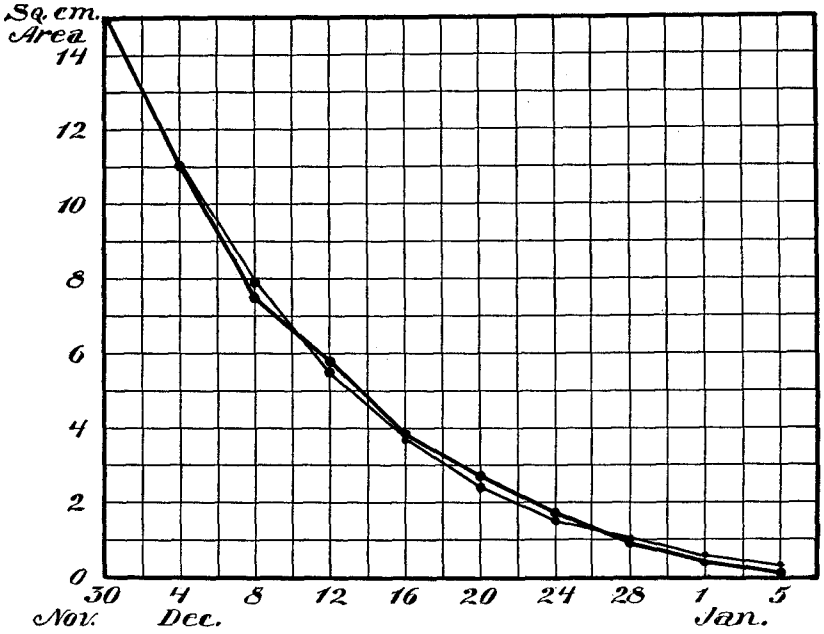
T represents the age of the wound from the time of the first observation S. Therefore in the formula (1) $T = t$, and practically $t = t' = 4$ days.

t' represents the time between the last observation S' and the time of the theoretical surface S'' of the wound.

i is a constant coefficient characterizing each wound.

Thus the first equation tends to establish an index of cicatrization i which is carried into the second in order to calculate the surface of the wound at a given time. It should be noticed that the best approximation is obtained when the time t is the same as the time t'. Therefore, after two observations, 3 or 4 days apart, of a wound which heals aseptically, the area that it should have 4, 10, 20, or 30 days later, and the day on which it should be healed can be computed. Accidents, of course, may retard temporarily the progress of the phenomenon. But generally the time lost is regained by a rapid acceleration as shown in Wounds 4, 6, and 7.

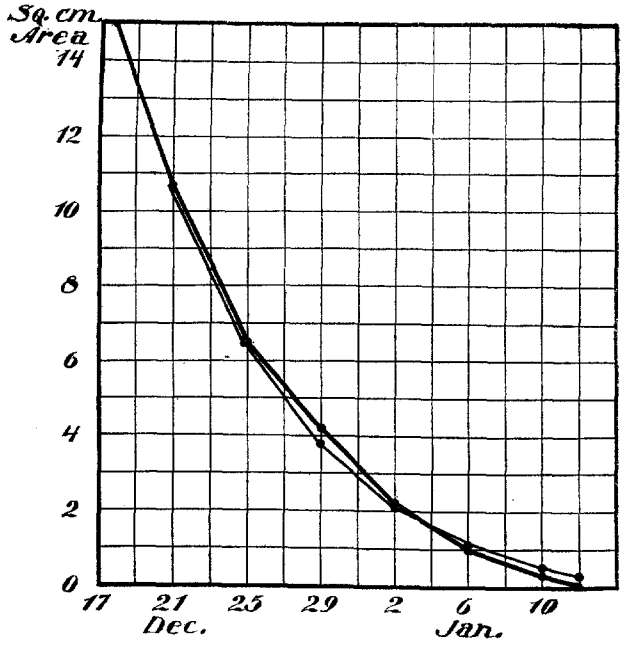
In the following experiments the calculated areas are compared with the observed areas.



TEXT-FIG. 1.

