SKIN FLAP FAILURE:

RECOGNITION, PATHOPHYSIOLOGY,

AND TREATMENT

A Thesis

by

© Carolyn L. Kerrigan, M.D.

Submitted to the Faculty of Graduate Studies
and Research,
in partial fulfilment of the requirements
for the degree of Master of Science

Department of Surgery,
Division of Surgical Research,
McGill University,
Montreal
August, 1981

SKIN FLAP FAILURE

ABSTRACT

The history of clinical skin flaps and experimental flap research was reviewed. Despite advancements in flap transfer and design, skin flap failure continues to cause significant patient morbidity. A new experimental flap model in a fixed skin animal was developed and its versatility demonstrated. The length of time that a skin flap can withstand an ischemic insult was measured. Thirteen hours of ischemia was tolerated by 50% of the flaps. The etiology and pathophysiology of skin flap failure was investigated by assessing a new objective monitoring technique (stab wound blood analysis) and by measuring flow with radioisotope techniques. It was shown that skin flaps fail because of arterial insufficiency rather than venous insufficiency. Based on this data, attempts to salvage the failing flap were made surgically and pharmacologically. Flap survival length was increased by surgical augmentation of arterial inflow but not by venous drainage, phenoxybenzamine, isoxsuprine or reserpine. Salvage of the failing skin flap remains a challenge to the clinician.

RESUME

Un relevé de l'évolution des lambeaux cutanés effectués chez des patients ainsi qu'en laboratoire a été réalisé. Malgré les progrès accomplis dans le choix du site donneur et dans la mèthode de transfert des lambeaux, la nécrose de ces lambeaux cutanés continue de causer une morbidité considérable. Un model expérimental de lambeau cutané a été établi à partir d'un animal dont la peau est intimement liée au tissus sous-cutanés, comme chez l'homme. Nous avons mesuré pendant combien de temps la peau pouvait résister à l'ischémie. La moitié des lambeaux ont resisté a 13 heures d'ischémie. L'étiologie et la pathophysiologie de la nécrose des lambeaux ont été examinées à l'aide d'une nouvelle méthode (prélèvement de sang par microméthode sur le lambeaux) et en mesurant le flot sanguin aux moyens de techniques radioisotopiques. Il a été démontré que c'est l'insuffisance artérielle qui est la cause de la nécrose des lambeaux cutanées. En se fondant sur ces conclusions on a tenté de sauver des lambeaux en voie de nécrose en faisant une intervention chirurgicale ou pharmacologique. Le temps de survie des lambeaux a pu etre prolongé en augmentant la vascularisation artérielle de façon chirurgicale mais aucune survie accrue ne fut associée à l'utilisation des medicaments

phenoxybenzamine, isoxsuprine ou de la réserpine.

Sauver un lambeau cutané en voie de nécrose demeure un défi pour le clinicien.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. Rollin K. Daniel for his encouragement and enthusiasm throughout the conception and execution of this project. His appropriate criticisms and assistance in the preparation of the manuscript have been invaluable.

My introduction to radioisotopes, their handling and use would have been impossible without the assistance of Pauline Crocilla, Tony Robinson, Bill Brown, and Lise. I appreciate their willingness to teach and advise.

David Wheatley, Paul Ballard and Derek Priest I thank for their technical assistance, particularly at inconvenient hours of the day. The rest of the staff in the Microsurgical laboratories have been a pleasure to work with and I am indebted to those who have patiently initiated me into the ways of the computer and word processor.

The statistical analysis of experiment 2 and 6 would have been overwhelming without the assistance of my aunt, Sydney Duder and Dr. Duncan Thomas. For the typing, proof reading and corrections of the manuscript I would like to sincerely thank Genevieve and Diane Holding, Paula Diadori and Ron Zelt.

This work was supported in part by the Medical Research Council of Canada, Grant No. 7240.

TABLE OF CONTENTS

INTRODUCTION

Skin flaps are utilized to close large tissue defects on every surgical service, including extremity injuries (Orthopaedics), major facial defects (Head and Neck Surgery), radiation ulcers (General Surgery, Gynecology), and pressure sores in paraplegics (Plastic and Pediatric Surgery). Failure of a major skin flap secondary to inadequate intrinsic blood supply occurs in 10-15% of cases with increased patient morbidity ranging from prolonged hospitalization to death. Salvage of the distal portion of a failing flap is presently impossible because its pathophysiology is poorly understood. Methods for early detection and reversal of the failing flap have not been devised.

The principal objectives of the present thesis were the following: 1) develop accurate methods of monitoring skin flap viability, 2) to determine the etiology of skin flap failure, and 3) to evaluate pharmacological agents for salvaging failing flaps. In contrast to previous investigators who studied the mechanism of the delay phenomenon, this report concentrates on the failing skin flap during its initial, 0-12 hours postoperatively.

BACKGROUND

Throughout history, the closure of large skin defects has plagued patients and challenged surgeons. The etiology of these defects has included trauma, infection, congenital abnormalities, and most recently surgery and radiation. During the past fifty years, reconstructive surgery has evolved as a specialty to overcome this pan-surgical problem. Numerous imaginative operations have been devised to utilize adjacent tissue or to move skin from a distance. The incidence of major necrosis ranges from 10-15% and minor necrosis may approach 30%. Unfortunately, it is a clinically proven rule that the portion of a skin flap which fails is the part that was to have provided the essential coverage. Flap failure results in increased hospitalization and may cause significant morbidity including sepsis, amputation, and even death. Surprisingly, previous plastic surgery research has concentrated on how to make flaps longer rather than how to recognize and prevent flap failure. This report represents a new approach to a frequent problem which continues to cause significant patient morbidity and to compromise surgical results.

It must be emphasized that the subject of why skin flaps fail has not been directly addressed in the literature prior to this review. Therefore, the following background material is drawn from related

fields concerning the vascular anatomy of the skin, clinical skin flaps, and research into the delay phenomenon. The resulting synthesis helps provide the critical information necessary to solve the question of why skin flaps fail.

DEFINITION AND CLASSIFICATION

Biological closure of skin defects can be achieved with either skin grafts or skin flaps. For the uninitiated, the distinction between these two procedures is often confused. A skin graft is composed of epidermis and dermis which is moved from one part of the body to another and whose initial survival is dependent upon a plasmatic circulation from the underlying recipient bed (188). In contrast, a skin flap is composed of epidermis, dermis and subcutaneous tissue whose survival following transfer is dependent upon a functioning intravascular circulation through the flaps intrinsic blood vessels. A knowledge of the anatomy and vascular supply of normal skin is essential for a basic understanding of current research in skin flaps.

Skin is composed of two layers: the epidermis and dermis. Underlying the dermis is the subcutaneous

tissue through which runs the blood vessels that supply the skin. As proposed by Daniel (41,42,52) the vascular supply to the skin may be conceived of on three levels - segmental, perforator and cutaneous. Segmental arteries are large branch vessels which are in continuity with the aorta as regards their pressure. They usually course in a plane deep to the muscles (eg. intercostal vessels). The perforator vessels function primarily to supply the muscles through which they pass and to serve as conduits from the segmental vessels to the cutaneous circulation (eg. thoracoacromial). Cutaneous vessels are of two types: musculocutaneous and direct cutaneous. The main blood supply to the skin is via numerous musculocutaneous arteries which penetrate directly from the underlying muscle through the subcutaneous tissues and into the overlying dermal-subdermal plexi. Each individual vessel supplies a relatively small area of skin. This supply is augmented by a limited number of direct cutaneous arteries which course parallel rather than perpendicular to the skin (eg. dorsalis pedis). These vessels course in a plane between muscle and skin.

Simplistically, skin grafts may be classified as split thickness or full thickness. Skin flaps are thicker and incorporate a portion of the subcutaneous tissue which insures preservation of the subdermal vascular plexus. When skin coverage is required, the

simpler procedure of grafting is utilized provided an adequately vascularized bed is available. In contrast, a skin flap is a more complicated and uncertain procedure which is reserved for cases where an inadequate recipient bed is present or other extenuating circumstances exist. Commonly encountered situations are defects overlying bare bone, tendon or nerve, radiation damage, burn scars or coverage of essential structures (eg. major blood vessels). Flaps may also be considered if future surgery is planned through the site.

The original classification of skin flaps was based on the method of movement from donor to recipient site. For local movement, single pedicle flaps were advanced, rotated or interpolated (186). For distal movement, a mobile donor site was brought to a fixed recipient site or a mobile recipient site was approximated to a fixed donor site. If both donor and recipient sites were fixed, then a temporary mobile attachment was used to jump (tumble or caterpillar) a skin flap from one area to another.

A new classification of skin flaps has evolved because of an improved knowledge of the cutaneous blood supply and refinements in the methods of movement. Daniel (41) has classified skin flaps on the basis of their blood supply into 3 major groups: random

cutaneous, myocutaneous and arterial flaps. A random cutaneous skin flap can be designed anywhere on the body and is supplied by terminal branches of the musculocutaneous vessels (89). A specific arteriovenous system is not incorporated into the pedicle of these flaps. A myocutaneous flap is designed in relationship to an underlying muscle. The blood supply of these "compound" muscle skin flaps is from the muscles dominant arteriovenous pedicle which subdivides into multiple musculocutaneous arteries terminating in the dermal vascular plexi. An arterial flap (190) is designed in relationship to a specific direct cutaneous artery (e.g. superficial temporal artery, dorsalis pedis artery, superficial inferior epigastric artery).

Concurrently, this appreciation of the blood supply to the skin has allowed more sophisticated methods of movement which minimize wastage of time and tissue. An island skin flap has as its pedicle only the essential blood vessels. With less pedicle wastage and restraint, the flap can achieve a greater axis of rotation and utilization. A free skin flap is essentially an island flap which is detached from the body and moved to a distant site where it is revascularized via microvascular anastomoses to blood vessels in the recipient bed.

HISTORY - CLINICAL

Skin flaps were devised long before skin grafts. In ancient India, local advancement flaps were used to close skin defects secondary to infection or trauma. In 1597, Tagliacozzi (210) of Bologna reported the use of a distant pedicle skin flap from the arm to reconstruct an amputated nose. Periodically skin flaps were "rediscovered" and popularized. However it was not until World War I that skin flaps became a common surgical procedure. Due to trench warfare and its associated facial injuries, reconstruction with distant tissue became a necessity if otherwise healthy young men were to return to society. Filatov and Gillies (210) independently began tubing (sewing parallel edges together) flaps to reduce infection, scarring and shrinkage. Numerous techniques were devised to move skin from one area of the body to another but they often required multiple operations with prolonged hospitalization. For example, a large 30cm long X 10cm wide flap, (hereinafter flap length is given first followed by flap width) would be tubed on the abdomen for a three week "delay" period. Then one end would be divided and attached to the wrist. Three weeks later, the opposite end would be divided and the wrist with its dangling tube flap would be sutured to the facial defect

and the patient immobilized in a "harness bandage" for four to six weeks. Once the flap gained its blood supply from the face, the arm attachment would be divided and the flap completely sutured to the face where it would be inserted over a 6-8 week period. As reviewed by Strange (197,198) the average reconstructive period was 6.8 months and required 5 operations.

Since many of these flaps failed due to tissue necrosis, improved techniques were developed. The most commonly employed method was the delay procedure which was introduced by Hamilton (193) and popularized by Blair (17). The delay procedure involved parallel incisions with elevation and undermining of the intervening skin which was then returned to its bed. Three weeks later, one base would be divided and the resulting skin flap elevated and transferred as a single pedicle flap into the recipient bed. Viability of the longer flap was significantly improved but at the cost of tissue fibrosis and additional surgery. However, the reward justified the expense and the delay procedure became the only method available for achieving additional flap length.

Concurrent with the development of the tubed flap, a second school of flap design had evolved. It was based on a detailed knowledge of the cutaneous vascular anatomy. In 1889, Manchot 117), a German anatomist,

did extensive anatomical dissections of the blood supply to the skin. Esser (63,64) and others (3) utilized this knowledge in the design of numerous arterial and island flaps of the face (211). Webster (211) extrapolated this concept to the torso and introduced the thoracoepigastric skin flap. In the 1940's, Littler (114) pioneered an island sensory flap based on the digital neurovascular bundles for restoring sensation to critical areas of the hand. This ability to restore discriminatory tactile sensation to the pinch area of the hand was one of the procedures upon which the rise of modern reconstructive hand surgery was based.

The next advance was recognition of the role of the blood supply in skin flap design as proposed clinically by McGregor (136) and experimentally by Milton (149) and Daniel (52). Skin flaps could be divided into those with a random blood supply and those with a specific arterial supply. With this concept the anatomy of the skin vasculature was restudied and additional flaps designed including the groin (35,191) and deltopectoral (8) flaps. The development of arterial flaps from the torso was a milestone in the evolution of head and neck surgery. Prior to the 1960's primary reconstruction of large facial defects following cancer resection was not possible due to the paucity of nonirradiated local skin. Soft tissue reconstruction (146,217) required multiple

preoperative delay procedures which precluded early surgical excision and had a high risk of necrosis. Due to its axial arterial blood supply from the anterior thoracic perforators, the deltopectoral flap (44) offered a large amount of skin (40 X 15cm) without delay from beyond the area of irradiation. Thus the introduction of new arterial skin flaps (forehead and deltopectoral) has revolutionized head and neck surgery by permitting larger resections with lessened morbidity and primary reconstruction.

Following introduction of the modern operating microscope (49) and extensive research (76,111,199), it became possible to directly transfer an island flap from one part of the body to another by microvascular anastomoses (85). New flaps were designed to retain their essential sensory nerve supply (46,50,51,106,120,126) and to incorporate viable bone (161,202). The perfection of free tissue transfers by microvascular anastomoses has significantly altered the approach to combined osteocutaneous defects of the lower extremity. Conventional techniques consisted of skin coverage with a cross-leg flap (26,192) followed by secondary bone grafting over several months. The one-stage free osteocutaneous groin flap provides a vascularized bone graft with more rapid incorporation than conventional bone grafts, as well as the requisite

skin coverage (202).

Concurrent with the evolution of free flaps, a separate group of investigators deduced that the vascularity of many random pattern flaps could be improved by elevating the underlying muscle with the skin as a single unit (118,123,124,129). The blood supply to muscle was originally detailed by Campbell and Pennefather (25) but it was not utilized by reconstructive surgeons for skin flap design until the last decade (163,164). McCraw (123,124) has pioneered the experimental and clinical design of myocutaneous flaps. Myocutaneous flaps are of particular value for covering exposed vascular prosthesis in the lower extremity. Due to the prevalent ischemic and/or diabetic condition, conventional skin flaps have an unacceptable high complication rate. Myocutaneous flaps, especially the medial gastrocnemius (65,125) and tensor fascia lata (30), can provide essential skin coverage with a minimal complication rate (15). In addition, the gracilis myocutaneous flap (127) allows vaginal reconstruction and closure of large irradiated lesions in the perineum.

During the past decade an increased knowledge of the blood supply to the skin plus utilization of the operating microscope (85,161) has initiated a renaissance in reconstructive surgery which has been

manifested in all surgical specialities. Reconstructive procedures that previously were either impossible or required multiple operations can now be done often in one operation with enormous benefit for the patient (18,43,48).

CLINICAL COMPLICATIONS

Since the principle purpose of a skin flap is to provide skin coverage, full-thickness necrosis of a flap is a catastrophic complication. Clinically, skin flap failure can result in sepsis (occult orocutaneous fistulas), exposure of critical structures (major vessels, pericardium), extremity amputations and even death (carotid blow-out). The extrinsic causes of flap failure include systemic factors (infection, malnutrition, hypotension, arteriosclerosis) and local flap factors (kinking, compression or tension). In most cases, the extrinsic factors can be prevented by preoperative patient preparation and attentive postoperative nursing care. As extrinsic factors are controllable, the primary cause of skin flap failure is an intrinsic factor - inadequate nutrient blood flow. The precise pathophysiology of this poor flow state is inadequately understood. It has been theorized by some that insufficient venous drainage is the primary event (97), and by others that a decreased arterial inflow is

to blame (168). Still others postulate that flow is shunted away from the nutrient capillaries through arteriovenous anastomoses (174). The validity of each of these concepts is still questionned. Surgeons do not understand why flaps fail.

The complexity and imprecision involved in the treatment of this complication is illustrated in the method of execution of a conventional skin flap. The flap is designed to cover a defect on the basis of generalized guidelines derived from a knowledge of the cutaneous blood supply. The flap is then elevated, transferred and sutured into the recipient bed. If the color of the flap looks "good" to the surgeon, dressings are applied and the operation is finished. If the color looks "bad", then the compromised portion is resected and alternate methods utilized. If the flap slowly fails postoperatively, nothing is done because it is an "instrinsic factor". Thus, a total ignorance exists as to why flaps fail as well as to how to recognize flap failure early and what can be done to salvage the failing flap.

Only a few review studies of flap failure exist in the literature. Complication rates of random cutaneous flaps for paraplegic pressure sores is reported at 15% (72). Dawson (54) reported that random cutaneous cross leg flaps had some form of necrosis in 40% of cases with

12% attributed to intrinsic factors and 28% to infection. In a review of 196 tubed pedicle flaps (random cutaneous type) Stranc (197) reported the incidence of instrinsic necrosis to be between 9 and 20%. Statistics for failure of myocutaneous flaps have not been reported but distal flap necrosis does occur. Arterial skin flap failure rates have been reported primarily for the deltopectoral flap. Gingrass et al (74) noted that necrosis of the distal portion was due principally to inadequate vascularity and secondarily to extrinsic kinking or tension. Krizek (110) evaluated 57 deltopectoral flaps and found major necrosis in 10% with minor necrosis in 24%.

The failure pattern of free flap transfers by microvascular anastomoses represents an interesting contrast to those of conventional skin flaps (185). Since a free flap usually has a single artery and vein, it is generally accepted that arterial thrombosis causes a white flap whereas venous thrombosis causes a cyanotic flap. If the problem is recognized and corrected within 6-8 hours of its occurrence, then the flap will survive. If the anastomoses can not be revised then the entire flap usually necroses. It is tempting to postulate that salvage of a failing free flap is comparable to the problem existing in the distal portion of a standard flap that fails. However, detailed analysis

demonstrates significant differences in the two situations. Rather than representing reversal of an intrinsic failure, revision of an anastomosis is merely correction of a factor external to the flap itself. In addition, a failing free flap is either totally ischemic from blocked arterial input or undergoing engorgement due to blocked venous drainage. In contrast, the imbalance of the microcirculation in the distal portion of a skin flap is probably shunt perfusion or inadequate perfusion of the capillary bed. Whereas external events will permit salvage of the failing free flap, successful manipulation of the microcirculation has not been achieved for conventional skin flaps.

In summary, despite advances in skin flap design and methods of movement, complications continue to occur. Since current reconstructive procedures are often more extensive than previously, flap failures cause greater complications. The exact pathophysiologic mechanism behind this failure is not understood. Thus it is imperative that a technique for early detection of impending flap failure be developed, that we understand the etiology of the failure and that treatment be available to reverse the process.

HISTORY - EXPERIMENTAL STUDIES

Since Filatov's (53) initial description of the tubed pedicle flap in 1917 which was based on experimental flaps in rabbits, skin flap research has continued to improve clinical techniques. Until recently the main goal of this research was to develop clinical guidelines for the safe timing of flap transfer. Unfortunately, numerous skin flap designs have been investigated in a wide variety of experimental animals. Data obtained in different species are probably not comparable and substantial differences exist between flaps of various design.

Popular experimental models have included those in loose skin animals - rat (130,218), rabbit (121,151,184), and dog (60,204) and more recently fixed skin animals-pig (105,168,194). In loose skin animals, survival patterns are extremely variable and usually only one flap per animal is created. Thus each animal does not act as his own control and separate control groups are required. Finseth et al (69) developed a rat abdominal flap whose control survival area was 10.4cm2 $\pm$ 6.2cm2, a greater than 50% variability. Myers and Cherry (151) have employed a rabbit back flap whose survival ranged from 2 to 8 cm with a mean of 4.5 cm. In these experiments large series are required. In

fixed skin animals (pig), numerous flaps may be designed on each animal permitting multiple experimental designs while retaining a control. Milton (141) was able to achieve a consistent survival length in pig arterial flaps with a mean survival of 11.3 cm ± 0.4 cm.

As our understanding of the skin's vascular anatomy improved it became apparent that loose skin animals possess a significantly different cutaneous blood supply than man, a fixed skin animal. Rabbits, rats and dogs have a densely hairy fur which is loosely attached to the underlying muscle by areolar tissue devoid of numerous blood vessels. The skin vessels enter cephalad and caudad as direct cutaneous vessels then run longitudinally in close association with the panniculus carnosus. In man and pig, the skin is sparsely covered with hair, firmly attached to underlying muscle and penetrated by numerous musculocutaneous arteries. Although the panniculus carnosus is present over the abdomen in swine, it is without special vascular properties and is comparable to the avascular Scarpa's fascia. Since the panniculus carnosus is absent over the buttock, this area provides an ideal site for the design of experimental flaps for research. For this reason, prior experimental studies can not be completely accepted and must be interpreted with caution. Previous experimental skin flap studies can be divided into three

major areas: 1) anatomical changes in an elevated flap, 2) physiologic changes, and 3) methods of augmenting flap survival (delay phenomenon).

ANATOMICAL CONSIDERATIONS

Morphologic changes in skin flaps have been studied in regards to flap design, change in blood vessel caliber and orientation, as well as evidence of denervation. Prior to 1970, skin flap design was based on a length to width ratio (195), ie. a flap would survive as long as its length was not greater than twice its width. However, the experimental studies of Milton (140) and of Daniel (42,52) have demonstrated that the length to width ratio is not applicable to random, arterial or island flaps. This research demonstrated that a flap's surviving length is determined principally by its blood supply, not by its width. Therefore, the best means of achieving increased surviving length, is to augment the blood supply, not to increase the flap's width. Augmentation of blood supply is done by designing the flap in the area of a direct cutaneous artery or over a muscle that has a dominant vascular pedicle. Previously, clinical skin flaps were designed on a length - width ratio, they are now designed in regard to the underlying vascular anatomy.

Anatomical changes of the vasculature in skin flaps

have been documented by histology and microangiography. German et al (73) investigated changes in dog tube flaps and found that within 10-14 days following flap elevation there was an increase in the size and number of vessels as well as reorientation along the flap's axis (19). Conway (34) and later DeHaan (55) observed rabbit tube flaps and confirmed that their vessels became longitudinally organized, tortuous and more numerous. Bellman and Veiland'r (14) studied a rabbit ear flap with in vivo microangiography and demonstrated enlarged vessels with longitudinal reorientation. Vessel ingrowth from surrounding tissues has been shown by several investigators to occur by the fourth to fifth day (16,184). It appears that blood flow in skin flaps is based on a dilation of and reorientation in preexisting channels and not development of new vessels. Wound edge healing leads to supplementary vascularization from the periphery.

Histologic changes in both autonomic and cutaneous sensory nerves have been documented in skin flaps with histochemical techniques. Palmer (165), using a rat dorsal flap (a random cutaneous flap) studied the catecholamine content of sympathetic nerve terminals by the formaldehyde induced fluorescence technique. He documented disappearence of catecholamines by 30 hours following surgical incision. Reinnervation and

accumulation of catecholamines began 4-8 weeks postoperatively. Waris (209) also using a dorsal rat flap investigated catecholamines with both formaldehyde and glyoxylic acid induced fluorescence. His findings confirmed those of Palmer. Waris simultaneously observed cutaneous sensory nerves by the nonspecific acetylcholinesterase (nsAch) reaction. The nsAch had disappeared by the 14th postoperative day and began to reappear between 4 & weeks postoperatively. Edstrom (61) studied catecholamine with the glyoxylic acid technique in both rats and pigs and he found disappearance of the neurotransmitter to be complete by the 4th postoperative day. He also noted that severing the major nerve to the rat abdominal flap did not cause a sympathectomy as previously assumed. Rather, flap denervation occurred following undermining of the skin thus effectively sympathectomizing the flap.

Vascular changes in the distal portion of a failing flap have not been studied histologically or by microangiography. In addition, the status of the sympathetic or sensory innervation of island and myocutaneous flaps have not been evaluated. Most previous projects have utilized loose skin animals and therefore need to be repeated and expanded in an acceptable fixed skin animal model.

PHYSIOLOGICAL CONSIDERATIONS

Physiological changes affecting both the metabolic and blood flow characteristics were investigated to better define the timing of flap transfers. Metabolic changes were measured by tissue pH and tissue gas levels (83,156,214), both of which had a positive correlation with flap viability. Glinz and Cardius (75) showed that a pH difference of less than 1.35 between control areas and a skin flap was compatible with survival whereas acidosis in excess of this level indicated impending necrosis. Myers et al (156) found that pO2 levels increased within an hour following flap incision but returned to normal within 8 hours in the viable portion. Guthrie (83) concluded that survival occurs if the pO2 is greater than 43mmHg and the pCO2 is less than 64mmHg. However, necrosis occurs if the pO2 is less than 50mmHg and the pCO2 is greater than 80mmHg. The above studies provided useful information about metabolic changes in skin flaps but were apparently abandoned due to the cumbersome equipment required and the potential trauma to the flap by the technique employed. If simpler techniques were available to gain the same information, they would contribute significantly to our understanding of skin flap physiology.

Intravenous fluorescein is the most widely utilized test (56,99,112,128,147,203). Following

injection and circulation, fluorescein diffuses into the interstitial spaces (37,38) where it can be detected by direct visualization under ultra-violet illumination. Fluorescein in the tissue appears yellow while nonfluorescent areas appear purple. The fluorescent portion of the flap corresponds with the viable portion. Additional qualitative assessment of blood flow can be duplicated with the intravenous injection of other dyes, ie. trisulphine blue. Experimental both fluorescein and trisulphine blue has been extensively used to predict flap survival and to measure the effect of a specific manipulation. Myers and Terzis also showed that in the rabbit, fluorescein penetration correlated within 0.5 - 1.0cm with the ultimate surviving length. Fluorescein was not reliable in the prediction of the viability of delayed pedicle flaps. Our impression clinically is that false negatives are the most frequent cause of inaccuracy with this test.

Quantitative estimates of blood flow can be obtained by two different techniques: cutaneous clearance of a substance (saline, atropine, heat, or radioisotopes) or by the intraarterial injection of radioactive labelled microspheres. Utilizing the intradermal saline injection test, Conway (33) found that tubed flaps at three weeks had a greater clearance rate than control areas (ie. an increase in blood flow).

Hynes (95) employed the intradermal atropine test and concluded that if the systemic effects of the cleared atropine were evidenced within 15 minutes then flow was adequate for flap division. As demonstrated by Brown (24), heat clearance provides a noninvasive measurement of local blood flow (93,206). However, instead of measuring actual absolute blood flow, he detected relative changes between denervated flaps and a control site. He reported an immediate decrease in blood flow and attributed it to vasoconstriction caused by surgical manipulation. Continuation of low flow during the first four postoperative days was considered secondary to flap edema. Increased flow between the 4th and 5th days following surgery correlated with resolution of flap edema.

Isotope clearance measurements can be divided into two groups: diffusion limited substances (Na, I, Tc) and freely diffusible flow limited substances (Xe, Kr, antipyrine) (7). Early investigators used radioactive Na24 (13,22,23,33,92) and I131 (38). They concluded that a flap was ready for division when clearance rates had returned to control rates, usually 7-10 days postoperatively. For unclear reasons, technetium99 has been favored more recently (145). Young (235) evaluated blood flow in viable pig skin flaps with Tc99 clearance rates beginning 24 hours postoperatively and continuing

at daily intervals for 2 weeks. Blood flow decreased for 2-3 days before increasing to its maximum by the 6th-10th day, with return to or below control values by 2 weeks. The major problem with the Na24 and Tc99 clearance techniques is that diffusible limited isotopes are influenced by flap edema in the early postoperative period thus producing false data. More accurate studies may be carried out using Xenon133 (20) or Krypton85 (175). With Xe133 Palmer (166,167) found that flow at the base of a pedicle flap remained at 100% of control whereas the tip flow decreased to 18% on the first postoperative day. A gradual increase in tip flow up to 65% occurred in the first week and became 75-90% of normal by 2 weeks.

Most recently, radioactive microspheres (84,88) have been used for quantitative assessment of blood flow in experimental flaps. The first study which employed this technique revolutionized our concept of and our approach to skin flap pathophysiology. In his key paper, Reinisch (174) reported a discrepancy between 15 micron microsphere distribution (capillary flow) and radioactive red blood cell distribution in the viable and nonviable portion of a pig skin flap. He demonstrated the presence of red blood cells in the portion of the flap that was destined to necrose. He hypothesized that this data demonstrated flow through

non-nutrient anatomical shunts (arteriovenous anastomoses) thus "stealing" from the nutrient capillary circulation. Subsequent microsphere flow studies have focussed on the flow changes in cable flaps and delayed flaps. From data on cable dog flaps, Nathanson (158) reported that control cutaneous flow rates were .02 - .24 ml/min 100gm. Following flap incision and elevation blood flow in the proximal part of the flap was significantly above control (highest 29%) while in the distal portion blood flow was significantly below control (lowest 1%). In cable canine flaps, Guba (82) found cutaneous flow rates of 8.. ml min 100gm. In pigs, the same author (80,81) had control cutaneous flow rates of 0.5 - 5 ml min 100gm and flap flow rates of 2 ml/min/100gm. Following a delay procedure, maximal flow (4.6 ml/min/100gm) occurred on the 6th postoperative day.

