EFFECTS OF DIFFERENT SUBSTANCES ON WOUND HEALING

THESIS SUBMITTED IN PART FULFILLMENT OF

M.CH. SURGERY

BY

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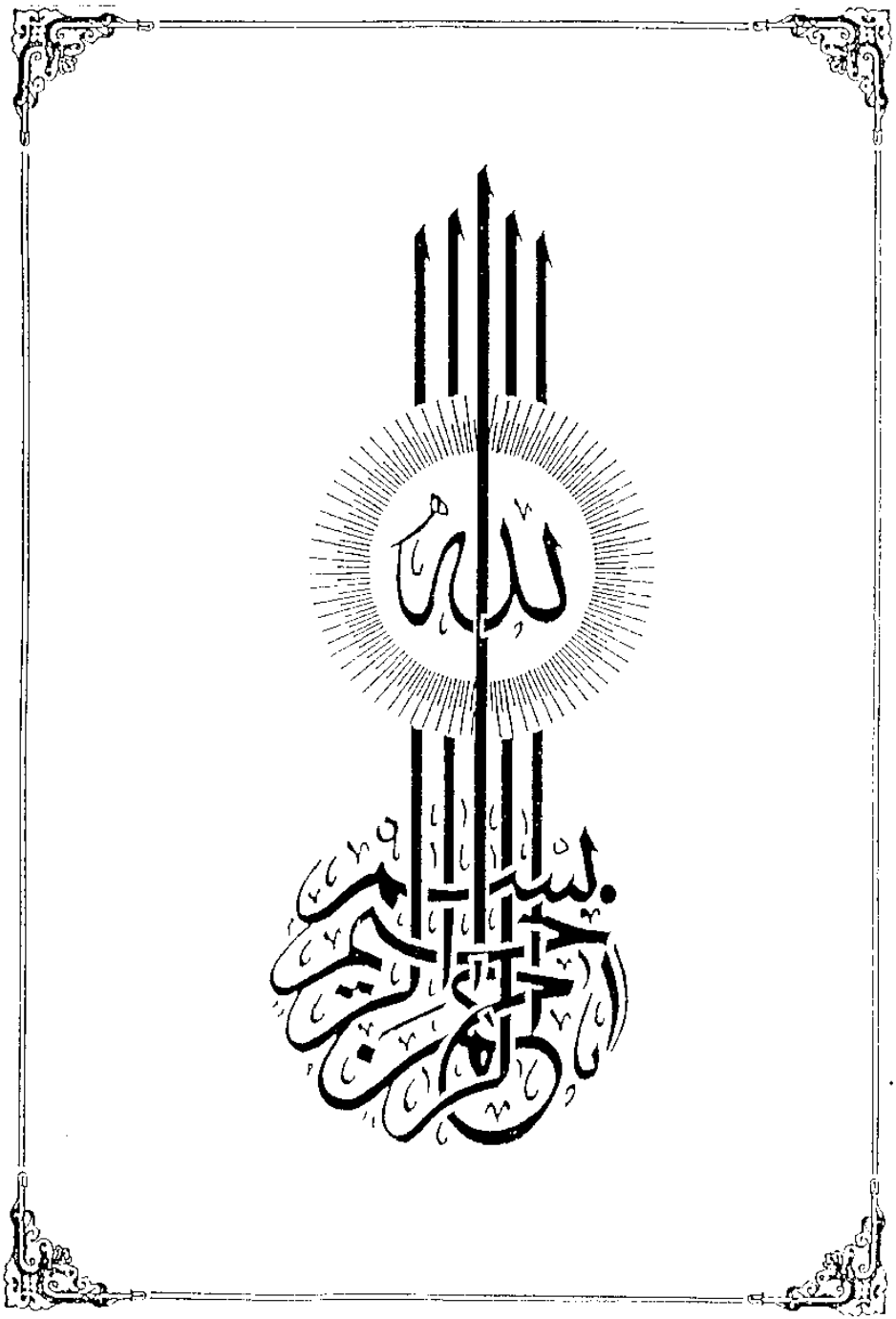

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PART I

I. INTRODUCTION

I N T R O D U C T I O N

The phenomenon of wound healing is a fundamental one in all surgical problems. It occurs in lacerations and contusions as well as in clean surgical incisions. The same process may be followed in the liver after poisoning and in a clot on the wall of a blood vessel. It proceeds in the bed of a chronic ulcer and around an invading cancer. All of these states are characterised by repair or attempts at repair of the injured tissue. Hence, a knowledge of the basic principles of wound healing as observed in surgical incisions is necessary to all surgeons to get best results of healing.