Experiment 1.—Patient 217, age 37 years. Wound of the arm. On Nov. 30, the size was 15.3 sq. cm. Index = 0.041 (Text-fig. 1). Between Dec. 18 and 24, a few bacteria appeared on the films (1 to 3 per microscopic field).

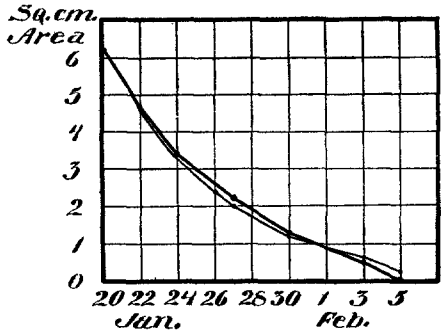
	1915 Dec. 4	8	12	16	20	24	28	1916 Jan. 1	5
Observed area..	11.0	7.5	5.8	3.8	2.7	1.7	0.9	0.4	Cicatrization.
Calculated "..		7.9	5.5	3.7	2.4	1.55	0.96	0.58	"



TEXT-FIG. 2.

Experiment 2.—Patient 221, age 27 years. On Dec. 17 the area of the wound was 16.2 sq. cm. Index = 0.057 (Text-fig. 2). There was a slight infection between Dec. 27 and 29 (1 microorganism in two microscopic fields).

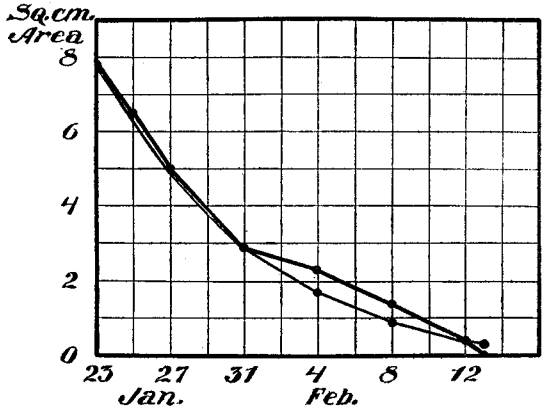
	1915 Dec. 21	25	29	1916 Jan. 2	6	10	12
Observed area.....	10.7	6.5	4.2	2.2	1.0	0.3	Cicatrization.
Calculated "		6.5	3.8	2.1	1.1	0.5	"



TEXT-FIG. 3.

Experiment 3.—Patient 354, age 40 years. On Dec. 20 the area of the wound was 6.2 sq. cm. Index = 0.07 (Text-fig. 3).

	1916 Jan. 22	24	27	30	Feb. 3	5
Observed area.....	4.7	3.4	2.2	1.3	0.5	Cicatrization.
Calculated "		3.4	2.4	1.2	0.54	"

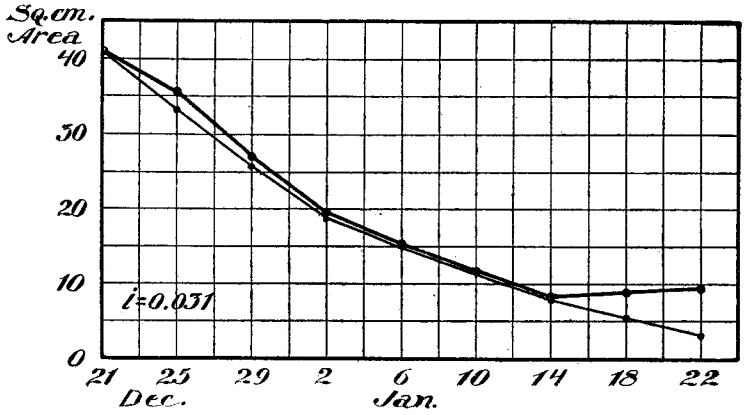


TEXT-FIG. 4.

Experiment 4.—Patient 330, age 31 years. On Jan. 23 the area of the wound was 7.8 sq. cm. Index = 0.059 (Text-fig. 4).

