Studies on Wound Healing, with Special Reference to the Phenomenon of Contracture in Experimental Wounds in Rabbits' Skin *

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INTRODUCTION

IN MAMMALS, which possess but limited capacity to regenerate specialized tissues and structures, wounds that are accompanied by a loss of tissue substance—or which gape so that their margins fail to approximate of their own accord—are normally repaired, with a varying degree of success, by the process of contracture. As a result of contracture the undamaged tissues bounding the lesion are gradually brought towards one another.

The healing of such wounds may be said to take place in two phases which overlap in time and which may be considered to provide in turn a temporary and a definitive repair. Initially the defect becomes filled with granulation tissue which provides a sort of *ad hoc* mesenchymal ground work. The latter, in wounds that involve epithelial surfaces, as in the bowel or integument, is rapidly resurfaced by the migratory activity of epithelium from the wound margins. Through contracture the histological and functional continuity of the damaged tissue may be restored with minimal disruption.

This mechanism for the restoration of continuity of tissues can sometimes be entirely beneficial particularly where reduction of free surface is of no functional consequence. For example, contracture may virtually restore muscular continuity with a satisfactory functional result following myocardial infarction. On the other hand, in regions of the human body where the integument is firmly united to underlying tissues, full-thickness loss of skin, particularly from such places as the extensor surfaces of the extremities, may be followed by severe impairment of mobility as contracture of the wound becomes manifest. The narrowing, and sometimes complete obstruction, of the duodenum following repeated ulceration and healing exemplifies a similar undesirable side-effect of contracture in wound healing.

The extent to which the process of contracture contributes to repair of a wound is highly variable and appears to depend among other things upon: a) the species of the individual, b) the tissue involved, and c) the anatomical location of the damaged tissue.

Experimental wounds in the integument are most accessible for studies on the processes of healing, especially contracture. The subject matter of this paper is the healing of extensive areas of full-thickness skin loss in rabbits and some of the factors that influence it. This species was chosen since, as previous work had shown, the contracture of cutaneous wounds proceeds very nearly to completion; moreover, relatively large wounds can be conveniently made

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and maintained under conditions which closely resemble those encountered clinically.

The literature on the subject of repair of cutaneous wounds, particularly that concerned with its quantitative aspects, is confused by inconsistencies and lack of precision in terminology. One important cause of this confusion appears to be a failure to separate clearly the contributions of epithelial and connective tissue to repair which, so we propose (see below), are nearly independent. The convenient end point of complete epithelial coverage may be held to constitute "wound closure," but it is hardly the completion of the healing process, as some investigators have assumed. Healing is only complete when a wound ceases to contract—when the process of re-apposition and functional reunion of the separated tissues has progressed as far as it is ever likely to do. The rate at which a wound becomes epithelialized cannot, therefore, be a measure of definitive healing but is at most a single component of the complex.

In the present study special attention has been paid to the rate of progress of contracture as derived from repeated and successive observations. The significance of the results of our various experiments has been assessed throughout on a purely statistical basis. While this necessarily restricted the scope of the comparison that could be made between one group of experimental findings and another to a single important parameter—so that much subsidiary information had to be neglected in the final analysis—we feel that an adequate compensation for this shortcoming was the gain in objectivity of the method.

PLAN OF THE EXPERIMENTS

Previous work (Billingham and Reynolds;[9] Billingham and Medawar[8]) had established that the process of contracture of extensive full-thickness cutaneous wounds in rabbits usually proceeds so nearly to completion that the original margins are almost approximated and the final scar is little more than a thin line. To provide the basis for the present study, these earlier observations were first placed on a strictly quantitative footing by following the course of contracture in a series of extensive wounds of standard dimensions. The influence of variation in depth, shape, and area on contracture of wounds was then investigated. Next, in their turn, the quantitative effects on contracture of each of the following has been studied: a) the age of the animal, b) the presence of different types of recently healed wounds of the skin in a remote location, c) the administration of cortisone, and d) the application of various types of autologous cutaneous grafts.

MATERIALS AND METHODS

Subjects of the work to be described were full-grown adult male agouti rabbits weighing 2.3 to 3.5 Kg. and ranging in age from about nine to 18 months.

Preparation of the Experimental Wounds. All operations were carried out aseptically under intravenous nembutal anesthesia supplemented by ether. The fur was removed closely from the dorso-lateral thoracic wall with a mechanical clipper and a thin layer of mildly antiseptic ointment was applied over the area.

With the animal on its side, and its legs tied out in full extension in a uniform and easily reproducible position, the outline of the intended wound was first marked accurately on the prepared skin with India ink. This was then incised down to, but not through, the panniculus carnosus, a thin layer of striated muscle closely bound to the corium but loosely united to the deep fascia. The full thickness of the skin within the incision was then carefully stripped away by sharp dissection from its underlying muscle and discarded. In spite of the close union between panniculus and corium it is possible to separate the integument

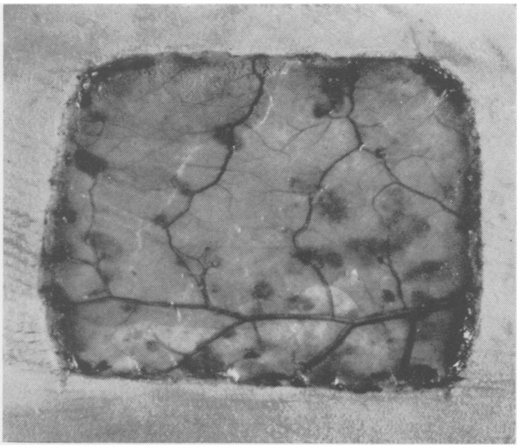

FIG. 1. Standard, rectangular full-thickness wound prepared in the skin of the side of a rabbit's chest. Note the prominent cutaneous vessels that course over the panniculus carnosus. (× ¾)

very cleanly in this plane; the panniculus with its rich vascular supply thus remains intact and provides an anatomically constant wound bed, the margins of which are united to underlying muscle (Fig. 1).

Dressings (tulle gras, gauze pad, bandage, and light plaster sheath) were applied in the way that has been described in detail and figured by Billingham and Medawar.[7]

Measurements. Immediately after its preparation the outline of the wound was traced as accurately as possible on a superimposed sheet of sterile cellophane. This outline was then transferred directly to a sheet of tracing paper and the area within it determined with a radial planimeter (Carrel and Hartmann[14]). Subsequent measurements of the area of the wound were made at regularly spaced intervals as healing progressed, each measurement being taken with the animal under deep anesthesia in the standard position. Besides the total area included within the full-thickness margins of the defect, the outline of the advancing front of epithelium growing in over the central granulations was also recorded.

OBSERVATIONS

1.1 *The process of healing of the standard wound.* The full-thickness wound forming the basis of this study was that resulting after excision of a rectangle of skin measuring 6 ×5 cm. before cutting, the long axis being disposed antero-posteriorly on the thoracic wall (Fig. 1). After cutting, these wounds gaped as a result of the natural elasticity of the integument so that their final area ranged from 35 to 40 cm^2.

The natural history of the repair of this type of wound has been described in detail elsewhere[9] so that it need only be briefly recapitulated here.

By the sixth postoperative day a thin layer of granulation tissue covers the floor of the wound, but the main vessels coursing on the surface of the panniculus can still be plainly seen. The vertically cut edges of the wound are rounded off and resurfaced by epithelial migration. By the ninth day the granulations have increased in thickness so that only the largest vessels can barely be distinguished through them, and a distinct border of native epithelium has migrated inwards over the developing granulations. By the twelfth day the surface of the granulation tissue may become elevated above the level of the surrounding skin. Meanwhile the wound as a whole has been contracting in such a way that the mid-points of the opposite sides are approaching one another. The combined processes of contracture and epithelial ingrowth result in the complete resurfacing of the wound within about 20 days.

