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(立法會秘書處譯本，只供參考用)

我是博昂志(Andrew Burd)教授，1976 年於蘇格蘭阿伯丁(Aberdeen)大學醫學系畢業，其後取得該大學頒發的醫學博士。我是英國愛丁堡皇家醫學院院士，並取得該學院整形外科專科醫生的認可資格。我亦是香港醫學專科學院院士，持有整形外科的考試證書。

我現任香港中文大學副教授兼外科學系整形外科部主管，另外亦出任香港整形外科醫生協會成員及香港燒傷學會會長。現以香港燒傷學會會長身分提出意見。

我特別關注的問題是，《人體器官移植條例》尚未界定不能生長的同種異體皮膚的性質。我亦關注到資料提供及保障方面的利益衝突，令本港醫生從歐洲皮膚庫(Euroskin Bank)進口甘油同種異體皮膚時，難以遵行條例的規定，因而嚴重影響爲港人提供的燒傷治療。若燒傷專科醫生在緊急情況下，主動進口甘油皮膚(glycerolized skin)，便須面對法律行動。

對於其他源自人體的皮膚代用品及以組織加工的物料，我亦深切關注。現時，人體器官移植委員會並沒有將該等物料確定爲移植器官。然而，根據條例無限制衍生的定義，該等物料被納入移植器官之列。爲此，有需要澄清條例對器官一詞的定義所提述的“亦包括任何器官的一部分”的陳述。

有關皮膚方面的意見，詳述於隨附文件，該份文件曾於最近一次國際座談會上提交。

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My name is Professor Andrew Burd. I qualified in medicine from the University of Aberdeen, Scotland in 1976. I have a Doctorate in Medicine from the same University. I am a Fellow of the Royal College of Surgeons of Edinburgh and have a specialist accreditation in Plastic Surgery from that College. I am a Fellow of the Hong Kong Academy of Medicine and have a Board Certification in Plastic Surgery.

I am an Associate Professor of the Chinese University of Hong Kong and am the Chief of the Division of Plastic and Reconstructive Surgery in the Department of Surgery. I am a member of the Hong Kong Society of Plastic and Reconstructive Surgeons and the President of the Hong Kong Burns Society. It is in this later capacity that I make this deputation.

My concern focuses specifically on the unresolved issue of the nature of non-viable allogenic skin which is not defined in the Ordinance. I am also concerned about the conflict of interest in data release and protection that prevents Doctors in Hong Kong from complying with the requirements of the Ordinance with regard to importing, specifically, glycerolized allogenic skin from the Euroskin Bank. This could have serious implications on the delivery of Burns Care to the people of Hong Kong and leave the Burns specialists open to legal action if they pro-actively import glycerolized skin in the event of an emergency.

Additional concern is expressed regarding the nature of other skin substitutes and tissue engineered materials that do have human origin. At present these have not been identified as transplants by the Human Organ Transplant Board. Nevertheless by strict inclusion in the unqualified derivative definition of the ordinance, they are transplants. To this extent clarification is needed with regard to the statement ‘and includes part of an organ’ in the definition of Organ as covered by the Ordinance.

The position with regard to skin is detailed in the accompanying paper which was presented at a recent international Burns symposium.

Glycerolised Allogenic Skin: Transplant or Dressing?

A Medico-legal Question

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Abstract

The use of non-viable allogenic skin in burn patients raises significant legal issues amongst regulatory authorities. Is such a material a transplant, device, pharmaceutical product or a dressing? This is not an academic question. In this paper the specific regulatory problems raised by ordering Euroskin from an Asian country are described and discussed. The solution to regulatory problems must involve active and constructive discussions with legislative bodies.

The emphasis should be on a the precise definition of the terminology of existing legislation. This may be a more effective approach to determining acceptable practice than changing legislation, a far more prolonged process.

Introduction

On Friday 28th July 2000 a previously fit and healthy 39 y/o male Hong Kong resident was involved in a domestic explosion in the Mainland. He was admitted to hospital for emergency escharotomies to all four limbs, tracheostomy and fluid resuscitation. He was subsequently transferred to the Prince of Wales Hospital in Hong Kong SAR and admitted to the Intensive Care Unit. He was assessed to have 85% BSA burns; 70% BSA was full thickness.

The patient was taken to theatre the following day and in a six hour procedure had 50% BSA full thickness burn excised (leaving a surgical defect in excess of 8,500 cm^2). The dorsum of the hands were covered in meshed auto graft and the remaining excised wound was covered with cadaver skin (1,600 cm^2) and pigskin. A further 140 pieces of cadaver skin were awaiting sterilization and could not be used.