	1916 Jan. 25	27	31	Feb. 4	8	12	13
Observed area.....	6.5	5.0	2.9	2.3	1.4	0.4	Cicatrization.
Calculated "		5.0	2.98	1.7	0.9	0.44	"

Between February 3 and 8 the wound became infected and deviated from the theoretical curve. However, it overtook the latter on February 12 after it was again sterilized. This shows that acceleration of the cicatrization has occurred, which always happened in the cases which we studied.

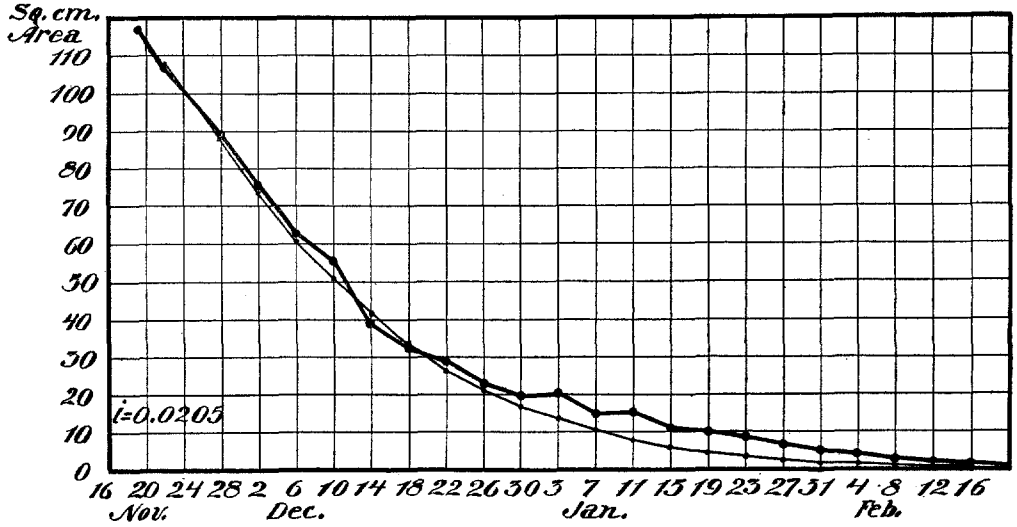


TEXT-FIG. 5.

Experiment 5.—Patient 266, age 33 years. On Dec. 25 the area of the wound was 35.4 sq. cm. Index = 0.031 (Text-fig. 5). On Jan. 14 the wound became infected and began to increase in size. It deviated from the theoretical curve and did not meet it again.

	1915 Dec. 29	1916 Jan. 2	6	10	14	18
Observed area.....	27.3	19.4	15.4	11.7	8.2	9.0
Calculated "		19.1	15.6	11.3	8.0	5.6

The following experiment was similar, but the observed curve coincided with the calculated curve before healing. The date of healing could be predicted 90 days in advance.

