THE RATE OF HEALING OF WOUNDS.

By JOHN BROWNLEE, M.D.

(From the National Institute for Medical Research, London, England.)

(Received for publication, November 2, 1923.)

During recent years a number of papers by Carrel and others concerning the rate of healing of wounds have been published. Du Noüy has also applied some mathematical treatment to these observations and constructed some graduation formulæ. In the application of these formulæ, however, I think that the meaning of the figures has been in some measure obscured and that a different treatment reveals some interesting relations.

Personally I do not feel inclined to make a special formula for any individual case until those which occur so commonly in nature have been investigated. The formula which seems to apply in all cases in which the data are sufficient is the geometrical progression. A geometrical progression is found to arise in nature in many different ways from the theory of chance. It might be assumed that at the beginning of the healing of a wound, the impulse to heal is great and the factors on which this impulse to heal depends, decay according to the ordinary monomolecular reaction, but the geometrical progression turns up in so many different ways and for reasons which at present we cannot understand that this is nothing but a tentative suggestion. To say more is going beyond the evidence.

To clear the ground, a further point requires mention; namely, that it is not necessary to assume that the process of healing is continuous and not subject to sudden change. Take the recent work of Glenny and Hopkins¹ on the disappearance of diphtheria antitoxin from the blood of animals into which intravenous injections have been made. In these experiments it is found that the rate of disappearance of the antitoxin is not continuous. During the

¹ Glenny, A. T., and Hopkins, B. E., *J. Hyg.*, 1922-23, xxi, 144.

first day and a half after injection a very large quantity of antitoxin disappears. Thereafter the decrease is much more gradual and obeys the law of the monomolecular reaction, the amount decreasing in the terms of a geometrical progression. After an incubation period of 9 or 10 days has passed, when antibodies begin to form, the destruction of the antitoxin becomes suddenly much more rapid. There is no use in trying to fit a continuous curve to a case like this in which, from the nature of the change which takes place, a fundamental break in the physiological or pathological processes is introduced.

When the figures published by Carrel are examined, something similar to this will I think be at once evident.

In the second column of Table I, the figures relating to the healing of a wound in the thigh, in a male aged 38 years are shown, the measurements of the area of the wound being given at intervals of 4 days. In the fourth and fifth columns, the logarithms of these numbers are given and the differences between the successive values of the logarithms. From the figures it would appear that at a date between February 29 and March 4 healing began. It will be noticed that from this date up to March 24, the mean difference of the successive logarithms is about 0.1, whereas following March 24 it is much nearer 0.2. By graduating the observations to two geometrical progressions with a break at about March 24, the figures in the third column have been obtained. The fit can only be considered exceedingly good. The ratio in the first half of the observation period from 4 days to 4 days is 0.793 and in the second half 0.652, the second value being very nearly the square of the first.

If the preceding case were a solitary one it might be considered as due to chance, but the same phenomenon is seen in practically every case given by Carrel. Two more examples are shown in Tables II and III and a third in Table VII.

In an experimental case of shorter duration, a female dog of 13 years of age had a rectangular flap of skin excised from the dorsal region. For 6 days no sign of reaction appeared, when, as is the rule in these cases, a rapid healing began. From the time healing began, about May 18, until June 9, the process can be graduated

very closely to a geometrical progression with a ratio of 0.785. This healing went on uninterruptedly until June 9 when again a sudden change took place and a wound which was 2.7 cm. was practically healed in 10 days. The area of the wound which would

TABLE I.
Male, Age 38 Years. Wound of the Thigh.

Date.	Area of wound.	Theoretical* area.	Ratio.	Log.	Difference.
1916	sq. cm.	sq. cm.			
Feb. 29	46.7	51.4	0.793	1.669	
Mar. 4	40.5	40.8		1.608	0.115
" 8	31.1	32.3		1.493	0.062
" 12	27.0	25.6		1.431	0.107
" 16	21.1	20.4		1.324	0.120
" 20	16.0	16.1		1.204	0.107
" 24	12.5	12.8		1.097	0.178
" 28	8.3	8.3		0.919	0.220
Apr. 1	5.0	5.4	0.652	0.699	0.097
" 5	4.0	3.5		0.602	0.240
" 9	2.3	2.3		0.362	0.216
" 13	1.4	1.5		0.146	0.146
" 17	1.0	0.8		0.000	

The data for this table were taken from du Noüy, P. L., *J. Exp. Med.*, 1916, xxiv, 465.