Skin Banking in Hong Kong

There are two skin banks in Hong Kong run by the two University Hospitals. The skin bank in Queen Mary Hospital stores viable allograft in liquid nitrogen. The skin bank at the Prince of Wales Hospital gamma irradiates the cadaver skin and subsequently stores it in liquid nitrogen, prior to application. The use of cadaver skin in Hong Kong is limited due to the low number of donors in the Chinese community. The prevailing cultural belief is that the body should not be disturbed after death and despite having a potential population of over three million, less than thirty cadavers are harvested each year by the PWH team.

The Clinical Applications of Cadaver Skin

There are three principle uses for cadaver skin.

a) Both viable and non-viable cadaver skin are used as temporary skin substitutes after the excision of full thickness cutaneous burns. Rejection will occur in both but the period of take can be extended by the use of immunosuppression.

b) A more common use of non-viable allogenic skin is to act as a temporary cover to widely meshed autograft which is placed on a bed of viable tissue after the excision of a full thickness or very deep partial thickness burn (Figure 1). The autograft will take and the interstices of the mesh will close but this process takes time. The allogenic skin prevents desiccation from occurring in the viable exposed graft bed in the interstices of the meshed autograft. Once re-epithelialization has occurred the allograft, the non-viable allogenic skin 'falls' off. It has acted as a temporary dressing.

c) The third use for non-viable allograft is as a dressing for intermediate depth partial thickness burns. The burn is not excised, but is cleaned and dressed with the allogenic skin. The cadaver skin adheres to the wound and protects it whilst healing occurs underneath. When the underlying skin heals the allogenic skin desiccates and 'falls' off (Figure 2a-d).

Pig skin is used as a standard biological dressing for superficial partial thickness wounds.

Immigration Tower Incident

On Wednesday 2nd August 2000 an arson attack occurred in the Immigration Tower when 'right of abode' protesters staged a demonstration that escalated out of control. Forty victims suffered burn injuries and a state of emergency was declared. After stabilization at the nearest hospital the major burns were distributed amongst the hospitals with specialized burns care. By Friday 4th of August there were four ventilated patients on the ICU in the Prince of Wales Hospital (PWH). Three of the patients were from the Immigration Tower incident but did not present skin cover problems. The patient with 85% BSA burn was extremely stable and the overriding priority was to complete the burn excision and continue definitive resurfacing.

At this stage the supplies of skin from the other Hong Kong skin bank were reported as being 'marginal' and so the decision was made to make an immediate order of Integra™ from Johnson and Johnson and also a fax was sent to the European Skin Bank requesting 5,000 cm^2 of skin. The European skin bank supplies 'non-viable' glycerolized human cadaver skin which has a shelf life of over five years. An Import Licence was faxed to the Port Authority and the Euroskin arrived within 20 hours.

On Monday 7th of August, the organizational Head of the Skin Bank returned from vacation and raised a concern about the use of the glycerolized Euroskin. The concern related to the implications of Human Organ Transplant Ordinance. In view of these concern the Euroskin was not used as planned on that day. The following day, however, with no remaining alternative skin supplies available, the Euroskin was applied to the patient, over widely meshed autograft.

All four ventilated patients went onto survive and were discharged from hospital.

The Human Organ Transplant Ordinance

In 1993, a local newspaper in Hong Kong ran a story suggesting that Hong Kong residents had transplants in the Peoples' Republic of China using organs procured there. There were rumours that this process was facilitated by Hong Kong doctors and the Hong Kong Medical Association adopted guidelines against the practice of buying and selling human organs for purposes of transplant. Continuing controversy led to the Human Organ Transplant Bill, modeled on the English Human Organ Transplants Act of 1989. The Bill became operational on 1st April 1998. It prohibits commercial dealing in organs and restricts the transplanting of organs between unrelated persons[1].

The practice of buying and selling human organs is both morally and ethically repugnant. As such, the HOTO is essential to protect against such practices. At the same time, however, it is important that such an Ordinance is both precise in its terminology and practical in its application. In both respects, the current ordinance is lacking but medical terminology and understanding are equally imprecise on these issues.