Unfortunately, none of the previous research has measured flow rates during the critical first 12 hours following flap elevation. It is known from investigations of tissue ischemia that skin can withstand up to 12 hours of normothermic ischemia (121,213). Thus it is during this critical first 12 hours following flap elevation that our efforts have been focussed to delireate what changes are occurring and how we can modify them to gain increase flap

survival. Physiologic studies of flow changes in skin flaps have utilized clearance and microsphere methods in various animal species. Conflicting information renders analysis difficult. These accepted methods of studying flow have not been applied to answering the critical question: "What happens to a skin flap with impending distal necrosis during the first 6 hours following surgery?" The etiology of skin flap failure remains unknown and it is through expansion of physiologic studies begun by Reinisch that an answer will be found.

AUGMENTING FLAP SURVIVAL - THE DELAY PHENOMENON

Conventional rand m cutaneous flaps often necrose due to inadequate blood supply. To circumvent this problem, a surgical technique known as the "delay procedure" was devised. It consists of incising the two longitudinal sides of a potential skin flap plus undermining the intervening skin. The newly created bipedicle flap is sutured back in place and then converted three weeks later into the definitive single pedicle flap. Hamilton (19 introduced the delay technique which was later popularized by Blair (17). The timing of the delay procedure and subsequent flap transfer was originally based on empirical observations and later by physiologic tests. The vast majority of skin flap research was designed to understand the delay

mechanism (154) and to duplicate it by non-surgical means.

To prevent necrosis secondary to inadequate nutrient blood flow, the delay phenomenon must cause either a decrease[d] nutrient requirement or an increased nutrient deliver[y] (94). Thus it has been postulated that the delay phenomen[on] works by conditioning a skin flap to ischemia or by improving nutrient blood flow.

Conditioning to ischemia was first proposed by Brown and McDowe[ll] (23). McFarlane (130), expanded this concept with his angiographic and intraarterial radioisotope studies of rat flaps. He concluded that the delay procedure conditions the skin to hypoxia. However, recent work by Milton (142) showed that an acutely elevated skin flap could survive 13 hours of total ischemia whereas delayed flaps could withstand only 4 hours of ischemia.

Thus improved vascularity is now considered the mechanism governing the delay phenomenon, but what does this actually mean? Is it a result of vasodilation secondary to sympathectomy as proposed by Hynes (96,97)? Is it due to a locally induced reactive hyperemia as postulated by Braithwaite (20)? Is it due to an inflammatory reaction as theorized by Velander (207)? Or is it due to an arteriovenous shunt adjustment as suggested by Reinisch (174)? Changes in flow of the

microcirculation are regulated by multiple factors (45). Therefore, adjustment of any single factor could account for the improved nutrient circulation induced by the delay procedure. All of the above hypothese may in fact be correct, or at least in part.

The sympathetic nervous system is the dominant regulating factor in skin blood flow. With the incision and elevation of a skin flap, the sympathetic neurotransmitters are depleted within 36 hours (61,165,209). Vasodilatation in response to delay must occur. Efforts to lengthen flap survival have concentrated on manipulation of sympathetic nerves and their receptors prior to flap elevation. Sympathetic axon blockers including reserpine (40,102) bretylium (101), guanethidine (101) and 6-OH dopamine (101,174) improve flap survival. Alpha adrenergic receptor blockers including phentolamine (100,160,212), phenoxybenzamine (153,212), thymoxamine (12) and alpha methyl-p-tyrosine (101) improve flap survival. Both a beta adrenergic receptor blocker, propanolol (100), and an agonist, isoxsuprine (66,68,216) have increased flap survival.

Locally induced reactive hyperemia also regulates the microcirculation. Factors including bradykinin, histamine, prostaglandins, hypercarbia, hypoxia and acidosis cause vasodilatation. Skin flap survival has

been augmented with histamine (107), DMSO (4,5,131) and other prostaglandin inhibitors (181) as well as hyperbarbic oxygen (79,102,132,169,170). Other experiments with the same agents have not increased flap survival (143). Skin flap survival has also been increased by an inflammatory reaction induced by the injection of formic acid (62). Other investigators have successfully augmented skin flap survival by altering the rheological properties of blood (176). Arteriovenous anastomoses have been experimentally manipulated by Reinisch (174) and found to increase flap survival. However, during maipulation, blood flow was not monitored and it is unclear if the effects were in fact on the arteriovenous anastomoses or on another portion of the microcirculation.

In summary, the mechanism by which delay procedures augment skin flap survival is still poorly understood. There have been multiple scattered attempts to duplicate the beneficial effects of delay by pharmacological manipulation. However, in none of these studies was the drug induced effect investigated on an anatomical or physiological level. The reasons for the beneficial effects were only postulated. In addition, most manipulations were utilized as a pretreatment prior to skin flap elevation to increase the surviving length of a flap. At present, pretreatment is not a clinical

necessity. Rather, it is salvage of an already elevated failing flap that demands assistance. The effects of pharmocologic manipulation require more careful delineation and an acceptable mode of treating the failing flap must be developed.

SPECIFIC AIMS

Skin flap failure is a significant clinical problem which has not been adequately investigated. Previous research concentrated on the mechanism of the delay phenomenon, an increasingly antiquated procedure, and has ignored the critical question: why do skin flaps fail?

The present thesis is divided into six papers each dealing with a specific aspect of experimental skin flap failure. The first paper reports the development of a new and versatile experimental skin flap model in the pig, a fixed skin animal. Numerous uses of this flap are demonstrated. The second study was designed to evaluate the duration of the ischemia time that island flaps and conventional flaps can tolerate and still remain viable. This critical ischemia time was used as a guide in subsequent studies to determine the frequency and duration of monitoring or the timing of treatment. In the third paper, currently employed subjective and objective methods of monitoring skin flaps were appraised and compared to an evaluation of new techniques. These new methods (stab wound blood analysis) are ones that have previously been proven useful for monitoring neonates. In the fourth paper, the pathophysiologic changes occurring in a failing skin flap during the critical ischemia period were

investigated. Acutely elevated flaps were studied for changes in total flow, nutrient flow and shunt flow. Based on these findings, a new hypothesis of skin flap failure is proposed. The fifth study is designed to determine the vascular basis of intrinsic distal flap necrosis. Do flaps fail because of arterial insufficiency, venous inadequacy or both? The flap model described in the first paper was modified to permit selective augmentation of the venous or arterial supply to the failing portion of the skin flap. The final study describes the systemic treatment of pigs with various drugs. The drugs were chosen because of their theoretical ability to increase cutaneous blood flow. This is the first report of a double blind experimental design in the treatment of failing skin flaps. Pigs are used because of their fixed skin and treatment is begun postoperatively so as to parallel the clinical situation.

EXPERIMENT 1:

THE OMNIPOTENTIAL

PIG BUTTOCK FLAP

INTRODUCTION

Since Filatov's (210) initial research with tubed pedicle flaps in rabbits, plastic surgeons have used experimental skin flaps as a method of improving clinical techniques. Early experiments were designed to investigate relevant clinical problems. When could pedicle flaps be safely transferred? What is the etiology of the delay phenomenon? Numerous experimental animals and flap models were utilized resulting in a diverse and often confusing literature.

Recent emphasis on the importance of cutaneous blood supply in skin flap design (42, 140) and a change in the type of flap used clinically (45) has forced a reevaluation of previous research models. Thus, it was necessary to develop a new experimental skin flap which would allow more accurate replication of clinical techniques. Based on these considerations, an omnipotential buttock flap in the pig has been designed for skin flap research.

MATERIALS AND METHODS

The pig buttock flap measures 18 x 10 cm and is located with its cephalo-dorsal corner at the anterior

superior iliac spine (Fig. 1-1). This area of the pig is devoid of panniculus carnosus and the skin is supplied by musculocutaneous perforators and a direct cutaneous artery. The neurovascular pedicle of the flap contains the direct cutaneous artery (the deep circumflex iliac artery), paired venae comitantes and a single cutaneous nerve (the lateral femoral cutaneous nerve). The cutaneous distribution of this nerve has been mapped electrophysiologically prior to and following skin flap elevation (5). With varying experimental requirements, this neurovascular supply can be altered to create a wide variety of flaps including the random cutaneous flaps (distally or proximally based), arterial flaps, island flaps (vascular or neurovascular) and free flaps (vascular or neurovascular).

OPERATIVE TECHNIQUE

White Poland-China pigs weighing 20 ± 2 kg are used. Animals sedated with acepromazine are anesthetized with intravenous sodium thiopental, intubated and then maintained on a mixture of oxygen, nitrous oxide and halothane. Using a standard grid, with the pig in the lateral decubitus position, the flap is outlined on the buttock (Fig. 1-2). Cross hatches are marked to facilitate correct alignment at closure. The standard

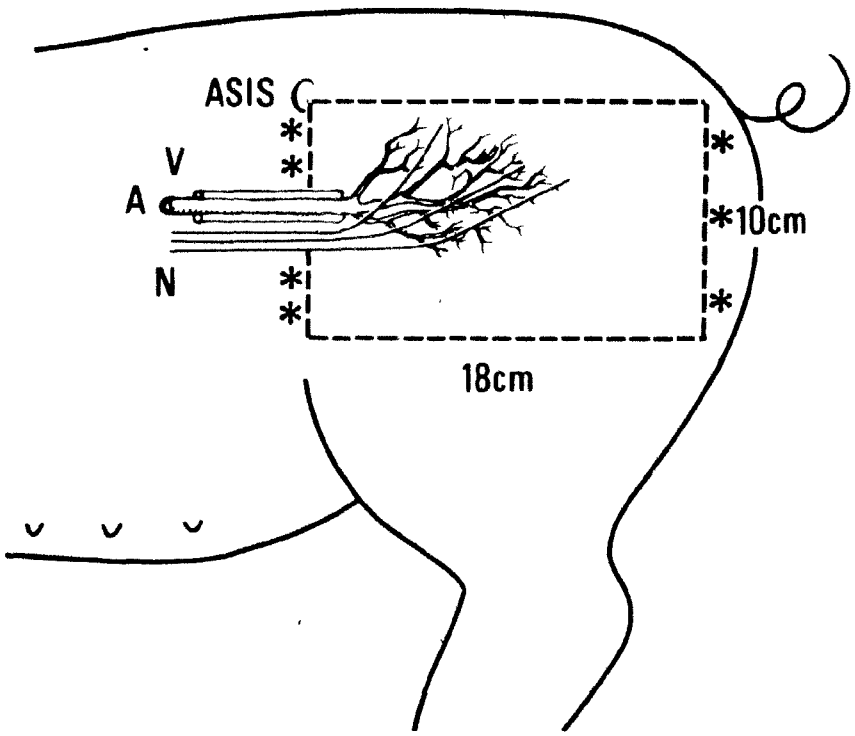

Fig. 1-1 Schematic anatomy of the pig buttock flap. ASIS = anterior superior iliac spine, A = deep circumflex iliac artery, V = vena comitan, N = lateral femoral cutaneous nerve, * = musculocutaneous perforators.

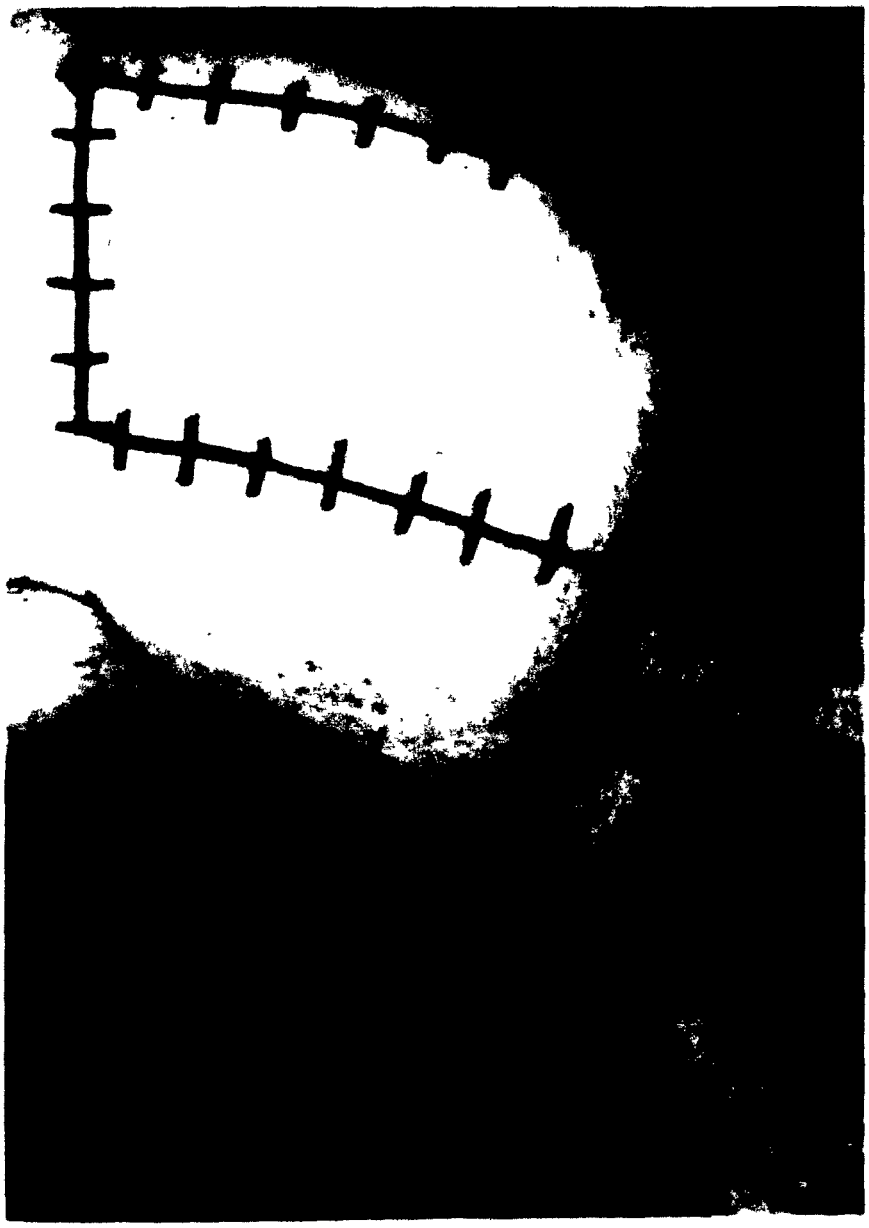

Fig. 1-2 The standard 18 X 10 cm buttock flap design.

arterial flap is created by incising on three sides and elevating the flap on to its proximal base. The essential neurovascular bundle is easily visualized on the undersurface of the flap in a central position. A proximally based random cutaneous flap is created by ligating the major vascular bundle at the base of the flap rendering it dependent on multiple musculocutaneous arteries. Alternately, a distally based random cutaneous flap is created by incising the flap on three sides and preserving the distal base. A delayed flap is constructed by incising the two long sides of the flap and undermining the central portion thereby leaving both proximal (arterial) and distal (random cutaneous) bases intact.

In creating island or free flaps, the standard arterial flap is elevated, the proximal cutaneous attachment is divided and the neurovascular bundle carefully preserved. The animal is turned from the lateral decubitus to a supine position and the skin incision is extended into the groin. The subiliac lymph node is identified as a landmark and then the neurovascular pedicle to the flap is dissected free from the medial aspect of the thigh (Fig. 1-3). Multiple muscular branches are ligated and the inguinal ligament approached. At this level, the femoral vessels and external iliac vessels are identified. In this

Fig. 1-3 Pig supine for isolation of 10 cm neurovascular stalk.

configuration, the flaps vascular stalk measures 10-12 cm in length. The artery is 1 mm in diameter and the fragile venae comitantes are 2-3 mm in diameter. To convert this island flap into a free flap, the vessels are divided at the level of the inguinal ligament. The flap may be replanted in situ or transferred to a distant site. Anastomoses of the artery and one vena comitan are performed using standard microvascular techniques.

EXPERIMENTAL DESIGN

During the past 5 years, we have created 152 buttock flaps of varied blood supply. The versatility of this flap is shown in the following four groups.

1. Standard survival lengths. In 10 animals, 20 buttock flaps with varied vascular supply (arterial, proximal cutaneous, distal cutaneous) were elevated and their surviving lengths measured at seven days.
2. Surviving length of Island flaps vs. Free flaps. Bilateral island flaps were elevated in eight animals with the vascular stalk dissected to the inguinal ligament. One flap was sutured back in situ as a control island flap whereas the vascular stalk of the opposite island flap was transected and thus converted to a free flap. Microvascular

anastomoses were performed and survival measured and photographed on the 7th postoperative day.

3. Onset of Delay Phenomenon. In 8 animals, 16 bipedicle buttock flaps were constructed. At 1 to 8 days postoperatively the flaps were reelevated and the random end of the bipedicle flap transected, thereby converting it to a delayed arterial flap. Survival was measured on the 7th postoperative day.

4. Monitors of Flap Viability. In pilot studies, the buttock flap was elevated bilaterally in 5 pigs. Skin temperature was measured using a thermistor surface probe (Digitec Thermometer 5800). Fluorescence was determined after injection of 5 cc of 10% fluorescein and ultimately correlated with survival. Capillary blood from stab wounds was collected in heparinized tubes. This blood was analyzed for pO_2, pCO_2, and pH using a Corning 175 blood gas analyzer. A Roche oxygen monitor #5301 was employed for continuous transcutaneous pO_2 monitoring. In one flap, an arterial failure was created and in two flaps, venous failures were created.

RESULTS

The standard survival patterns are depicted in Fig. 1-4 and Table 1-I. As expected, the arterial buttock flap survived to a greater length than the random cutaneous flap. The proximal cutaneous flap survived to a significantly greater length ($p<.01$) than the distally based random cutaneous flap. Innervated island flaps and denervated free flaps did not differ in their survival lengths nor did they differ from the survival length of arterial flaps.

The effect of delay was present by the 4th postoperative day (45). Survival of flaps delayed for 1-3 days did not differ from standard arterial flaps.

Fluorescein administered 5 hours postoperatively predicted a survival of 10.68 $\pm$ .94cm whereas actual survival on the 7th postoperative day was 12.62 $\pm$ 1.24cm. This difference was statistically significant at $p < .01$. Temperature readings revealed flap temperatures to be below control, the fluorescent flap being 2.06 $\pm$ .5 C cooler than control and the nonfluorescent flap 3.76 $\pm$ .4 C cooler than control. Capillary gas analysis showed a mean pH for the control, viable and nonviable flaps to be 7.3, 7.2 and 6.9 respectively. Transcutaneous pO2 readings from flaps with arterial or venous failure showed accurate trends

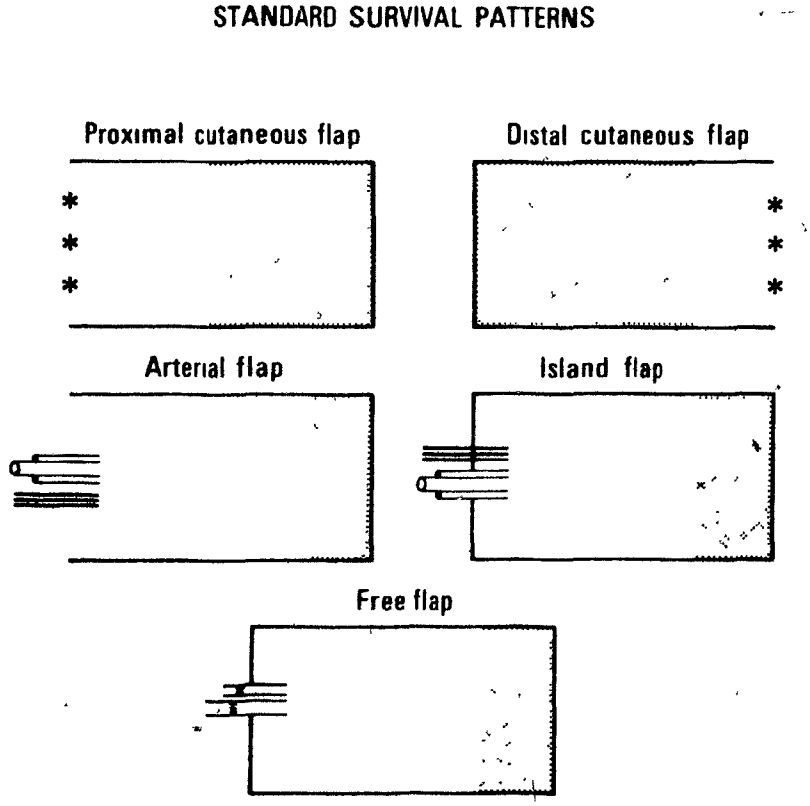

Fig. 1-4 Standard survival patterns.

Table 1-I

Flap	N	Mean Survival (cm)	Standard Deviation	Range
Arterial	7	13.3	1.56	11.4-15.6
Proximal Cutaneous	7	8.3	1.5	6.4-10.3
Distal Cutaneous	6	4.6	1.9	3.0-7.2
Island	5	13.2	2.4	11.5-17.5
Free	5	13.5	2.9	10.5-17.5

but inaccurate p02 values.

DISCUSSION

As previously reported (52, 141, 168), we found arterial flaps to survive longer than random cutaneous flaps. Also, the proximally based random flaps survived to a greater length than the distally based random flaps. This difference may be attributed to regional variation in patterns of musculocutaneous arteries. arteries.

The observation that denervated free flaps survive to the same length as innervated island flaps indicates that in the acute flaps, sensory innervation plays no significant role in determining flap viability.

The benefits of delay occured by the fourth postoperative day, confirming the studies of Myers and Cherry (154). Previous studies (61, 165) have shown that sympathetic denervation in skin flaps is profound by 48 hours and complete by 96 hours. It is our opinion that the relationship between the loss of cutaneous catecholamines from adrenergic terminals and the onset of the benefits of delay is important.

The discrepancy between fluorescein predicted and observed suvival is not surprising. Studies documenting

flow changes in acutely elevated flaps (158, 167) show that flow does increase with time. If the critical ischemia time of skin is 12 hours (142), then any spontaneous increase in flow up to that time will cause an increase in flap survival. Skin surface temperature varies directly with the cutaneous blood flow through shunts. Lower temperatures in skin flaps may represent a decrease in cutaneous blood flow, especially shunted blood flow. The low pH in nonviable flaps is a reflection of anaerobic metabolism in inadequately oxygenated tissue. Results with the transcutaneous oxygen monitor are only preliminary, but show promise.

Skin flap research currently falls into two major categories, 1) studies of the macrocirculation and its role in skin flap design, and 2) studies of the microcirculation and its role in skin flap survival. During the past decade tremendous emphasis has been placed on the design of skin flaps as related to their vascular supply (8, 51, 136). New classifications of skin flaps have evolved based on either blood supply or method of movement (45). Unfortunately this broad variability in clinical flap design cannot be duplicated in most experimental models. The pig, however is an excellent experimental animal for studying the relationship between vascular supply and survival patterns because it is fixed skin and has both

musculocutaneous and direct cutaneous arteries.

Physiologically, the regulation of the microcirculation is at the arteriolar level or beyond. Differences in regulating mechanisms between loose and fixed skin animals have not been defined in the literature. To study microcirculatory changes it is unclear which species is more appropriate and research using either type of animal may be acceptable.

There still remain, however, drawbacks to each of the loose skinned animals. Under most research protocols, rats are too small to have experimental and control flaps elevated on the same animal. Survival lengths from one animal to another in both rats (69) and rabbits (151) are highly variable. Thus, groups of animals are used and must be large enough to ensure statistical significance. In rats there is a high rate of autocannabilization of flaps. Dogs and rabbits offer an improvement over rats in that contralateral control flaps can be created. When using dogs, their dark skin does not allow for the subjective observations of color which may be important when monitoring flaps for viability. Dogs offer no economic advantages over pigs although for long term studies (eg. greater than 4 weeks), they offer the advantage of not growing to unmanageable sizes.

There are multiple flap models available in the

pig. In the original work of Kernahan (104) dorsally-based random cutaneous skin flaps were located over the rib cage of pigs. Milton (141) extended this work and devised a standard flap, either arterial or island, based ventrally 4 cm from the nipple line. Prior to the development of our buttock flap, a comparable flap over the flank was used with the same supplying blood vessels (77). The flap was originally extended in a cephalad direction from the vascular pedicle rather than a caudal direction. A portion of panniculus carnosus was included in the former flap and for this reason the buttock flap, without panniculus carnosus, was more acceptable. Skin flaps based on the inferior epigastric vessels have also been employed (172). Myocutaneous flaps have been designed to include the rectus muscle (16, 52), the gracilis muscle (70), the intercostal muscle (46), or the lattissimus dorsi muscle (87).

In conclusion, we have found the pig and its buttock flap very versatile.

Advantages of Pig Flap Research

1) Accurate replication of the vascular supply of the skin in man.
2) Large surface area allowing multiple flaps with inclusion of controls.

3) Multiple flap configurations available : random, arterial, island, free, myocutaneous.
4) Skin color allows subjective observations similar to those used clinically.

Disadvantages of Pig Flap Research

1) Cost as compared to rats (but comparable to dogs).
2) Rapid weight gain therefore limiting the use of pigs in experiments designed to last more than a few weeks.

Advantages of Buttock Flap

1) Consistent survival lengths.
2) Reliable anatomy.
3) Multiple vascular configuration available.
4) Easily visible area of body to make postop observations.
5) Free flaps located here are technically easier than those flaps located over the thorax or abdomen which move with each respiration.
6) Virtually no disadvantages.

SUMMARY

An experimental pig flap model is presented with detailed operative technique. Studies employing this model are reported showing that differences in survival patterns depend on vascular configuration. Innervated island flaps were found to survive to the same length as denervated free flaps and the onset of the benefits of the delay procedure occurred by the 4th postoperative day. The advantages of the pig and the pig buttock flap are discussed in detail.

EXPERIMENT 2:

CRITICAL ISCHEMIA TIME

AND THE

FAILING SKIN FLAP

INTRODUCTION

Ischemia may be defined as a condition of inadequate blood supply to an area of tissue(208). The degree and duration of the ischemic insult will determine the extent of tissue damage. The critical ischemia time refers to the maximum duration of the ischemic insult which tissue can withstand and subsequently remain viable. If we are to salvage the failing distal end of a skin flap, it is important to determine its critical ischemia time. If we have this knowledge it will allow appropiate initiation of treatment and possible salvage of the failing skin flap.

It has been demonstrated experimentally that island flaps in the pig(142) and free flaps in the rabbit(121) can withstand 8 hours of normothermic ischemia induced by clamping or cutting their vascular supply. Yet one cannot equate this type of complete flap ischemia, as characterized by the above studies, with the failing distal portion of a skin flap. In contrast to the former's complete circulatory arrest, the distal flap may have a marginal capillary circulation or even an extensive arteriovenous shunt circulation(174). The present study is designed to determine if there is a significant difference in the critical ischemia time for the island flap with its vascular pedicle clamped versus

the failing distal end of a random flap.

METHODS AND MATERIALS

White Poland-China pigs (21±3Kg) were sedated, anesthetized and intubated. Anesthesia was maintained throughout the experiment by spontaneous inhalation of a mixture of oxygen, nitrous oxide and halothane. In 14 animals, bilateral longitudinal incisions were made 4 cm lateral to the nipple line. Numerous direct cutaneous arteries were identified and subsequently used to create island flaps(52, 140). Two experimental groups were studied (Fig. 2-1).

TOTAL ISCHEMIA OF ISLAND FLAPS.