In the late 18th Century, John Hunter was the first to describe systematically the gross phenomenon of wound healing as known to us today. He defined healing by first intension and by second intension, and recognized the role of granulation tissue, which he believed to be composed of the coagulable lymph (the name that he gave for exudates containing plasma) and new blood vessels. He named the process of epithelization "skinning". He clearly described the contraction of wounds (called by him cicaterisation) and noted that it occurred more readily in a rectangular wound than in a circular one.

A knowledge of the microscopic feature of repair had to await Virchow (1858) and the era of cellular pathology. Virchow himself had less to say about repair than about inflammation, but his successors (Marchand 1901, Aschoff, 1924) described the chronology and the microscopic appearance of granulation, fibroplasia, and epithelization. At first it was the pathologists who explored the phenomenon of repair under the microscope. Surgeons began to inquire into the nature of healing in clean wounds, when it became apparent that suppuration, which previously overshadowed all other events in the wound, is not inevitable in the process of healing. Remarkable observations were made by Paget in 1853, and other surgeons that were interested in the nature of repair in the late 19th Century were Warren (1886) who described the organization of a thrombus that occurs after arterial ligation, and Halsted (1890) who was among the first to show that healing could be promoted in an open wound by the presence of a blood clot. Chlusky (1899) used tensile strength as a measurement of the factors that effect healing. It remained, however, for Howes (1929) to use measurements of the tensile strength as the basis for the quantitative studies for repair. The splendid review of Arey summarizes the known facts about wound healing up to 1936.

In recent years, considerable attention has been directed to wound contraction (Billingham 1956, Crill 1958). Important histologic features in epithelial repair, with particular reference to remnants of epithelium in the wound, have been extensively studied by Gillman 1955. The cytologic features of healing of the body surface in mammals have been reviewed in detail by Johnson 1960. The biochemical events occurring in wound healing have been the subject of considerable study (Dumphy 1955, Edward 1958, Jackson 1958 and Dumphy 1960).

The search for a surgical "touchstone", the substance or agent which will stimulate wound healing, is never ending. Many claims have been, and still are being made but none is fully convincing. It would seem rather that there is an optimum rate of healing and this can best be achieved by avoiding or correcting all factors which may inhibit it or slow it down. Of the general factors, the most important is anaemia. Skin grafts rarely take if the Hb concentration is less than 70% of the normal. Protein deficiency in rats has been shown to cause a reduction in number of fibroblasts in wounds and scarcity of the new collagen formation, and similar effects may be noted clinically in the hypoproteinaemia of extensive burns. Vitamin C deficiency also

has well known effects. Infection is the most inhibitory local factor. It can prevent the migration of epithelial cells or even cause their regression; certain organisms almost inevitably prevent the take of skin grafts, and the excess of granulation tissue which ensues in badly infected wounds may result in excessive scarring.

In this work, a trial is made to throw light upon the different measures that promote healing. There is not an ideal method that may be used to dress a wound and to promote healing. Comparing and contrasting the different methods for dressing a wound, may lead us to recognise better methods that encourage the healing process. Application of different substances may be tried to know which is better for healing. In this work, petroleum (petroleum, paraffin, or vasiline) dressings, scarlet red, anabolic agents, agents containing amino-acids are used as topical applications for wounds and their results are compared with those of homografts. The patients chosen are those admitted to Maadi Armed Forces Hospital in the Plastic Surgery Section during the 2 years 1967 and 1968. The age chosen is between 15 and 50 years. The chemical substances are applied to a standard wound and the degree of healing is estimated.

The details for such work are mentioned later.