The Human Organ Transplant Board were contacted with full details of the importation of the cadaver skin from the Euroskin bank and its subsequent use. Their position was stated as follows, "The Board agrees that the ordinary dictionary definition of 'transplant' applies to the Human Organ Transplant Ordinance (Cap 465) (HOTO), that is, the transfer of an organ from one person to another during a grafting or transplant operation,

regardless of permanence. Therefore, the application of glycerolized cadaver skin, the so-called 'temporary life saving measure' is a transplant operation which falls within the ambit of the HOTO even though it does not involve permanent skin replacement. If cadaver skin is imported for the purpose of performing such 'temporary life saving measure', section 7 of the HOTO will apply, that is, it must be accompanied by a certificate containing the required information with an acceptable signatory and the certificate must be submitted to the Board before the procedure commences. In addition, section 6 of the HOTO must be complied with by submitting Form 2 upon the transplant of organ in Hong Kong or Form 3 as to the final disposal of an organ imported but not transplanted to the Board within 30 days after these procedures are conducted. A person who fails to comply with such requirements may be guilty of an offence and is liable upon conviction to a fine at level 5 and to imprisonment for 3 months."

The threat of litigation is an incentive to action and two avenues were explored. The immediate concern was to comply with the requirements of the Ordinance albeit retrospectively and the second avenue was to question the terminology of the ordinance and thus clarify and define the law.

The requirements of the ordinance

The Ordinance defines an 'organ' as 'any part of the human body consisting of a structured arrangement of tissues which, if wholly removed, cannot be regenerated by the body, and includes part of an organ'. The list of human organs subject to the provision

of the Ordinance include the skin. It is noted that the list may be updated from time to time taking into account state-of-the-art technology in transplant surgery.

The import of human organs is covered in considerable detail by the ordinance. Any person importing an organ for the purpose of transplant in Hong Kong must

a) apply for an Import License from the Port Health Office of the Department of Health and

b) ensure that the organ is accompanied by a Certificate, signed by a person in the country of origin who is acceptable to the Board, and by the required supporting documents.

The Certificate for the import of human organs for transplant requires the following declarations to be signed either by the medical practitioner who removed the organ in the country of origin or the Medical Director of the Institute/Hospital which provided the organ.

This is to certify that

(1) In obtaining the organ, all applicable laws of _____, the country of origin, were complied with;

(2) The source of the organ, as far as can be ascertained, is not infected with any disease that could be transmitted to the recipient of the organ through transplanting;

(3) The organ was removed in a hospital in which the government of the country of origin has authorized organs to be removed for transplanting;

(4) As far as can be ascertained, no person in the country of origin has made/received or intends to make/receive a payment for supplying the organ; and information on the donor is provided below

a) Name

b) Age

c) Sex

d) Date of removal of organ

e) Where the donor is deceased

i) Time and date of death

ii) Cause of death (if known)

This form was sent to the Medical Director of the Euroskin bank for completion. The form was returned partially completed with the following statement.

"In compliance with European tissue banking regulations, details of all skin donors are kept on file at the Euro Skin Bank. However, the Dutch laws on personal privacy prevent us from disclosing these details to third parties. Quality certificates, attesting to the viral and bacteriological safety of the batch were sent with the order.

For your information, the Euro Skin Bank is a non-profit division of the Dutch Burns Foundation, which is a national charity. Glycerol-preserved allografts are non-viable and were developed as a temporary biological dressing for the treatment of burns and other conditions involving skin loss. In the Netherlands, the product is classified as a pharmaceutical product and is prepared under the auspices of J Prins, PhD, pharmacist.

Allograft procurement and processing comply with the guidelines of both the American and the European Tissue Bank Societies. The product has been passed by the regulatory bodies of all European countries.

I trust that the above information will reassure you of the legitimacy of the glycerol-preserved allografts which are provided by the Euro Skin Bank. If you have further comments or queries, I will be happy to respond."

This situation has remained unresolved and not withstanding that the certificate was submitted late it still remains unacceptable to the HOTB. Discussions continue to clarify this issue.

In the meantime the terminology of the law is being questioned and refined.

Evolving Terminology

In 1890, Billings Medical Dictionary defined a 'graft' as, 'A portion of living tissue transplanted from one place to another on the same or another organism, with a view to its adhesion and growth; also, the operation or its result, the adhesion and growth of such new tissue'. Surgeons borrowed the term from horticulturists who have practiced grafting for centuries, whereby a scion or a shoot is inserted into a groove or slit made in another stock so as to allow the sap of the latter to circulate through the former and thereby maintain its viability. Transplant and transplantation are terms the surgeon has similarly borrowed from the horticulturist.

In Horticultural terms, the word ‘transplant’ is derived from the Latin ‘transplantare’ – where ‘plantare’ is to plant. ‘Trans’ a standard prefix which signifies ‘across’ or ‘beyond’. ‘Plant’ as a transitive verb therefore is used to describe the action of putting into the ground for growth. The Latin word ‘planta’, a noun, refers to a shoot, a slip or a cutting. Transplantation is therefore the process of removing a shoot, slip or cutting from the ground where it grows and planting it in another place. Such an action has been the practice for millennia in the field of horticulture, which long preceeded the practice of surgery. It is a very necessary part of thinning out a densely seeded bed and the onward planting of seedlings into a definitive position for mature growth.