In 8 pigs, ventrally based flaps (12 X 4 cm) were created on each of the available segmental vessels resulting in a total of 77 flaps. After all flaps were elevated, Acland microvascular clamps (A3) were applied to each vascular pedicle and the flaps sutured back in place. A vital dye (fluorescein or alphazurine blue) was administered to verify complete occlusion of the pedicle. At time intervals varying from 0-16 hours postoperatively (times being randomly assigned to flaps) the vascular clamps were removed. Following removal of

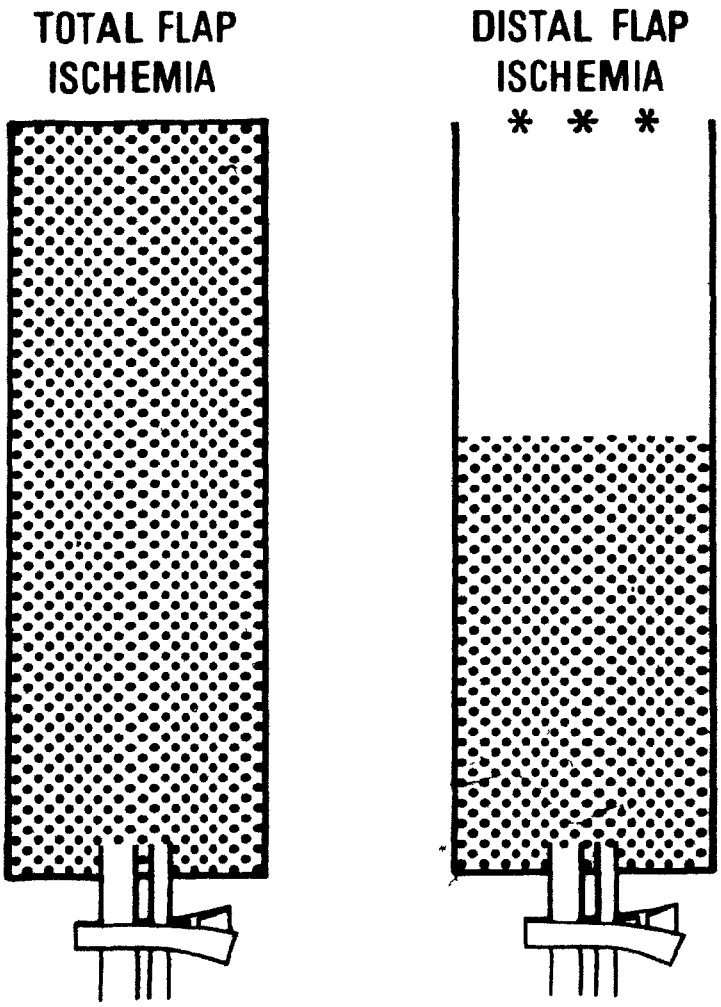

Fig. 2-1 Schematic flap designs. Shaded area is ischemic.

the last clamp, a second vital dye was injected to detect the presence or absence of blood flow. One week postoperatively, survival or necrosis of the flap was noted and recorded.

DISTAL ISCHEMIA OF A RANDOM FLAP.

In an additional 6 animals, 12 X 4 cm bipedicle flaps were elevated. Pilot studies indicated that these flaps would survive completely as a bipedicle with a dorsal random end and a ventral island attachment. In essence, these flaps were similar to the previous group except that the distal end was not severed. A total of 57 bipedicle flaps were constructed. Vascular clamps were applied to all island pedicles and a vital dye injected intravenously to assure perfusion from the random pedicle and occlusion of the island pedicle. Therefore, the flap received its blood supply solely from musculocutaneous arteries in its random base. Clamps were removed from the island pedicle between 0 and 16 hours postoperatively. Restoration of blood flow via the direct cutaneous arteries of the island pedicle was confirmed by a second dye injection. Survival or necrosis of the distal (island portion) flap was assessed one week postoperatively.

The method of probit analysis was utilized to derive the equation of the relationship between ischemia

time and the probability of necrosis.

RESULTS

In both groups, several patterns of necrosis were observed: 1) accidental severance of the island vascular pedicle, 2) traumatic injury of the island vascular pedicle by the microclamp or dessication, 3) infection in the late postoperative period, and 4) no reflow. In the total flap ischemia group there were 2 accidental losses, 10 traumatic losses and 2 late losses from infection. These flaps were excluded from the study leaving 63 flaps for analysis of which 21 died and 42 survived. In the distal flap ischemia group there were 3 accidental losses leaving 54 flaps of which 23 died and 33 survived.

The observed necrosis rates at the time intervals tested and the probit derived curves are shown (Fig. 2-2 & 2-3). The tolerance to ischemia was highly variable from one animal to another. In some animals, necrosis occured after 8 hours of ischemia, whereas in others there was survival after 16 hours. It can be predicted from the probit analysis that 50% of totally ischemic flaps will die after 13.05 hours, 10% after 7.5 hours and 1% after 3 hours. For the distally ischemic flaps,

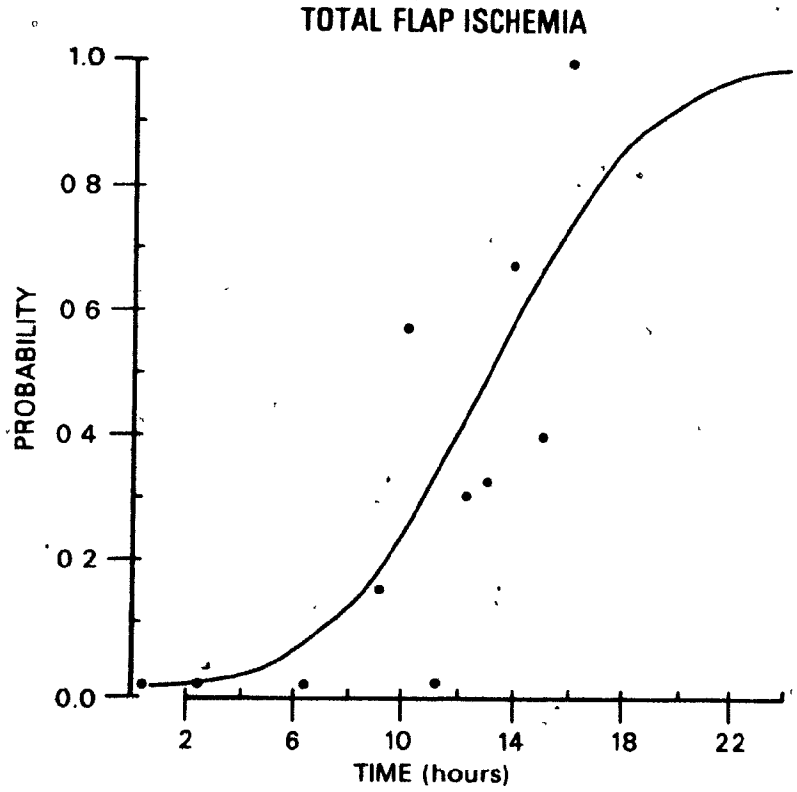

Fig. 2-2 Critical ischemia time of island flaps. Dot equals observed necrosis rates. Line equals probit derived curve.

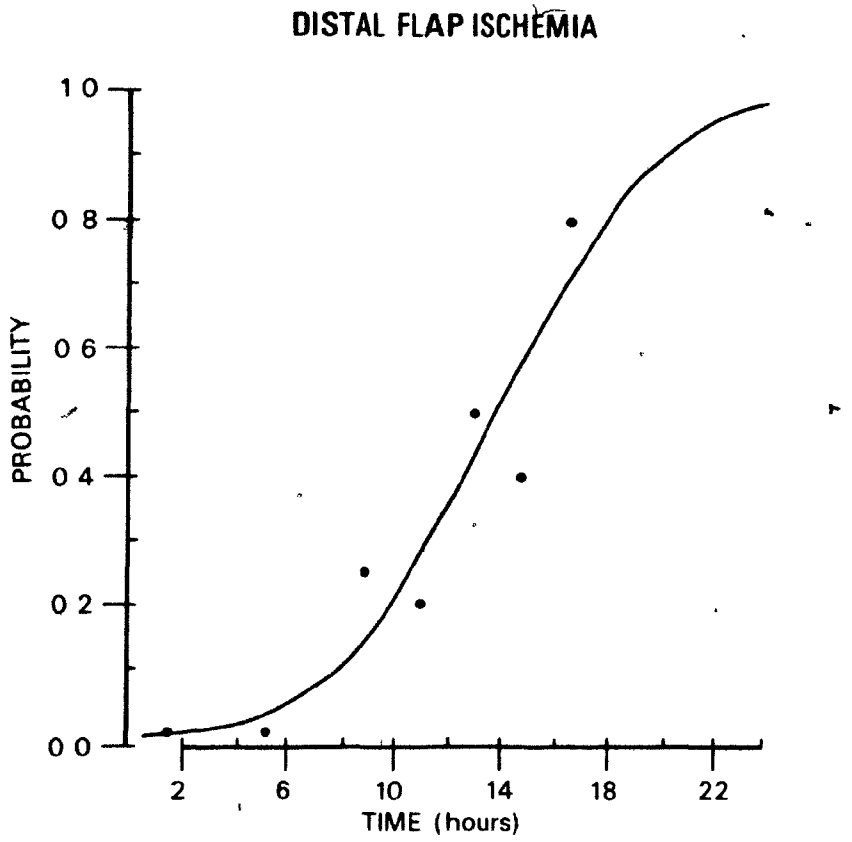

Fig. 2-3 Critical ischemia time of distal flap. Dot equals observed necrosis rates. Line equals probit derived curve.

50% will die after 13.14 hours of ischemia, 10% after 7.0 hours and 1% after 2 hours. There is no significant difference between these two groups.

DISCUSSION

In pigs, both island flaps and the failing end of a random flap tolerated the same duration of ischemia despite their striking difference in histological appearance. From pilot studies, we found that the dermal vessels of an ischemic island flap appear normal whereas those in the failing portion of a random flap are dramatically altered. The capillaries, venules and arterioles are distended and filled with red blood cells. There is partial degradation of the endothelial lining with lysis of many cytoplasmic structures. This observed difference is not reflected in a change of the critical ischemia time. The average ischemia time (50% necrosis, 50% survival) tolerated by pig skin flaps was 13 hours and the projected safe ischemia time (10% necrosis, 90% survival) was 7 hours.

Inadequate blood supply to an area of tissue produces harmful effects because of hypoxia and failure to remove waste products. Pathophysiologically, the metabolic rate of the tissue being studied and the time

duration of the ischemic insult will determine the extent of damage produced. Ischemia may have several influences, ranging in severity from no effect, to physiological disturbances which may include cellular degeneration with replacement fibrosis or even to frank necrosis(208). When cell damage occurs, a characteristic inflammatory response is elicited. This results in vasodilation, increased capillary permeability, increased blood viscosity, stasis, leukocyte adherence and endothelial cell swelling. If severe enough, this can perpetuate and magnify the original ischemic insult. When the ischemic damage results in obstruction to bood reflow in the tissues the no- reflow phenomenon is observed. The critical ischemia time is the duration of ischemia necessary to elicit irreversible no- reflow.

Under normothermic conditions, experimental studies have shown that rat skin is able to tolerate 6(213) to 9(183) hours of ischemia, rabbit free skin flaps more than 8 hours of ischemia (121) and pig island flaps between 8 and 13 hours of ischemia (142). Clinical experience has shown that free skin flaps and amputated digits are able to tolerate 6-8 hours of normothermic ischemia (122).

Under hypothermic conditions, cellular metabolism is decreased and the critical ischemia time of tissues

can be prolonged. At 3-4 degrees centigrade, skin grafts can tolerate up to 3 weeks of complete ischemia (23). Storage of experimental rat free skin flaps (10) at 4 degrees centigrade has prolonged their critical ischemia time from 8 hours to greater than 72 hours. Similarly, rabbit free skin flaps stored at 6-7 degrees centigrade can tolerate up to 3.8 days of complete ischemia (57). Clinically there are reported cases of viable human free flaps after 30 hours of hypothermic ischemia (6) and human digits after 28 hours (119) and 36 hours (113).

How does understanding the effects of ischemia assist us in our clinical goal of salvaging the failing flap? It defines for us three theoretical approaches. First, the presence of no re-flow and the critical ischemia time limit the number of hours postoperatively to successfully treat the failing flap. By decreasing metabolism to prolong this time (as with hypothermia), the skin flap can further benefit from spontaneous or drug induced increases in blood flow. Secondly, both ischemia and surgical trauma stimulate an inflammatory reaction which in the case of skin flaps appears to be detrimental to blood flow. The use of anti-inflammatory agents (133, 134) may decrease the damage induced and increase flap survival. Thirdly, if ischemia is what causes skin flap necrosis, then increasing flow by

pharmacologic means, before no-reflow is reached, will minimize the ultimate area of necrosis.

Further experimental studies will facilitate the postoperative management of clinical cases. The normothermic and hypothermic critical ischemia times of myocutaneous flaps should be defined. Milton's observation that delayed skin flaps could only tolerate 4 hours of ischemia (in contrast to acute flaps tolerating 8 hours) may be of relevance to free skin flaps subjected to early or late postoperative thrombosis. Delayed flaps and free flaps both suffer an initial ischemic insult at the time of flap elevation. This insult may deplete many-of the cellular metabolic stores. With a subsequent second ischemic episode, the flap may be less able to tolerate the ischemic insult. We are currently studying the critical ischemia time of this secondary insult in pig skin flaps. Clinically, it is important to know how long a secondary ischemic period a free flap can withstand. By increasing our understanding and awareness of the characteristics of critical ischemia time for different flaps under different conditions, perioperative patient management will be optimized. Results of the present study lead us to conclude that guidelines previously defined for management of the ischemic free flap can be used for the ischemic distal portion of a random flap.

SUMMARY

An experimental pig model has been used to measure the critical ischemia time for total flap ischemia versus the more common distal flap ischemia. Both flaps were found to tolerate an average 13 hours of ischemia. The importance of critical ischemia time to skin flap pathophysiology is discussed.

EXPERIMENT 3:

MONITORING ACUTE

SKIN FLAP FAILURE

INTRODUCTION

If failing free flaps are to be salvaged by reoperation and failing conventional flaps resurrected by pharmacologic intervention then a reliable method of detecting impending flap failure must be devised. The ideal technique for evaluating flap circulation should have the following characteristics: 1) accuracy, 2) repeatability, 3) applicability to all types of flaps, 4) simplicity, 5) low cost, as well as being quick and noninvasive. The usefulness of subjective methods (color, capillary blanching and refill, dermal bleeding, healing and hair growth) increases with the experience of the user, but is of limited value to the inexperienced. Objective methods (temperature, vital dyes, photoelectric tests, metabolic tests, cutaneous clearance tests) are employed less frequently. With the exception of fluorescein and temperature, objective methods tend to be expensive without convincing evidence of their efficacy.

For years, capillary blood samples collected from heel stab wounds in premature infants have been analyzed for their pH and gas content. The results thus obtained are used to monitor the infants and to effectively adjust therapeutic measures. Most hospital settings have preexisting facilities for carrying out such

analyses. In the present study, blood samples are collected from the site of a dermal bleeding test in experimental pig flaps. The blood is analyzed for hematocrit, pH and gases and the results are compared to the conventional standards of fluorescein and surface temperature. If this technique is valuable for monitoring a premature infant, then why not a skin flap?

METHODS AND MATERIALS

White Poland China pigs (15-30Kg) were sedated with acepromazine. Anesthesia was induced with intravenous pentobarbital and maintained via endotracheal intubation with spontaneous inhalation of a mixture of oxygen, nitrous oxide and halothane. The animal's rectal and room temperature were monitored for the duration of the experiment. Island buttock flaps (see Experiment 1) were designed on all animals, surgically constructed, and sutured back in their bed.

EXPERIMENTAL GROUPS

Viable Flaps. In 3 animals 6 10x10cm buttock flaps were created to have 100% viability. Monitoring was carried out at an unoperated control site cephalad to the anterior superior iliac spine and at one flap site (Fig. 3-1). Observations were made at 1/2, 2, 6 and 10 hours postoperatively.

Vascular Failure. In 5 animals, 6 10x10cm totally viable flaps were designed and elevated. One hour later either the draining veins (3 flaps) or supplying artery (3 flaps) were ligated. One flap site and one control site were monitored 2, 6 and 9 hours postoperatively in venous failures and 1, 3 and 7 hours in arterial failures.

Distal Flap Necrosis. In 6 animals, 8 18x10cm flaps were designed to insure distal flap necrosis. Fluorescein demarcation indicated which portion of the flap was at risk of necrosis. A control site and 3 flap sites (proximal fluorescent portion (A), borderline fluorescent nonfluorescent portion(B), and distal nonfluorescent portion (C)) were monitored 1, 5 and 9 hours postoperatively (Fig. 3-2).

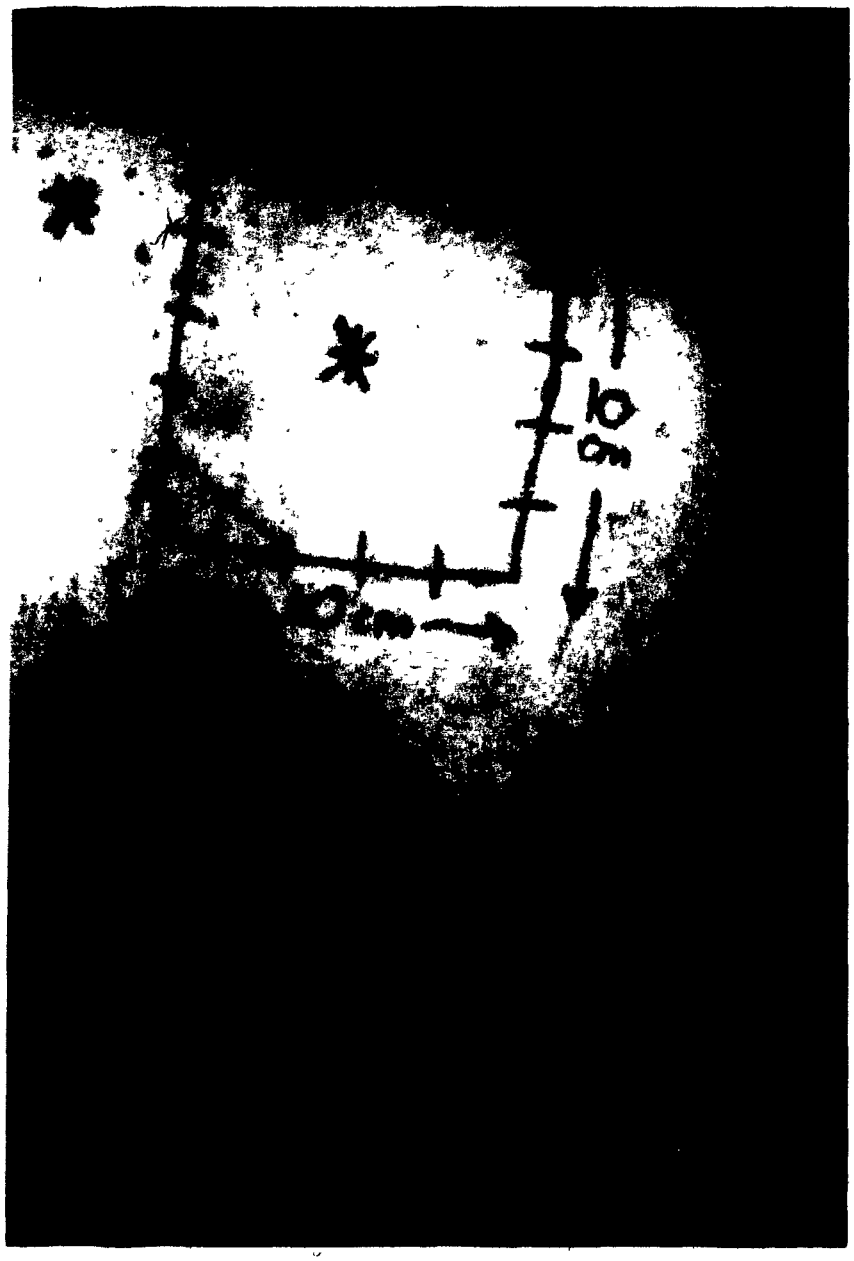

Fig. 3-1 Viable 10x10cm flap with * denoting monitoring sites.

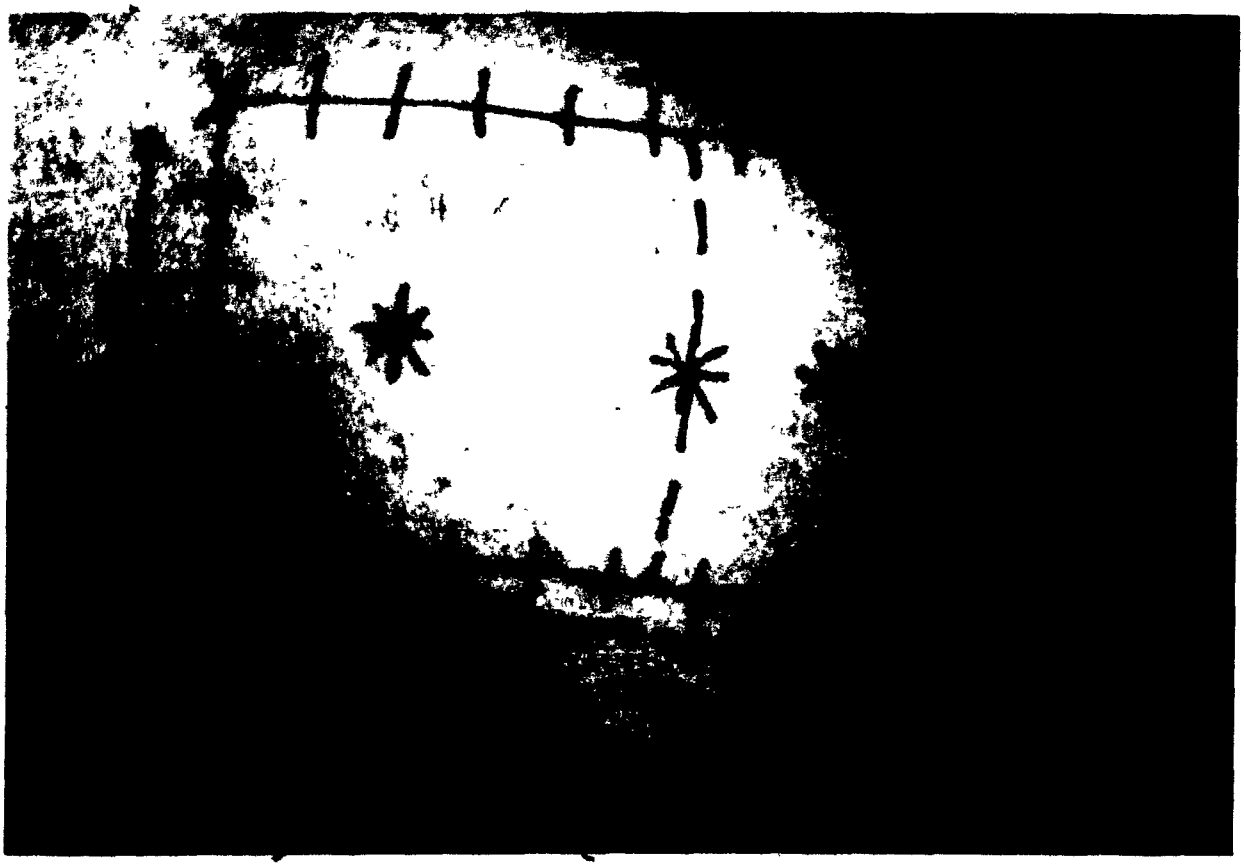

Fig. 3-2 18x10cm flap with * denoting monitoring sites. Dotted line represents average fluorescein penetration.

MONITORING TECHNIQUES

All flap sites and control sites were assessed at various time intervals after flap construction by subjective and objective techniques. Subjective observations of color, capillary blanching, and bleeding from stab wounds were made. Three objective measures were used. Fluorescein staining was obtained by administration of 500mg of fluorescein (10% solution) intravenously to all animals 1 hour after flap construction and again 8 hours later. Dye penetration along the flap was recorded and compared to ultimate survival. Temperature readings were obtained with a surface thermistor probe (YSI No.708) with readout on a digital (Digitec No.5800) display unit. Temperatures are reported as mean differences plus or minus a standard deviation from control values taken at the same time. Stab wound blood analysis was made by using a No.11 scalpel blade to create wounds in flaps and control sites. If bleeding was present, the blood was collected in heparinized capillary tubes (40ul or 150ul). Hematocrit was measured by standard centrifugation for 5 min and pO2, pCO2, pH were measured in a Corning 175 blood gas analyzer on microsample mode. Results are reported as mean differences plus or minus a standard deviation from control values taken at the same time.

RESULTS

Animals had a mean rectal temperature of 36.7±1 degrees celsius throughout the experiment and room temperature averaged 22.6± .4 degrees celsius.

Viable Flaps. In 10x10cm viable flaps, subjective assessment showed all flaps to be of similar color to the surrounding skin. Blanching was not as easily visible as in humans but could be elicited. There was active bleeding from all stab wounds. This blood was usually bright red but on occasion appeared dark red as if a vein had been pierced. Objective assessment with fluorescein at 1 hour showed the distal dorsal corner of the flap, an area of approximately 3 cm2, to be nonfluorescent. At 8 hours, readministration of fluorescein demonstrated fluorescence of the whole flap. All flaps survived completely. Temperature readings (Table 3-I) from the flap were 1.24 degrees celsius cooler than at the control site. This difference was present 1/2 hour after flap elevation and did not change significantly in the 10 hours the flaps were monitored. Hematocrit readings from both the flaps and control sites were consistently 35%. Blood gas analysis from control sites showed a mean pH of 7.4, pCO2 51 and pO2 230. The high dermal pO2 is consistent with the

TABLE 3-I

10 x 10 cm Flaps

	Viable Flap	Venous Failure	Arterial Failure
Temp- (°C)			
Control	35.1 ± .7	34.3 ± 1.8	34.6 ± 1.1
Δctrl 2	-1.2 ± .3	-2.4 ± 1.2	-1.7 ± .6
6	-1.2 ± .7	-2.7 ± 1.8	-2.2 ± .9
10	-1.4 ± .9	-2.7 ± 1.1	-3.0 ± 1.3
Hct-			
Control	35%	36.5%	
flap	35%	42 %	
pH			
Control	7.40 ± .03	7.30 ± .04	
Δctrl 2	-.02 ± .15	-.24 ± .07	
6	.05 ± .04	-.34 ± .07	
10	.16 ± .27	-.40 ± .05	
pCO2 (mm Hg)			
Control	51.86 ± 4.1	52.3 ± 10.8	
Δctrl 2	2.17 ± 7.2	32.7 ± 12.9	
6	4.57 ± 5.7	38.2 ± 22.1	
10	6.48 ± 12	64.0 ± 7.7	
pO2 (mm Hg)			
Control	230.45 ± 29.3	195.5 ± 35.3	
Δctrl 2	-72.96 ± 60.7	-161.2 ± 29.5	
6	-152.37 ± 53.4	-132.2 ± 18	
10	-112.62 ± 82.9	-184.7 ± 34.8	

arterial blood pO2 and is secondary to the high oxygen flow rates used for inhalation anesthesia. The flap sites had a pH 0.05 units lower than control, a pCO2 3.2 mmHg higher than control and a pO2 119.4 mmHg lower than control.

Vascular Failure. In 10x10cm flaps subjected to venous failure, cyanosis rapidly developed with brisk capillary refill on blanching. Bleeding from stab wounds was profuse, initially of dark red blood and then of bright red blood. After wounding, the area of flap around this site became transiently less cyanotic in color. Following fluorescein administration, all flaps fluoresced but in a splotchy pattern. All flaps underwent necrosis. Temperature readings of the flap were on the average 2.6 degrees celsius cooler than control sites. This difference, when compared to that of the 10x10cm viable flaps is statistically significant ($p<.05$). Stab wound blood was easily obtained. Mean flap hematocrit was 42% compared to a control of 36.5%. Blood gas analysis showed increasing deviation from control with time. At 2 hours pH was 0.24 units less than control, pCO2 was 32 mmHg greater than control and pO2 was 161 mmHg lower than control. By 9 hours, pH was 0.4 units less than control, pCO2 64 mmHg greater and pO2 184 mmHg less.

In the 10x10cm flaps subjected to arterial ligation, all flaps appeared paler than the surrounding tissue and capillary blanching could not be detected. Stab wounds did not bleed actively or enough to allow blood collection for analysis. The flaps did not fluoresce and all died. Temperature readings in the flap were 2.4 degrees celsius cooler than control sites and this did not change significantly during the 7 hour observation period.

Distal Flap Necrosis. In 18x10cm flaps with impending distal flap necrosis, cyanosis of the distal portion gradually developed and increased with time. Capillary blanching could be elicited in all parts of the flap. Stab wounds in the proximal flap bled easily while those in the distal flap sometimes bled briskly and at other times bled sluggishly. Fluorescein penetration at 2 hours averaged 9.4$\pm$ 1.3cm, at 8 hours 11.3$\pm$ 2cm, and survival at 7 days was 13.4$\pm$ 1.1cm. The transitional zone of partial fluorescence between proximal and distal flap was more sharply demarcated at 8 hours than at 2 hours. Temperature readings (Table 3-II) obtained from proximal, transitional and distal flap were respectively 1.25, 2.42 and 3.11 degrees celsius cooler than control. Stab wound blood analysis showed a control hematocrit of 35.5%, a proximal flap

TABLE 3-II

18 x 10 cm Flaps

		Proximal Flap	Transitional Zone	Distal Flap
Temp- (°C)				
Control		33.6 ± 1.1		
Δ Ctrl	1	-1.48 ± .9	-2.42 ± .67	-2.84 ± .3
	5	-1.02 ± .6	-2.26 ± .65	-3.12 ± .4
	9	-1.24 ± .6	-2.58 ± .94	-3.38 ± .8
Hct				
Control		35.5%	35.5%	35.5%
Flap	1	34.2 ± .9	39.5 ± 5.4	49.5 ± 2.4
	5	35.5 ± 1.3	39.5 ± 2.4	53.5 ± 1.7
	9	36.0 ± 1.4	38.0 ± 2.7	58.2 ± 3.9
pH				
Control		7.32 ± .1		
Δ Ctrl	1	-.02 ± .02		-.46 ± .01
	5	-.02 ± .02		-.52 ± .06
	9	-.003 ± .01		-.44 ± .03
pCO2 (mm Hg)				
Control		51.5 ± 14.6		
Δ Ctrl	1	+3.3 ± 3.5		+46.7 ± 10.3
	5	+4 ± 4		+53.6 ± 2.1
	9	0 ± 5.3		+43.1 ± 18.2
pO2 (mm Hg)				
Control		161.9 ± 11.1		
Δ Ctrl	1	-8.3 ± 79		-144.5 ± 25.2
	5	-24.7 ± 40.7		-146.9 ± 12.8
	9	-25.3 ± 50.1		-136.7 ± 18.7

hematocrit of 35.3%, a transitional zone hematocrit of 39% and a distal flap hematocrit of 53.8%. The latter two hematocrits were significantly greater than control and significantly different from each other ($p<.03$). Blood gas analysis showed animals to have a mean pH of 7.3, pCO2 of 51 mmHg and pO2 of 162 mmHg. In the proximal fluorescent portion of the flap, pH was 0.02 below control, pCO2 3 mmHg above control and pO2 20 mmHg below control. In the distal nonfluorescent portion of the flap, the pH was 0.49 units below control, pCO2 47.8 mmHg above control and pO2 142.7 mmHg below control. These changes were apparent as early as 1 hour and did not change significantly when measured at 5 and 9 hours.