1.2 *Quantitative analysis of contracture of the standard wound.* After an initial lag period of one to two days the rate of contracture of the wound (given by the tangent to the curve in which area of the wound is plotted against time) is rapid at first, declining progressively to approach zero asymptotically in its final stages. By the 45th day the wound area rarely exceeds about 2 cm^2. A typical curve of contracture

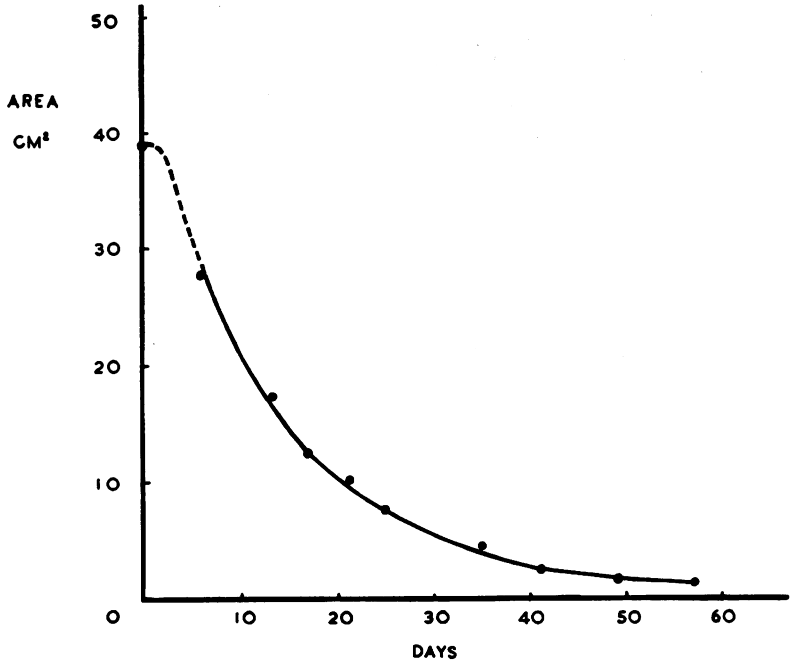

FIG. 2. Animal RX-1. Illustrating the contracture of a standard rectangular wound. (For explanation of the broken line see text.)

of a standard wound is presented in Figure 2. The beginning of the curve is represented by a broken line because the primary inspection was not carried out until the 6th day. The shape of this earlier part of the curve was based upon inspections carried out on several animals. By the 50th day contracture had brought the margins of the wound so close together that only a small linear external scar remained (Fig. 3) and the process was virtually complete.

When the logarithm of the area of the wound was plotted against time (Fig. 4) the relationship was found to be strikingly linear between the 6th and 40th days during which time the greater part of the reduction in area of the wound took place; in other words, the area diminished by a constant percentage or proportion of the existing area in each interval of time over this period. This linear relationship between log area and time was found to obtain for all the wounds in our control panel of seven animals and indeed for all types of full-thickness cutaneous wounds studied under these conditions.

The linear relationship between the logarithm of the area of the wound and time may be expressed in the form:

$$\log_e A = \log_e A_0 - at$$

where A and t represent area of the wound in cm² and time in days respectively; a is the slope of the straight line, and A_0 is the initial area of the wound on the day of operation. Alternatively the relationship beteen A and t can be stated as:

$$A = A_0 \cdot e^{-at}$$

which emphasizes that contracture of the wound obeys the exact opposite of the more familiar compound interest law of growth—contracture may be regarded as *negative* growth in this sense.

For each of the seven animals in the control series measurements of the actual total area of the wound were taken at eight to nine regularly spaced inspections over the range 0 to 50 days. However, since the linear relationship, illustrated in Figure 4, does not strictly hold at either extreme of the healing process, i.e. between 0 and 6 days and after about the 45th day, the statistical

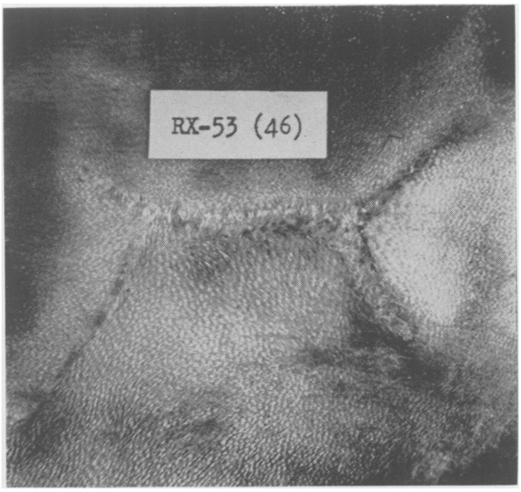

FIG. 3. The small linear scar remaining after completion of contracture of a standard wound prepared 46 days previously. (× ¾)

analysis of contracture has been confined to the period 6 to 44 days.

The value of a, together with its standard error, has been computed for each wound by analysis of the regression line. The "pooled value" of a with its standard error was obtained (see Table 1) by dividing the pooled values of sums of squares and products for each series of observations by the appropriate number of degrees of freedom.

The parameter a has a simple biological meaning. It is the *specific rate of contracture* and, since a is small, it approximates closely enough for all practical purposes the amount by which a unit area of wound diminished in one day.

From a another useful characteristic can be calculated, the "half-life," which is defined as the time in days that it takes for a wound at any given time within the linear period of contracture to reduce its area by one half and which is numerically equal to $\log_e 2/a = 0.693/a$. Because of the slight irregularity of the relationship between area and time during the initial period, the "half-life" is only an approximation of the actual time required for the initial wound to reach half size.

TABLE 1. *Specific Rates of Contracture and "Half-Lives" of Standard, Rectangular Full-Thickness Wounds (Controls)*

Animal Number	Initial Wound Area (cm.^{2})	Specific Rate of Contracture "a" ± Standard Error	"Half-Life" (days)
RX-1	39.4	−0.06977 ± 0.002680	9.96
RX-12	36.0	−0.07444 ± 0.005957	9.31
RX-13	37.2	−0.06991 ± 0.008727	9.91
RX-16	35.0	−0.07016 ± 0.003911	9.88
RX-53	33.2	−0.08330 ± 0.004588	8.32
RX-92	37.5	−0.09102 ± 0.004617	7.62
RX-101	39.0	−0.07929 ± 0.005712	8.74
Pooled Values		−0.07554 ± 0.002230	9.18

This group is statistically homogeneous ($P > 0.2$).

Results. The data obtained from the study of seven standard-sized wounds are set out in Table 1. The comparatively low values of the standard errors of the individual estimates of a provide a numerical confirmation of the precision with which a straight line may be fitted to the data in each case. When tested for statistical homogeneity by the method of covariance (see Snedecor[32]) this group was found to be homogeneous ($P > 0.2$). The pooled value of the seven individual estimates of a was found to be − 0.07554 ± 0.002230, the corresponding "half-life" being 9.18 days.

1.3 *Contracture in full-thickness wounds made through the panniculus.* Wounds from which the panniculus has been removed gape widely; their mobile edges can easily be lifted away from the underlying, relatively avascular fascia and are slow to become fixed. The forces of contracture generated within the wound can only become effective when its margins are fixed. Moreover, until fixation occurs the free edges allow easy entry for infection which can spread widely beneath the integument.