In surgical terms, ‘transplantation’ was again defined in Billings Medical Dictionary as ‘the removal of a portion of living tissue from its normal position, and uniting it with living tissue in another place, in order to repair a defect or lessen deformity’.

Definitions do change and Longmans Dictionary of Contemporary English defines the medical term transplant as, ‘to move an organ, piece of skin, hair, etc. from one part of the body to another or from one person or animal to another: e.g. to transplant a heart’. Whilst graft is defined as: ‘a piece of healthy living substance, skin or bone, placed instead of such a substance in another part of the body which has been damaged e.g. a skin graft on the burnt leg’. Meanwhile Collins Cobuild English Language Dictionary defines the terms as: transplant – ‘a transplant is a surgical operation in which a diseased or missing part of a person’s body, such as their kidney, their heart, or a part of their skin or their hair, is replaced by a part from another person’s body or from a different part of

their own body'; graft – 'a piece of healthy skin or bone, or a healthy organ, which is attached to a damaged part of your body by a medical operation in order to replace it'.

The reference to transplantation and grafts from Billings Medical Dictionary, dates from 1890. The significance of this is that the history of skin grafting evolved through the 1800's. In 1804, Baronio performed the first well documented experiments of successful skin autografts in a sheep model. In 1869, Reverdin, working in La Charite in Paris treated an avulsion injury with a skin autograft[2] and reported the use of a skin allograft the following year[3]. Meanwhile in the UK, Lawson, an ophthalmologist used full thickness autografts to repair eyelids[4]. Pollock was the first to report the use of skin grafts in burn wounds[5]. In the United States of America, Girdner was the first to use cadaveric allograft skin, taken from a suicide victim, to treat a patient with a severe burn from a lightning injury and reported an immediate take of 75%[6]. Brown popularized the use of allograft skin with his experiences in the second world war when he used the ready supply of allogenic skin as a 'dressing'[7-8].

The mechanism of autogenic skin graft 'take' has been the focus of much research interest for many years. From this has developed enquiry into the nature of allogenic skin 'take', including vascularization. In turn, this has led to significant advances in the understanding of the biological processes of immunology. Medewar and Gibson, observing the behaviour of viable allograft described the stages of rejection and in particular the second set reaction[9]. Rapaport, working with another Plastic Surgeon, Converse, received the Noble Prize for his investigation and elaboration of the HLA system[9].

It is my contention that it is the method and circumstances of use which determines the nature of a biological material. The determination of 'take' of a skin graft remains an elusive phenomenon as it has not been adequately defined. Features of 'take' are adherence, re-vascularization and viability. Adherence is necessary for viable skin grafts to 'take' but it is evident that adherence is a phenomenon associated with non-viable skin grafts and indeed other dressing materials. It has been suggested that there are two modes of adherence[10-11].

i) direct chemical bonding between fibrin in the wound and the dressing material

ii) entrapment of fibrin

Thus non-viable allograft will adhere to the wound as a 'collagen prosthesis' but will not undergo true chemical bonding.

The process of re-vascularization has been attributed to a number of processes either singly or in combination: 1) direct connection of host and graft vessels, referred to an 'inosculation'; 2) in growth of host vessels into endothelial channels of the graft; and 3) random penetration of the host vessels into the graft dermis thereby creating new endothelial channels. It is evident that both viable and non-viable allogenic skin can undergo re-vascularization. Rejection in the allogenic skin is heralded by distension in the vascular system, followed by the appearance of a sluggish circulation with clumped elements. Complete cessation of blood flow and vascular dissipation occurs in most human skin viable allografts within seven to ten days. It is possible, however, to extend this period considerably by the use of immuno suppressive agents.

The survival of viable allogenic skin will depend upon its 1) ability to access nutritive materials; 2) ability to dispose of metabolic waste products; 3) anatomic distinction from the recipient, and 4) taxanomic and immunogenic relationship to the recipient. It is quite evident that in terms of adherence, re-vascularization and viability, viable allogenic skin can be transplanted. However, in the strict definition of transplantation, it is not possible to transplant non-viable allogenic skin. It is possible for such skin to adhere to a wound bed and exhibit features of re-vascularization. Such 'incorporation' into the host would be similar to that observed if a piece of gauze was left on a wound bed. The incorporation is at the level of the dermal collagenous matrix. Non-viable allogenic skin can never be rendered 'viable' by transplantation. A schema is proposed in Figure 3 to clarify the nature of allograft skin.