DISCUSSION

It has previously been documented that skin flap failure is a significant clinical problem (54, 74, 110, 198) Two types of flap failure occur clinically for which different kinds of monitoring may be beneficial. Free tissue transfers suffer predominantly an all or none vascular compromise. Monitors that assess one flap site will give an accurate reflection of total flap viability. Free skin flaps can be monitored externally whereas other types of free tissue transfers (bone,

dermis and bowel) require more sophisticated monitoring devices for the supplying vessels (flow probes (11, 144), temperature probes (115), doppler (9)). In direct contrast, conventional skin flaps are usually jeopardized only in their distal portion. Thus sampling from one site will often be an innacurate index of flap viability.

Monitors may be intermittent or continuous and they can assess only one site or the total flap. As flaps are persistently in a dynamic flow state, continuous objective monitoring is more accurate than intermittent assessment, although most continuous monitors tend to be cumbersome and expensive (tcpO2 (2), photoplethysmographs (36)). When intermittent monitoring is utilized, it is often begun only after subjective signs cause the physician to be suspicious of vascular compromise. Fluorescein and thermography are the only techniques that act as total flap monitors. Since they assess the whole flap, they are not subject to sampling error.

With current techniques, free skin flaps are best monitored at one site by continuous means and conventional flaps assessed by vital dyes on an intermittent basis. The experimental investigation of new monitoring methods is worthwhile because of the potential clinical benefits and the improved

understanding of skin flap pathophysiology that is often obtained.

SUBJECTIVE TESTS

Skin color is dependent on the state of blood flow, dilatation of cutaneous capillaries, oxygen content of the blood, and natural skin pigmentation. In dark skinned individuals and certain experimental animals (eg. dogs), color cannot be used as a guide to flap vascularity. For the experienced surgeon, subtle changes in color remain the earliest method of recognizing a threatened flap (49). Despite attempts to simplify the accurate observation of color (3) it remains an unreliable test for inexperienced eyes. In pig flaps with complete vascular failure, color changes were immediate and striking. In flaps with distal failure, color changes evolve with time and only became obvious 4-6 hours postoperatively. Capillary refill and blanching is a very imprecise index as documented by its presence in the nonfluorescent portion of the pig flaps. Stab wound bleeding occurs from subpapillary and deep dermal vascular plexi. The spontaneity and color of the blood are helpful in assessing free flaps, but can be misleading in evaluation of the failing distal portion of conventional flaps. Subjective monitoring has long been used as the sole guide for postoperative patient

management.

OBJECTIVE TESTS

Fluorescein is currently the most widely used and accepted agent for predicting the survival-necrosis interface of a skin flap (128, 147). Fluorescein has a plasma half life of approximately 20 minutes and tissue fluorescence is maximal by 15-20 minutes after dye administration (38). Clearance of fluorescein from the tissue takes up to 12 hours and therefore limits the repeatablility of this test. However, the usefulness of fluorescein has been increased by the development of a fiberoptic dermofluorometer (187) which allows objective quantitation of tissue fluorescence. A new photographic technique has also been devised (149) that may improve the objectivity of fluorescein evaluation. The major limitation of fluorescein is that it only tests vascularity at one point in time. Subsequent changes in flow, detrimental or beneficial, go undetected. The major advantage of fluorescein is that it is the only available technique for simultaneously assessing the whole flap. It is therefore not subject to sampling error. The results of our pig studies are in accordance with previous rat studies (180) in that fluorescence at 8 hours post flap construction is a better predictor of flap survival than is fluorescence at 2 hours. This

observation is most likely a reflection of spontaneous increases in flap blood flow during the early postoperative period.

Temperature readings are a gross reflection of the state of the microcirculation. Since skin surface temperature is variable, it is beneficial to use a control site for reference. Viable flaps are cooler than control sites and nonviable flap sites are cooler than both the viable and control sites. This temperature difference obviously corresponds to a decrease in blood flow to the skin flap. However, it remains too variable an index, when employed on an intermittent basis, to state precisely what magnitude of temperature change will be representative of a jeopardized flap. Continuous monitoring of temperature as used in digital replants (196) and around microvascular anastomoses (115) provides more meaningful information.

Monitoring flap hematocrit proved to be a suprisingly useful technique. As a predictor of impending flap failure, it was more accurate and reliable than temperature readings. The elevated hematocrits found in jeopardized flaps is a reflection of pathophysiologic events. An ischemic insult leads to cellular injury, especially endothelial cell damage, which causes increased capillary permeability.

Subsequent to plasmatic leakage, there is hemoconcentration within the vascular bed which, in itself, is detrimental to blood flow. The increased blood viscosity creates an increase in functional, peripheral vascular resistance which jeopardizes blood flow.

Metabolic tests measure flap circulation at its most critical level, ie. cellular perfusion. With reduced blood supply, oxygen concentration decreases. This results in anaerobic metabolism and increased local acidity as the tissues' buffering capacity is depleted. Both tissue pH and tissue gas levels have been studied experimentally with positive correlation to flap viability (31, 75, 156, 214) However, these previous methods had significant drawbacks as they required traumatic insertion of catheters into the flap and expensive, tempermental equipment for analysis. In contrast, capillary blood analysis, a technique routinely performed on premature infants, is simple, inexpensive and has not previously been applied for study on skin flaps. Our results in pig flaps have shown that pH values can be reliably used to predict flap jeopardy. The pCO2 and pO2 values are highly variable and thus an inferior index when compared to pH.

SUMMARY

Reliable and repeatable means for objective postoperative monitoring of skin flaps is a necessity. If a failing free flap can be recognized early, it can be salvaged by revision of the appropriate anastomoses. For the threatened distal portion of a conventional flap, external factors, such as kinking or hematoma, may be corrected or drug therapy instituted. We have analyzed blood from stab wounds in experimental pig flaps for pO2, pCO2, pH and hematocrit. The results were compared to fluorescein penetration and flap surface temperature. Hematocrit readings of threatened flaps (54%) were elevated above control (35%). The pH readings in the jeopardized flaps were 0.4 units below control. These two measures proved to be more reliable than intermittent temperature readings. In contrast to the fluorescein test, which can only be used once, stab wound analysis is repeatable at any time in the postoperative period and can be effectively used to follow dynamic changes within a skin flap.

EXPERIMENT 4:

SKIN FLAP

FAILURE

INTRODUCTION

Skin flaps are utilized to provide essential skin coverage, therefore survival is their most fundamental requirement. Despite careful flap design, full thickness necrosis of skin flaps occurs and may lead to catastrophic complications. To avoid this problem, a clearer understanding of the physiological changes which occur in normal skin, following its conversion into a skin flap, is necessary. Of particular concern are the effects on the microcirculation which, in itself, determines ultimate flap viability.

With an understanding of both the etiology and pathophysiology of skin flap failure, it may be possible to salvage the failing flap with pharmacologic agents. The present study has evaluated experimental pig flaps in an effort to clarify the pathophysiology of skin flap failure. Temperature patterns, red blood cell distribution and skin blood flow have been measured in acutely elevated flaps.

CLINICAL SKIN FLAP FAILURES

Skin flap failure is due to either extrinsic or intrinsic causes. Extrinsic causes include systemic

factors (infection, arteriosclerosis, hypotension, malnutrition) and local factors (compression, tension, thrombosis or kinking of a pedicle). Several of these extrinsic causes can be minimized by careful perioperative managment. In contrast to the plurality of extrinsic factors, the only intrinsic cause is inadequate nutrient blood flow within the skin flap. This reduction in normal cutaneous blood flow is probably secondary to surgical incisions. Reviews of clinical skin flaps have shown infection and intrinsic factors to be the leading causes of flap failure (54). Conventional skin flaps suffer from distal necrosis due to inadequate vascularity whereas free flaps usually undergo total necrosis following thrombosis of their vascular pedicle. The former is an intrinsic microcirculatory failure while the latter is an extrinsic macrocirculatory failure. Myocutaneous flaps also undergo necrosis although an assessment of their etiology has not been reviewed in the literature.

Total necrosis of a failed free flap is usually due to thrombosis of an arterial or venous anastomoses, with partial distal necrosis being a rare event. Revision of the appropriate anastomosis allows salvage of the failing free flap in a high pecentage of cases (47). In direct contrast, the pattern of partial flap failure, as seen in conventional skin flaps, is much more complex.

The precise pathophysiological events occurring in the distal dying portion is poorly understood and currently, we have no reliable means of reversing the situation. It is unclear from previous experimental studies whether the inadequate nutrient flow is secondary to poor venous drainage, arterial insufficiency or shunting of blood through arteriovenous anastomoses. The present report investigates the pattern of conventional flap failure.

PREVIOUS EXPERIMENTAL WORK

To date, there have not been any major experimental studies directly addressing the pathophysiology of conventional skin flap failure. Past research has been directed towards an understanding of the delay phenomenon. However, with improved flap design and the development of microsurgical techniques in the last decade, there are few clinical requirements for delayed flaps. Experimental studies have been slow at paralleling the change in clinical emphasis. As there are no previous papers dealing specifically with acute skin flap failure, a literature review must draw on related areas. Several theories as to the mechanism of the delay phenomenon have evolved. Through an analysis of these theories, the pathophysiologic events

occurring in an acutely elevated flap may be better understood.

ISCHEMIA THEORY

It was originally proposed by Brown & McDowell (23) that a delay operation conditions the skin flap to ischemia. Multiple investigators (156, 214, see Experiment 2) have documented that acutely elevated skin flaps, both delayed and undelayed, are indeed ischemic. When their tolerance to ischemia was tested, Milton (142) showed that delayed flaps are more susceptible to ischemic necrosis than acute flaps. These data do not support the ischemia theory of delay. Acutely elevated flaps are suffering an ischemic insult, but delayed flaps do not have an increased tolerance to ischemia.

SYMPATHECTOMY THEORY

The role of sympathetic denervation of the cutaneous vasculature in the delay phenomenon was first proposed by Hynes (98). He demonstrated by simple nilhydrin sweat tests that skin flaps are sympathectomized. Subsequent researchers (61, 165, 209) have shown histological loss of catecholamines in experimental flaps by 36 hours postoperatively. The relationship between the delay phenomenon and sympathectomy is still unclear. In acutely elevated

flaps a cut sympathetic nerve spontaneously discharges catecholamines. This release may have an initial vasoconstricting effect on the cutaneous blood vessels which is detrimental to flap survival.

REACTIVE HYPEREMIA THEORY

Based on histological observations of clinical tubed flaps, Braithwaite (20) proposed that the delay procedure worked because of reactive hyperemia. He observed that certain vessels of the dermal plexus became enlarged under the influence of local metabolites. He postulated that this dilatation led to an improvement in venous drainage and a decrease in the overall hemodynamic resistance of the flap. Local vasodilatation due to an accumulation of metabolites in ischemic tissue is a well accepted fact, but its role in the delay phenomenon is much less clear. It can be postulated that in an acutely elevated ischemic flap, the balance between vasodilating metabolites and vasoconstricting catecholamines will help determine the rate of blood flow through nutrient channels.

INFLAMMATION THEORY

Velander (207) proposed that the benefits of the delay procedure were from the inflammatory reaction induced by surgical trauma. He felt that if the

transfer of the flap was optimally timed, this inflammatoy state would lead to a "rapid vascular link-up over a maximal area". By injecting formic acid to cause an inflammatory reaction at the site of future flap elevation, Erikson and Robson (62) were able to increase the survival of experimental rat flaps. An acutely elevated flap suffers from two major insults, surgical trauma and ischemia, both leading to an inflammatory reaction. Whether this inflammatoy state is beneficial or detrimental to delayed or acute flaps has not been adequately defined.

ARTERIOVENOUS SHUNT THEORY

Acute flaps fail because of inadequate nutrient flow. Reinisch (174) has proposed that this state of low capillary flow occurs in the presence of a high arteriovenous shunt flow. Arteriovenous shunts, dilated because of sympathectomy, are postulated to offer the pathway of least resistance to flow thereby "stealing" from the higher resistance capillaries. With time, the shunts are thought to undergo a relative vasoconstriction and a substantial proportion of the total flow is redirected to nutrient channels. Based on indirect observations of temperature, dynamic flow studies and radioactive red blood cell distribution, Reinisch postulated that delay works because of this

redirection of flow. If this theory is correct, then attempts to mimic delay should be directed towards closing arteriovenous shunts, not at increasing arterial inflow. Subsequently, Prather (172) was unable to find temperature patterns or red blood cell distributions that supported the shunt hypothesis. Guba (80) attempted to quantitate total, nutrient and shunt flow in pig flaps using the microsphere technique. He did not find a significant decrease in absolute shunt flow in delayed flaps. Whether shunt flow does play an important role in acute skin flap failure is still unclear. Both indirect and quantitative studies need to be repeated so that the shunt theory can be rejected or accepted.

The relative importance of ischemia, inflammation and sympathectomy in skin flap failure remains undefined. The presence or absence of detrimental arteriovenous shunt flow is controversial. None of these factors have been carefully examined in the acutely elevated flap (0-12 hours). If our long term goal is to successfully salvage a failing flap, then it is imperative that its basic pathophysiologic mechanisms be more carefully defined. The primary goal of the present study is to quantitate changes of total, nutrient and shunt flow in acutely elevated flaps.

METHOD AND MATERIALS

White Poland China pigs (21±2kg) were sedated with acepromazine and anesthetized with thiopental. Anesthesia was maintained by either pentobarbital, or by intubation and spontaneous inhalation of a mixture of oxygen, nitrous oxide and halothane (.25-1%). Four flap designs were used in the experiments (Fig. 4-1). Dorsal random (DR) and ventral arterial (VA) flaps, both 18 x 4 cm were based 3cm from the dorsal midline or 4cm from the nipple line respectively. Random buttock (RB) and arterial buttock (AB) flaps, both 18 x 10 cm were designed with the anterior superior iliac spine as a key landmark (see Experiment 1). After flap construction, all animals recieved 5cc of 10% fluorescein solution. Under Wood's lamp illumination, the pattern of fluorescence was noted and recorded. The nonfluorescent portion of the flap was considered at risk of failure. Five separate experiments were performed.

TEMPERATURE

Under nembutal anesthesia, six pigs had 34 flaps constructed (20 DR, 8 VA, 3 RB, and 3 AB). Flap surface temperature was measured wih a surface thermistor probe (YSI #708) and digital readout display (Digitec 5800). Data was obtained both preoperatively and one hour

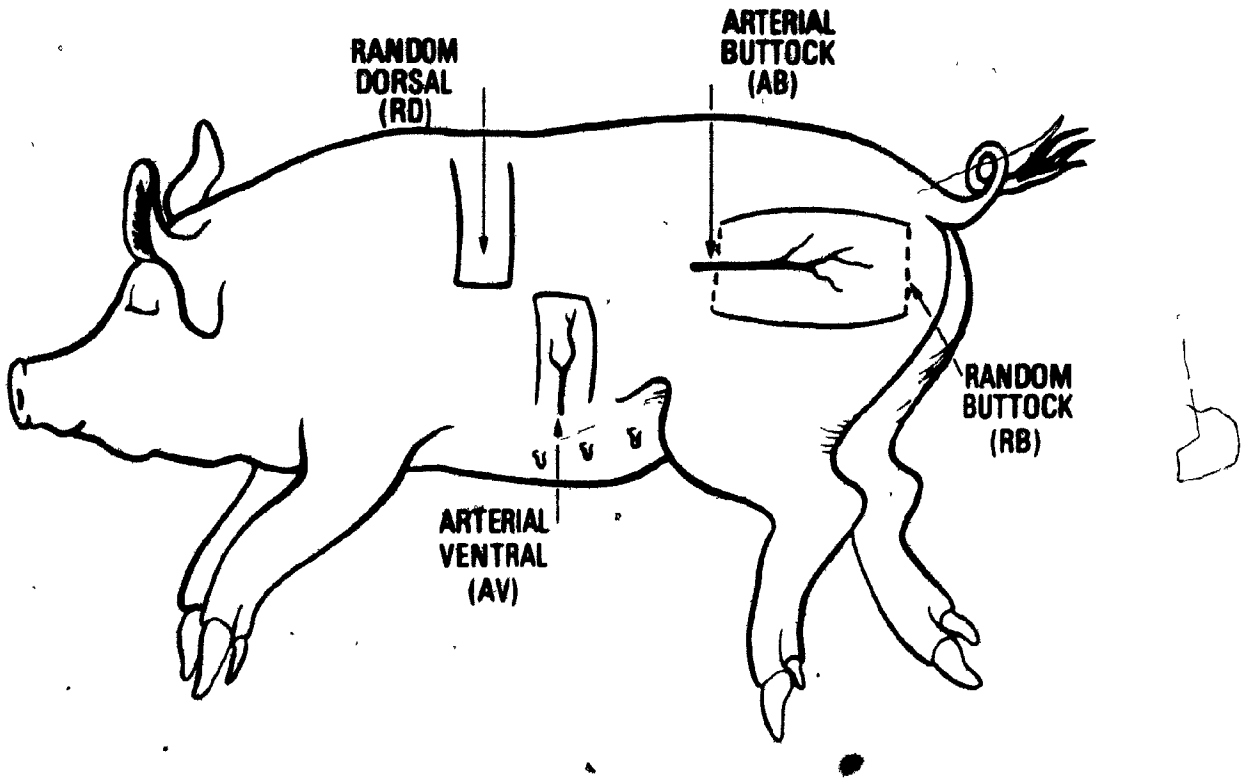

Fig. 4-1 Standard flap designs.

postoperatively at 2cm intervals along the length of the flap. For graphic presentation of the data, the preoperative temperature at the base of the flap was arbitrarily assigned 0 (mean base temperature = 34.5°C). The mean temperature changes from this value for the four flap types are presented. In one pig under nembutal anesthesia, a thermogram was obtained of acutely elevated DR flaps.

CHROMIUM TAGGED RED BLOOD CELLS

Five animals under pentobarbital anesthesia and four animals under halothane anesthesia had four DR flaps outlined on one or both sides. The flaps were elevated at different time intervals (1-24 hours) before administration of radioactive red blood cells. Each animal's blood was tagged with chromium51 in the standard fashion. In a sterile vial, the following ingredients were mixed and incubated at 37 degrees celsius for 15 minutes: 30cc of blood, 10cc of A-C-D solution and 200uCi of sodium chromate51. The vial was centrifuged, the plasma discarded and replaced with an equal volume of normal saline and 250 units of vitamin C. Washing of the plasma was repeated 3 times. After the appropriate period, the pig was fluoresced, the radioactive red blood cells were administered and precisely 2 minutes later, most flaps were transected at

their base. In four animals, the flaps which had not been divided at 2 minutes were transected at 20, 40 or 60 minutes. All specimens were pinned out to length on cardboard and placed in a freezer. Once frozen, biopsies (1.5cm in diameter) were obtained along the length of the flap using a corkborer. The flap biopsies were placed in scintillation vials and radioactivity counted for 10 or 20 minutes in a Beckman Gamma 8000. The window employed for chromium51 was 250-400 keV. Counts were corrected for background and plotted in histogram format.

DYNAMIC SCANS

Under nembutal anesthesia, two pigs were used to assess the value of dynamic scanning of skin flaps. Dorsal random flaps were designed, elevated and fluoresced in the standard fashion. Lead shielding was positioned under the flaps and over the rest of the pig to minimize background counts. One pig recieved 10mCi of technetium99 free ion and the other 50mCi of technetium99 tagged albumin. Starting from the time of isotope injection, the gamma camera was programmed to make thirty 3sec exposures, the scan thus lasted for 90 seconds. Flaps were then excised 2, 20, 40 and 60 minutes after isotope injection and a static, 10 minute, exposure of the flaps' radioactiviy was made.

TAGGED RED BLOOD CELLS AND 15U MICROSPHERES.

Strontium labelled 15u microspheres suspended in normal saline with 0.01% Tween 80 were obtained at a nominal specific activiy of 1mCi/g. The spheres were examined microscopically and standards of 100-400 spheres were prepared to calculate average counts per bead. The red blood cells were tagged with chromium51 as previously described. Two DR and two VA flaps were designed and elevated on three pigs under pentobarbital anesthesia. Through a carotid artery cutdown, a size 5 catheter was positioned at the base of the aorta. Following fluorescein administration, 75uCi of Sr85 15 micron spheres were injected via the aortic catheter. The radioactive red blood cells were then injected intravenously and all flaps excised 2 minutes later. The flaps were frozen, biopsied and counted for radioactivity. Chromium was counted at 180-400keV and strontium at 400-700keV. Counts were corrected for background and crossover and then plotted as histograms.

TOTAL FLOW AND NUTRIENT FLOW

Nutrient flow was measured with 15u spheres and total flow with 50u spheres. The 50u spheres, tagged with cerium141 were obtained in the same form and inspected as previously described. In five animals, 2 under pentobarbital anesthesia and 3 under halothane

anesthesia, 4 DR and 2 AB flaps were designed. The left ventricle was catheterized with a size 5 catheter under manometric guidance. A femoral arterial line was positioned for blood pressure monitoring and reference sample withdrawal. Three of the DR flaps were elevated and one left unoperated for measurement of control blood flow. The AB flaps were elevated as island flaps and the draining vein was catheterized with PE50 tubing.

Prior to sphere injection, blood pressure was recorded and reference sample withdrawal was initiated at a rate of 7.64cc/min using a Harvard pump. The 15u spheres, which had been placed in an injection vial (177) and counted, were injected over a 20 second period and the line flushed with 10cc of normal saline. The whole procedure was then repeated for the 50u spheres. The venous effluent of the AB flaps was collected for 30 seconds before and 7.5 minutes after each sphere injection.

Skin flaps were excised and cut into nine 4 x 2 cm strips. The strips were weighed and counted for radioactivity along with the reference blood samples, venous drainage samples and the sphere standards. The Beckman Gamma 8000 was programmed to count each specimen for 10 minutes in two windows (20-180keV for ceriuml4l and 400-700keV for strontium85). A computer program was written and used to correct counts for background and

crossover and to calculate flow according to the equation:

$$\text{FLOW TO SPECIMEN (CC/MIN/100GM)} = \frac{\text{REF FLOW(CC/MIN)} \times \text{SPECIMEN RADIOACT(CPM)} \times 100}{\text{REF RADIOACT(CPM)} \times \text{SPECIMEN WT(GM)}}$$

The calculated flow rates for each 2 x 4cm segment along the flap were then plotted as histograms. The mean flow rates of control skin, fluorescent flap skin and nonfluorescent flap skin were calculated for two types of anesthesia.

To estimate the accuracy of 15u and 50u spheres in their determination of shunt flow, the radioactivity of the venous effluent of the AB flaps was divided by the sum of the radioactivity of the total flap and the venous effluent. Shunt flow for DR flaps was calculated by subtracting nutrient flow (15u spheres) from total flow (50u spheres.) The number of spheres per skin specimen was determined by comparing radioactivity to that of the standard preparations. This enabled us to assure at least 400 beads per specimen.

RESULTS

Fluorescein administration in the early postoperative period (1-4 hours) resulted in a poorly defined borderline between fluorescent and nonfluorescent segments of the flap. After 8 hours however, the demarcation line of fluorescence was well defined.

TEMPERATURE

The mean temperature patterns for the four flap types show consistent differences from control (Fig. 4-2). Distal to the level of fluorescein penetration, flap temperature was 1.5-2.5°C below control preoperative values. In the fluorescent portion of the flap, proximal temperatures in arterial flaps were closer to control than were those in random flaps. Thermograms showed all flaps to be cooler than control skin (Fig. 4-3). If surface temperature is an accurate reflection of cutaneous blood flow, there is a gradual decrease in flow as one progresses distally along the flap. Without exception, the flap was always cooler than controls in marked contrast to previous reports (174).

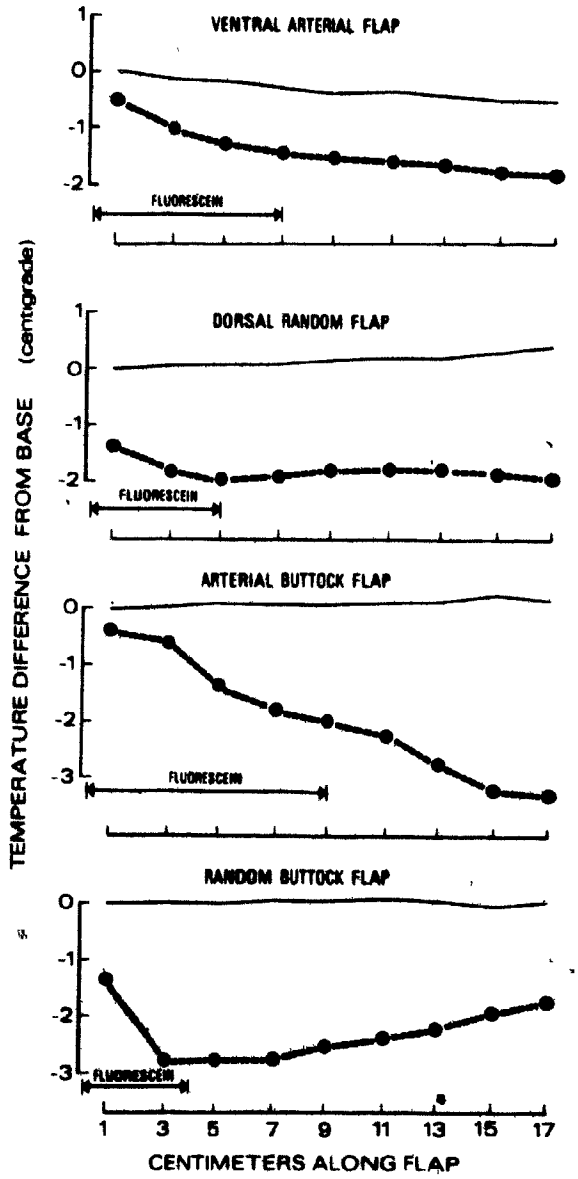

Fig. 4-2 Average temperature patterns in acutely elevated flaps.

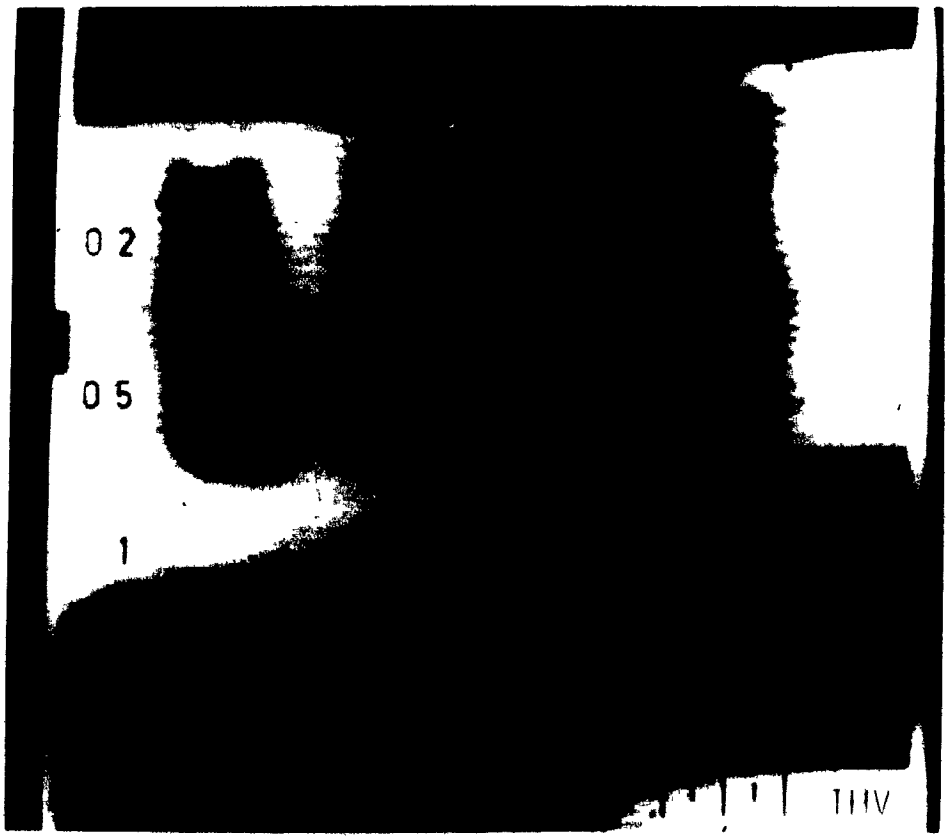

Fig. 4-3 Thermogram of 4 acutely elevated dorsal random flaps.