To investigate the effect of these differences a wound of standard size was made through the panniculus in each of three rabbits. Only by the 15th to 18th day had these wounds become filled with granulations, and this marked the beginning of the logarithmic phase of contracture. The results of these experiments are presented in Table 2. The group is not homogeneous statistically ($P < 0.05$). The pooled value of a (− 0.06567 ± 0.001835) was somewhat lower than the control value, the difference being statistically significant ($P < 0.01$). We believe that the variable and somewhat

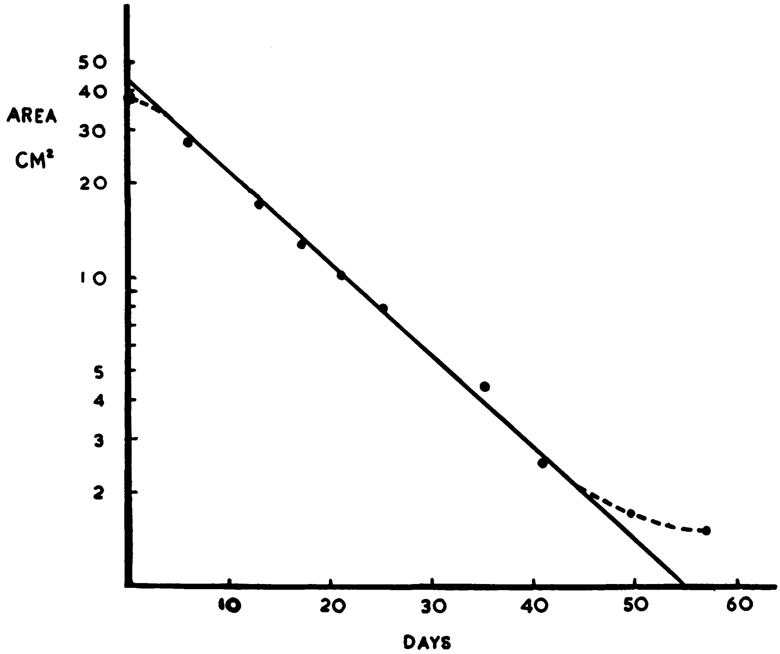

FIG. 4. Animal RX-1 (see also Table 1). Illustrating the linear decrease of the area of a standard wound, plotted as its logarithm, between the 6th and 45th days.

TABLE 2. *Specific Rates of Contracture and "Half-Lives" of Standard Size Rectangular Wounds through the Panniculus Carnosus Muscle*

Animal Number	Initial Wound Area (cm.²)	Specific Rate of Contracture "a" ± Standard Error	"Half-Life" (days)
RX-8	40.2	−0.05860 ± 0.000927	11.83
RX-62	48.7	−0.06499 ± 0.003819	10.67
RX-64	44.0	−0.07052 ± 0.002338	9.83
Pooled Values		−0.06567 ± 0.001835	10.55

This group is *not* homogeneous statistically ($P < 0.05$) and it differs significantly from the control group ($P < 0.01$).

slow rates of contracture observed in these wounds are ascribable to one or more of the following: 1) The tendency of these wounds to assume a circular configuration. (The influence of circular shape will be discussed below.) 2) The constant centrifugal traction exerted on the margins of the wound by the cut muscle fibers which are attached to the wound edges and are no longer continuous across the wound bed. 3) The difficulty of excluding low grade infection following on the early drawbacks cited above.

The fact that the pooled value of a for these deeper wounds does not differ very greatly from that of the shallower control wounds suggests that thickness of the mesenchymal wound-fill does not strikingly influence the rate of contracture; certainly thicker layers do not speed the process.

1.4 *The role of the panniculus in the healing of the standard wound.* Since dissection of completely contracted wounds yielded no evidence of a central "bunching up" of the underlying panniculus carnosus, it appeared likely that its surface was the fixed base across which the skin moved. This supposition was confirmed in the following way. In each of three rabbits a full-thickness standard wound was prepared. Small pieces of fine, stainless steel ribbon, measuring about 3 × 1 mm., were then implanted in photographically-recorded positions into tiny slits cut in the panniculus itself. When contracture of the wounds was

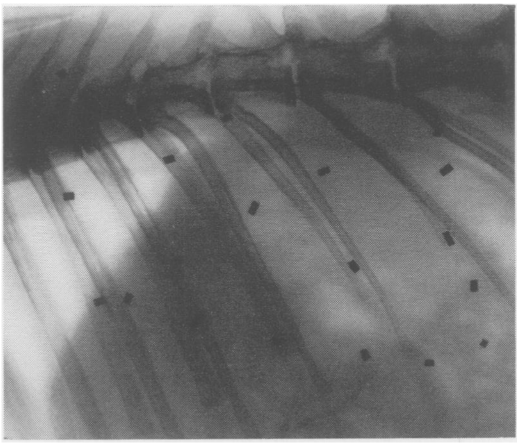

FIG. 5. Radiograph of the thorax of rabbit RX-53, to show the position of the stainless steel markers 46 days after their insertion into the panniculus carnosus which formed the bed of a freshly prepared standard rectangular wound. The wound has undergone complete contracture (see Fig. 3) but the position of the markers remains virtually unaltered. (× ¾)

complete the final disposition of the markers was determined by radiography (Fig. 5). In all three wounds this revealed that, in spite of complete contracture, the distribution of the markers had remained virtually unchanged.

2. *The influence of shape upon the rate of contracture of wounds.* To find out what influence the initial shape of a wound has upon the course of its contracture, the healing of three equilateral triangular and three circular wounds has been compared with the standard rectangular wounds of the control group. Care was taken to be sure that the final areas of these wounds were similar. The radius of the circle as marked out on the skin before cutting was 3.1 cm. (area = 30.0 cm.²), and the length of side of the equilateral triangular wound was 8.3 cm. (area = 29.8 cm.²). The rectangular control wounds were 6 × 5 cm. in lengths of side (area = 30.0 cm.²). After excision the wounds gaped about equally in the three groups.

Again a strictly linear relationship between the logarithm of the area and time obtained in these widely varying shapes.

Results: a) *Triangular wounds* (Table 3a).The rates of specific contracture for the wounds in this series form a statistically homogeneous group ($P > 0.05$), the pooled value of a being -0.07363 ± 0.003206. This value a does not differ significantly from that of the control group of rectangular wounds ($P > 0.2$).

TABLE 3a. *Specific Rates of Contracture for Triangular Wounds*

Animal Number	Initial Wound Area (cm.²)	Specific Rate of Contracture "a" ± Standard Error	"Half-Life" (days)
RX-51	38.8	-0.06907 ± 0.003711	10.03
RX-61	38.1	-0.07516 ± 0.002252	9.22
RX-98	30.2	-0.08009 ± 0.003154	8.65
Pooled Values		-0.07363 ± 0.003206	9.41

This group is statistically homogeneous ($P > 0.05$) and does not differ from the controls ($P > 0.2$).

b) *Circular wounds* (Table 3b). Again, the three individual estimates of a form an homogeneous group ($P > 0.05$). The pooled value of a, -0.05443 ± 0.002754, however, is very significantly lower than that of the controls ($P < 0.01$).

TABLE 3b. *Specific Rates of Contracture for Circular Wounds*

Animal Number	Initial Wound Area (cm.²)	Specific Rate of Contracture "a" ± Standard Error	"Half-Life" (days)
RX-40	39.6	-0.06195 ± 0.002826	11.19
RX-56	31.5	-0.04891 ± 0.003930	14.17
RX-109	34.0	-0.05798 ± 0.015490	11.95
Pooled Values		-0.05443 ± 0.002754	12.73

This group is statistically homogeneous ($P > 0.05$). It differs significantly from the control group ($P < 0.01$).

c) *Rectangular border wounds* (Table 3c). To obtain further data on the influence of shape on contracture we studied the healing of a rectangular wound in which a central square island of intact skin had been left behind. Four wounds of this type

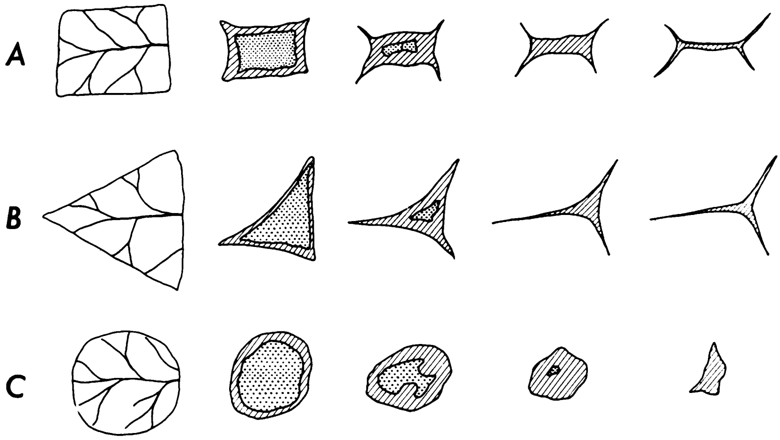

FIG. 6. Illustrating the patterns of contracture and changes in length of perimeter of a rectangular wound (A), a triangular wound (B), and a circular wound (C). Unsurfaced granulations are represented by stippling, marginal ingrowth of epithelium by hatching.

were prepared, the central islands measuring 1.5 × 1.5 cm. The area of the wound was obtained by subtracting the area of the central island from that included by the outer margin of the wound. The individual values of *a* were statistically homogeneous ($P > 0.2$), the pooled value being – 0.07126 ± 0.001649. This does not differ significantly from the control group ($P > 0.2$).