* Healing would begin by this theory on Mar. 2.

have been present had the process remained continuous is given in the third column. In comparison with this two other short cases are given in Tables V and VI, in both of which the graduation to a geometrical progression is nearly perfect and in both of which towards the end a rapid quickening in the rate takes place.

TABLE II.
Male, Age 32 Years.

Date.	Area of wound.	Theoretical area.	Ratio.	Log.	Difference.
1916	sq. cm.	sq. cm.			
Feb. 6	56.6	57.5	0.839	2.753	0.107
" 10	44.3	48.2		2.646	0.023
" 14	42.0	40.5		2.623	0.097
" 18	33.6	34.0		2.526	0.046
" 22	30.2	28.4		2.480	0.096
" 26	24.2	23.9		2.384	0.040
Mar. 1	22.1	20.0		2.344	0.114
" 5	17.0	16.8		2.230	0.096
" 9	13.6	14.1		2.134	0.093
" 13	11.0	11.8		2.041	0.077
" 17	9.2	9.8	0.660	1.964	0.151
" 21	6.5	6.4		1.813	0.190
" 25	4.2	4.2		1.623	0.132
" 29	3.1	2.8		1.491	0.236
Apr. 2	1.8	1.8		1.255	0.194
" 6	1.15	1.2		1.061	0.158
" 10	0.8	0.8		0.903	

The data for this table were taken from du Noüy, P. L., *J. Exp. Med.*, 1916, **xxiv**, 464.

The interpretation of these phenomena is conjectural. The first phenomenon is the sudden commencement of healing; this is so obvious that it cannot be overlooked. There seems, however, to

TABLE III.

Patient, Age 21 Years. Shell Wound of the Posterior Thoracic Region.

Date.	Area of wound.	Theoretical area.	Ratio.
	<i>sq. cm.</i>	<i>sq. cm.</i>	
Feb. 2	40.2		0.788
" 6	40.0	38.3	
" 10	29.3	30.7	
" 14	24.0	24.6	
" 16	19.8	19.6	
" 18	16.0	15.7	0.675
" 22	11.0	10.8	
" 26	7.1	7.3	
May 1	5.0	4.9	
" 5	2.0		

The data for this table were taken from Carrel, A., and Hartmann, A., *J. Exp. Med.*, 1916, xxiv, Text-fig. 15 between pp. 444 and 445.

TABLE IV.

Female Dog, Age 13 Years. Resection of a Rectangular Flap of Skin on the Dorsal Region.

Date.	Area of wound.	Theoretical area.	Ratio.
	<i>sq. cm.</i>	<i>sq. cm.</i>	
1919			
May 13	39.4		0.785
" 17	38.7	43.3*	
" 19	33.5	34.0	
" 20	30.2	30.2	
" 23	20.3	20.9	
" 24	18.7	18.6	
" 26	14.3	14.6	
" 27	12.2	12.9	
" 28	11.5	11.5	
" 29	9.2	10.2	
" 31	7.7	8.0	
June 4	4.0	4.9	
" 9	2.7	2.7	
" 13	1.1	2.1	
" 17	0.5	1.6	

The data for this table were taken from Carrel, A., and du Noüy, P. L., *J. Exp. Med.*, 1921, xxxiv, 341.

* Healing would begin on May 18.

TABLE V.

Patient, Age 36 years. Wound of the Left Iliac Region; Slightly Infected.

Date.	Area of wound.	Theoretical area.	Ratio.
	<i>sq. cm.</i>	<i>sq. cm.</i>	
Nov. 30	15.3	15.8	0.697
Dec. 4	11.0	11.0	
" 8	7.5	7.7	
" 12	5.8	5.4	
" 16	3.8	3.7	
" 20	2.7	2.6	
" 24	1.7	1.8	
" 28	0.7	1.2	

The data for this table were taken from Carrel, A., and Hartmann, A., *J. Exp. Med.*, 1916, xxiv, 433.

TABLE VI.

Male, Age 38 Years. Wound of the Arm.