CHROMIUM TAGGED RED BLOOD CELLS

The mean distribution of chromium51 tagged red blood cells to random pattern flaps, elevated for 0-24 hours (mean=10 hours) and left in situ for 2 minutes, is limited primarily to the fluorescent portion of the flap (Fig. 4-4). There is a gradual decline in radioactivity as one progresses distally away from the flap's base. If 4 hour old flaps are left in situ for 20, 40 or 60 minutes, there is a gradual increase in radioactivity in the nonfluorescent portion of the flap (Fig. 4-5). The 15u spheres are trapped in the capillary bed during their first circulation and their level of radioactiviy is representative of flow rates. With recirculation through the vascular system, radioactive red blood cells are distributed to all vascular spaces regardless of flow rates. This may explain the discrepancy of the distribution of these two vascular markers. The use of halothane as compared to nembutal did not alter the distribution of red blood cells in the failing pig flaps.

DYNAMIC SCANS

With the dynamic flow studies, no radioactivity was detected in the flaps on 3 second exposures (Fig. 4-6). However, radioactivity was detected when the static scan was performed on the same flaps for 10

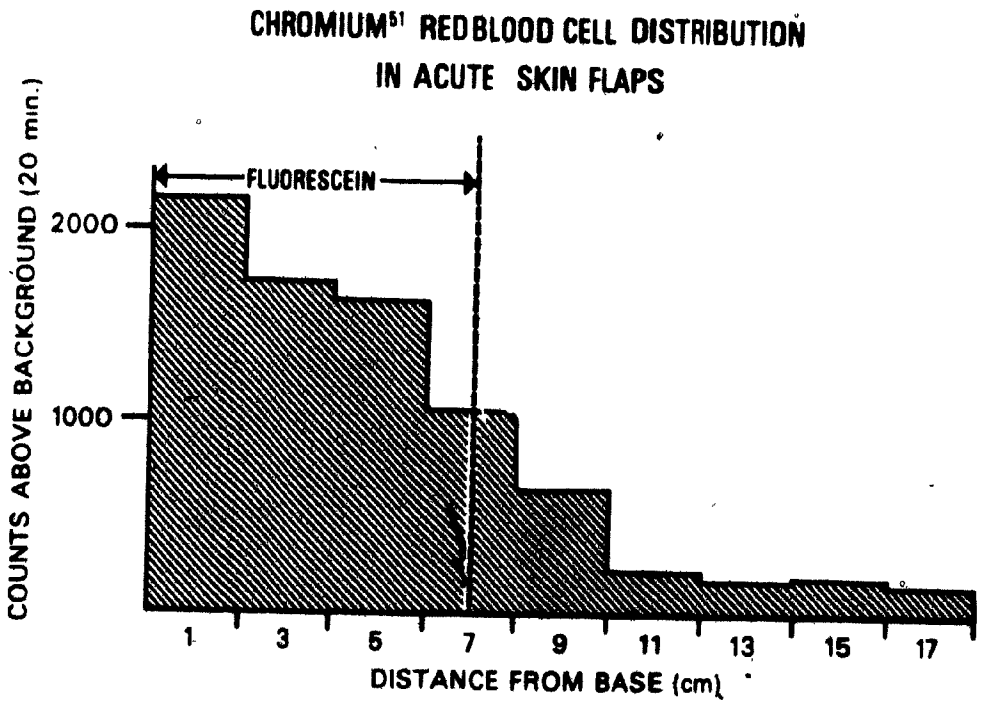

Fig. 4-4 Mean distribution of red blood cells in an acute skin flap.

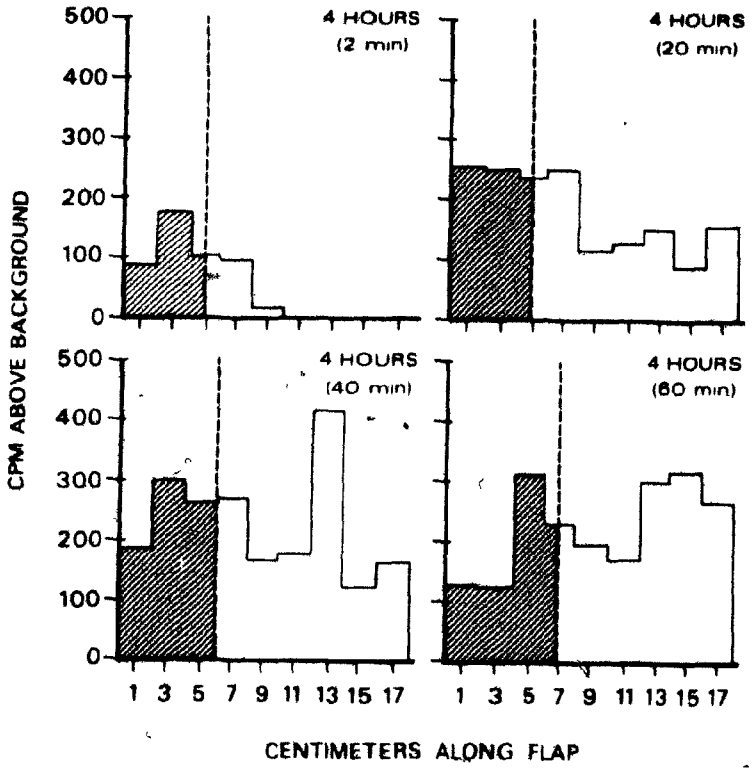

Fig. 4-5 Radioactivity of 4 hour old flaps excised at 2, 20, 40, or 60 minutes post rbc injection.

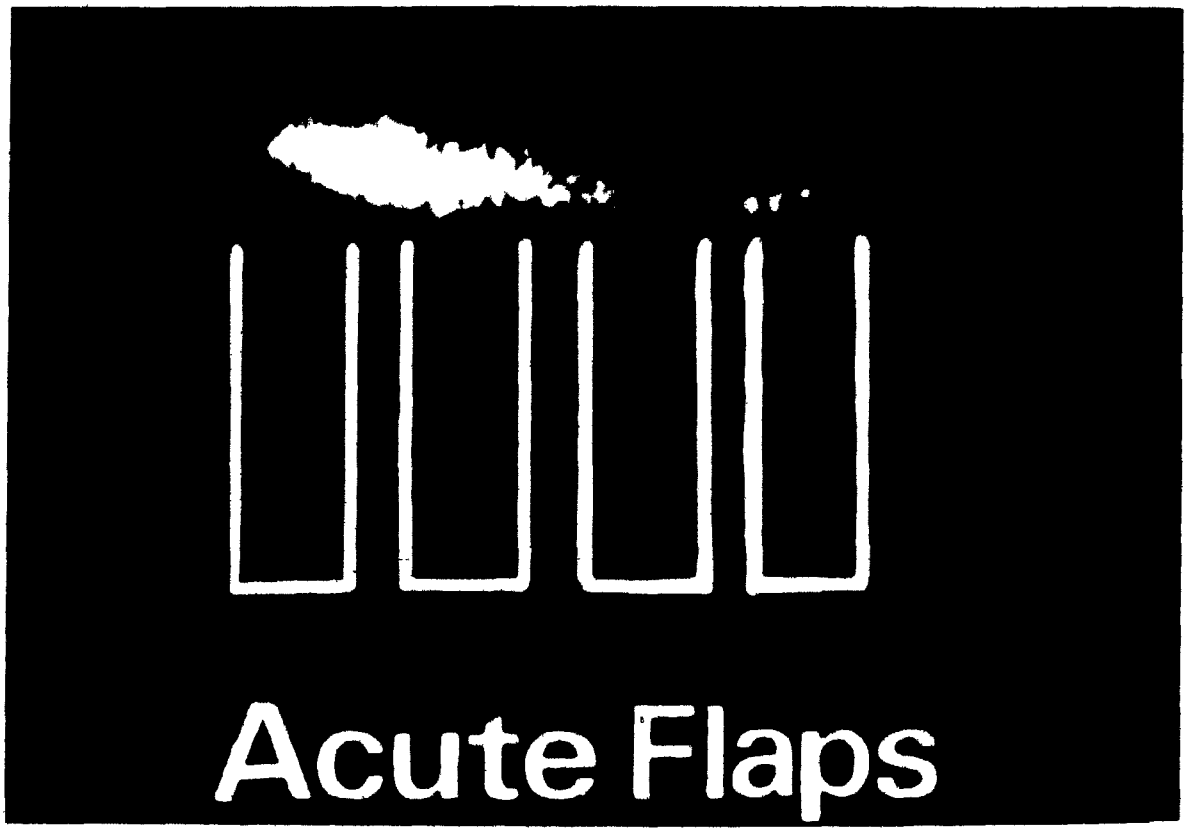

Fig. 4-6 Dynamic flow scan. Note absence of radioactivity in the flaps.

minutes (Fig. 4-7). As with the red blood cell distribution, both the free ion and albumin were distributed principally to the fluorescent portion of the flap. The radioactivity in the nonfluorescent portion of the flap increased with the length of time the flap was left in situ. In contrast to previous reports (174), dynamic scans were unable to assess blood flow in skin flaps.

SPHERES VS. RED BLOOD CELLS

In comparing 15u spheres and chromium51 tagged red blood cell distribution (Fig. 4-8), both vascular markers were primarily limited to the fluorescent portion of the flap. By excising flaps at 2 minutes, we were unable to replicate previous findings (174). However, if the flaps had been left in situ longer, it is presumed that the recirculation of the red blood cells and their equilibration in the distal flap would lead to a discrepancy in their distribution as compared to spheres.

TOTAL AND NUTRIENT FLOW

Quantitative flow studies with the microspheres show that under nembutal or halothane anesthesia (Fig. 4-9) there is insignificant flow, both total and nutrient, in the nonfluorescent portion of an acutely

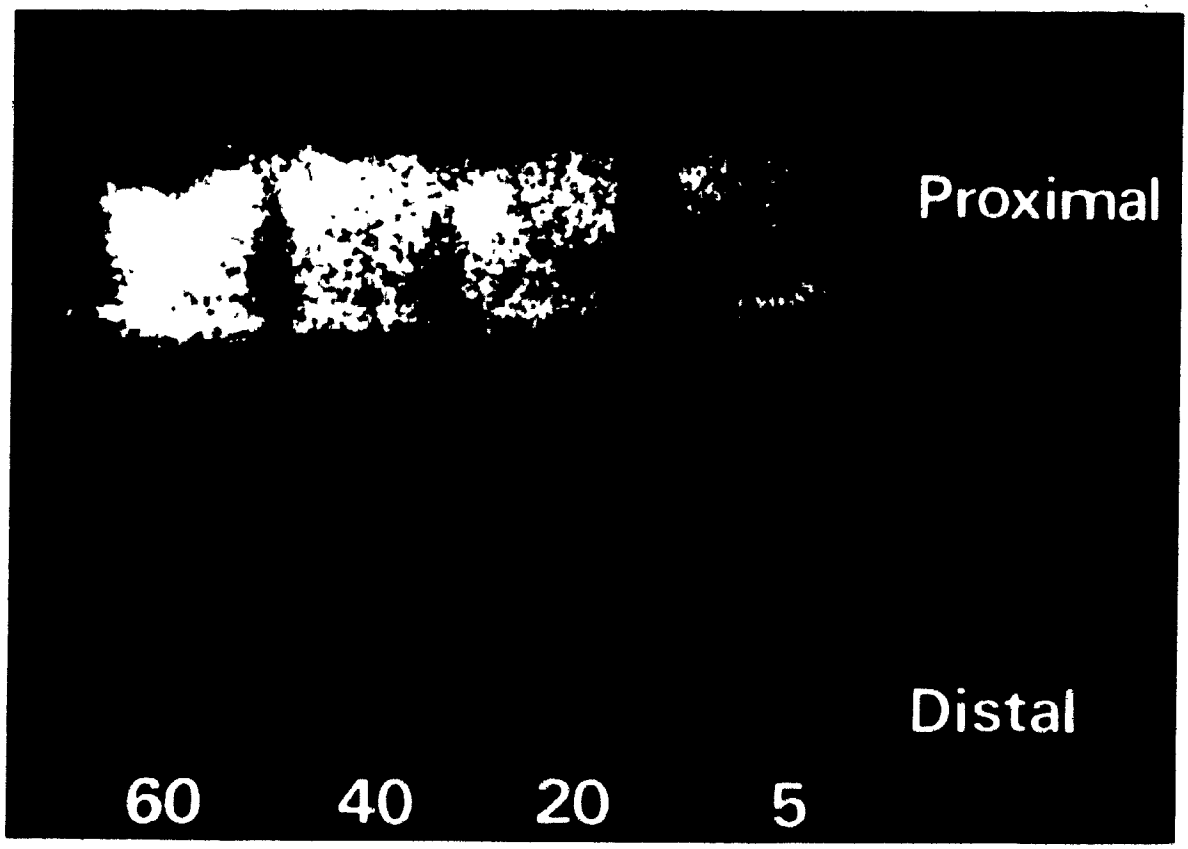

Fig. 4-7 Static scan of same flaps seen in Fig 6.

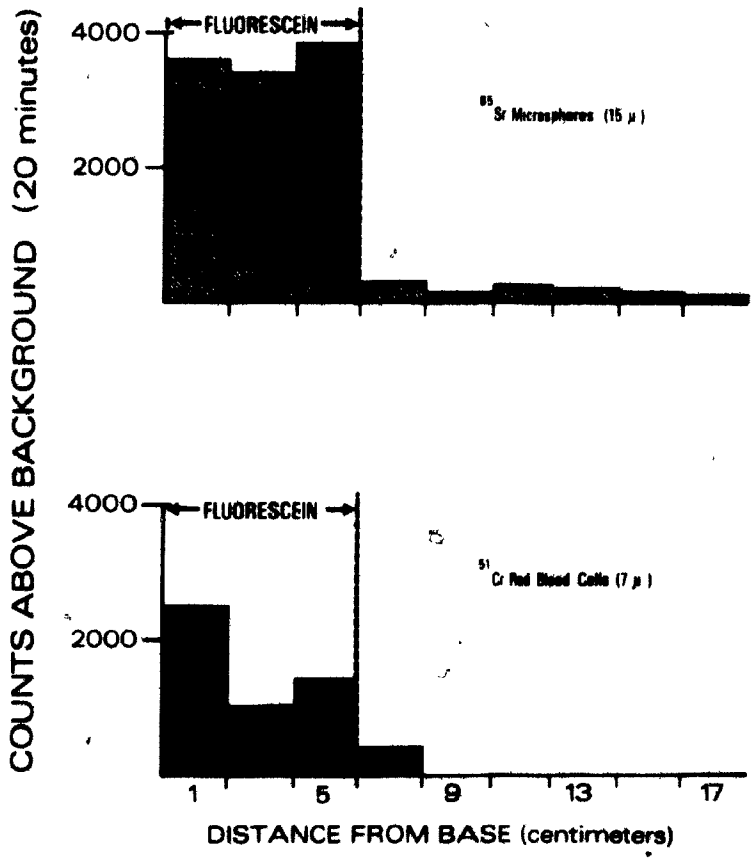

Fig. 4-8 Cr51 rbc's vs 15u sphere distribution.

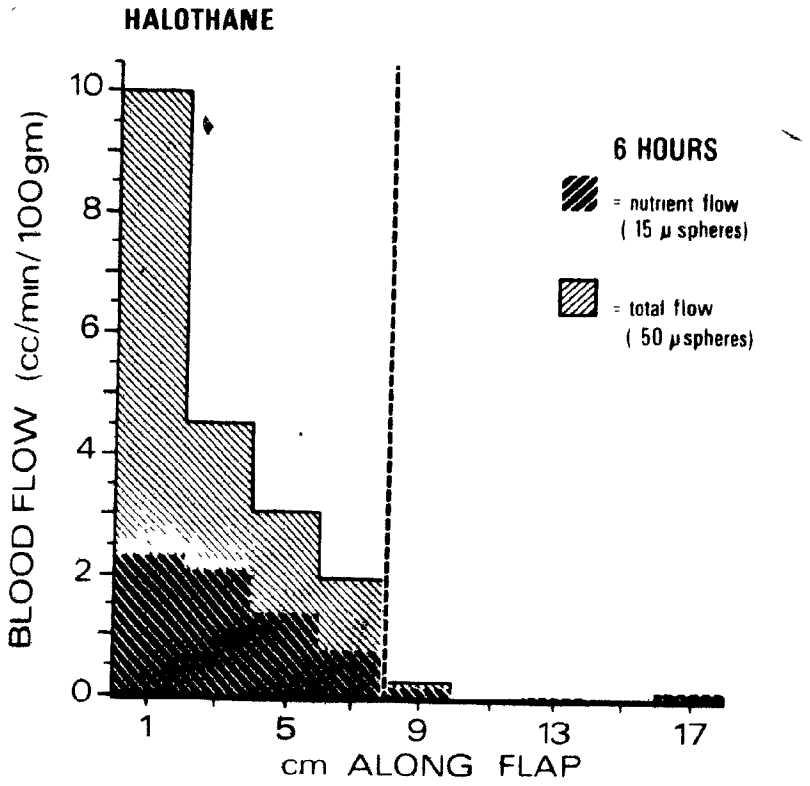

Fig. 4-9 Mean flow rates under halothane anesthesia.

elevated flap. In the fluorescent flap, flow gradually decreases as one progresses distally from the base. This pattern of diminishing distal flow was consistent in all the flaps examined. In both these acute flaps, the absolute and relative shunt flow also decrease as one progresses distally.

The average flow rates for control skin and the fluorescent and non fluorescent portions of the flap were calculated (Fig. 4-10). Total blood flow was found to be significantly higher in control skin than in the fluorescent flap. Nutrient blood flow does not differ between control skin and fluorescent flap. The nonfluorescent flap has virtually no measurable flow, neither total nor nutrient. From the data obtained by collecting the venous effluent of arterial buttock flaps, 4.4% of the 50u spheres were shunted and 84% of the 15u spheres were shunted. We interpret this to show that flow as determined by 50u spheres is an accurate index of total flow to the flaps. Shunt flow, computed from total flow less nutrient flow, was significantly less in the flap than in control skin. The act of flap construction induces profound changes in cutaneous blood flow.

Anesthetic agents also have a profound effect on cutaneous blood flow. Pigs under halothane anesthesia had control cutaneous total blood flows significantly

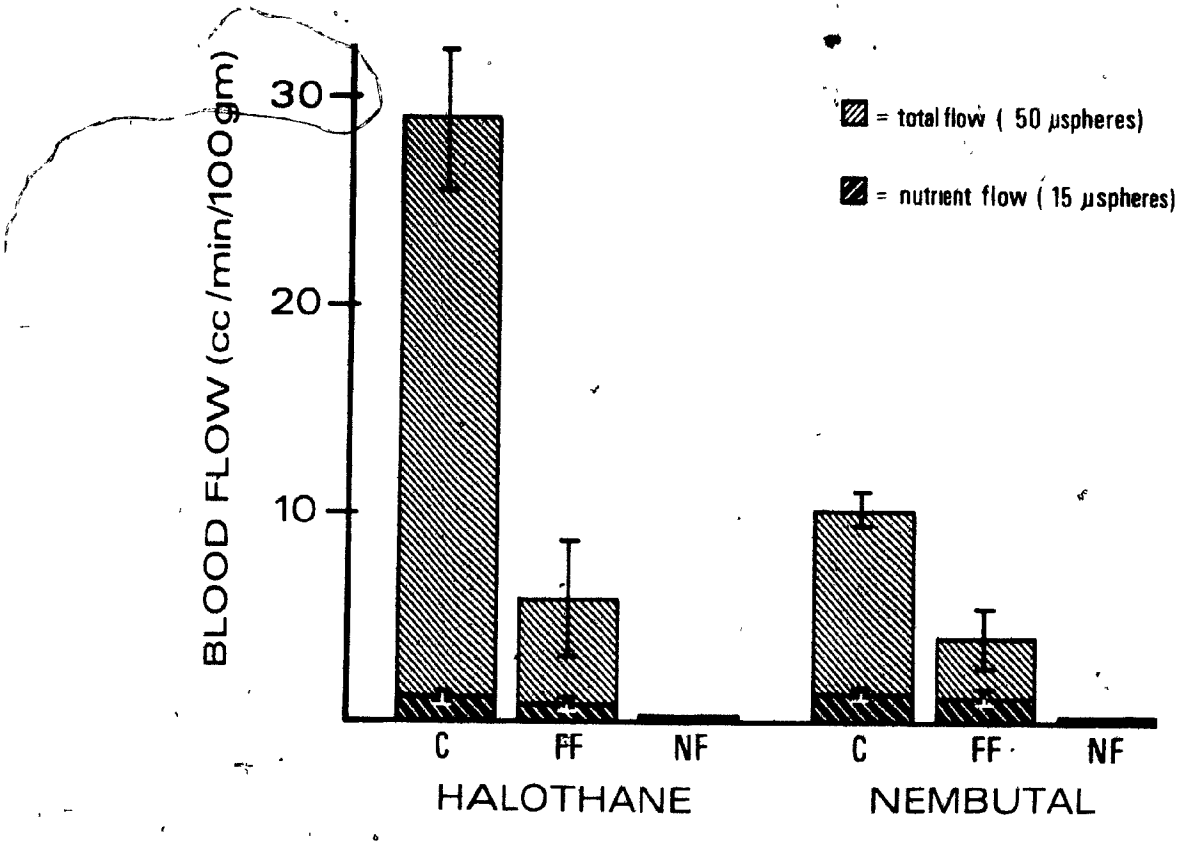

Fig. 4-10 Mean flow rates for control skin, fluorescent flap and nonfluorescent flap.

higher than pigs under nembutal anesthesia ($p<.01$). Nutrient blood flow was lower under halothane than under nembutal. Shunt flow in both control skin and fluorescent flap skin was greater under halothane than nembutal (Table 4-I & 4-II). The type of anesthesia employed significantly affects measurements of cutaneous blood flow. Ideally, animals should be awake while assessing skin blood flow rates.

DISCUSSION

The importance of understanding the pathophysiology of skin flap failure is related to our ultimate ability to prevent the complications of skin flap necrosis. Data from the present study on experimental pig flaps indicate that flaps fail because of arterial insufficiency. Arteriovenous shunts do not play an important role in acute skin flap failure.

OBJECTIVE EVALUATION

Surface temperature readings indicate that flap blood flow becomes progressively less than control as one moves distally along a flap. If shunt flow is the cause of inadequate capillary flow, one would expect to find higher temperatures as one progresses distally.

TABLE 4-I

CUTANEOUS FLOW RATES
(cc/min/100gm)

HALOTHANE ANESTHESIA

	CONTROL SKIN	FLUORESCENT FLAP	NONFLUORESCENT FLAP
50u flow	29.17 ± 6.9	5.59 ± 2.3	.08 ± .1
15u flow	.87 ± .72	.62 ± .49	.08 ± .22
shunt flow	28.3	4.97	0
	(97%)	(89%)	(0%)

TABLE 4-II

CUTANEOUS FLOW RATES
(cc/min/100gm)

NEMBUTAL ANESTHESIA

	CONTROL SKIN	FLUORESCENT FLAP	NONFLUORESCENT FLAP
50u flow	10.25 ± 1.7	4.100 ± 3.1	.05 ± .06
15u flow	1.34 ± .20	1.21 ± .8	.07 ± .08
shunt flow	8.9	2.89	0
	(87%)	(70%)	(0%)

After approximately 6-8 circulation times (2 minutes), the distribution of radioactive red blood cells also indicate a gradual decrease in flow towards the distal end of the flap. However, after multiple recirculations (20-60 min) the concentration of radioactive cells in the distal flap increases to greater than control. Blood is getting into the flap but at such a slow rate that flow and oxygen delivery are insignificant. The high red blood cell concentration is a reflection of the hemoconcentration that we have previously documented (see Experiment 3). The vascular channels in the failing distal flap are patent. This observation has important implications for the systemic treatment of skin flaps.

Dynamic scans provided no useful information about blood flow to acute skin flaps. Skin flap flow is so low when compared to the rest of the body that gamma cameras are unable to detect the presence of radioactivity in a 3 second exposure. However, static scans of the technetim ion and technetium albumin distribution in the flaps was in accord with the observed distribution of red blood cells.

Utilizing the radioactive microsphere technique, we were able to measure total flow by the 50u spheres, nutrient flow by 15u spheres and shunt flow by subtracting nutrient flow from total flow. By

collecting venous effluent from selected flaps we were able to test the accuracy of 50u spheres in measuring total flow. Flow (total, nutrient and shunt) unquestionably decreases as one progresses distally along an acutely elevated pig skin flap.

ACUTE FLAP BLOOD FLOW

Why do skin flaps fail? Inadequate nutrient blood flow appears to be a consequence of a decrease in arterial inflow (see Experiment 5). This decrease is secondary to the surgical severance of the normal cutaneous vasculature. Poor flap design and anatomical variations in skin blood supply make this an unavoidable consequence. Our findings of decreased flow rates in random pig flaps correspond well with previous experimental studies. However, these studies did not look specifically at the failing portion of the flap. Nathanson (158) measured skin blood flow in viable random dog flaps during their construction. Incising the flap sides caused an increase in nutrient flow as compared to control. Flap undermining caused a dramatic decrease in nutrient blood flow. Guba (82) assessed nutrient blood flow to viable arterial flaps on dogs in the early postoperative period. Control flow measures were made prior to flap construction. At both 30 and 90 minutes post construction, cutaneous flow in the

arterial portion of the flap was significantly greater than preoperatively. However, flow rates in the viable random portion of the flap were significantly below control flow at 30 and 90 minutes. Sasaki (180) studied flow rates and microsphere distribution in acutely elevated rat flaps. Measurements of control skin blood flow or control sphere distribution were not reported. The 15u sphere distribution was initially (2-6 hour old flaps) limited to the arterial portion of the flaps. However, in 12-24 hour old flaps, spheres were also seen in the distal random portion. Flow rates were measured for the total flap but were not subdivided into arterial or random, viable or nonviable segments. Flow to the total flap was found to increase with time after surgery, reaching a maximum by 24 hours.

INSULTS

Flaps fail from arterial insufficiency (see Experiment 5). What are the physiological consequences of this and are they beneficial or detrimental to flap circulation (Fig. 4-11)? One must first realize that flaps are in essence a type of end organ without collateral circulation. The distal flap is totally dependent on the proximal flap. Changes in the distal flap are always more severe than those in the proximal flap. There are 3 major interrelated insults initiated

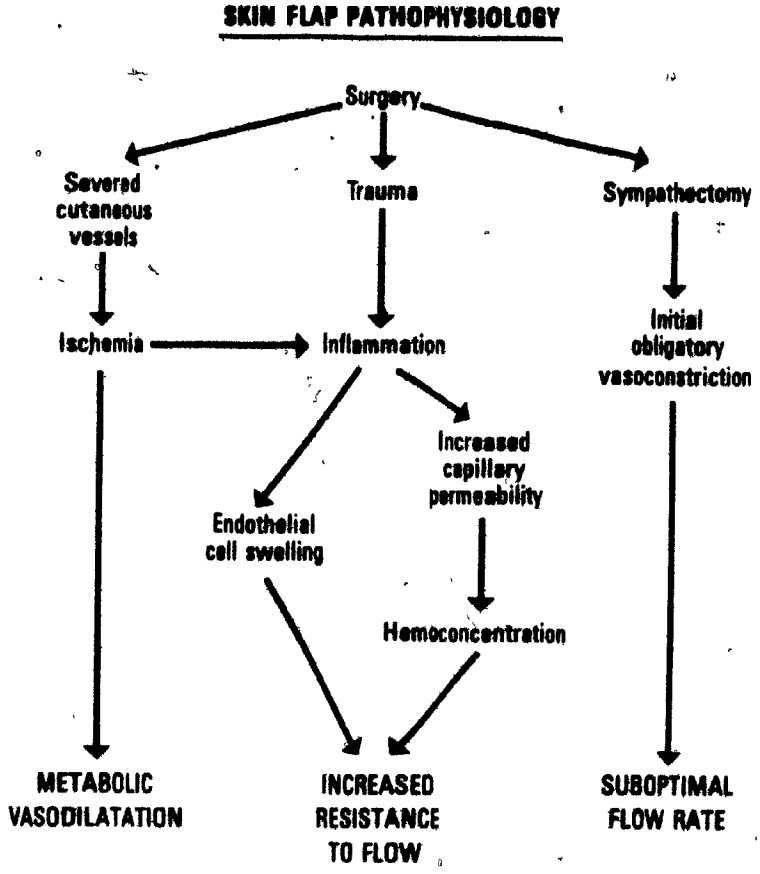

Fig. 4-11 Pathophysiological events occurring in an acutely elevated flap.

by flap elevation: 1) severed vessels producing ischemia, 2) surgical trauma causing inflammation, and 3) severed nerves resulting in sympathectomy.