There is no doubt that the timely arrival of 5,000 cm^2 of glycerolized human cadaver skin played an instrumental role in saving the life of a major burn patient. It would have been ironic if the dedicated medical staff treating the patient had gone to prison for their part in the treatment and care of this patient.

Whilst this paper has focused on a specific issue related to a specific regulatory ordinance, it is evident that this is not a unique problem. Regulatory bodies are going to come under increasing pressure to ensure that any human organs, tissues, cells and even cell products used for any purpose are done so only with the full and informed consent of the source. Laws will become more sophisticated to ensure the safety of recipients and the dignity of donors. There will be a period of confusion whilst the legal system on the one hand and

the medical system on the other, work at refining definitions and procedures and develop mutually acceptable terms of reference. In the meantime, the most constructive approach is to work in co-operation with the present legal systems as much as possible and when grey areas occur, take pro-active steps in terms of education, not only of the legal profession but also of the public who influence the politicians to modify the law.

References

1) Law and Medicine. Current Legal Issues 2000. Freeman M, Lewis ADE (Eds). Oxford University Press. Volume 3.

2) Reverdin JL. Sur la greffe epidermique. CR Acad Sc (Paris) 1871;73:1280.

3) Reverdin JL. De la greffe epidermique. Arch Gen Med (suppl 6) 1872;19:276.

4) Lawson G. Cases of skin grafting. Lancet 1870;2:567.

5) Pollock G. Cases of skin grafting and skin transplantation. Trans Clin Soc Lond 1871;4:37.

6) Girdner JJ. Skin grafting with skin grafts taken from the dead subject. Med Rec NY 1881;20:119.

7) Brown JB, McDowell F. Massive repairs of burns with thick split skin grafts: emergency 'dressings' with homografts. Ann Surg 1942;115:658-674.

8) Brown JB, Fryer MP, Randall P, Lu M. Postmortem homografts as 'biological dressings' for extensive burns and denuded areas. Ann Surg 1953;138:618-630.

9) Plastic Surgery. Joseph G McCarthy (Ed), W B Saunders Co, 1990 Volume 1.

10) Tavis MJ, Thornton JW, Harney JH, Woodroof EA and Bartlett RH. Graft adherence to deepithelialized surfaces: a comparative study. Ann Surg 1976;184:594-600.

11) Thornton JW, Tavis MJ, Harney JH, Pirkle H and Bartlett RH. Graft adherence to wound surfaces: collagen fibrin interactions. Burns 1977;3:23-7.

Legends

Figure 1 The sandwich technique with overlying allograft protecting the wound bed and allowing re-epithelialization of the interstices of the mesh.

Figure 2
a) An eleven month old child with a deep dermal scald exhibiting fixed staining in the wound.
b) Covered with closed meshed glycerolized human allograft.
c) Two weeks later the allograft is dry and spontaineously separating.
d) Allogenic skin all removed, healed burn that did not develop hypertrophy.

Figure 3 Schema for determining nature of allogenic skin.