Date.	Area of wound.	Theoretical area.	Ratio.
	<i>sq. cm.</i>	<i>sq. cm.</i>	
1916			
Mar. 12	25.8	28.3*	0.750
" 16	21.1	21.3	
" 20	16.0	16.0	
" 24	13.0	12.0	
" 28	9.9	9.0	
Apr. 1	6.5	6.7	
" 5	5.6	5.1	
" 9	3.6	3.8	
" 13	2.7	2.9	
" 17	2.0	2.1	
" 21	1.7	1.6	
" 25	0.9	1.2	
" 29	0.5	0.9	
May 3	0.3	0.7	

The data for this table were taken from du Noüy, P. L., *J. Exp. Med.*, 1916, xxiv, 466.

* Healing would begin Mar. 13.

TABLE VII.
Patient, Age 22 Years.

Date.	Area of wound.	Theoretical area.	Ratio.	Log.	Difference.
1916	sq. cms.	sq. cms.			
Feb. 6	129.4	171.8		2.112	
" 10	111.0	137.4		2.045	0.067
" 14	105.5	109.9		2.023	0.022
" 18	99.5	87.7		1.998	0.025
" 22	67.5	70.0		1.829	0.169
" 26	57.0	55.9		1.756	0.073
Mar. 1	45.0	44.7		1.653	0.103
" 5	37.0	35.7		1.568	0.085
" 9	27.5	28.4		1.439	0.129
" 13	23.9	22.7	0.789	1.378	0.061
" 17	17.6	18.1		1.246	0.132
" 21	14.0	14.5		1.146	0.100
" 25	11.8	11.6		1.072	0.074
" 29	9.2	8.8	9.2	0.964	0.108
Apr. 2	5.9	6.1		0.771	0.193
" 6	4.1	4.2		0.613	0.158
" 10	3.0	3.0		0.477	0.136
" 14	1.7	2.0	0.695	0.230	0.247
" 18	1.8	1.4		0.255	-0.025
" 22	1.0	1.0		0.000	0.255
" 26	0.65	0.7		1.813	0.187

The data for this table were taken from du Noüy, P. L., *J. Exp. Med.*, 1916, xxiv, 457.

be a second phenomenon. A point comes in the healing when an extra healing power suddenly develops. This change in the process seems to show that in surgical disease as in medical, there are more factors at work than might be thought probable. It is possible that a search into the conditions would furnish results of practical value.

A final note may be made on the case of the male, aged 22 years, in whom septic infection of the wound occurred and decreased the rate of healing (Table VII). After sterilization of the wound on February 22 and until March 29, healing progressed uninterruptedly with a ratio of 0.789. About March 29 a marked change took place, the ratio for the rest of the healing being 0.695. Du Noüy in fitting his formula obtained a curve which represents very closely the observations before and after sepsis and makes the inference that the sepsis had no permanent effect on the rate of healing. I have calculated back from the first portion of my curve and find very much larger values for the size of the wound than those given by the actual figures. As the geometrical progression has been found to hold in all the examples given with very considerable accuracy, I am inclined to think that du Noüy's interpretation is wrong and that the sepsis did make a permanent difference in the rate of healing.

APPENDIX.

Let it be assumed first that the wound be circular and that the rate of advance of the epithelium in the direction of the radius diminishes in a geometrical progression.

If the radius at any time be r , and A is the area, since

$$A = \pi r^2$$

we have at once

$$\frac{dA}{dt} = 2\pi r \frac{dr}{dt}$$

in which t is the time. But it has been assumed that $\frac{dr}{dt}$ diminishes in a geometrical progression so that

$$\frac{dr}{dt} = -ake^{-k}$$

in which a is the radius at commencement of healing, whence

$$\begin{aligned} r &= -ak \int e^{-kt} dt \\ &= a_0 e^{-kt} \end{aligned}$$

so that we have

$$\frac{dA}{dt} = -2\pi a^2 e^{-2k}$$

or

$$A = \pi a^2 e^{-2k}$$

so that the area also decreases in a geometrical progression. This applies to a circular wound. In many of the experiments, the wound has been rectangular. Consequently, at the beginning of healing, the area covered by the advancing edge is rather greater than it would be were the edge circular, because the peripheral border of a square is greater in relation to the contained area than in the case of a circle, but the difference is not sufficient to interfere seriously with the analysis given above.