cess hyaluronidase should have no further significance.

To test this hypothesis, highly concentrated hyaluronidase solutions (3.3–333 μg./cc.) plus indicator were placed on superficial epidermal incisions for as long as 90 minutes and their spread compared to indicator solutions not containing the enzyme. No significant spreading effect of hyaluronidase was evident in these experiments wherein fluid was administered under zero pressure. In the next experiments, varying skin interstitial pressures were obtained by varying the volume of hyaluronidase administered intradermally (the enzyme concentration, 3.33 μg./cc., was kept constant).

Table 2 shows these results. The value "T" is calculated from T = volume administered/area spread

TABLE 2

Vol. (cm.³)	Initial T (mm.)	Initial rate (cm.²/min.)	Area increase over control at 10 min. (cm.²)	T at 10 min. (mm.)
1.0	3.3	7.41	9.86	0.64
0.5	3.2	6.95	8.37	0.43
0.25	1.9	3.26	3.06	0.45
0.10	1.3	1.39	1.01	0.38

(assuming that there is neither gain nor loss of fluid from the injected fluid volume). "T" is thus an index of the average "thickness" of the injected bleb and is regarded as a value proportional to the increased interstitial pressure produced by intradermal fluid administration. Table 2 demonstrates that:

(1) The initial rate and final areas of spread of hyaluronidase solutions are directly related to volume from 0.1 to 0.5 cc. and thereafter level off.

(2) The initial rate is directly proportional to "T," the thickness of the bleb at that time.

(3) The "T" values at 10 minutes, independent of the volume injected and initial "T" values, are approximately the same.

TABLE 3

Vol. (cm.³)	Enzyme concentration (μg./cc.)	Initial rate (cm.²/min.)	Area increase over control at 10 min. (cm.²)
0.25	13.4	2.97	3.04
0.10	33.3	1.53	1.03

Another experiment, the results of which are shown in Table 3, answers possible objections that the results in Table 2 are due to differences in the total amounts of hyaluronidase administered. Here the total amounts of enzyme were kept constant (3.3 μg.), but the volumes were varied. As will be seen, the solution administered in largest volume (but lowest concentration) spread to a greater extent than did the solution injected in smaller volume and highest concentration.

The finding that hyaluronidase induces spreading only when local interstitial pressure is increased by fluid administration, coupled with the demonstrated correspondence between spreading and interstitial pressure-volume relationships, helps to elucidate many obscure points of S.F. action. Space does not permit adequate treatment of this material, which will be discussed in subsequent reports. However, the significance of these findings as regards the relation of S.F. to bacterial invasiveness through skin might briefly be mentioned. Bacteria usually penetrate the skin through abrasions with only minimal amounts of fluid accompanying the invading organism. Thus, the spread of organisms through the interstitial spaces will depend as much upon the ability of the bacteria to stimulate the production of edema-inducing "leukotaxin-like" substances (*5*) as it does upon S.F. production.

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Grafts of Free Muscle Transplants Upon the Myocardium

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Within recent years the introduction of nerve-muscle transplants and pedicle-muscle grafts has made possible remarkable advances in many branches of clinical surgery. It is now becoming feasible to replace necrotized and nonfunctioning tissue destroyed by trauma and infection with free muscle grafts.

Experiments of Beck (*1*) and O'Shaughnessy (*4*) have demonstrated that pedicle-muscle grafts onto the heart resulted in the creation of a significant vascular anastomosis between the two tissues, particularly if the myocardium were rendered ischemic. Such grafts not only brought extra cardiac blood to the heart but also served as an anastomotic channel for the transport of blood between healthy and diseased coronary beds. Although this method gave great experimental promise, the clinical application of large pedicle-muscle grafts was necessarily limited because of the extensive surgical manipulation involved in its adaptation to human cardiac surgery. Therefore, simpler methods obviating past difficulties have been sought.