To investigate why circular wounds consistently contract more slowly than those of triangular or rectangular outline a careful comparison was made of the actual patterns of contracture and of the changes in length of perimeter for wounds of each type (see Fig. 6 and Table 3d).

As Figure 6 shows, in both the straight-sided figures contracture proceeds by the apparent drawing in of the mid-points of the opposite sides towards the center, the corners of the wounds undergoing practically no displacement. This is the pattern of contracture to be expected on the assumption that the tensile forces generated within the wound act perpendicularly to its margins at all points. Collapse of a wound in this manner must necessarily be accompanied by a slight lengthening of its perimeter. Because of the elastic nature of the skin and the fact that tension results in a

TABLE 3c. *Specific Rates of Contracture and "Half-Lives" of Rectangular Bordered Wounds*

Animal Number	Initial Wound Area (cm.²)	Specific Rate of Contracture "*a*" ± Standard Error	"Half-Life" (days)
RX-2	41.9	−0.07814 ± 0.004772	8.87
RX-6	44.0	−0.06912 ± 0.002031	9.88
RX-18	34.6	−0.06962 ± 0.003014	9.96
RX-34	35.6	−0.07196 ± 0.001030	9.63
Pooled Values		−0.07126 ± 0.001649	9.76

This group is homogeneous statistically ($P > 0.2$) and does not differ significantly from the control group ($P > 0.2$).

true intussusceptive growth—an intercalary growth of new skin substance within the original framework of stretched dermal tissue (see Billingham and Medawar [8])—this can easily occur and no great resistance is therefore likely to be offered to the forces of contracture.

If a circular wound is to collapse without gross distortion of its shape, then it follows that some perimeter reduction is inevitable. This would entail a circumferential compression of the skin edges as the margin is drawn inwards. Since the skin is fairly firmly united to its bed and provided that only very slight buckling or folding of its surface can occur, some resistance to col-

TABLE 3d. *The Relationship Between the Specific Rates of Contracture and Changes of the Perimeter in Wounds of Different Shape*

Animal Number	Type of Wound	Initial Perimeter (cm.)	Final Perimeter (cm.)	% Change of Perimeter (±)	Specific Rate of Contracture
RX–12	Standard Control Rectangle	24.1	24.8	+ 2.6%	−0.07444
RX–16	Standard Control Rectangle	22.9	23.8	+ 4.2%	−0.07016
RX–53	Standard Control Rectangle	21.6	22.9	+ 5.9%	−0.08330
Averages		22.9	23.8	+ 4.2%	
RX–51	Equilateral Triangle	27.3	29.0	+ 6.0%	−0.06907
RX–61	Equilateral Triangle	25.4	27.3	+ 7.0%	−0.07516
RX–98	Equilateral Triangle	24.1	26.0	+ 7.5%	−0.08009
Averages		25.6	27.4	+ 6.6%	
RX–40	Circle	22.9	14.0	−39.0%	−0.06195
RX–56	Circle	20.3	14.0	−31.0%	−0.04891
RX–109	Circle	21.2	12.0	−43.0%	−0.05798
Averages		21.5	13.3	−37.7%	

lapse of a wound of this shape might be anticipated.

Comparison of the initial and final lengths of the perimeters of the various wounds shows clearly that contracture of those with straight sides is in fact accompanied by a slight increase in perimeter whereas in the case of circular wounds there is a very considerable *decrease* in the length of the original perimeter.

It can now be seen that the marked tendency for wounds carried through the panniculus to assume a circular outline (par. 1.3) as they gape may also have contributed to their demonstrably slow rate of contracture.

3. *The influence of size of wound upon contracture.* The influence of the initial size of a wound upon contracture has been under question for some time (Carrel and Hartmann;[14] Spain and Loeb[33]). This relationship was reinvestigated simply by preparing on two groups of animals rectangular wounds which, before cutting, were respectively one-half and one-quarter of the area of the original standard control wound. These two experiments are summarized in Tables 4a and b.

TABLE 4a. *Specific Rates of Contracture and "Half-Lives" of Half-Size Wounds*

Animal Number	Initial Wound Area ($cm.^2$)	Specific Rate of Contracture "*a*" ± Standard Error	"Half-Life" (days)
RX–33	22.7	−0.06205 ± 0.001204	11.17
RX–41	19.3	−0.06234 ± 0.006808	11.12
RX–108	20.6	−0.06982 ± 0.008986	9.93
Pooled Values		−0.06317 ± 0.003449	10.97

This group is homogeneous statistically ($P > 0.2$). It differs significantly from the control group, however ($P < 0.01$).

Results: a) For the half-size wounds the rates of specific contracture form a statistically homogeneous group ($P > 0.2$), the pooled value of *a* being − 0.06317 ± 0.003449. It will be seen that this figure is lower than that for the control group and statistically the difference is considered significant ($P < 0.01$).

b) The three values of *a* determined for the "quarter-size" wounds also constitute a uniform group ($P > 0.2$), with a pooled figure of − 0.08102 ± 0.000653 for the specific rate of contracture. This is closely

TABLE 4b. *Specific Rates of Contracture and "Half-Lives" of Quarter-Size Wounds*

Animal Number	Initial Wound Area (cm.^{2})	Specific Rate of Contracture "a" ± Standard Error	"Half-Life" (days)
RX–82	11.3	−0.07872 ± 0.01040	8.80
RX–89	11.7	−0.08112 ± 0.003701	8.54
RX–90	12.2	−0.08273 ± 0.002030	8.38
Pooled Values		−0.08102 ± 0.000653	8.55

This group is homogeneous statistically ($P > 0.2$). It is also homogeneous with the control group ($P > 0.2$).

comparable with the control figure ($P > 0.2$).

There are two possible explanations for the anomalously slow rate of contracture of the half-size wounds; either a) wounds of about 20 cm.^{2} do indeed heal more slowly than wounds of twice or of half that area, or b) the values of a for the 20 cm.^{2} wounds (Table 4a) represent a vagary of sampling. The second explanation is much more reasonable, inasmuch as a 40 cm.^{2} wound is at one stage a 20 cm.^{2} area in the course of contracting.

Summarizing: the results in the various experiments described so far show that the specific rates of contracture remain remarkably constant for full-thickness cutaneous wounds over a wide range of size and shape.