Ischemia. Conversion of a skin area to a skin flap necessitates severance of cutaneous vessels with resulting ischemia. The degree of ischemia tends to increase with distance from the vascular supply to the flap. The consequences of ischemia are fourfold. First, cellular death will result within 13 hours (see Experiment 2) unless flow is restored to the tissues. Second, there is a buildup of by-products from anaerobic metabolism which act as local vasodilators. This vasodilating effect will only be beneficial if the arterial pressure is adequate to insure continued flow with this decrease in vascular resistance. Third, ischemia results in an inflammatory type reaction leading to endothelial cell swelling and in the extreme, intraluminal obstruction. Fourth, the ischemic tissue will be more susceptible to infection which in itself will be detrimental to flap survival.

Trauma. Surgical trauma causes an additional inflammation that compounds the insult of ischemia. With the inflammatory reaction, multiple agents including bradykinin, histamine, and prostaglandins are

released causing local vasodilatation and an increase in capillary permeability. There is a resultant shift or leakage of fluid into the extravascular space. This leakage has two important consequences. Intravascularly, there is hemoconcentration which alters the rheologic properties of blood. Resistance to flow is increased. Extravascularly, interstitial edema develops as does intracellular swelling.

Sympathectomy. When a sympathetic axon is severed from its cell body, there is an obligatory loss of catecholamine from the nerve terminal. This release causes a vasoconstricting influence on the alpha adrenergic receptors. Whether this is offset by opposing vasodilating forces will depend on the ultimate balance between the two. It is our impression that in the proximal flap, where ischemia is not so severe, the vasoconstriction predominates causing submaximal flow. However, in the distal flap which is severely ischemic the vasodilating factors are predominant. More importantly the distal flap is entirely dependent on the proximal flap for its blood flow. Thus, despite vasodilatation in the distal flap, flow cannot increase because of the proximal regulation of arterial inflow.

FLAP SALVAGE

With this postulated information, how can we attempt to salvage the failing flap? If we could increase arterial inflow, we could minimize the ischemic insult. Theoretically, this increase flow could be accomplished by blocking the vasoconstricting factors affecting the proximal flap. A variety of alpha blockers have been employed in several animal species with somewhat varied results. Alternatively, vasodilating forces could be made stronger so as to overcome the vaoconstricting forces. Direct acting vasodilators have been utilized both successfully (67) and unsuccessfully (189) in rats. If proximal flap flow is suboptimal, continued efforts to find effective vasoactive agents should prove beneficial to the failing flap. Detrimental effects of infection have been indirectly demonstrated by an increase in skin flap survival in germ free rats as compared to controls (116). Experimental flaps treated with topical silver sulfadiazine (133) also have increased survival when compared to untreated animals. Control of the natural skin flora by topical therapies has exciting possibilities for the failing flap.

The inflammatory response elicited by both ischemia and surgical trauma is detrimental to acute flap survival. Antiinflammatory agents such as

corticosteroids can protect the cells against ischemia by stabilizing cell membranes. This effect will minimize increases in capillary permeability and fluid extravasation. The use of systemic steroids in experimental animals with skin flaps (137, 138) has been found beneficial. Topical application of steroid creams has not yet been utilized. Prostaglandin synthesis inhibitors have also been demonstrated to increase experimental flap survival (181). Whether this effect is due to blocking the inflammatory or vasoactive characteristics of prostaglandins is unclear.

Manipulation of the hemoconcentration, and thus the resultant increase in vascular resistance, that develops in the failing portion of a skin flap is another potential means for improving flap survival. Experimental animals have been made both hypoproteinemic (176) and anemic (59, 159) in order to improve flap survival lengths. Flaps in rabbits treated with systemic heparin have also shown increased survival length (182).

Skin flaps fail because of arterial insufficiency. Ischemia is the primary insult which is compounded by surgical trauma, inflamation and sympathectomy. Hopefully, with this improved understanding of the pathophysiology of skin flap failure, attempts to increase flap survival length will be more fruitful than

in the past.

SUMMARY

The pathophysiology of skin flap failure was investigated in acutely elevated pig random skin flaps. Temperature patterns were observed as was the distribution of radioactive red blood cells. Microspheres were utilized to quantitate nutrient and total flow. Acutely elevated flaps were fluoresced and it was found that the nonfluorescent portion of the flap had insignificant circulation as determined by each of the above techniques. The consequences of this decrease in flow are discussed with respect to the potential treatment of the failing skin flap.

EXPERIMENT 5:

SALVAGE OF THE FAILING FLAP BY CONTROLLED VASCULAR AUGMENTATION

INTRODUCTION

The etiology of intrinsic skin flap failure is attributed to either arterial insufficiency or venous inadequacy (77). In the past few decades, three different experimental approaches were employed to resolve this problem. Clinical observations by Hynes (96) and experiments by Myers et al (155) and Cherry et al (30) assessed the effect of gravitational forces on blood flow in sympathectomized skin flaps. Flaps were made dependent to increase venous drainage. These studies had conflicting results and no conclusion as to the relative importance of arterial or venous factors could be made.

The second method was based on the corollary that conversion of an arterial flap to a random flap resulted in a shorter surviving length. Experiments were designed (152, 168) to determine if the critical manoeuvre was the division of the segmental artery, vein or both. Arterial supply was found to be the most important factor. If decreasing the arterial input decreases flap survival length then what effect will increasing arterial input or venous drainage have on flap survival length?

The present paper describes a third approach to the problem. Selective augmentation of either venous or

arterial supply is effected to the nonfluorescent portion of a random flap.

METHODS AND MATERIALS

White Poland-China pigs (16-23kg) were sedated with acepromazine and anesthetized with thiopental. Following intubation, anesthesia was maintained with a mixture of halothane, nitrous oxide and oxygen. In 9 pigs, bilateral standard buttock flaps 18 x 10 cm were designed to have a random pedicle distally and an island pedicle proximally (see Experiment 1) The flap was incised, elevated and sutured back in its bed. The animal was turned to a supine position to allow dissection of the vascular pedicle to the level of the inguinal ligament. The vascular island pedicle was manipulated in one of three ways: 1) all structures were divided, 2) nerve and vein were divided, or 3) the nerve and artery were divided (Fig. 5-1). Three experimental groups were thus created: control (C), arterial augmentation (AA) and venous augmentation (VA). The wounds were closed and all animals observed. One week postoperatively, the animals were sacrificed and the flaps photographed.

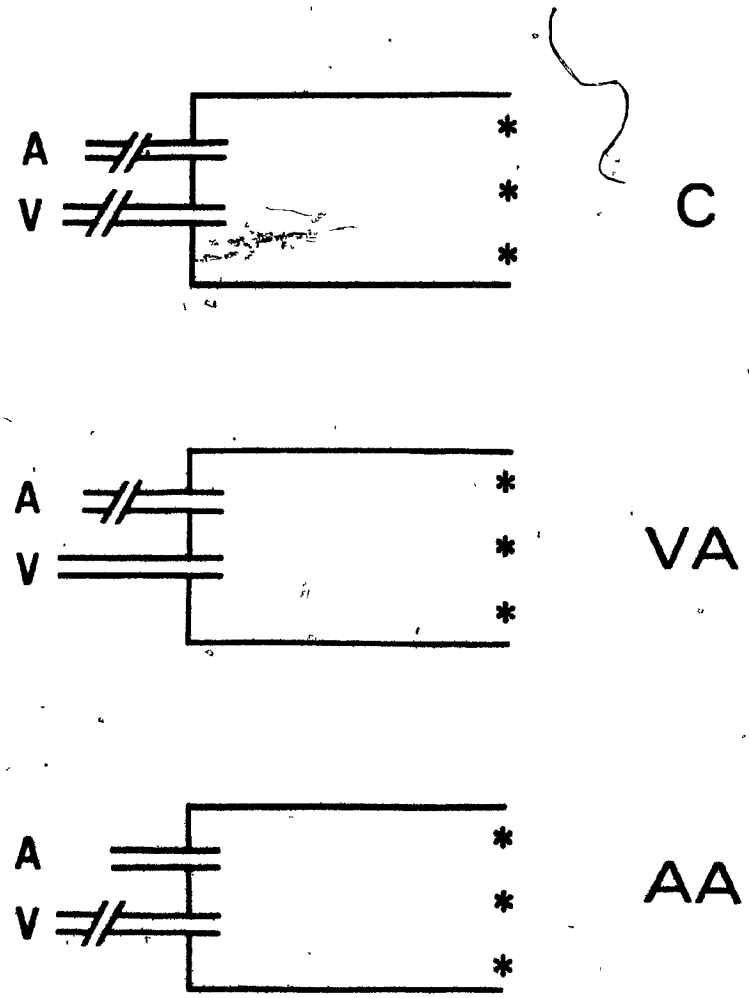

Fig. 5-1 Flap designs. C=control. VA=venous augmentation. AA=arterial augmentation.

RESULTS

All flaps in the control and venous augmentation group underwent necrosis of the island end of the flap and survival of the random end of the flap (Fig. 5-2 & 5-3). The mean survival of control flaps was 7.67 cm (43%), VA flaps 8.33 cm (46%) and AA flaps 18 cm (100%) (Fig. 5-4). The AA flaps were significantly longer than either VA or C flaps ($p<0.01$). The survival lengths of VA and C flaps were not significantly different ($p>0.33$).

DISCUSSION

In order to salvage a failing flap it is critical to understand the physiological basis of skin flap failure. Since the dying flap often appears blue, the etiology was considered congestion secondary to venous insufficiency (134). Histologically, one sees dilated capillaries packed with red blood cells. But does this observed state represent passive distension from venous inadequacy or is it the active vasodilatation of anoxia secondary to arterial insufficiency? Clinically, Hynes (96) noted that "blue" flaps could be made white and "white" flaps made blue by changing gravitational forces. He postulated that flaps failed because of

Fig. 5-2 Survival of control flaps, random pedicle only.

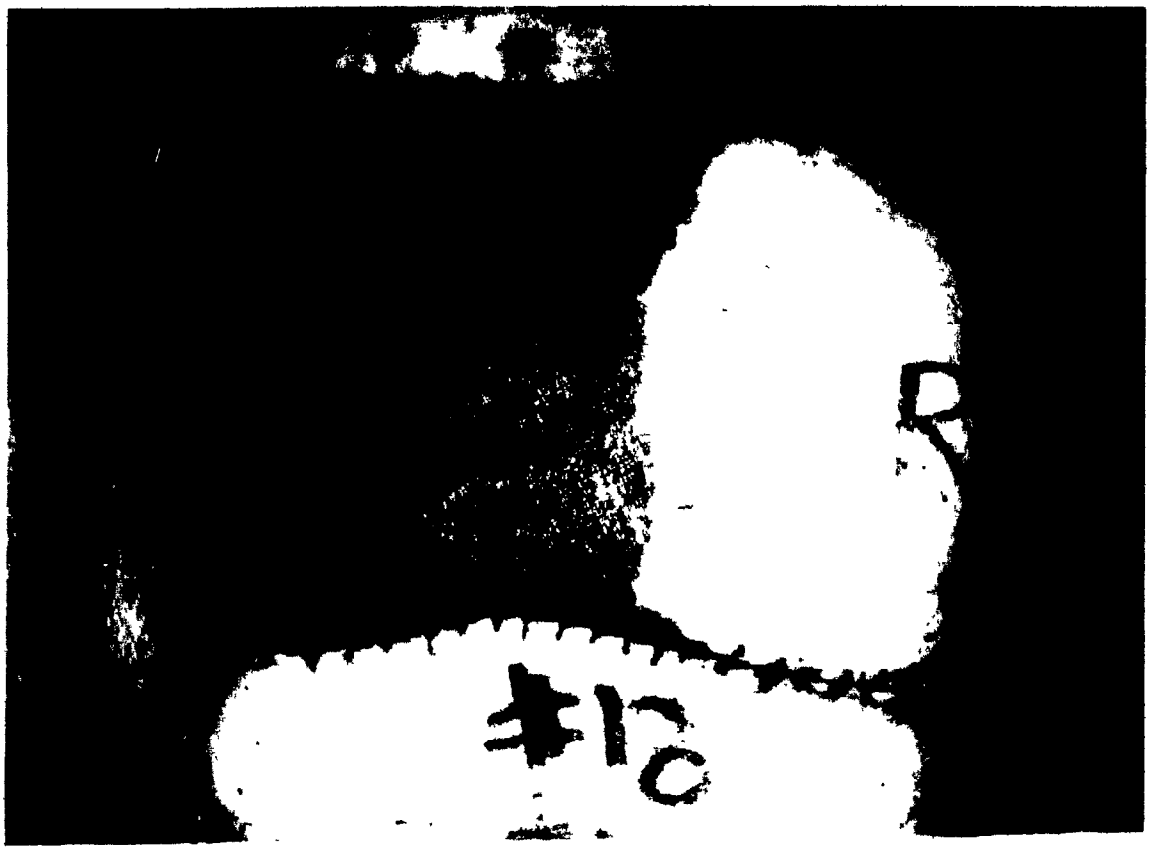

Fig. 5-3 Survival of VA flaps, random pedicle with augmented venous supply.

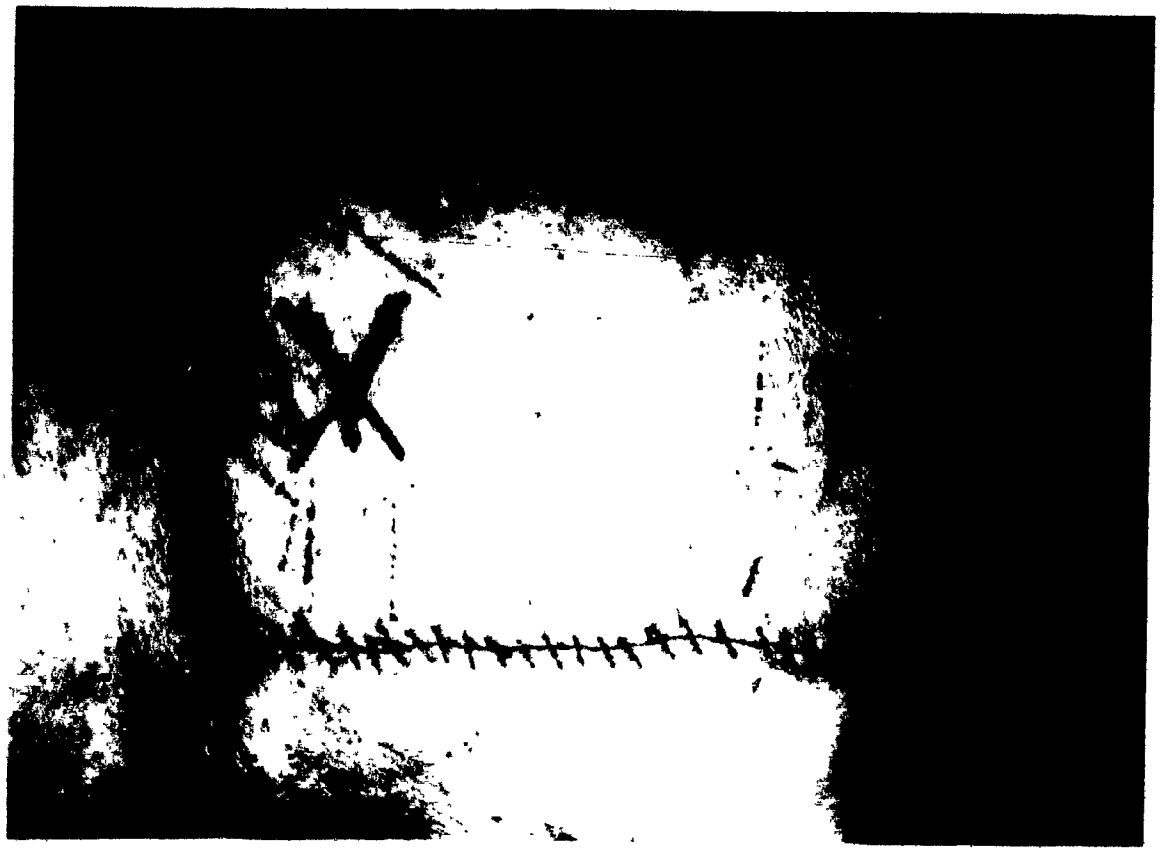

Fig. 5-4 Survival of AA flaps, random pedicle with augmented arterial supply.

arterial insufficiency. Myers et al (155) subsequently used gravitational force in experimental rabbit and pig flaps to increase arterial inflow. They found no change in survival length. Cherry et al (30) extended these studies to include delayed flaps subjected to more severe gravitational forces. He found a decrease, not an increase, in survival length of dependent delayed flaps. These conflicting studies confuse the issue as it is questionable whether gravity really does alter arterial inflow. Myogenic factors in the autoregulation of the cutaneous microcirculation may limit the effect of gravity (86).

Studies in the rabbit and pig (155, 168) showed that survival of arterial flaps was decreased if their segmental artery was ligated. In contrast, ligation of the segmental vein did not alter survival length. Salvage of a flap tip destined to necrose by increasing arterial inflow has not been shown by the foregoing studies. However, our data show clearly, that selective augmentation of arterial inflow does prevent necrosis in that portion of a pig skin flap that is destined to fail. Clinically, it will be difficult to increase arterial inflow. First, there is rarely a segmental artery in the distal end anatomically. Even with microsurgical techniques, there is rarely a segmental artery in the distal end of a clinical flap (135). A

convenient donor artery is also unavailable (157). Thus, salvage of the failing distal portion of a skin flap must be by pharmacologic manipulation of the microcirculation, especially arterial inflow. Currently, double blind drug studies are being done with phenoxybenzamine (an alpha adrenergic receptor blocker), isoxsuprine (a beta receptor agonist and a direct smooth muscle relaxant) and reserpine (a catecholamine depletor) to determine their efficacy.

SUMMARY

The role of arterial supply and venous drainage in skin flap necrosis has been examined using a pig skin flap model. Augmentation of arterial inflow to the distal portion of the flap significantly increased flap survival. Augmentation of venous drainage had no effect on flap survival. Attempts to salvage failing skin flaps should be directed towards increasing arterial inflow.

EXPERIMENT 6:

PHARMACOLOGIC TREATMENT

OF THE

FAILING SKIN FLAP

INTRODUCTION

Salvaging the failing skin flap remains a challenge for plastic surgeons. Despite an improved understanding of the cutaneous vasculature, skin flap necrosis still occurs. Effective and reliable treatment of the failing skin flap remains an elusive goal. Necrosis occurs in all types of skin flaps including random flaps, arterial flaps, myocutaneous flaps and free flaps. The present study was designed to investigate failure in random skin flaps.

CLINICAL TRIALS

To date clinical reports regarding the treatment of failing flaps are based primarily on isolated cases, not on clinical series. Adamson (4) elevated random skin flaps in the lower extremities of a paraplegic patient. Flaps on the leg were treated with topical dimethylsulfoxide. The treated flaps survived to a longer length than untreated flaps on the contralateral limb. The difference seen in viability was suggestive of a beneficial drug effect but may also be explained by chance variation. Barisoni (12) studied the effects of thymoxamine, an alpha adrenergic receptor blocker, on

control skin and flap skin blood flow. Systemic thymoxamine and locally injected thymoxamine were found to increase Na22 clearance in flaps but not control skin. Unfortunately this increase in blood flow did not correlate with survival. Finseth (66) has published case reports of salvaging failing flaps with isoxsuprine. Fluorescence of the flaps was the control measure of viability before drug treatment. As fluorescence is not always an accurate index, the benefit of isoxsuprine, or any other drug, cannot be accurately assessed by isolated case reports. Perrins (169) has studied the effect of hyperbaric oxygen in a more systematic way. Clinical skin flaps threatened with failure, as defined by subjective observations, underwent intermittent treatment. There were obvious improvements in flap color and flap viability. The overall incidence of flap failure during the year that the therapy was instituted was less than in previous years at the same hospital. Unfortunately this treatment has not become widely accepted because it involves potential hazards to the patient, cumbersome equipment and the need for highly trained professionals.

EXPERIMENTAL STUDIES

More than 45 papers have been published on the treatment of experimental failing skin flaps. The results of these studies are conflicting and therefore difficult to interpret. The literature can be simplified by defining certain pertinent factors 1) therapeutic agent employed, 2) timing of treatment, 3) route of administration, 4) animal species employed, and 5)repeatibility of the study. The therapeutic agents utilized to increase flap survival can be subdivided according to their theoretical mode of action.

INCREASED BLOOD FLOW

Sympatholytics

Phenoxybenzamine has been successful at increasing flap survival when used both pre- and postoperatively in rats (67, 153, 212) It has been administered by both the systemic route and by direct injection into the base of the flap. However, the same drug employed by different researchers in rats (189) and pigs (148) has shown no beneficial effects. Pretreatment of rats with systemic reserpine (40, 102) 6-OHdopa (174, 212) and propranolol (67, 100) have been found successful by some authors but unsuccessful by others (103, 189). Pretreatment of rats

wih guanethidine has been successful and repeatable (1, 67, 102). If our current understanding of skin flap failure is correct, the pharmacologic manipulation of the sympathetic regulation of cutaneous microcirculation should increase flap survival. However, past attempts to do this have not been consistently successful. Our current theories need closer examination and our pharmacologic studies require more careful planning and monitoring.

Direct Vasodilators

Topical dimethylsulfoxide has been used postoperatively in both rats and rabbits showing both beneficial (5, 78, 107) and no effects (109, 153) on skin flap survival. Histamine in rabbits (107, 143) and hydralazine in rats (67, 189) have also been both successful and unsuccessful at increasing flap survival length. Isoxsuprine, given pre- and postoperatively to rats has increased flap survival in some researchers hands (67) but not others (29, 179). The use of prostaglandin inhibitors in rats has been found to increase flap survival (180) but there are no confirmatory investigations in the literature. Whether or not vasodilators can increase flap survival is questionable. Pharmacologic agents are usually complex having more than one effect. For drugs such as

dimethylsulfoxide and prostaglandins, it is uncertain whether it is their vasodilating or anti-inflammatory effects that are beneficial to flap circulation. Even in the treatment of medical illnesses, the precise mode of action of many drugs is uncertain. Plastic surgeons might be wiser to limit their experimentation to the use of drugs whose actions are clearly understood by the pharmacologists.

Altering Rheology of Blood

Postoperative treatment of skin flaps with pentoxifylline (rats, 200) and heparin (rabbits, 182) has increased flap suvival. Anemia, in dogs (59) and rabbits (159), and protein depletion in rats (176) has shown an increase in flap survival length. The use of dextran (150) has not improved flap viability. Perfusion of rat flaps with solutions of varying viscosity have shown that decreasing perfusate viscosity results in a significant increase in flap blood flow (39). No attempts to replicate these findings have yet been published. Alteration of the rheologic properties of blood may indeed improve flap survival. However, it is not acceptable to make patients anemic or hypoprotenemic to achieve this goal.

INCREASING TOLERANCE TO ISCHEMIA

Systemic steriods have been used both pre- and postoperatively in rabbits (138) and pigs (137) with a significant increase in flap survival. No replications of these findings have been published. Hyperbaric oxygen has been used successfully in rats postoperatively (7). Cooling has also been effective postoperatively in rabbit flaps (108). Topical flamazine (133) and moist dressings (178) in rats have been found successful at increasing flap survival length. Although corticosteroids show exciting possibilities, more experimental studies must be carried out to document their benefit to the failing flap. Clinical trials will not be justified until such a time.

Our previous work led us to conclude that flaps fail because of arterial insufficiency, resulting in ischemic necrosis. Treatment of the failing flap should be directed towards increasing arterial inflow or minimizing the effects of ischemia. Clinically, recognition and treatment of a failing flap does not occur until the postoperative period. In designing the present study, pigs were chosen for their fixed skin and multiple flap sites. Treatment was begun postoperatively so as to mimic the clinical situation. Three vasoactive drugs were tested. Phenoxybenzamine,

an alpha adrenergic receptor blocker, was choosen because of its ability to minimize the vasoconstricting effects of catecholamines, especially those being spontaneously released from the surgically cut sympathetic nerves. Isoxsuprine, a direct acting smooth muscle relaxant was choosen for its vasodilating effects and for its controversy in the current literature. Reserpine, a catecholamine depletor, was used to theoretically hasten the depletion of catecholamines from the cut sympathetic nerves. Drug induced changes in flow were measured by the microsphere technique.

METHODS

White Poland-China pigs (21±2kg) were sedated with acepromazine, anesthetized with sodium thiopental and endotracheal anesthesia maintained with a mixture of oxygen, nitrous oxide and halothane. Following anesthesia, four dorsally based random skin flaps were outlined on one flank (Fig. 6-1). Following skin preparation with proviodine, the flaps were elevated, then sutured back in their beds and 5cc of 10% flourescein was given intravenously. Under Wood's lamp illumination the furthest penetration of flourescein was recorded. This could be expected to correlate (±1cm)

Fig. 6-1 Pig with outline of four 14 x 4 cm dorsally based random flaps.

with survival as based on our previous data from comparable flaps. Three experiments were carried out.

EXPERIMENT 1

Twenty pigs (17.4 ± 2 kg, mean ± S.D.) were divided into four groups. All animals underwent two operations (Fig. 6-2). Following flap elevation, fluorescein was administered. At the first operation all animals had four 14 x 4 cm dorsally based random flaps constructed. No treatment was received for the next three days. On the third postoperative day the second operation was performed. Four 14 x 4 cm similar flaps were elevated on the unoperated side. Immediately after surgery and fluorescein evaluation, animals received an intramuscular drug and an intravenous drug (Table 6-I). The IM drug was administered every 8 hours for 5 days and the IV drug once a day for 5 days. On the seventh day after the second operation the animals were sacrificed and the flap survival lengths measured. Animals were operated on, treated and housed in groups of four, there being one animal under each treatment condition.

Phenoxybenzamine, 2 mg/kg, or its placebo was administered intravenously once a day. The drug was supplied in powder form and a 10 mg/cc solution

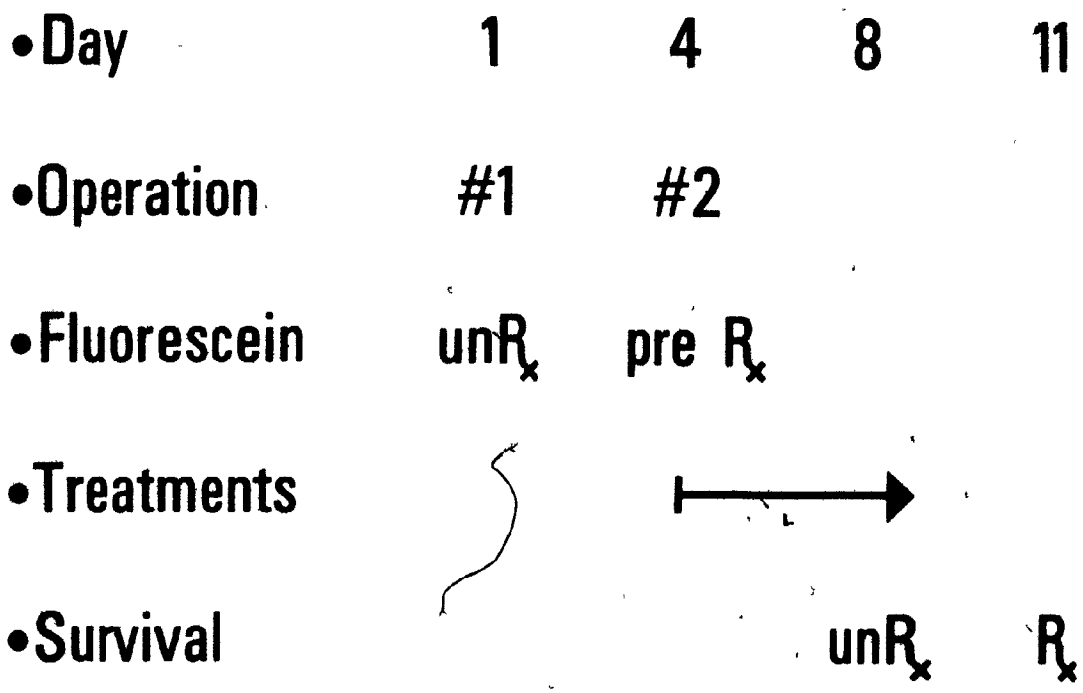

Fig. 6-2 Sequence of events in experiment 1.

TABLE 6-I

EXPERIMENT 1

	Placebo I .1cc/kg 1M g8h	Isoxsuprine .5mg/kg 1Mg8h
Placebo P .2cc/kg IV g24h	Group 1	Group 3
Phenoxybenzamine 2mg/kg IV g24h	Group 2	Group 4

prepared. One gram of powder was dissolved in 50 cc of 100% ethanol which was then mixed with an equal volume of 0.01N HCl acid. The solution was sterilized with 0.22u millipore filter paper and stored in a freezer until used. The placebo solution was the solvent without drug (placebo P, 0.2 cc/kg). Isoxsuprine, 0.5 mg/kg, was given intramuscularly every 8 hours. It was supplied as 5 mg/cc in a 2.5% glycerin solution. This same solution, without isoxsuprine was used for placebo injections (placebo I, 0.1cc/kg). All drugs were placed in coded vials and the researchers were unaware of their contents until the conclusion of the experiment. A true double-blind study was effected.