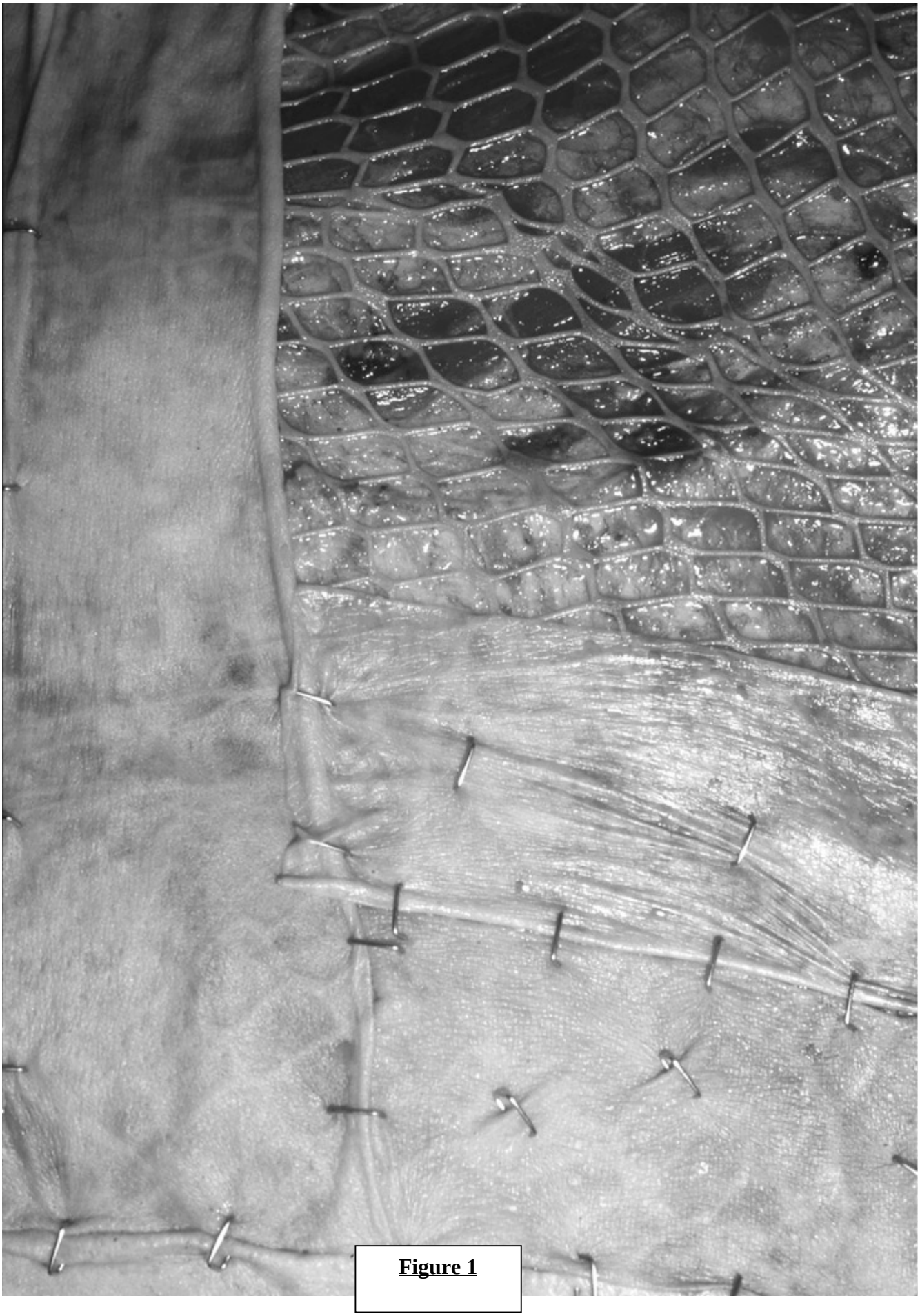


Figure 1