4. *The influence of age upon contracture of wounds.* The experiments now to be described were carried out to determine whether the age of the subject exerts any influence on contracture (cp. du Nöuy,[17-19] Howes and Harvey,[23] Bourlière and Gouré-vitch[11]). The specific rates of contracture have been obtained for wounds prepared on groups of very young and fairly old animals respectively and then compared with the control data obtained for the animals within the age group 9 to 18 months.

a) *Contracture in young animals* was investigated in a group of five 50-day old rabbits (0.9 – 1.1 Kg.) on each of which

TABLE 5a. *Specific Rates of Contracture and "Half-Lives" of Wounds on 50-day old Animals*

Animal Number	Initial Wound Area (cm.^{2})	Specific Rate of Contracture "a" ± Standard Error	"Half-Life" (days)
RX–76	17.3	−0.11330 ± 0.005093	6.12
RX–77	19.0	−0.08641 ± 0.012890	8.02
RX–79	17.5	−0.08680 ± 0.004037	7.99
RX–102	17.8	−0.10420 ± 0.006330	6.65
RX–103	17.4	−0.11690 ± 0.003859	5.93
Pooled Values		−0.09957 ± 0.003312	6.96

This group is *not* homogeneous ($P < 0.01$). It differs significantly from the control group ($P < 0.001$).

a "half-size" wound (marked area before cutting: 3.75 × 4.0 cm.) was prepared. Table 5a shows that, despite their variability ($P < 0.01$), the determined values of a (pooled value – 0.09957 ± 0.003312) are strikingly and significantly higher than the controls ($P < 0.001$).

b) *Contracture in old animals.* It was our intention to obtain an extensive panel of rabbits at least four years old with dates of birth established and of the same breed as our controls. Unfortunately, however, only three animals satisfying these requirements could be obtained. Standard sized wounds were prepared on these and the data relating to their contracture appear in Table 5b. This group shows greater uniformity than the young animals but falls short of true statistical homogeneity ($P < 0.05$). The pooled value of a for this group is – 0.06703 ± 0.002552, which is significantly lower than that for the controls ($P < 0.05$).

The "half-lives" corresponding to the pooled values for a in the three age groups studied, i.e. 50 days, 9 to 18 months, and 4 years, are 6.96 days, 9.18 days, and 10.34 days respectively, which indicates a downward trend in the specific rate of contracture with advancing age. However, less weight can be placed on the results derived from the group of old animals because of its small size.

TABLE 5b. *Specific Rates of Contracture and "Half-Lives" of Wounds on Old Animals*

Animal Number	Initial Wound Area (cm.^{2})	Specific Rate of Contracture "a" ± Standard Error	"Half-Life" (days)	Age of Animal (yrs.)
RX-70	32.0	-0.07287 ± 0.004218	9.51	6
RX-71	35.1	$= 0.06968 \pm 0.002097$	9.95	5
RX-72	32.5	-0.05566 ± 0.003199	12.51	4
Pooled Values		-0.06703 ± 0.002552	10.34	

This group is *not* homogeneous statistically ($P < 0.05$). It differs significantly from the controls ($P < 0.05$).

TABLE 5c. *The Effect of Age on the Percentage Contracture of Wounds*

Animal Number	Age at Operation (days)	Initial Wound Area (cm.^{2})	Wound Area on 12th Day (cm.^{2})	Percentage Contracture
3.1	50	20.16	8.58	57.4*
4.1	50	18.49	4.84	73.8*
5.1	50	25.97	6.67	74.3*
6.6	50	18.06	6.82	62.2*
2.2	100	27.0	8.4	68.9*
3.2	100	38.19	15.96	58.2*
6.4	175	43.56	17.76	59.2*
2.3	200	37.2	20.65	44.5
3.3	200	30.25	10.2	66.3*
4.2	200	35.34	14.85	58.0*
2.4	300	37.2	19.35	48.0
4.3	300	43.56	22.79	47.7
2.5	400	42.16	21.16	49.8
6.5	400	36.0	15.98	55.6
3.4	500	42.09	21.62	48.6
4.6	700	52.93	26.95	49.1
2.6	800	41.76	19.61	53.0

Note: Percentage contractures of 57% or over are marked *. Percentage contracture

$$= \frac{\text{loss of wound area between 0 and 12 days}}{\text{initial wound area}}.$$

Further evidence to the same effect was obtained indirectly in the course of an experiment not specifically designed to obtain data on contracture of wounds. Rectangular full-thickness wounds of rather variable extent were prepared in the skins of 17 rabbits, varying in age from 50 to 800 days. Measurements of the length and breadth of each wound were taken immediately after operation and subsequently on the 12th day; the wounds remained approximately rectangular so that the products of their lengths and breadths were taken as reasonable approximations of their areas. The *percentage contracture* over the 12 day period for each wound is set out in Table 5c: within the age range 50 to 200 days the percentage contracture on all animals, with only one exception, was greater than that in animals whose ages fell between 300 and 800 days. Thus these findings corroborate the previous conclusion.

5. *The influence of a recently-healed primary wound upon the process of contracture of a secondary wound.* It has not infrequently been contended from clinical evidence that patients who have undergone repeated operations or injuries show an increased rate of repair of a subsequent wound in a remote location (Lorin-Epstein[27]). This postulated acceleration in the healing process was ascribed to some systemic factor—a "wound hormone" or "trephone" (Carrel[15]) liberated by damaged or healing tissues.[27] The early literature on this subject is well covered in reviews by Arey,[3] Davidson [16] and Cameron.[13] Efforts to demonstrate the existence of this "second wound" phenomenon on an experimental basis have yielded conflicting results,[21, 31, 34, 38] and the subject is still controversial. In the present section an account will be given of experiments carried out to examine the influence of a primary cutaneous wound on the contracture of a secondary one.

The primary wound was produced in the skin of one side of the thorax and, after eight to seventeen days, a secondary wound of standard rectangular dimensions was prepared on the opposite side. The specific rate of contracture was determined by the usual method. Two different types of primary wound have been employed: full-thickness rectangular wounds of approximately the same area as those of the control series; and a set of three parallel,

TABLE 6a. *Specific Rates of Contracture and "Half-Lives" of Secondary Wounds (First Series)*

Animal Number	Initial Wound Area (cm.²)	Specific Rate of Contracture "*a*" ± Standard Error	"Half-Life" (days)	Interval between Wounds (days)
RX-11	39.4	−0.08555±0.009997	9.12	17
RX-38	38.1	−0.07263±0.003403	9.54	14
RX-57	34.1	−0.07514±0.006152	9.22	17
RX-58	37.3	−0.08080±0.005604	8.48	17
RX-59	42.2	−0.08680±0.008692	7.99	17
Pooled Values		−0.07886±0.003018	8.79	

This group is homogeneous statistically ($P > 0.2$). It is also statistically indistinguishable from the control group ($P > 0.2$).

TABLE 6b. *Specific Rates of Contracture and "Half-Lives" of Secondary Wounds (Second Series)*

Animal Number	Initial Wound Area (cm.²)	Specific Rate of Contracture "*a*" ± Standard Error	"Half-Life" (days)	Interval between Wounds (days)
RX-65	42.5	−0.07056±0.003579	9.82	15
RX-91	35.0	−0.05786±0.001969	11.98	13
RX-93	38.3	−0.07937±0.005628	8.73	14
RX-106	33.8	−0.08079±0.002943	8.58	8
RX-107	32.3	−0.07802±0.008750	8.88	8
Pooled Values		−0.07258±0.002533	9.55	

This group is *not* homogeneous statistically ($P < 0.01$). It is statistically indistinguishable from the control group, however ($P > 0.2$). This group likewise does not differ significantly from the first series of secondary wounds ($P > 0.2$).

longitudinal incised wounds through the panniculus, about 6 cm. in length, which were immediately closed with sutures. The utility of the open type of "stimulus" wound was that, besides providing an extensive area of damaged tissue, it initiated a prolonged period of active proliferation of tissue. On the other hand, the incised wounds, although perhaps producing less damage to tissue, had the advantage of healing without contracture, thereby leaving the contralateral skin with its normal tension unchanged. The interval between the two operations was such that the secondary wound was made when healing of the primary wound was well advanced but still far from complete.

Results. The influence of an extensive open "stimulus wound" on the contracture of its secondary partner is summarized in Table 6a. The results of the five experiments are very uniform ($P > 0.2$), giving a pooled value for *a* of − 0.07886 ± 0.003018 which is statistically indistinguishable from that of the control group ($P > 0.2$).