The data collected included two measures, fluorescence and survival, for each of 8 flaps in 20 animals. Initially, a 6-way analysis of variance was performed and showed no benefit from including the fluorescein data. Therefore, data interpretation was simplified to a 4-way analysis of variance. The variables were isoxsuprine, phenoxybenzamine, flaps and animals. The first null hypothesis tested was that the difference between survival of untreated and treated flaps was 0. The second null hypothesis stated that this difference is the same in one drug group as compared to the other drug groups. The differences were tested against an error variance estimated between

animals and averaged across flaps.

EXPERIMENT 2

In five pigs (21 ± 1.5 kg) flaps were elevated in two operations as in the previous study. Immediately postoperative, all animals recieved one dose each of IV phenoxybenzamine (2 mg/kg) and IV reserpine (2.5 mg/kg). Reserpine was prepared from the powder form by dissolving in a small amount of acetic acid and then 10cc of distilled water. Survival lengths of the treated and untreated sides were subjected to a one tailed t-test.

EXPERIMENT 3

In ten animals (22.3 ± 1.7 kg), the microsphere technique was utilized to measure changes in cutaneous blood flow. The 15 micron spheres, suspended in normal saline, labelled with Ce141, Cr51 or Nb95 were obtained, examined and placed in injection vials (88). Following anesthesia of the pig, three of four dorsal random flaps (18 x 4 cm) were elevated and sutured back in place (Fig. 6-3). The unelevated flap was used for control skin blood flow measurements. A left ventricular catheter and femoral catheter were positioned for sphere injection and reference sample withdrawal. The first spheres, Ce141 labelled, were administered approximately

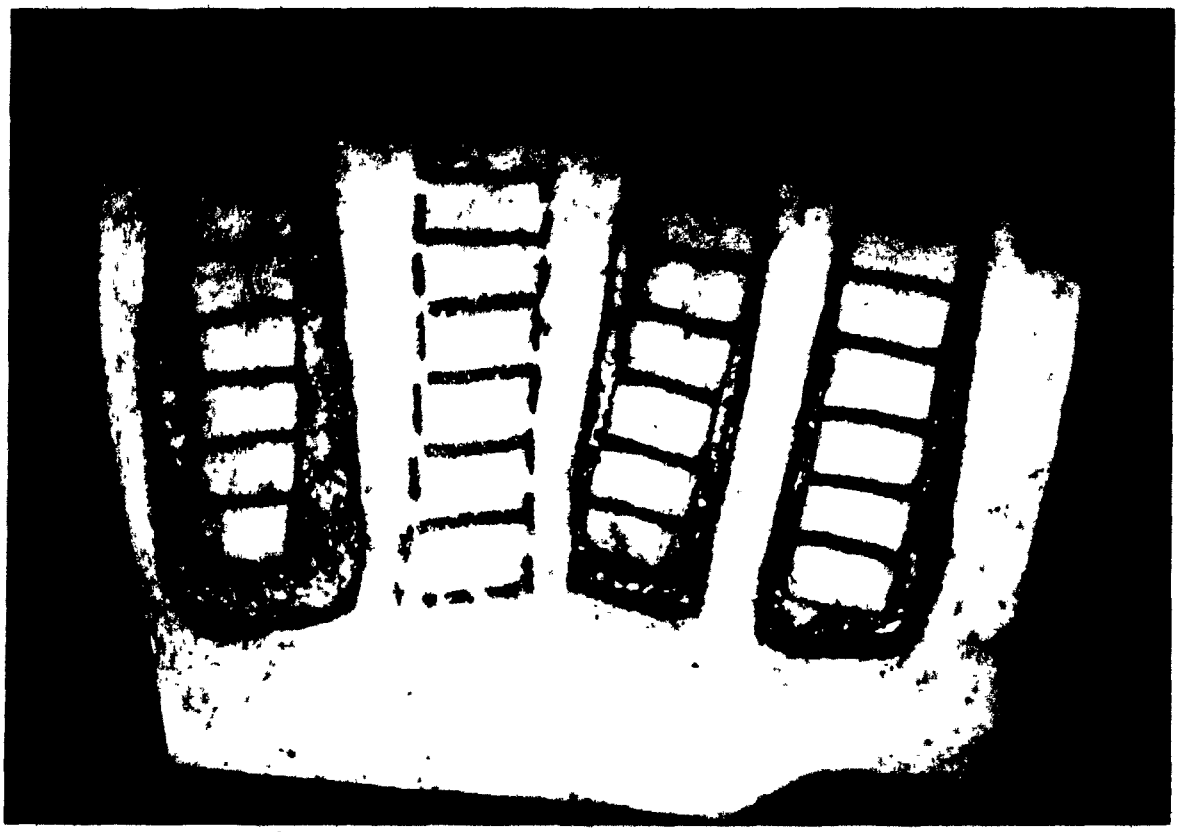

Fig. 6-3 Pig with 3 out of 4 18 x 4 cm flaps elevated. Stripes on flaps represent cuts to be made for division of flaps into 9 segments for counting radioactivity.

two hours after flap construction and reference sample obtained at a rate of 7.64 cc/min for 1 minute. The drug to be tested was then given and 1 hour later the second sphere injection, Cr51 labelled, was carried out. The third sphere injection, Nb95, was given at the dosing interval of the drug being tested, either 8 or 24 hours. Flaps were excised from the pig after the last sphere injection and each flap divided into nine 4 x 2 cm strips. The strips were weighed, placed in scintillation vials with formalin and counted for radioactiviy along with the reference blood samples and standard sphere preparations. Using a Beckman Gamma 8000, specimens were counted for 5 minutes in three windows (0-200 keV for cerium141, 220-400 keV for chromium51 and 400-850 keV for niobium95). The raw counts were entered into the computer which was programed to adjust for background counts and crossover. Flow rates for each strip of skin and average flow rates for control skin, flourescent flap and nonfluorescent flap were calculated for each animal.

Ten animals were tested, two for each of five drug effects: 1) phenoxybenzamine 2 mg/kg IV, 2) placebo P 0.2cc/kg IV, 3) isoxsuprine 0.5 mg/kg IM, 4) placebo I 0.1 cc/kg IM and 5) phenoxybenzamine 2 mg/kg and reserpine 2.5 mg/kg IV. Animals recieving phenoxybenzamine were challenged 30 minutes later with

norepinephrine to test for alpha blockade.

RESULTS

All animals survived the drug treatments although those recieving reserpine ambulated poorly and were unable to eat for approximately 2-3 days after the second operation. Technical difficulties were encountered in administering the intravenous drugs on a daily basis and animals had to be sedated wih thiopental.

EXPERIMENT 1

An initial 6-way analysis of variance showed the only significant differences to be between fluorescein penetration and survival. The fluorescein penetration for all flaps was 5.07 $\pm$ .77 cm (mean $\pm$ S.D.) and the survival was 5.74 $\pm$ 1.38 cm. The difference between survival and fluorescein penetration was not greater for any one group compared to the others. A 4-way analysis of variance showed no statistically significant treatment effect on skin flap survival lengths. The mean difference in survival length between untreated and treated sides of the animals receiving both placebo drugs was 0.57 cm. The difference for animals recieving

phenoxybenzamine was 0.34 cm, isoxsuprine 0.1 cm and the two drugs combined 0.17 cm. There are no significant differences between these differences. An additional observation was that variance between flaps within the same animal was much smaller (S.D.=0.38) than between flaps of different animals (S.D.=2.77). Thus neither phenoxybenzamine, isoxsuprine or placebo injections increase pig skin flap survival length at the doses tested.

EXPERIMENT 2

The mean survival of untreated control flaps was 6.75 $\pm$ .72 cm. The mean survival of treated flaps was 7.94 $\pm$ 1.15 cm. The difference between these approached, but did not reach, significance ($t=1.73$, $df=4$, $p=.08$). The mean fluorescein penetration of the control flaps was 4.98 $\pm$ .45 cm and of the flaps to be treated was 6.24 $\pm$ .55 cm. The difference between these is significant ($t=4.08$, $df=4$, $p<.01$). Reserpine, at the dose tested, did not increase flap survival length.

EXPERIMENT 3

In the placebo injected animals control skin blood flow was variable at the three time intervals tested (Table 6-II). At 8 or 24 hours after injection, flow was higher than preinjection and 1 hour after injection.

TABLE 6-II

	CONTROL SKIN			FLUORESCENT FLAP			NONFLUORESCENT FLAP		
	PRE DRUG	1-POST DRUG	2-POST DRUG	PRE DRUG	1-POST DRUG	2-POST DRUG	PRE DRUG	1-POST DRUG	2-POST DRUG
PLACEBO I	.85	1.27	2.58	.15	.53	.90	0.0	0.7	.20
ISOXSUPRINE	.8	.49	1.32	.56	.52	1.10	.01	.08	.20
PLACEBO P	1.46	.97	1.81	.93	1.01	2.87	.05	.09	.22
PHENOXYBENZ	2.56	1.19	1.81	.95	.86	2.91	.03	.12	.28
PENO+RESERP	2.12	6.9	3.02	.77	6.6	2.6	.08	.87	.29

In the same animals, the fluorescent flap blood flow was less than control at 8 hours but more than control at 24 hours. The nonfluorescent flap blood flow was initially insignificant but by 8 and 24 hours had increased. Reevaluation with fluorescein at 24 hours showed that fluorescein penetration had increased. However, flow calculations for fluorescent and nonfluorescent portions of the flap were based on the initial fluorescein evaluation.

In isoxsuprine and phenoxybenzamine treated animals, no differences from placebo treated animals could be detected in blood flow for control skin, fluorecent flap or nonfluorescent flap. However, in the animals recieving reserpine, flow 1 hour post drug injection was strikingly elevated. This increase was not sustained for 24 hours. Animals who were tested for alpha blockade 30 min after phenoxybenzamine administration all showed an increase in blood pressure in response to the norepinephrine. There appeared to be no alpha blockade effect from the dose of phenoxybenzamine employed.

DISCUSSION

Of the three systemic therapeutic agents tested none showed a significant effect on random flap survival length in pigs. In addition neither phenoxybenzamine or isoxsuprine showed a measurable effect on cutaneous blood flow. The effect of reserpine on random flap survival length approached significance and it did induce a significant increase in cutaneous blood flow.

The systemic and local injection effects of phenoxybenzamine have beed studied previously in rats and pigs but the drug was given both pre- and postoperatively. Myers and Cherry (153) found increased survival by local injection of rat flaps but not in pig flaps (148). Wexler (212) also found an increase survival with local injection into rat flaps. Finseth gave a 2 week pre- and 1 week postoperative intraperitoneal course of phenoxybenzamine to rats and found an increase in flap survival length (6). Unfortunately the control animals in these studies did not receive 2 placebo and thus the effects are difficult to interpret. Smith et al (189) on the other hand administered phenoxybenzamine to rats for 1 week preoperatively and 5 days postoperatively and found no increase in flap survival length.

Phenoxybenzamine is a haloalkylamine that inhibits

responses mediated by alpha adrenergic agonists. Its peak blockade effect develops about 1 hour after administration and disappears with a half life of 24 hours. If blood flow to acutely elevated flaps is being kept submaximal by an obligatory discharge of catecholamines from the surgically cut sympathetic nerves than theoretically blockade of alpha receptors will increase flap blood flow. Following administration of phenoxybenzamine to pigs we were unable to document either increased survival lengths or increased blood flow. One possible explanation of the latter is that the vasodilation induced by halothane anesthesia masked the drug effect. However, when challenged with norepinephrine, the pigs responded with an increase in blood pressure. This demonstrates an ineffective alpha receptor blockade by the dosage of phenoxybenzamine used in the present study. It is still possible that skin flap survival in pigs can be increased by phenoxybenzamine if effective alpha blockade can be achieved by higher doses.

Isoxsuprine has been used systemically in rats and pigs and found effective by one researcher (67) but ineffective by others (29, 179). An additional study in rats showed beneficial effects from isoxsuprine when hematomas were created under the flaps (91). Isoxsuprine is similar chemically to the sympathomimetic

amines and has often been described as a beta adrenergic agonist. However, the drug appears to act as a direct vascular smooth muscle relaxant as its effects are not inhibited by beta adrenergic receptor blockers (32). The pharmacokinetic properties of isoxsupine are poorly understood. When used in obstetrical cases, it is administered as a continuous intravenous drip and when used orally, it is taken three or four times daily. It is unlikely that any therapeutic benefits could be obtained by using the drug only once daily. In the present study, no increased flap survival and no increase in flap or control blood flow could be measured. In one animal, muscle specimens were obtained close to the site of isoxsuprine injection. There was a measurable increase in muscle blood flow at 1 hour but not 8 hours following drug administration. This may explain the increase survival seen with failing myocutaneous flaps (29, 71). We do not feel that there is any indication to continue further studies wih isoxsuprine. There are many other more suitable direct acting vasodilators on the market (eg. hydralazine).

Reserpine has been administered preoperatively to rats to test for its effect on skin flap survival. Two studies (10, 40) showed an increase in flap survival length and one study (103) showed no effect. In the latter study, flow was measured using the microsphere

technique. Flow in the flap base was less than control flow immediately after drug administration but the same as control by 24 hours. Reserpine is a rauwolfia alkaloid that depletes stores of catecholamines. Its effect on depletion is measurable by one hour and maximal by 24 hours. The depletion is partially dependent on nerve activity and can therefore be reduced by nerve section. Reserpine causes an initial sympathomimetic effect and then a subsequent fall in blood pressure with a decrease in peripheral vascular resistance. This is usually most marked in the skin and can cause an increase in cutaneous blood flow. In the present study, phenoxybenzamine was used in combination with reserpine to block the initial sympathomimetic effect induced by catecholamine release. The effect of this drug combination was to cause no increase in flap survival but a significant increase in blood flow to both the flap and control skin. This increase in blood flow occured along with an increase in blood pressure that was noted after reserpine administration. The flow induced changes may have been secondary to the increase in blood pressure caused by reserpine induced catecholamine release, and not secondary to the postulated blockade of adrenergic vasoconstricting factors. The use of anesthetized animals complicates the interpretation of drug induced changes in blood

flow. The fluorescein predicted survival of untreated flap was significantly less than that of the treated flaps. Why this is so, in contrast to experiment 1 where no difference was noted is unclear. Seemingly both groups of animals were subjected to the same stress. This difference in fluorescein staining of the untreated and treated flaps would tend to cancel out the trend towards significance seen in survival.

From the presented experiments it has become obvious that the design and execution of studies testing drug effect on flap survival is more complex than initially realized. The choice of agent to be tested is done on a theoretical basis and the choice of route of administration, dose and dosing interval are somewhat arbitrary. It is imperative that some attempts be made to measure serum or tissue drug levels or drug induced changes in cutaneous blood flow.

The ideal experimental design as related to timing of treatment should be based on the potential clinical applications. We feel strongly that therapeutic measures should not be instituted in experimental flaps until after flap elevation. The length of time that treatment should be continued is still unclear. In experimental pig studies collateral vascularization of flaps is present by 5-8 days (173), and the benefits of surgical delay are onset by 5 days (45). It would seem

clear that treatment should be maintained for at least 5 days to maximize its effectiveness.

When measuring therapeutic effects on skin flap survival length what is the best control measure? In the present study we have used three types of controls. Fluorescein was used as a baseline assessment of the flaps blood flow to ensure that all groups of flaps were starting with equal vascularity. The importance of this measure was noted in experiment 2 where the trend towards significance was cancelled by the unequal fluorescein indices. The second control measure was survival of untreated flaps on the same animal. The third control measure was survival of placebo treated flaps in a different group of animals. In experiment 1, there was no significant difference in these two types of survival control measures. The stress of treatment injections had no effect on flap survival.

When choosing an experimental animal, we prefer the pig not only because of its fixed skin but because many flaps can be created on each animal. The variance of flap survival lengths between animals was much greater than within an individual animal. If each animal serves as his own control the strength of the statistical argument is greatly increased. Ideally one would test several topical therapeutic measures all on each pig, each undergoing only one operation. Systemic

drug treatments necessitate the use of different pigs for each drug thus inducing a greater variance. The variance in studies using rats is so great that larger series need to be used than have in the past. In addition, it is of great importance that findings be reproducable by other researchers. Conclusions are often too quickly drawn and the drugs inappropriately used in clinical cases.

CRITERIA FOR FUTURE PHARMACOLOGIC STUDIES

1) Postoperative treatment only
2) Control flaps on same animal
3) Baseline fluorescein data
4) Double blind experimental design
5) Measurement of drug induced changes in flow

SUMMARY

Pigs with random skin flaps were treated with phenoxybenzamine, isoxsuprine or reserpine. No significant increase in flap survival was detected. In selected animals, cutaneous blood flow was measured using the microsphere technique. Of the drugs tested, reserpine was the only one to cause a significant increase in cutaneous blood flow. Previous clinical and experimental studies on the treatment of failing skin flaps are reviewed. The important criteria for designing future pharmacologic studies are discussed.

ACKNOWLEDGEMENTS

We wish to thank Bristol-Myers, CIBA and Smith, Kline & French for kindly supplying the drugs for this study.

CONCLUSIONS

The experimental investigation of skin flap failure was undertaken to improve our understanding and management of clinical skin flap failures. A new model was developed in a fixed skin animal. The vascular supply to skin in pigs is anatomically more similar to man's than loose skin animals, such as rats and rabbits. The survival patterns of the new pig buttock flap were reliable and reproducable. The length of time that skin flaps could endure an ischemic insult was tested. Both totally ischemic flaps and distally ischemic flaps were able to tolerate an average of thirteen hours of ischemia. Thus, subsequent experiments were designed to evaluate acutely elevated skin flaps within this initial critical thirteen hours. New methods (stab wound blood analysis) of detecting impending skin flap failure were utilized on standard pig buttock flaps. Both hematocrit readings and pH values were useful indices in predicting which region of the flap had questionable viability. Further investigations were made into the precise pathophysiological events of acute skin flap failure using the radioactive microsphere technique. Skin flap failure occurred because of a marked decrease in both nutrient capillary blood flow and total skin blood flow. Arteriovenous shunt flow within the flap had no detrimental effect on survival. Based on these flow studies, attempts to salvage the failing flap were made

both anatomically and pharmacologically. Anatomical augmentation of arterial flow improved flap survival whereas increasing venous drainage had no beneficial effect. The pharmacologic treatment of pigs with failing flaps with systemic phenoxybenzamine, isoxsuprine or reserpine was unsuccessful at increasing flap survival. Future attempts to treat flap failure pharmacologically should be aimed at increasing arterial inflow, or prolonging tolerance to ischemia.

REFERENCES

1 Aarts, H.R. Regional intravascular sympathetic blockade for better results in flap surgery: an experimental study of free flaps, island flaps and pedicle flaps in the rabbit ear. Plast. Reconstr. Surg. 66: 690, 1980.

2 Achaver, B.M., Black, K.S. and Litke, D.K. Transcutaneous pO2 in flaps: a new method of survival prediction. Plast. Reconstr. Surg. 65: 738, 1980.

3 Acland, R.D. A method of eliminating error in the perception of skin color. Br. J. Plast. Surg. 29: 97, 1976.

4 Adamson, J.E., Horton, C.E., Crawford, H.H., Ayers, W.T. The effects of Dimethyl Sulfoxide on the Experimental Pedicle Flap: A Preliminary report. Plast. Reconstr. Surg. 37: 105, 1966.

5 Adamson, J.E., Horton, C.E., Crawford, H.H., and Ayers, W.T. Studies on the Action of Dimethyl Sulfoxide on the Experimental Pedicle Flap. Plast. Reconstr. Surg. 39: 142, 1967.

6 Anderl, H. Storage of a free groin flap. Chir. Plastica (Berl) 4: 41, 1977.

7 Arturson, G., Khanna, N.N. The effects of hyperbaric oxygen, DMSO and complamin on survival of experimental skin flaps. Scand. J. Plast. Reconstr. Surg. 4: 8, 1970.

8 Bakamjian, V.Y. A two-stage method for pharyngoesophageal reconstruction with a primary pectoral skin flap. Plast. Reconstr. Surg. 36: 173, 1965.

9 Baker, D.W. and Holloway, G.A. Assessment of viability in transplanted tissue- doppler techniques using acoustic and optical techniques. In Microsurgical Composite Tissue Transplantation. Serafin, D., Buncke, H.J. (Eds) C.V. Mosby Co, 1979.

10 Ballantyne, D.L., Reid, C.A., Harper, A.D., and Shaw, W.W. The effects of short-term preservation on microvascular free groin flaps in rats. J. Microsurg. 2: 101, 1980.

11 Banis, J.C., Scwartz, K.S., Acland, R.D. Electromagnetic flowmetry - An experimental method for continuous blood flow measurement using a new island flap model. Plast. Reconstr. Surg. 66: 534, 1980.

12 Barisoni, D.M. and Veall, N. Effect of thymoxamine on circulation in skin flaps and in denervated skin. Lancet i: 400, 1969.

13 Barron, J.N., Veall, N. and Arnott, D.G. The measurement of the local clearance of radioactive sodium in tubed skin pedicles. Brit. Jour. Plast. Surg. 4: 16, 1951.

14 Bellman, S. and Velander, E. Vascular transformation in experimental tubed pedicles. Br. J. Plast. Surg. 12: 1, 1959.

15 Bhaquat, B.M., Pearl, R.M. and Laub, D.R. Uses of the rectus femoris myocutaneous flap. Plast. Reconstr. Surg. 62: 698, 1978.

16 Black, M.J.M., Chait L., O'Brien, B.McC., Sykes, P.J. and Sharzer, L.A. How soon may the axial vessels of a surviving free flap be safely ligated: A study in pigs. Brit. J. Plast. Surg. 31: 295, 1978.

17 Blair, V.P. The delayed transfer of long pedicle flaps in plastic surgery. Surg. Gynec. and Obst. 33: 261, 1921.

18 Bostwick, J., Vasconez, L.O., Jurkiewicz, M.J. Breast reconstruction after a radical mastectomy. Plast. Reconstr. Surg. 61: 682, 1978.

19 Braithwaite, F. Preliminary observations on the vascular channels in tubed pedicles. Brit. J. Plast. Surg. 3: 40, 1950.

20 Braithwaite, F. Some observations on the vascular channels in tubed pedicles - II. Brit. J. Plast. Surg 4: 28, 1951.

21 Braithwaite, F., Farmer, F.T., Edwards, J.R.G. and Inkster, J.S. Simultaneous measurements of blood flow and Sodium 24 clearance in the skin. Brit. J. Plast. Surg. 12: 189, 1959.

22 Braithwaite, F., Farmer, F.T. and Herbert, F.I. Observations on the vascular channels of tubed pedicles using radioactive sodium - III. Brit. J. Plast. Surg. 4: 38, 1951.

23 Brown, J. and McDowell, F. Skin Grafting. J.B. Lippincott Company, Philadelphia, Pa., 1959.

24 Brown, W.F., Litzow, T.J., Anderson, J.A. and Baldes, E.J. An experimental method of studying blood flow in canine bipedicle tube flaps. Mayo Clin Proc. 44: 742, 1969.

25 Campbell, J. and Pennefather, C.M. The Blood Supply of Muscles. Lancet I : 294, 1919.

26 Cannon, B., Lischer, C.E., Davis, W.B., Chasko, S., Moore, A., Murray, J.E. and McDowell, A. The use of open jump flaps in lower extremity repairs. Plast. Reconstr. Surg. 2: 336, 1947.

27 Challoner, A.V.J. Measurement of cutaneous blood flow by isotope clearance and thermal conductance methods. In Methods in Microcirculation Studies. T.J. Ryan, B. Jolles, and G. Holti, (Ed's) 43-50, H.K. Lewis, London, 1972.

28 Cherry, G.W. The effect of isoxsuprine on muscle and skin flap survival in the pig. Brit. J. Plast. Surg. 31: 295, 1978.

29 Cherry, G.W. The differing effects of isoxsuprine on muscle flap and skin flap survival in the pig. Plast. Reconstr. Surg. 64: 670, 1979.

30 Cherry, G.W., Myers, M.B., Ardran, G. and Ryan, T.J. The effects of gravity on delayed and transplanted delayed tubed flaps. Plast. Reconstr. Surg. 64: 156, 1976.

31 Cherry, G.W. and Ryan, T.J. The effect of ischemia and reperfusion on tissue survival. In Microvascular Injury, Major Problems in Dermatology Series. Ryan, T.J. (Ed) London, Saunders, 1976.

32 Coffman, J.D. Vasodilator drugs in peripheral vascular disease. N.E.J.M. 300: 713, 1979.

33 Conway, H. Radioactive Sodium Clearance as a test of Circulatory efficiency of tubed pedicles and flaps. Proc. Soc. Exp. Biol. 77: 348, 1949.

34 Conway, H., Stark, R.B. and Docktor, J.P. Vascularization of Tubed Pedicles. Plast. Reconstr. Surg. 4: 133, 1949.

35 Corso, P.F. Variations of the arterial, venous and capillary circulation of the soft tissues of the head by decades as demonstrated by the methyl methacrylate injection technique, and their application to the construction of flaps and pedicles. Plast. Reconstr. Surg. 27: 160, 1961.

36 Creech, B.J., Miller, S.H. Evaluation of Circulation in Skin Flaps. In Skin Flaps. Grabb, W.C., Myers, M.B. (Eds) Little, Brown & Company, Boston, 1975.

37 Crismon, J.M. and Fuhrman, F.A. The use of fluorescein as an indicator of local blood flow. Distribution of fluorescein in body fluids after IV injection. J. Clin. Invest. 26: 259, 1947.

38 Crismon, J.M. and Fuhrman, F.A. Studies on gangrene following cold injury. V The use of fluorescein as an indicator of local blood flow: Fluorescein tests in experimental frostbite. J. Clin. Invest. 26: 268, 1947.

39 Cutting, C., Ballantyne, D., Shaw, W. and McCarthy, J. Effect of blood pressure and viscosity on skin flap blood flow and fluorescein dye distance: a new experimental model. Paper presented at the 26th Annual Plastic Surgery Research Council Meeting, Springfield, Illinois, 1981.

40 Cutting, C.B., Koss, N. and Robson, M.C. Pharmacology and Flap Physiology. Surgical Forum, p.563, 1976

41 Daniel, R.K. The anatomy and Hemodynamics of the Cutaneous Circulation and their influence on Skin Flap Design. In Skin Flaps. Grabb, W.C., and Myers, B. (Eds) Boston, Little, Brown and Company, 1975.

42 Daniel, R.K. Towards and anatomical and hemodynamic classification of skin flaps. Plast. Reconstr. Surg. 56: 330, 1975.

43 Daniel, R.K. Mandibular reconstruction with free tissue transfers. Ann. Plast. Surg. 1: 346, 1978.

44 Daniel, R.K., Cunningham, D.M. and Taylor, G.I. The Deltopectoral Flap: An Anatomical and Hemodynamic Approach. Plast. Reconstr. Surg. 55: 275, 1975.

45 Daniel, R.K. and Kerrigan, C.L. Skin flaps: An anatomical and hemodynamic approach. Clin. Plast. Surg. 6: 181, 1979.

46 Daniel, R.K., Kerrigan, C.L. and Gard, D.A. The great potential of the intercostal flap for torso reconstruction. Plast. Reconstr. Surg. 61: 653, 1978.

47 Daniel, R.K., Lidman, D. and Charbonneau, R. Vascular complications in free flap transfers. Paper presented at the 49th Annual Convention of the American Society of Plastic and

Reconstructive Surgeons, New Orleans, 1980.

48 Daniel, R.K., and Taylor, G.I. Distant transfer of an island flap by microvascular anatomoses. Plast. Reconstr. Surg. 52: 111, 1973.

49 Daniel, R.K. and Terzis, J.K. Reconstructive Microsurgery. Little, Brown and Company, Boston, 1977.

50 Daniel, R.K., Terzis, J.K. and Cunningham, D.M. Sensory Skin Flaps for Coverage of Pressure Sores in Paraplegic patients: A premilinary report. Plast. Reconstr. Surg. 58: 317, 1976.

51 Daniel, R.K., Terzis, J.K. and Schwarz, G. Neurovascular Free Flaps. Plast. Reconstr. Surg. 56(1): 13, 1975.

52 Daniel, R.K. and Wiliams, H.B. The free transfer of skin flaps by microvascular anastomoses: an experimental study and a reappraisal. Plast. Reconstr. Surg. 52: 16, 1973.

53 Davis, J.S. Story of Plastic Surgery. Ann. Surg. 113: 641, 1941.

54 Dawson, R.L.G. Complications of the Cross-leg Flap Operation. Proc. Roy. Soc. Med. 65: 626, 1972.

55 DeHaan, C.R. and Stark, R.B. Vascular reinforcement of pedicled tissues: Quantitation by arteriography of increase in circulation obtained using histamine iontophoresis. Surg. Forum 8: 578, 1958.