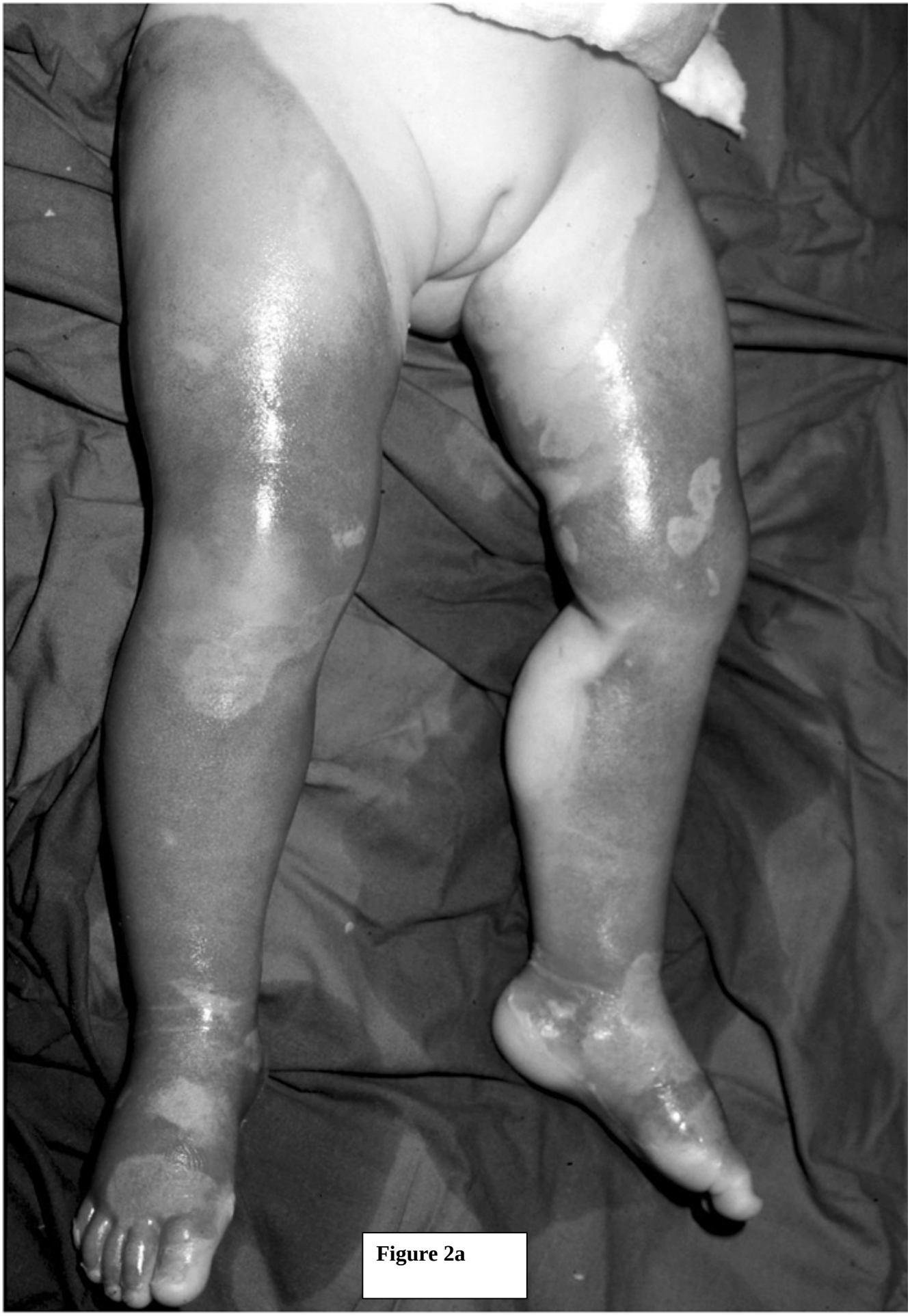
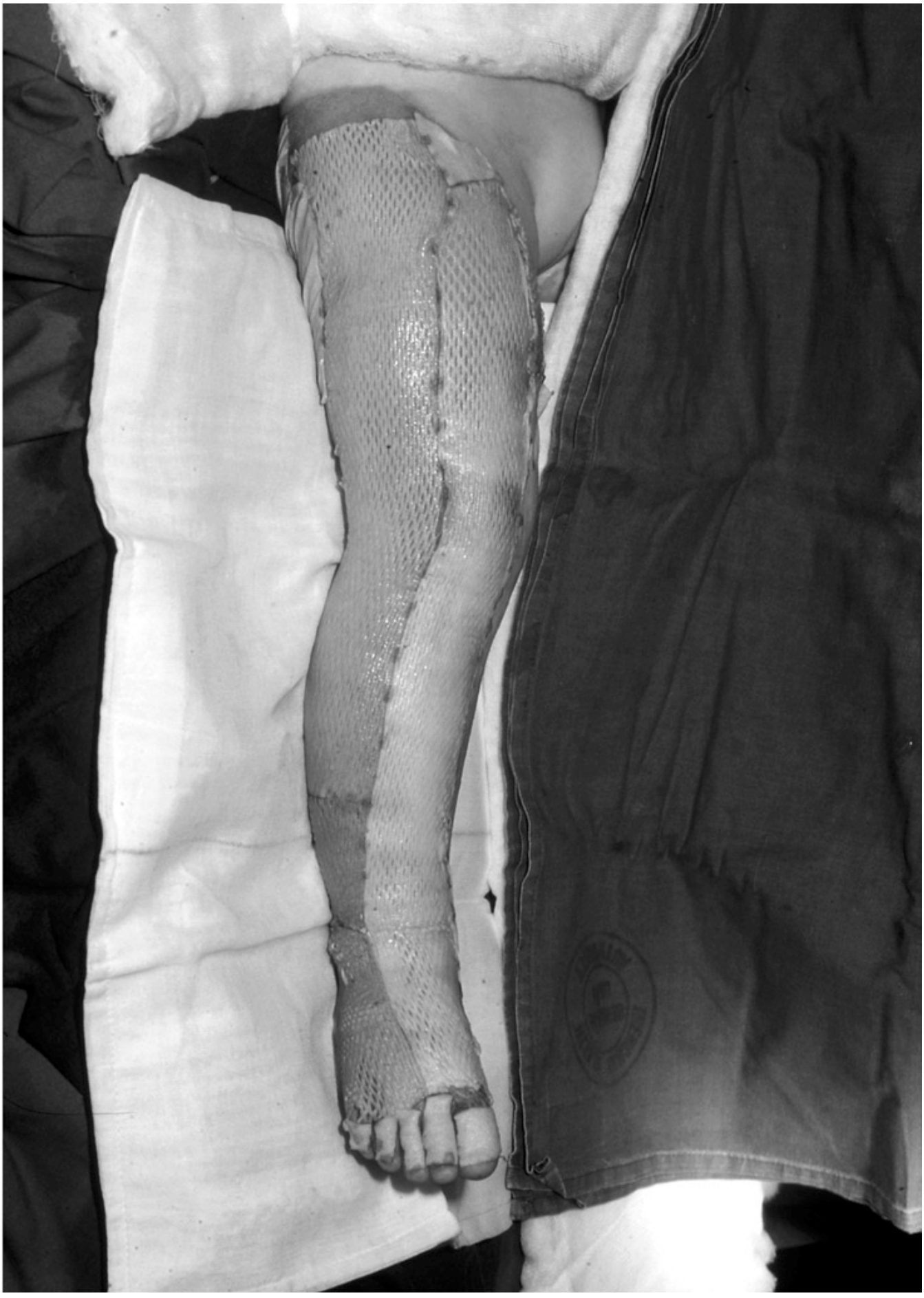