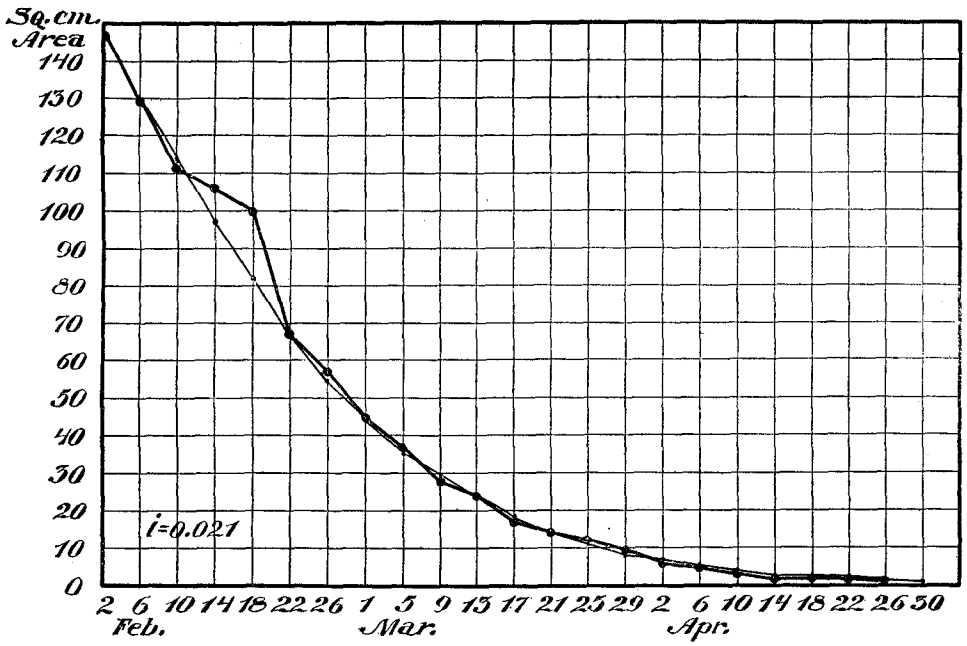


TEXT-FIG. 6.

Experiment 6.—Patient 263, age 36 years. On Nov. 19 the area of the wound was 118.5 sq. cm. Index = 0.0205 (Text-fig. 6). The fluctuations of the curve were due to infection. The observed curve has, as always, a tendency to regain time lost in order to rejoin the calculated curve (from Dec. 10 to 14, then from Jan. 27 to Feb. 18).

	1915 Nov. 22	28	Dec. 2	6	10	14	18	22	26	30
Observed area.....	107.0	89.6	76.0	62.1	55.1	39.7	32.5	29.1	23.0	19.5
Calculated "		88.0	74.2	61.8	51.0	41.6	33.6	26.9	21.3	16.8

	1916 Jan. 3	7	11	15	19	23	27	31	Feb. 4	8	12	16	18
Observed area.....	20.0	14.8	15.0	11.0	10.0	8.5	6.5	5.2	4.3	2.6	1.7	0.4	Cicatrization.
Calculated area..	13.1	10.1	7.8	5.9	4.5	3.4	2.5	1.9	1.4	1.0	0.74	0.5	"



TEXT-FIG. 7.

Experiment 7.—Patient 360, age 22 years. Index = 0.021 (Text-fig. 7). The deviation at the beginning (Feb. 18) was due to infection. After sterilization it overtook the calculated curve.

	1916 Feb. 6	10	14	18	22	26	Mar. 1	5
Observed area	129.4	111.0	105.5	99.5	67.5	57.0	45.0	37.0
Calculated "		113.0	96.8	81.6	67.9	55.9	45.5	36.6

	Mar. 9	13	17	21	25	29	Apr. 2
Observed area	27.5	23.9	17.6	14.0	11.8	9.2	5.9
Calculated "	29.2	23.1	18.1	14.0	10.8	8.26	6.27

	Apr. 6	10	14	18	22	26	30	May 4	6
Observed area	4.1	3.0	1.7	1.8	1.0	0.65	0.7		Cicatrization.
Calculated "	4.7	3.5	2.6	1.9	1.4	1.0	0.7	0.5	"

As shown by the above experiments, 0 of the formula, that is, the theoretical healing, corresponds to an area of about 0.4 sq. cm. This is required by the fact that if the calculation should be continued, 0 would be reduced to infinity. Experience has proved that the calculated number 0.4 nearly always represents complete healing of the wound.

The value of the index varies between 0.02 and 0.08. It depends on the age of the patient and the size of the wound, and is much larger when the wound is smaller and the subject younger.

In conclusion, it may be stated, that, under given conditions of asepsis and dressing, the area cicatrized in a day is directly proportional to the size of the wound, to the square root of its age, and to the relation between the rate of cicatrization and the square root of the age of the wound at the time of observation. The relation between the rate expressed in function of the total area, and the square root of the age of the wound is represented by the cicatrization index i, which acts in Formula 2 as a constant characterizing each wound.

Mechanism of the Formula.