56 Dingwall, J.A. and Lord, J.W. The fluorescein test in the management of tubed (pedicle) flaps. Bull. Johns Hopkins Hosp. 73: 129, 1943.

57 Donski, P.K., Franklin, J.D., Hurley, J.V., and O'Brien, B.M. The effects of cooling on experimental free flap survival. Brit. J. Plast. Surg. 33: 353, 1980.

58 Douglas, B. and McNeely, G. The role of absorption of radioactive isotopes as a test of the efficiency of the circulation in pedicle flaps. Plast. Reconstr. Surg. 20: 350, 1957.

59 Earle, A.S., Fratianne, R.B. and Nunez, R.D. The relationship of hematocrit levels to skin flap survival in the dog. Plast. Reconstr. Surg. 54: 341, 1974.

60 Edstrom, L.E., Dibbell, D.G. and Hedberg, J. A new model for the study of skin flap blood flow and the delay phenomenon. Proceedings of the 24th Annual Plastic Surgery Research Council Meeting, Dallas, Texas, 1979.

61 Edstrom, L.E., Hopp, D., Robson, M. and Surgeon, J.W. The use of a rapid new technique in the demonstration of cutaneous catecholamines. Paper presented at the 23rd Annual Plastic Surgery Research Council Meeting, Richmond, Virginia, 1978.

62 Erikson, E. and Robson, M.C. Experimental flap delay with formic acid. Br. J. Plast. Surg. 31: 238, 1978.

63 Esser, J.F.S. Studies in plastic surgery of the face. Ann. Surg. 65: 297, 1917.

64 Esser, J.F.S. Biological or Arterial Flaps of the Face. (English Language Ed.) London: Royal Society of Medicine, 1931.

65 Feldman, J.J., Cohen, B.E., and May, J.W. The medial gastocnemius myocutaneous flap. Plast. Reconstr. Surg. 61: 531, 1978.

66 Finseth, F. Clinical salvage of three failing skin flaps by treatment with a vasodilator drug. Plast. Reconstr. Surg. 63: 304, 1979.

67 Finseth, F. and Adelberg, M.G. Prevention of skin flap necrosis by a course of treatment with vasodilator drugs. Plast. Reconstr. Surg. 61: 738, 1978.

68 Finseth, F. and Adelberg, M.G. Experimental work with isoxuprine for prevention of skin flap necrosis and for treatment of the failing flap. Plat. Reconstr. Surg. 63: 94, 1979.

69 Finseth, F. and Cutting. An experimental neurovascular island skin flap for the study of the delay phenomenon. Plast. Reconstr. Surg. 61: 412, 1978.

70 Finseth, F. and Zimmerman, J. Prevention of necrosis in island myocutaneous flaps in the pig by treatment with isoxsuprine. Plast. Reconstr. Surg. 64: 536, 1979.

71 Finseth, F., Zimmerman, J. and Liggins, D. Prevention of muscle necrosis in an experimental neurovascular island flap by a vasodilator drug - isoxsuprine. Plast. Reconstr. Surg. 63: 774, 1979.

72 Fish, W.W. A multidisciplinary approach to the management of pressure sores in spinal cord injured patients. University of Southern California Research Seminars, Ranchos Los Amigos Hospital, 1975.

73 German, W., Finesilver, E.M. and Davis, J.S. Establishment of circulation in tubed skin flaps: experimental study. Arch. Surg. 26: 27, 1933.

74 Gingrass, R.P., Culf, N.K., Garrett, W.S. and Mladick, R.A. Complications with the deltopectoral flap. Plast. Reconstr. Surg. 49: 501, 1972.

75 Glinz, W. and Clodius, L. Measurement of tissue pH for predicting viability in pedicle flaps: experimental studies in pigs. Br. J. Plast. Surg. 25: 111, 1972.

76 Goldwyn, R.M., Lamb, D.L. and White, W.L. An experimental study of large island flaps in dogs. Plast. Reconstr. Surg. 31: 528, 1963.

77 Grabb, W. C. and Myers, M.B. Skin Flaps, Little, Brown and Company, Boston, 1975.

78 Grossman, J.A.I., McGonagle, B., Dowden, R.V. and Dinner, M.I. Effect of hyaluronidase and dimethylsulfoxide (DMSO) on skin flap survival. Paper presented at the 49th Annual Convention of the American Society of Plastic and Reconstructive Surgeons, New Orleans, 1980.

79 Gruber, R.P., Billy, L.I., Heitkamp, D.H. and Amato, J.J. Hyperbaric oxygenation of pedicle flaps without oxygen toxicity. Plast. Reconstr. Surg. 46: 477, 1970.

80 Guba, A.M. Study of the delay phenomenon in axial pattern flaps in pigs. Plast. Reconstr. Surg. 63: 550, 1979.

81 Guba, A.M. and Callahan, J. Nutrient blood flow in delayed axial pattern skin flaps in pigs. Plast. Reconstr. Surg. 64: 372, 1979.

82 Guba, A.M., Zinner, M.J., and Hobson, R.W. Regional hemodynamics of a pedicle flap: evaluation by distribution of radioactive microspheres. J. Surg. Res. 25: 274, 1978.

83 Guthrie, R.H., Goulian, D. and Cucin, R.L. Predicting the extent of viability in flaps by measurement of gas tensions, using a mass spectrometer. Plast. Reconstr. Surg. 50: 385, 1972.

84 Harell, G.S., Dickhoner, W.A. and Breman, R.A The simultaneous visualization of microspheres and blood flow in the microvascular bed of the hamster cheek pouch. Microvasc. Res. 13: 203, 1977.

85 Harii, K. and Ohmori, S. Free flap transfers. In Proceedings of the Sixth International Congress of Plastic and Reconstructive Surgery. Paris: Masson, 1975.

86 Heistad, D.D. and Abboud, F.M. Factors that influence blood flow in skeletal muscle and skin. Anesthesiology, 41: 139, 1974.

87 Heckler, F.R., White, T.Z. The effects of denervation on skin blood flow and skin survival in musculocutaneous flaps. Paper presented at the 26th Annual Plastic Surgery Research Council Meeting, Springfield, Illinois, May 1981.

88 Heymann, M.A., Payne, B.D., Hoffman, J.I.E., Rudolph, A.M. Blood flow measurements with radionuclide-labeled particles. Prog. cardiovasc. Dis. 70: 55, 1977.

89 Hill, H.L., Brown, R.G. and Jurkiewicz, M.J. The transverse lumbosacral back flap. Plast. Reconstr. Surg. 62: 177, 1978.

90 Hill, H.L., Nahai, F. and Vasconez, L.O. Tensor fascia lata myocutaneous free flap. Plast. Reconstr. Surg. 61: 517, 1978.

91 Hillelson, R.L., Glowacki, J., Healey, N.A. and Mulliken, J.B. A microangiographic study of hematoma associated flap necrosis and salvage with isoxsuprine. Paper presented at the 25th Annual Plastic Surgery Research Council Meeting, Hershey, Pennsylvania, 1980.

92 Hoffmeister, F.S. Studies on timing of tissue transfer in reconstructive surgery, I. Effect of delay on circulation in flaps. Plast. Reconstr. Surg. 19: 283, 1957.

93 Holti, G. and Mitchell, K.W. Estimation of the nutrient skin blood flow using a segmented thermal clearance probe. Clin. Exp. Dermatol. 3: 189, 1978.

94 Hoopes, J.E. Pedicle Flaps - An Overview. In Symposium on Basic Science in Plastic Surgery. Krizek, T.J. and Hoopes, J.E. (Ed's). The C.V. Mosby Company, Saint Louis, 1976.

95 Hynes, W. A simple method of estimating blood flow with special reference to the circulation in pedicled skin flaps and tubes. Brit. J. Plast. Surg. 1: 159, 1948.

96 Hynes, W. The blood vessels in skin tubes and flaps. Brit. J. Plast. Surg. 3: 165, 1950-1951.

97 Hynes, W. The Blue Flap: A Method of Treatment. Brit. J. Plast. Surg. 4: 166, 1951.

98 Hynes. W. The determination of the changes in the small vessels of a flap after division of its pedicle. Brit. J. Plast. Surg. 9: 251, 1956-1957.

99 Hynes, W. and MacGregor, A.G. The use of fluorescein in estimating the blood flow in pedicled skin flaps. Br. J. Plast. Surg. 2: 4, 1949

100 Jonsson, C.E., Jurell, G., Nylen, B. and Pardeya, N. Effect of phentolamine and propranolol on the survival of experimental skin flaps. Scand. J. Plast. Reconstr. Surg. 9: 98, 1975.

101 Jurell, G. and Jonsson, C.E. Increased survival of experimental skin flaps in rats following treatment with antiadrenergic drugs. Scand. J. Plast. Reconstr. Surg. 10: 169, 1976.

102 Jurell, G., and Kaijser, L. The influence of varying pressure and duration of treatment with hyperbaric oxygen on the survival of skin flaps. Scand. J. Plast. Reconstr. Surg. 7: 25, 1973.

103 Kennedy, T.J., Pistone, G. and Miller, S.H. The effect of reserpine on microcirculatory flow in rat flaps. Plast. Reconstr. Surg. 63: 101, 1979.

104 Kernahan, D.A., Zingg, W. and Kay, C.W. The effect of hyperbaric oxygen on the survival of experimental skin flaps. Plast. Reconstr. Surg. 36: 19, 1965.

105 Kerrigan, C.L. and Daniel, R.K. An analysis of experimental free flap models. Paper presented at the 24th Annual Plastic Surgery Research Council Meeting, Dallas, Texas, 1979.

106 Kerrigan, C.L. and Daniel, R.K. The intercostal flap: An anatomical and hemodynamic approach Ann. Plast. Surg. 2: 411, 1979.

107 Ketchum, L.D., Ellis, S.S., Robinson, D.W. and Masters, F.W. Vascular augmentation of pedicled tissue by combined histamine iontophoresis and hypertensive perfusion. Plast. Reconstr. Surg. 39: 138, 1967.

108 Kiehn, C.L. and des Prez, J.D. Effects of local hypothermia on pedicle flap tissue. I Enhancement of survival of experimental pedicles. Plast. Reconstr. Surg. 25: 349, 1960.

109 Koehnlein, H.E. and Lemperle, G. Experimental studies on the effect of DMSO on pedicle flaps. Surg. 67: 672, 1970.

110 Krizek, T.J. and Robson, M.C. Potential pitfalls in the use of the deltopectoral flap. Plast. Reconstr. Surg. 50: 326, 1972.

111 Krizek, T.J., Tani, T., Desprez, J.D., and Kiehn, C.L. Experimental transplantation of composite grafts by microsurgical vascular anastomoses. Plast. Reconstr. Surg. 36: 538, 1965.

112 Lange, K. and Boyd, L.J. The use of fluorescein to determine adequacy of circulation. Med. Clin. N. Amer. 26: 943, 1942.

113 Leung, P.C. Prolonged refrigeration in toe-to-hand transfer- Case report. J. Hand Surg. 6: 152, 1981.

114 Littler, J. W. The neurovascular pedicle method of digital transposition for reconstruction of the thumb. Plast. Reconstr. Surg. 12: 303, 1953.

115 Lukash, F.N. and May, J.W. Vessel patency assessment with heat sensing monitors. Paper presented at the 26th Annual Plastic Surgery Research Council Meeting, Springfield, Illinois, 1981.

116 Macht, S.D. and Frazier, W.H. The role of endogenous bacterial flora in skin flap survival. Plast. Reconstr. Surg. 65: 50, 1980.

117 Manchot, C. Die Hautarterien des menschlichen Koreers. Leipzig: Vogel, p.1-56, 1889.

118 Mathes, S.J., Nahai, F. and Vasconez, L.O. Myocutaneous free flap transfer: anatomical and experimental considerations. Plast. Reconstr. Surg. 62: 162, 1978.

119 May, J.W. Digit replantation with full survival after 28 hours of cold ischemia. Plast. Reconstr. Surg. 67: 566, 1981.

120 May, J.W., Chait, L.A., Cohen, B.E. and O'Brien, B.M. Free neurovascular flap from the first web of the foot in hand reconstruction. J. Hand. Surg. 2: 387, 1977.

121 May, J.W., Chait, L.A., O'Brien, B.M. and Hurley, J.V. The no-reflow phenomenon in experimental free flaps. Plast. Reconstr. Surg. 61: 256, 1978.

122 May, J.W., and Gallico, G.G. Upper extremity replantation. Curr. Probl. Surg. 17: 635, 1980.

123 McCraw, J.B. and Dibbell, D.G. Experimental definition of independent myocutaneous vascular territories. Plast. Reconstr. Surg. 60: 212, 1977.

124 McCraw, J.B., Dibbell, D.G. and Carraway, J.H. Clinical definition of independent myocutaneous vascular territories. Plast. Reconstr. Surg. 60 341, 1977.

125 McCraw, J.B., Fishman, J.H. and Sharzer, L. The versatile gastrocnemius myocutaneous flap. Plast. Reconstr. Surg. 62: 15, 1978.

126 McCraw, J.B. and Furlow, L.T. The dorsalis pedis arterialized flap: A clinical study. Plast. Reconstr. Surg. 55: 177, 1975.

127 McCraw, J.B., Massey, F.M., Shanklin, K.D. and Horton, C.E. Vaginal reconstruction with gracilis myocutaneous flaps. Plast. Reconstr. Surg. 58: 176, 1976.

128 McCraw, J.B., Myers, B. and Shanklin, K.D. The value of fluorescein in predicting the viability of arterialized flaps. Plast. Reconstr. Surg. 60: 710, 1977.

129 McCraw, J.B., Penix, J.O. and Baker, J.W. Repair of major defects of the chest wall and spine with the latissimus dorsi myocutaneous flap. Plast. Reconstr. Surg. 62: 197, 1978.

130 McFarlane, R.M., Heagy, F.C., Radin, S., Aust, J.C. and Wermuth, R.E. A study of the delay phenomenon in experimental pedicle flaps. Plast. Reconstr. Surg. 35: 245, 1965.

131 McFarlane, R.M., Laird, J.J., Lamon, R., Finlayson, A.J.R. and Johnson, R. Evaluation of dextran and DMSO in experimental pedicle flaps. Plast. Reconstr. Surg. 41: 64, 1968.

132 McFarlane, R.M. and Wermuth, R.E. Use of hyperbaric oxygen to prevent necrosis in experimental pedicle flaps and composite skin grafts. Plast. Reconstr. Surg. 37: 422, 1966.

133 McGrath, M.H. How topical dressings salvage "questionable" flaps: experimental study. Plast. Reconstr. Surg. 67: 653, 1981.

134 McGregor, I.A. Fundamental Techniques of Plastic Surgery 7th edition. Churchill Livingstone, Edinburgh, 1980.

135 McGregor, I.A. and Jackson, I.T. The groin flap. Brit. J. Plast. Surg. 25: 3, 1972.

136 McGregor, I.A. and Morgan, G. Axial and random pattern flaps. Brit. J. Plast, Surg. 26: 202, 1973.

137 Mendelson, B.C., and Woods, J.E. Effect of corticosteroids on the surviving length of skin flaps in pigs. Brit. J. Plast. Surg. 31: 293, 1978.

138 Mes, L.G.B. Improving flap survival by sustaining cell metabolism within ischemic cells: A study using rabbits. Plast. Reconstr. Surg. 65: 56, 1980.

139 Milton, S.H. Survival of experimental pedicled skin flaps. Doctoral thesis. Bodleian and Kilner Libraries, Oxford, England, 1970.

140 Milton, S.H. Pedicled skin flaps: The fallacy of the length/width ratio. Brit. J. Surg. 57: 502, 1970.

141 Milton, S.H. Experimental studies on island flaps. Plast. Reconstr. Surg. 48: 574, 1971.

142 Milton, S.H. Experimental studies on island flaps. II ischemia and delay. Plast. Reconstr. Surg. 49: 444, 1972.

143 Milton, S.H., and Corbett, J.L. Failure to increase the survival of experimental flaps by histamine and hypertension. Plast. Reconstr. Surg. 43: 235, 1969.

144 Morris, R., Polak, E and Serafin, D. Assessment of viability in transplanted tissue-electromagnetic flowmeter. In Microsurgical Composite Tissue Transplantation. Serafin, D., Buncke, H.J. (Eds). C.V. Mosby Co, 1979.

145 Moustafa, H.E. and Hopewell, J.W. The evaluation of an isotope clearance technique for the measurement of skin blood flow in the pig. Microvascular Res. II: 147, 1976.

146 Mutter, T.D. Cases of deformity from burns relieved by operations. Amer. J. Med. Sci. 4: 66, 1842.

147 Myers, M.B. Prediction of skin slough at the time of operation with the use of fluorescein dye. Surgery 51: 158, 1962.

148 Myers, M.B. Attempts to augment survival in skin flaps - Mechanism of the delay phenomenon. In Skin Flaps Grabb, W.C. and Myers, M.B. (eds) Little, Brown and Company, Boston, 1975.

149 Myers, M.B. How to photograph fluorescein in a normally illuminated room. Plast. Reconstr. Surg. 67: 809, 1981.

150 Myers, M.B. and Cherry, G. Design of skin flaps to study vascular insufficiency. J. Surg. Res. 7: 399, 1967.

151 Myers, M.B. and Cherry, G. Augmentation of tissue survival by delay: an experimental study in rabbits. Plast. Reconstr. Surg. 39: 397, 1967.

152 Myers, M.B. and Cherry, G. Causes of necrosis in pedicle flaps. Plast. Reconstr. Surg. 42: 43, 1968.

153 Myers, M.B. and Cherry, G. Enhancement of Survival in Devascularized Pedicles by the use of Phenoxybenzamine. Plast. Reconstr. Surg. 41: 254, 1968.

154 Myers, M.B. and Cherry, G. Differences in the delay phenomenon in the rabbit, rat and pig. Plast. Reconstr. Surg. 47: 73, 1971.

155 Myers, M.B., Cherry, G. and Bombet, R. On the lack of any effect of gravity on the survival of tubed flaps: An experimental study in rabbits and pigs. Plastic and Reconstructive Surgery 51: 428, 1973.

156 Myers, M.B., Cherry, G. and Milton, S. Tissue gas levels as an index of the adequacy of circulation: The relation between ischemia and the development of collateral circulation (delay phenomenon). Surgery 71: 15, 1972.

157 Nakayama, Y., Soeda, S. and Kasai, Y. Flaps nourished by arterial inflow through the venous system: An experimental investigation. Plast. Reconstr. Surg. 67: 328, 1981.

158 Nathanson, S.E. and Jackson, R.T. Blood flow measurements in skin flaps. Arch. Otolaryngol. 101: 354, 1975.

159 Neilsen, R.W. and Parkin, J.L. Skin flap survival; influence of infection, anemia and tubing. Arch. Otolaryng. 102:. 727, 1976.

160 Norberg, K.A. and Palmer, B. Improvement of blood circulation in experimental skin flaps by phentolamine. Europ. J. Pharm. 8: 36, 1969.

161 O'Brien, B.M., Morrison, W.A., Ishida, H., MacLeod, A.M. and Gilbert, A. Free flap transfers with microvascular anastomoses. Br. J. Plast. Surg. 27: 220, 1974.

162 Ohmori, K., Sekiguchi, J. and Ohmori, S. Total rhinoplasty with a free osteocutaneous flap. Plast. Reconstr. Surg. 63: 387, 1979.

163 Orticochea, M. The musculocutaneous flap method: An immediate and heroic substitute for the method of delay. Brit. J. Plast. Surg. 25: 196, 1972.

164 Owens, N. A compound neck pedicle designed for the repair of massive defects: formation, development and application. Plast. Reconstr. Surg. 15: 369, 1955.

165 Palmer, B. Sympathetic denervation and reinnervation of cutaneous blood vessels following surgery. Scand. J. Plast. Reconstr. Surg. 4: 93, 1970.

166 Palmer, B. Factors influencing the elimination rate of 133 Xenon injected intracutaneously. Scand. J. Plast. Reconstr. Surg. 6: 1, 1972.

167 Palmer, B., Jurell, G. and Norberg, K.A. The blood flow in experimental skin flaps in rats studied by means of Xenon 133 clearance method. Scand. J. Plast. Reconstr. Surg. 6: 6, 1972.

168 Patterson, I.J.S. The survival of skin flaps in the pig. Brit. J. Plast. Surg. 21: 113, 1968.

169 Perrins, D.J.D. The effect of hyperbaric oxygen on ischemic skin flaps. In Skin Flaps, Grabb, W.C. and Myers, M.B. (Ed's), Little, Brown and Company, Boston, 1975.

170 Perrins, D.J.D. Hyperbaric oxygenation of flaps. Brit. J. Plast. Surg. 19: 110, 1966.

171 Pless, J. and Sondergaard, W. The effect of halothane on tissue necrosis in pedicle skin flaps in pigs. Scand. J. Plast. Reconstr.Surg. 6: 13, 1972.

172 Prather, A., Blackburn, J.P., Williams, T.R. and Lynn, J.A. Evaluation of tests for predicting the viability of axial pattern skin flaps in the pig. Plast. Reconstr. Surg. 63: 250, 1979

173 Rasmussen, D.L. and Bennett, J.E. Aquisition of vascular supply by cutaneous flaps in pigs. Surg. Forum 27: 568, 1976.

174 Reinisch, J.F. The pathophysiology of skin flap circulation - the delay phenomenon. Plast. Reconstr. Surg. 54: 585, 1974.

175 Reller, C., Sheridan, J. and Aust, J.B. Capillary blood flow determination with Krypton 85. Fed. Proc. 23: 443, 1964.

176 Ruberg, R.L. and Falcone, R.E. Effect of Protein Depletion on the Surviving Length in Experimental Skin Flaps. Plast. Reconstr. Surg. 61: 581, 1978:

177 Rudolph, A.M. and Heymann, M.A. The circulation of the fetus in utero: methods for studying distribution of blood flow, cardiac output and organ blood flow. Circ. Res. 21: 163, 1967.

178 Sasaki, A., Fokuda, O. and Soeda, S. Attempts to increase the surviving length in skin flaps by a moist environment. Plast. Reconstr. Surg. 64: 526, 1979.

179 Sasaki, A. and Harii, K. Lack of effect of isoxsuprine on experimental random flaps in the rat. Plast. Reconstr. Surg. 66: 105, 1980.

180 Sasaki, G.H. and Pang, C.Y. Hemodynamics and viability of acute neurovascular island skin flaps in rats. Plast. Reconstr. Surg. 65: 152, 1980.

181 Sasaki, G.H. and Pang, C.Y. Experimental evidence for involvement of prostaglandins in viability of acute skin flaps: effects on viability and mode of action. Plast. Reconstr. Surg. 67: 335, 1981.

182 Sawhney, C.P. The role of heparin in restoring the blood supply in ischemic skin flaps: an experimental study in rabbits. Brit. J. Plast. Surg. 33: 430, 1980.

183 Selye, H. Ischemic necrosis: Prevention by stress. Science, 156: 1262, 1967.

184 Serafin, D., Shearin, J.C. and Georgiade, N.G. The vascularization of free flaps. Plast. Reconstr. Surg. 60: 233, 1977.

185 Serafin, D., Villareal, A. and Georgiade, N. Fourteen free groin flap transfers. Plast. Reconstr. Surg. 57: 707, 1976.

186 Shaw, D.T. and Payne, R.L. One-staged tubed abdominal flaps. Surg. Gynecol. Obstet. 83: 205, 1946.

187 Silverman, D.G., LaRossa, D.D., Barlow, C.H. et al. Quantification of tissue fluorescein delivery and prediction of flap viability with the fiberoptic dermofluorometer. Plast. Reconstr. Surg. 66: 545, 1980.

188 Smahel, J. and Clodius, L. The blood vessel system of free human skin grafts. Plast. Reconstr. Surg. 47: 61, 1971.

189 Smith, G., Weeks, P.M. and Wray, C. Pharmacologic delay of neurovascular island skin flaps in rats. Paper presented at the 25th Annual Plastic Surgery Research Council Meeting, Hershey, Pennsylvania, 1980.

190 Smith, P.J. The vascular basis of axial pattern flaps. Brit. J. Plast. Surg. 26: 150, 1973.

191 Smith, P.J., Foley, B., McGregor, I.A. and Jackson, I.T. The anatomical basis of the groin flap. Plast. Reconstr. Surg. 49: 41, 1976.

192 Stark, R.B. Blood supply of cross-leg pedicle flaps. Plast. Reconstr. Surg. 3: 694, 1948.

193 Stark, R.B. Plastic Surgery. New York, Hoeber, 1962.

194 Stell, P.M. The pig as an experimental model for skin flap behaviour: a reappraisal of previous studies. Brit. J. Plast. Surg. 30: 1, 1977.

195 Stell, P.M. The viability of skin flaps. Ann. Roy. Coll. Surg. Eng. 59: 236, 1977.

196 Stirrat, C.R., Seaber, A.V., Urbaniak, J.R. and Bright, D.S. Temperature monitoring in digital replantation. J. Hand Surg. 3: 342, 1978.

197 Stranc, M.F., Labandter, H. and Roy, A. A review of 196 tubed pedicles. Brit. J. Plast. Surg. 28: 54, 1975.

198 Stranc, M.F. and Stranc, W.E. Tubed Skin Flaps. Chapter 30 in Skin Flaps. Grabb, W.C. and Myers, M.B. (Ed's), Little, Brown and Company, 1975.

199 Strauch, B. and Murray, D.E. Transfer of composite graft with immediate suture anastomoses of its vascular pedicle measuring less than 1mm in external diameter using microsurgical techniques. Plast. Reconstr. Surg. 40: 325, 1967.

200 Takayanagi, S. and Ogawa, Y. Effects of pentoxifylline on flap survival. Plast. Reconstr. Surg. 65: 763, 1980.

201 Tauxe, W.N., Simons, J.N., Lipscomb, P.R. and Hamamoto, K. Determination of vascular status of pedicle skin flaps by use of radioactive pertechnetate (99m Tc). Surg. Gyn. Obst. 130: 87, 1970.

202 Taylor, G.I. and Watson, N. One stage repair of compound leg defects with free revascularized flaps of groin skin and iliac bone. Plast. Reconstr. Surg. 61: 494, 1978.

203 Thorvaldsson, S. E. and Grabb, W. C. The intravenous fluorescein test as a measure of skin flap viability. Plast. Reconstr. Surg. 53: 576, 1974.

204 Traaholt, L., Nas, R. and Statelid, O. Perfusion and reimplantation of a free skin flap in a dog. A preliminary report. Scand. J. Plast. Reconstr. Surg. 12: 163, 1978.

205 Tsuchida, Y. and Tsuya, A. Measurement of skin blood flow in delayed deltopectoral flaps using local clearance of 133 Xenon. Plast. Reconstr. Surg. 62: 763, 1978.

206 Van de Staak, W.J., Brakkee, A.J.M., DeRijke-Herweijer, H.E. Measurement of the thermal conductivity of the skin as an indication of skin blood flow. J. Invest. Derm. 51: 149, 1968.

207 Velander, E. Vascular changes in tubed pedicles: An animal experimental study. Acta. Chir. Scand. Suppl. 322, 1964.

208 Walter, J.B., and Israel, M.S. General Pathology 5th Ed, Churchill Livingstone, New york, 1979. (Chapters 6 and 42).

209 Waris, T. Degeneration and regeneration of nerves in a dorsal skin flap in the rat. Scand. J. Plast. Reconstr. Surg. 12: 95, 1978.

210 Webster, J.P. The early history of the tubed pedicle flap. Surg. Clin. North Am. 39: 261, 1959.

211 Webster, J.P. Thoraco-epigastric tubed pedicles. Surg. Clin. N. Am. 17: 145, 1937.

212 Wexler, M.R., Kalisman, M., Yeschua, R. and Neuman, Z. The effect of phenoxybenzamine, phentolamine and 6 hydroxydopamine on skin flap survival in rats. J. Surg. Res. 19: 83, 1975.

213 Willms-Kretschner, K. and Majno, G. Ischemia of the skin - electron microscopic study of vascular injury. Am. J. Path. 54: 329, 1969.

214 Wilson, W.R., Toomey, J.M. and Owens, G. Continuous measurements of local p02 and pCO2 during the creation of bipedicle skin flaps in dogs. Surg. Forum 23: 495, 1972.

215 Young, C.M.A. The measurement of blood flow in pedicle skin flaps in the pig. Bibl. Anat. 16: 185, 1977.

216 Zimmerman, J. and Finseth, F. An experimental neurovascular island myocutaneous flap in the pig: Prevention of necrosis by treatment with the vasodilator drug - isoxsuprine. Paper presented at the 24th Annual Plastic Surgery Research Council Meeting, Dallas, Texas, 1979.

217 Zovickian, A. Pharyngeal fistulas: Repair and prevention using mastoidocciput based shoulder flaps. Plast. Reconstr. Surg. 19: 355, 1957.

218 Zuker, R.M. and Harii, K. A random pattern flap borne on an axial pattern flap: Experimental study in rats. Br. J. Plast. Surg. 31: 286, 1978.