In 1933 Leriche and Fontaine (*3*) foresaw the value of free muscle grafts for the replacement of myocardial infarcts. However, their work was very limited and was never taken up by others.

Basic studies on the regeneration and reconstitution of free muscle grafts are indicative of the applicability of this method to clinical surgery. The regeneration of small sections of mammalian striped muscle grafted in situ and/or transplanted at right angles to its original orientation was studied by LeGros Clark (*2*). Reconstitution of muscle was manifested by fine plasmodial outgrowths from the ends of the surrounding muscle and by sarcoplasmic buds from the muscle graft. The initial fibroblastic union between recipient muscle and the donor graft was replaced rapidly by young muscle fibers crossing in parallel formation into the graft. The directional pathway was determined by the structure of the degenerating transplant rather than the course of the original muscle fibers. After 18 days the majority of new muscle fibers had penetrated the graft. Thereafter, maturation was rapid, and the usual skeletal striations were present histologically. These experimental studies have provided evidence in support of the practicability of the transplantation of free muscle grafts.

The present investigation consisted of an attempt to graft free skeletal muscle onto the intact myocardium of dogs. Nine dogs of variable age, and ranging in weight from 10 to 17 kg., were used. The animals were anesthetized by intravenous injections of sodium pentobarbital. Positive pressure in the lungs was maintained when the thoracic cage was opened. The muscle graft, rectangular in shape and averaging 7×4 cm., was obtained from the anterior abdominal wall (internal oblique) or from the lower extremity (vastus lateralis). It was placed around the heart and anchored thereto by means of three or four fine cotton sutures. The epicardial surface of the heart was not scarified. The pericardium was sutured over the graft, the latter being usually included in the suture line. The Emerson respirator proved a valuable adjunct in re-establishing voluntary respirations immediately following the operation.

Except in the infected cases, the postoperative course of the dogs was accompanied neither by shock nor by severe disability, and within two or three days they were up and about in their kennels. After recovery, the dogs were exercised daily. The animals showed no signs of cardiac incompetency or depletion of cardiac reserve. After a period of 10 to 15 weeks the animals were anesthetized and the cardiac transplants examined.

In this series of nine dogs, six animals were sacrificed and the other three preserved for special studies. In the former group two completely successful muscle-graft "takes" were found, while in a third, islands of regenerating muscle were present. In the other three dogs there was total absorption of the muscular elements of the graft with replacement by a connective tissue layer not unlike that of fascia. Signs of intrapleural, pulmonary, and pericardial infection were evident in these cases. The three dogs still alive have shown no signs of postoperative infection. One of them was reoperated upon after 15 weeks, and a branch of the left coronary artery was ligated. Upon opening the pericardium the graft was found to have taken completely.

Examination of the dogs with the free muscle-graft "takes" revealed several significant facts. The grafts were well fixed to the myocardium with little or no mobility. The transplant was easily identified over the ventricle and showed practically no shrinkage. However, the skeletal muscle graft had lost its reddish color and, on section, appeared tan-yellow with white trabeculae of connective tissue. Between the graft and myocardium the epicardium was thicker than normal with a rich vascular network. Sections taken through the graft showed a normal muscle histology with no histopathological variations in either the nuclei or the muscular components. The usual cross striations characteristic of skeletal muscle were present. On examination of the heart with the thoracic cage open, no deleterious effect on cardiac function and blood circulation from the standpoint of cardiac dilatation, extrapericardial adhesions, or intrapericardial pressure was observed.

Sufficient evidence has been accumulated from these experiments to state that free muscle transplants may successfully be grafted upon the myocardium of the dog's heart.

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Effect of Penicillin on Seed Germination

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Many clinical and biochemical differences have been reported between pure, crystalline penicillins and the crude, yellow grade of therapeutic penicillin used for clinical purposes. Lewis (*2*) reported a growth inhibition toward cancer tissues of therapeutic penicillin, but purified penicillin showed no such inhibition. It was hoped that seed germination tests could be used to measure this anticarcinogenic activity. Work done

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