The five subjects of the second group (Table 6b), in which the primary wounds were linear incisions, did not form a statistically homogeneous series ($P < 0.01$). Nevertheless, the pooled value of *a*, − 0.07258 ± 0.002533, again falls well within the control range ($P > 0.2$).

Considered together, the two groups of results from second wounds constitute a homogenous group ($P > 0.2$). The pooled value of *a* as determined from the entire battery of the ten secondary wounds is − 0.07667 ± 0.002047 (controls: 0.07554 ± 0.002230, Table 1).

This observation that primary wounds have no detectable influence on the contracture of secondary wounds is corroborated by the constant specific rate of the process of contracture in all types of wounds we have studied. The mere fact that the specific rate of contracture does not increase as the process advances is in itself a strong argument against the concept that stimulatory substances are released during the process of healing.

6. *The influence of cortisone on contracture of wounds.* Cortisone greatly delays the development of granulation tissue (Ragan, Howes, Plotz, Meyer and Blunt [30]), depresses the proliferation of capillaries (Baxter, Schiller, Whiteside and Straith [4]), and retards contracture of wounds (Billingham, Krohn and Medawar [6]). The present experiment was carried out to determine quantitatively the influence of the daily subcutaneous administration of 10 mg. of cortisone acetate

TABLE 7. *Specific Rates of Contracture and "Half-Lives" of Standard Wounds in Rabbits Treated with Cortisone*

Animal Number	Initial Wound Area (cm.^{2})	Specific Rate of Contracture "a" ± Standard Error	"Half-Life" (days)
RX-27	37.0	-0.03353 ± 0.001673	20.67
RX-28	40.0	-0.03820 ± 0.003431	18.14
RX-74	39.4	-0.03699 ± 0.002461	18.74
RX-86	39.2	-0.04287 ± 0.003440	16.17
Pooled Values		-0.03707 ± 0.001226	18.70

This group is statistically homogeneous ($P > 0.05$). It differs significantly from the controls ($P < 0.001$).

TABLE 8. *Specific Rates of Contracture and "Half-Lives" of Standard Size Rectangular Wounds Grafted with Pure Epidermis*

Animal Number	Initial Wound Area (cm.^{2})	Specific Rate of Contracture "a" ± Standard Error	"Half-Life" (days)
RX-3	43.2	-0.05730 ± 0.005690	12.00
RX-5	37.7	-0.05904 ± 0.006002	11.74
RX-15	37.5	-0.06843 ± 0.006340	10.13
Pooled Values		-0.06209 ± 0.003694	11.16

This group is homogeneous statistically ($P > 0.2$). It differs significantly from the controls ($P < 0.01$).

on the contracture of standard wounds prepared on a group of four rabbits (weights 2.3 to 3.9 Kg.).

In addition to being slow in developing, the sparse layers of granulation tissue on the floor of the wounds appeared pale and dry. Consequently the vascular pattern of the panniculus was clearly visible even as late as the 20th day, and only by about the 25th day were the wounds finally filled with granulations.

As in the controls, the wounds contracted at a constant specific rate. The cortisone-treated animals form a surprisingly homogeneous group ($P > 0.05$) with a pooled value for a (-0.03707 ± 0.001226, see Table 7) which shows a profoundly significant difference from the controls ($P < 0.001$). Cortisone, in the dosage administered, reduced the rate of specific contracture by about one half, correspondingly doubling the "half-life" (18.70 days).

In this dosage persistent administration of cortisone had a gradual debilitating effect on the animals in that they slowly lost about 1 Kg. of weight over the 50 day period of the experiment. Two animals died before completion of the experiment and are not included in Table 7. The others slowly regained their normal weights and vigor after treatment was over.

A similar experiment was likewise done in which a standard wound was prepared on each of two normal animals and the course of contracture followed in the usual manner. After 16 days, when granulation tissue filled the wounds, and evidence had been obtained as to the normality of their rates of contracture, the daily administration of 10 mg. of cortisone was commenced. This produced an almost immediate reduction in the rate of specific contracture and an abrupt change in the slope of the regression line (Fig. 7), which came to resemble that characteristic of wounds on animals which had received cortisone throughout.

On the other hand, sudden termination of cortisone treatment in animals which had received it from the day of wounding did not result in a prompt return of the normal rate of contracture; only gradually and irregularly did their wounds begin to contract in a normal manner. Sufficient local deposits of the hormone may have remained in the body to maintain an effective systemic level.

7. *Incomplete contracture and neogenesis of hair.* The process of contracture in about 60% of the large, full-thickness cutaneous wounds we have studied pursued a constant course until their original margins had become closely approximated, being separated by no more than a narrow, linear scar. However, for some as yet unexplained reason, in the remaining wounds this process terminated abruptly just before closure

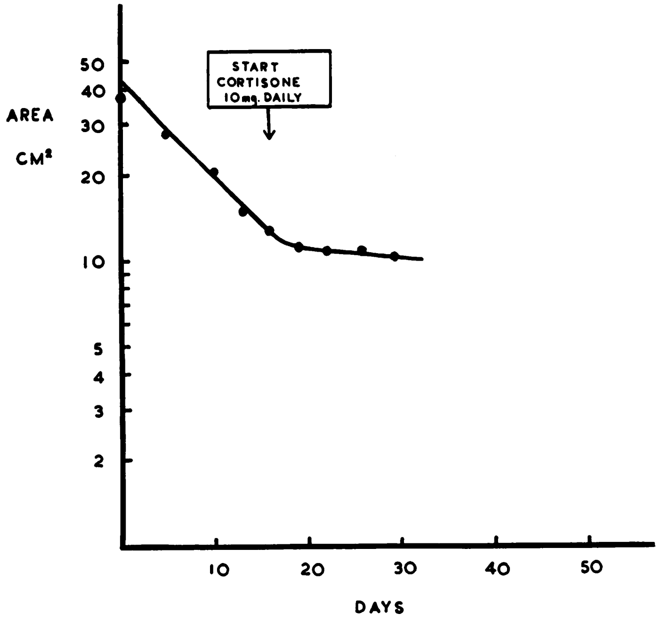

FIG. 7. Animal RX-95. Showing the influence of the delayed administration of cortisone on contracture. The hormone was not administered until the 16th day, when the wound was filled with granulation tissue and contracting normally.

was complete at a time when the area was no more than a few square centimeters. Subsequently, some of the wounds showing this arrested contracture near the end-point showed a slight *increase* in area. Invariably by about the 45th day, from all wounds which failed to contract completely there emerged dense crops of fine, non-pigmented hairs which, when they had grown long enough, stood out in marked contrast to the normally pigmented fur of the surrounding skin (Fig. 8). These newly-formed hairs developed from the periphery of the wound inwards, and lay wholly within the original perimeter of the wound where they must have formed *de novo* from the "adventitious skin" derived from resurfaced granulation tissue.