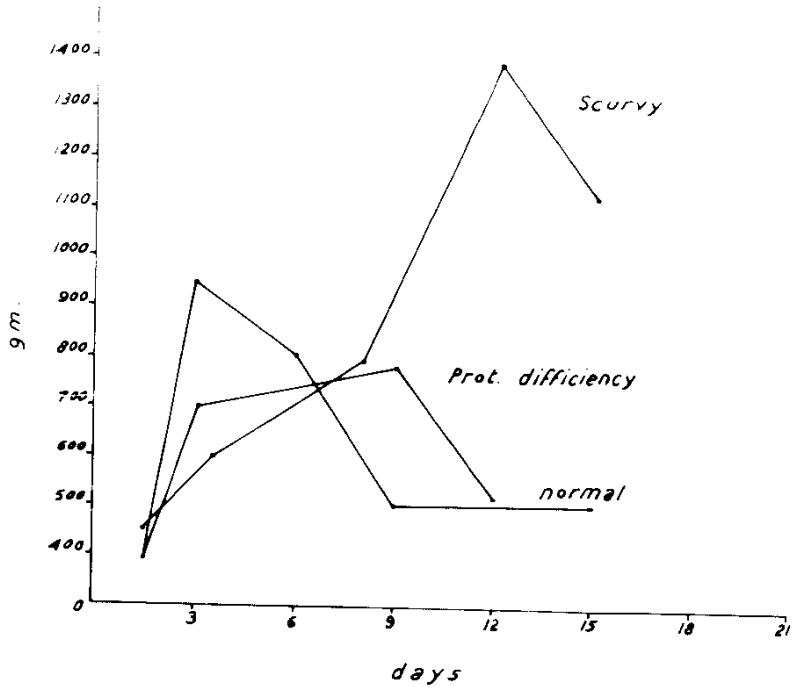
II. CHEMISTRY & PHYSIOLOGY OF WOUND HEALING

CHEMICAL CHANGES IN A HEALING WOUND

Edward and Dunphy carried out notable experiments in relation to chemical changes in wound healing. During the first 5 days there is a marked increase in hexosamine concentration. This is the chemical expression of the increased ground substance mucopolysaccharide as demonstrated histologically by metachromasia and the colloidal iron stain. About the 5th to 6th day a silver staining reticular material is present. Thus, the first few days are often regarded as a lag phase or latent period because of the absence of any visible sign of healing. It is in fact a period of active metabolic change leading to the formation of mucoproteins and polysaccharides. During this time the first stages in the biogenesis of soluble collagens are taking place which lead ultimately to the formation of insoluble collagen. (Fig.1).

From the 6th day onward the collagen content rises. The tensile strength of the wound also increases and the hexosamine content decreases sharply. By the 9th day collagen is abundant, and by the 12th day it is maximal and the fibroblasts become reduced. Edward and Dunphy concluded that the formation of mucopolysaccharide is an essential

preliminary step for collagen synthesis.



Hexosamine levels in normal, scorbutic, and prot. difficiency wd.

Fig. 1

(After Dunphy, J.E. in Surgical Progress).

In scorbutic animals during the first 5 days there is a high concentration of hexosamine but very little collagen. There is considerable intercellular material with immature fibroblasts, but collagen fibres are not demonstrable. The defect appears to be a lack of formation of collagen from pro-collagen.

Watts and Grose, using Ivalon sponges to sample granulation tissue found, not a rise by a steady fall in hexosamine, and this suggested that collagen formation might occur without antecedent production of mucopolysaccharides. However, they investigated the effect of local application of hyaluronidase upon wound healing to reduce the mucopolysaccharide. This did not alter the collagen concentration, but greatly reduced the total collagen in the wound. This points to matrix formation being an essential preliminary to collagen deposition. One incidental observation of these workers was that local hyaluronidase had a systemic effect in that the collagen content is reduced in a control wound, when another wound on the same animal is being treated simultaneously with hyoluronidase. (Fig.2).

The diagram illustrates the relationship between collagen content in a normal, a scorbutic, and a protein-deficient wound as compared with the tensile strength.

Enzymes and wound healing :

The evolution of methods for the microchemical assay of tissue enzymes and for the histochemical display of the localisation and the concentration of specific enzymes has lead naturally to the application of these techniques to wound healing. Alkaline phosphatase activity is marked in

collagen fibres in these experimental animals, as this enzyme has in vitro been found to become bound to collagen fibres. However, an essential role for alkaline phosphatase in fibrogenesis is not certain, since it has been claimed that collagen fibres can be formed under conditions when this enzyme cannot be demonstrated by histochemical methods. No effect on wound healing has been found following the application of phosphatase inhibitors directly to the surface of the wound. The amount and distribution of acid and alkaline phosphatases and leucine aminopeptidases in tissues during the immediate hours after wounding was studied by Raeballis (1960).

The first to appear was leucine aminopeptidase which was demonstrable within 2 hours and increased up to 32 hours. Acid phosphatase activity was definite in the uninjured epidermis and the dermis just beyond the wound edge after 4 hours. This increases steadily until the sixteenth hour. Later, after 8 hours, alkaline phosphatase appeared in the injured dermis and increased until 32 hours after the injury. Since this enzyme activity is present before the sixteenth hour when leucocytic invasion is evident, these enzymes cannot be derived from the invading white blood cells. The fibroblasts contain transaminases. This has been shown by