The study of a wound in the process of healing shows that the age of the wound seems to have no action whatever on the rate of cicatrization. On the other hand, since all wounds under a certain size cicatrize at about equal rate, the part of the constant i is no longer clear, as this index is not the same for every wound. If the age of the wound is of no consequence, it should be suppressed, and the index i, which has after all the dimensions of an acceleration $\frac{V}{T}$, should tend towards the same value for all wounds when they are nearly healed. Therefore i would not be a constant characterizing every wound. How then can this index be of value in the formula as a constant? And what part does the square root of the age of the wound play?

The explanation is simple. The most important factor of the rapidity with which a wound cicatrizes is its size. Consequently when a large wound cicatrizes and grows old, the measure of the progress of cicatrization is its age. Time is one of the factors of its dimensions. Then, if age itself does not influence the rate of cicatrization, the size plays an important part. Therefore a quantity representing the age, a known quantity, represents also in some measure the size of the wound, an unknown quantity. Thus a factor inactive in it-

self, such as age, plays the part of the principal factor, that is size. But it should be understood that the area is expressed in time.

Hence the part of the index i as a constant is explained. In order to express what really occurs, i should increase in a manner inversely proportional to the size, which conforms with the formula:

$$\frac{\frac{S-S'}{S}}{t}$$

but then, the unnecessary element T must be suppressed. Practically' the coefficient i is constant, but we arbitrarily maintain the quantity T in the formula. The result is the same, because, like i, T increases in inverse proportion to the area of the wound. So the progress of cicatrization can be indirectly expressed. This procedure was used, since time was the only factor at our disposal for the calculation of the entire curve of the wound after the first two observations had been made.

Details of the Calculation.

We see from Formula 2 that in order to continue the calculation and obtain successively the area S''' at the end of t'' days, S'''' at the end of t''' days, S_n at the end of t_m days, and so on, the last calculated area is brought into the formula in order to obtain the next area. Then the following calculations are made:

$$S'' = S' - [S' \times i \times (t' + \sqrt{T+t'})] = S'' \quad (\text{here: } T = t)$$
$$S''' = S'' - [S'' \times i \times (t'' + \sqrt{T+t''})] = S''' \quad (\text{“} \quad T = t + t')$$
$$S'''' = S''' - [S''' \times i \times (t''' + \sqrt{T+t'''})] = S'''' \quad (\text{“} \quad T = t + t' + t'')$$

....

$$S_n = S_{n-1} - [S_{n-1} \times i \times (t_m + \sqrt{T + t_m})], \qquad (T = t + t' + t'' + \cdots + t_{m-1})$$

Let us take for example a sterile wound of 12 sq. cm. 4 days later it measures 9 sq. cm.

(1) Calculation of the index i:

$$S = 12 \quad S' = 9 \quad t = 4 \quad T = 4 \qquad i = \frac{\frac{12-9}{12}}{4 + \sqrt{4}} = 0.0416$$

(2) Calculation of the surface:

(*a*) 4 days later $\begin{cases} S'' = S' - [S' \times i \times (t' + \sqrt{T + t'})] \\ = x = 9 - [9 \times 0.0416 \times (4 + \sqrt{4 + 4})] = 6.45 \text{ sq. cm.} \end{cases}$

(*b*) 3 days later $\begin{cases} S''' = S'' - [S'' \times i \times (t'' + \sqrt{T + t''})] \\ = 6.45 - [6.45 \times 0.0416 \times (3 + \sqrt{8 + 3})] = 4.84 \text{ sq. cm.} \end{cases}$

and so on.

11 days after the first observation, the area will be 4.8 sq. cm., if the wound has remained aseptic.

SUMMARY.

The cicatrization of sterile wounds may be studied in the same way as an ordinary physicochemical phenomenon. It is possible, therefore, to express the law of cicatrization by a mathematical equation as soon as an accurate measure of the wound can be obtained. By means of the equation, a curve is obtained which represents the theoretical evolution of the cicatrization of a wound. This curve, being an expression of what should happen on a normal wound, healing aseptically, on a normal man, is a daily point of comparison to what appears actually on the observed wound, and allows one to study accurately the fluctuations of cicatrization on a given individual, and the action of different dressings and antiseptic substances.