Convincing evidence that neogenesis of hair can occur from epithelialized scar tissue in experimental cutaneous wounds in rabbits has also been obtained by Breedis,[12] who deliberately prevented contracture of wounds by the insertion of metal splints. A more complete account of our findings with respect to this phenomenon appears elsewhere.[10]

8. *The effect of skin grafting upon contracture of wounds.* It is well recognized amongst surgeons that contracture of an open wound may be prevented by covering it with a live skin graft, the efficacy of the graft depending, at least to some degree, upon its thickness; thicker grafts being more effective than thin ones.[28]

A limited number of trials in which freshly-prepared standard, full-thickness wounds were completely resurfaced with accurately fitted split-thickness grafts, approximately 0.25 mm. in thickness, cut from the skin of the trunk with a Padget dermatome, convinced us that contracture is as completely inhibited in the rabbit as in man. The final area of the grafted wounds after more than 50 days was almost the same as it had been initially. A likely explanation of this inhibitory effect of grafting on a fresh wound is that by becoming rapidly united to its floor a graft restores the wound to a status very close to its

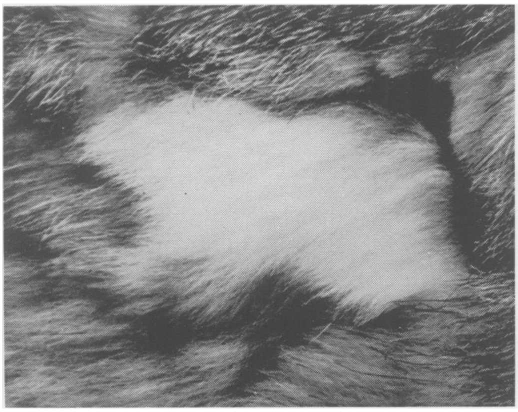

FIG. 8. Showing a dense crop of white hairs of new formation growing on the scar of a wound prepared 70 days previously which had failed to contract completely. (× 1)

initial condition, thus precluding one necessary condition for contracture, i.e. the formation of new mesenchymal tissue or "granulations."

Can *delayed* skin grafting arrest the process of contracture once it has commenced? In each of two rabbits a square, 2.5 × 2.5 cm., full-thickness graft was excised from the comparatively supple, thin skin of the dorsum of the ear and transplanted to the center of the granulations covering a rectangular, full-thickness wound prepared 10 days previously. These wounds were contracting normally up to the time of grafting. The grafts healed in perfectly, regenerating sparse crops of the hair characteristic of skin on the ear. Although the border of granulation tissue which initially separated the graft margin from the edge of the wound contracted completely, at no stage did the grafts themselves undergo any diminution in size. This demonstrates that not only does a cutaneous graft prevent the inception of contracture in a fresh wound, but it also brings the process abruptly to a standstill when it is actively under way in a previously ungrafted wound.

8.2 *The effect of pure epidermal grafts on contracture.* For a complete analysis of the mechanism of the inhibition of contracture by a cutaneous graft the relative contributions of the epidermis and dermis must be assessed independently. Billingham and Reynolds,[9] who employed pure epidermal grafts to bring about the rapid resurfacing of full-thickness cutaneous wounds in rabbits, found that epithelial coverage prevented neither the formation of granulation tissue beneath it nor the process of contracture of the wound. Moreover, the constancy of the specific rate of contracture of ungrafted wounds is clear evidence of the ineffectiveness of epithelial coverage in preventing or even seriously retarding contracture—for although most of our wounds were completely resurfaced by about the 20th day, contracture continued at a constant specific rate. The results of our own quantitative studies of the influence of pure epidermal grafts on contracture are summarized in Table 8. It can be seen that the grafts do in fact retard the process very slightly.

8.3 *The influence of frozen-dried grafts on contracture.* So far it has been shown that the capacity of a skin graft to prevent contracture resides almost entirely in its dermal component. The present experiments will show that even "devitalized" grafts can retard contracture. "Devitalization" of the grafts was achieved by freeze-drying, a process which produces minimal change in the fine anatomical and biochemical constitution of tissues.[5, 37]

Transplantation of frozen-dried grafts to freshly prepared wounds was performed in each of two animals. An extensive sheet of split-thickness skin was removed with a dermatome and secured under light tension to a sheet of perforated metal of appropriate size. The latter was intended to prevent the graft from rolling up and so reducing the rate of desiccation. Lyophilization was then performed from the frozen state according to the method of Eastcott, Holt, Peacock, and Rob.[20] The desiccated grafts were reconstituted in excess normal saline and were anchored in place on full-

TABLE 9. *The Effect of Frozen-Dried Grafts on Contracture of Wounds*

Animal Number	Type of Graft Bed	Specific Rate of Contracture "a" ± Standard Error	"Half-Life" (days)
RX-21	Freshly Prepared	−0.04007 ± 0.006563	17.3
RX-25	Freshly Prepared	−0.04496 ± 0.002090	15.42
RX-75	Granulating	−0.03784 ± 0.002240	18.32
RX-94	Granulating	−0.03319 ± 0.002637	20.88

thickness rectangular wounds by multiple, interrupted sutures.

At the primary inspection the grafts appeared to be fairly well united to their beds and their surfaces were smooth, dry and supple. At this stage their pallid appearance was the only outward indication of lack of viability. However, by about the 10th day, the entire remains of the superficial epidermis came away with the dressings, exposing the moist graft dermis. The latter remained firmly united to its bed. It was thought that inward migration of native epithelium over the surface of this fibrous remnant of the graft, combined with its invasion by mesenchymal cells from beneath, might bring about a histologic repopulation and reconstruction of the type which occurs in frozen-dried blood vessel grafts.[24] This did not happen, however, for the inception of epithelial migration was delayed and epithelialization, when it did occur, took place *beneath* the fibrous remains of the graft and eventually caused it to slough away. Nevertheless, the presence of these frozen-dried grafts reduced the rate of contracture to little more than half its normal value (see Table 9).

It has likewise been shown that the delayed grafting of lyophilized skin to a granulating and actively contracting wound-bed arrested the process of contracture (see Table 9).

9. *The effect of dressings on healing of wounds.* All the wounds on which the present study has been based have been maintained under dressings throughout the observation period, and in none of our wounds did scabs form. That the presence of dressings profoundly modifies the course of healing of cutaneous wounds is common knowledge. For completeness' sake we have studied the process of contracture in undressed "half-size" rectangular wounds in rabbits: the employment of larger wounds for this purpose was contraindicated by the greater risk of infection. In two wounds the panniculus was left intact and in another pair it was excised.

Results. The most striking difference between these four undressed wounds and all our previous ones was their tremendous reduction in area over the first two days—there was virtually no latent period at all—resulting in a loss of well over 50% of their initial area. Most of this reduction took place in the antero-posterior direction, greatly foreshortening the original rectangle. After about 24 hours these wounds had fairly dry, pliable surfaces which became progressively drier and less supple as the scabs consolidated. Indeed, it seems highly probable that the formation of these tough, adherent eschars was responsible for terminating the precipitous early reduction in area. This early phase of rapid reduction of area takes place long before there can have been any response of mesenchymal tissue to wounding, and it seems quite obvious that its underlying mechanism is quite different from that we have been studying.

In these undressed wounds, only by the sixth or eighth day, when the area had long been enormously reduced, was there a layer of new mesenchymal tissue beneath the scab, and our rather limited observations indicate that only from this time on is the process of contracture similar to that we have seen in dressed wounds, save that in the present case the scab somewhat impedes contracture.

What is the cause of this early reduction in area in the undressed wound which makes by far the greatest contribution to their closure? The fact that the remarkably asymmetrical antero-posterior foreshortening, seen in the first day after wounding, lies parallel to the fibers of the panniculus muscle seems to implicate muscular spasm as an important factor in this particular instance. However, the same sort of change in shape, though a little less marked, occurs after the panniculus has been removed from the wound bed, in which circumstance only those muscle fibers passing dorsal and ventral to the wound could be active. At any rate it seems likely that the cutaneous muscle effects the closure of an open, undressed wound differently from a covered one, and that it may have a hitherto unrecognized function in helping to appose the margins of naturally occurring open cutaneous wounds of this type in animals which are so equipped.

The sudden discontinuation of dressings from wounds which had been previously covered, at a time when contracture was far advanced and the central portion of the wound had been completely resurfaced by ingrowing epidermis from the wound margins, resulted in an almost immediate increase in the rate of contracture. It is difficult to account for this acceleration. Two factors which might influence the process are: an increased rate of dehydration of the wound as a result of exposure; and a possible increase in the tonus of the panniculus carnosus.

10. *The fate of the content of wounds during contracture.* Little attention has been paid to the apparent loss of content of wounds that contracture must necessarily entail. This apparent loss of substance becomes particularly striking in wounds of the type we have studied where the end-result of healing may be the virtually complete occlusion of the wound. Water loss undoubtedly accounts for some of the loss of substance since the water content of healing cutaneous wounds is initially abnormally high.[29] Abercrombie, Flint and James [1] found that the loss of wet weight of small full-thickness cutaneous wounds in rats parallels the process of contracture.

To obtain further information concerning the fate of the derivatives of the granulation tissue, careful dissections were made of a series of completely contracted wounds. The distribution of white, collagenous, scar tissue was found not to be restricted to the site of the narrow linear scar presenting on the surface; scar tissue was present in varying amount over the entire surface of that part of the panniculus which had originally been laid bare as the wound bed. Experiments in which the original granulations were tattooed with India ink at an early stage of contracture made this particularly clear, since on subsequent dissection, when contracture was complete, the pigment was found in association with the collagen extending out to the original perimeter of the wound. Despite its widespread distribution this collagen layer was not of even thickness. It was exceedingly thin peripherally, increasing in thickness towards the centre where it reached a maximum at the site of the outwardly visible scar.

This pattern of collagen distribution over the original bed of the wound suggests very strongly that the formation of new connective tissue fibers by the granulation tissue "fill" of the wound only continued so long as the granulations remained unsurfaced by the incoming skin from the margins of the wound. The site last to be resurfaced—i.e. the central area of the wound—was the site where the collagen attained its maximal thickness. Histological examination of the scar tissue indicated that the collagen fibers were mainly disposed in a horizontal plane, their orientation being along the lines of action of the tensile forces which were presumed to have acted on the margin of the wound. This was to be expected since fibroblasts are known to adopt an orientation that conforms to the lines of superimposed tensions (Weiss [35, 36]).

On completion of contracture only a very sparse population of mesenchymal cells was present in what remained of the initial "filling" of the wound—i.e. the scar tissue. The fate of the enormous transitory population of cells that once filled the wound has yet to be elucidated.

DISCUSSION

The findings reported in this paper are in complete accordance with the now generally held view that the tensile forces that bring about contracture of wounds originate within the substance of the mesenchymal reparative tissue (in these surface wounds, "granulation tissue") which fills the defect. The work of Lindquist [25] may be cited as providing a sound experimental basis for this belief and at the same time decisively refuting any attempt to explain contracture as the outcome of a sphincter-like action on the part of the tissue bounding the perimeter of the wound. Granulation tissue may therefore be said to constitute an adventitious and more or less ephemeral "organ" of contracture, one function of which is the re-apposition of the margins of the wound. As we have found, its effect is remarkably constant in full-thickness wounds of a wide range of shapes and sizes maintained under dressings.

Agreement has yet to be reached on the intrinsic *modus operandi* of the "organ of contracture." It has long been recognized that the formation of new collagen fibers accompanies contracture of wounds and studies on closed incisional wounds have shown almost unequivocally that the increase in their tensile strength accompanies, and is attributable to, the laying down of new collagen. At present most authorities believe that contracture is the outcome of the formation of collagen fibers and a subsequent shortening in length of these fibrils (see Loeb,[26] Arey [3]). Direct evidence in support of this theory has never been presented. The marked inhibitory effect of cortisone on contracture of wounds might suggest that fiber maturation is in some way responsible for contracture.

The validity of the "fibrillogenetic" theory of contracture has recently been questioned by Abercrombie et al.,[1] who found that although contracture and formation of collagen accompany one another in the early stages of healing of small, undressed full-thickness cutaneous wounds in rats, formation of collagen continued after cessation of contracture. Subsequently these workers obtained strong evidence against the existence of a causal relationship between fiber formation and contracture when they demonstrated that although contracture was not impaired in scorbutic guinea pigs, formation of collagen was severely inhibited.[2] On the basis of this and other evidence they have presented a cogent argument that the contractile forces are generated by the mesenchymal *cells* of the repair tissue. This theory is attractive and merits careful consideration. It does not deny that fibrillogenesis plays an important role in healing of wounds, making the major contribution to increasing tensile strength. The present authors wish to suggest that during the course of contracture the collagen fibers may actually be responsible for temporarily anchoring the margins of the wound at all stages as they are drawn inwards by forces originating principally within the mesenchymal cells.

Our demonstration that the incoming full-thickness edges of the wound appear to transform the underlying granulation tissue into mature, less cellular, fibrous tissue, rich in collagen, simultaneously terminating its contribution to further contracture, is consistent with the fibrillogenetic theory. Likewise, as Gillman, Penn, Bronks, and Roux [22] have demonstrated, the presence of a skin graft on exuberant granulations rapidly transforms them into dense, rather avascular fibrous tissue. This transformation is accompanied by a great reduction in tissue volume and cell population. Moreover, the action of delayed cortisone in arresting contracture may easily be accounted for on the basis of the "cellular" theory. This hormone is known to have a profound influence on the activity of all mesenchymal tissues. It delays the development of connective tissue fibers, and by so doing it may also deprive the mesenchymal cells of the mechanical assistance afforded by the tensile strength of the developing collagen fibers. Not only would the mesenchymal cells have to generate the necessary forces to pull in the cutaneous margins, but in the absence of connective tissue fibers, they would have to maintain these forces continuously.

Finally we wish to draw attention to the profound difference between the course of healing in dressed and undressed wounds of the integument and the fact that leaving off dressings from a completely resurfaced wound is not without considerable influence on the rate of contracture. It is our belief that only if wounds are maintained under dressings in experimental animals can the effect of the panniculus be minimized, and the physical conditions in the neighborhood of the surface of the wound be kept reasonably constant so that contracture can take place in a manner representative of that which occurs in lesions involving nonexposed tissues of the body.

SUMMARY AND CONCLUSIONS

1. The definitive repair of full-thickness cutaneous wounds in rabbits is the outcome of contracture, a forced inward movement of the margins of the wound in response to tensile forces generated within the wound. As a consequence of contracture the restoration of the histologic and functional continuity of the skin is almost complete.

2. For any wound, from a series of measurements of its area at known times, a valuable parameter or numerical characteristic—its *specific rate of contracture*—may be computed. This approximates the amount by which unit area of the wound diminishes in one day. The specific rate of contracture has been employed as a quantitative measure of the influence of a variety of factors on healing of wounds.

3. The specific rate of contracture was found to be remarkably uniform for rectangular wounds whose initial areas ranged from about 50 $cm.^2$ to 10 $cm.^2$, and for wounds of triangular and other straight-sided outlines. Circular wounds, however, contracted at a perceptibly slower rate, because—so it is argued—they present a greater resistance to the contractile forces.

4. Wounds on very young animals contracted faster than those on adults, and evidence has been obtained suggesting that even during adult life there is a slight progressive decline of the specific rate of contracture.

5. The presence of healed or healing "primary" wounds in remote locations has been found to be without demonstrable influence upon the contracture of "secondary" wounds. This finding lends no support to the belief that a primary wound releases stimulatory substances—growth hormones or "trephones"—which accelerate the healing processes of subsequent wounds.

6. The systemic administration of 10 mg. of cortisone acetate per day approximately halved the rate of contracture. Even when its administration was delayed until a wound was filled with granulation tissue and was contracting normally, cortisone promptly retarded contracture. Thus the effect of this hormone on contracture cannot be ascribed merely to its inhibition of the development of granulations.

7. Coverage either of freshly prepared, or of granulating and actively contracting, full-thickness cutaneous wounds with full-thickness cutaneous grafts completely inhibited contracture. Grafts of frozen-dried skin only reduce the rate of contracture.

Viable "pure" epidermal grafts, which bring about very rapid epithelial coverage of a wound, are almost ineffective in retarding contracture.

8. The experimental findings are discussed in relation to possible mechanisms of contracture of wounds, and it is argued that granulation tissue provides an ephemeral 'organ of contracture' which may bring about the functional repair of lesions involving many other tissues of the body besides the integument.

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