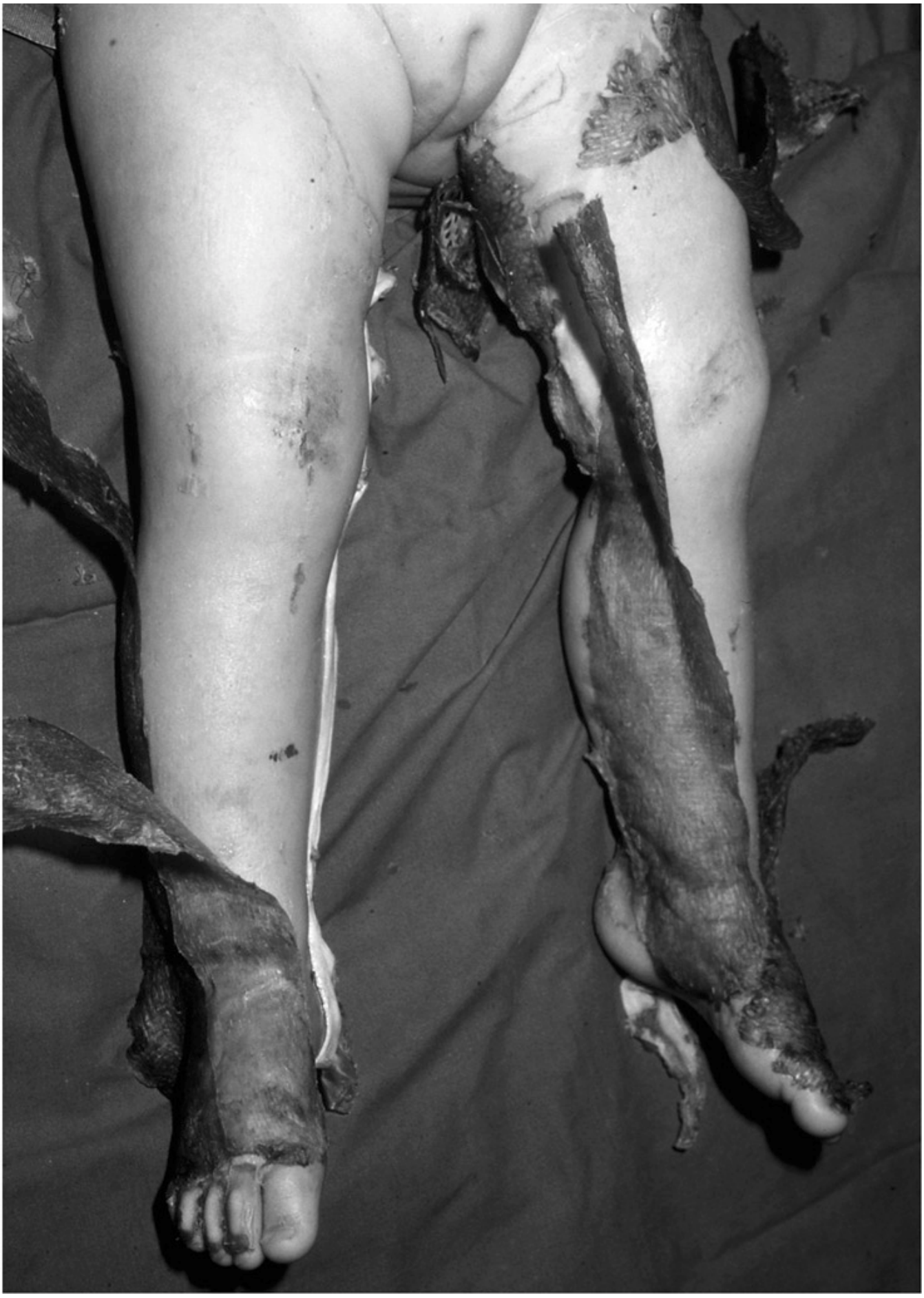
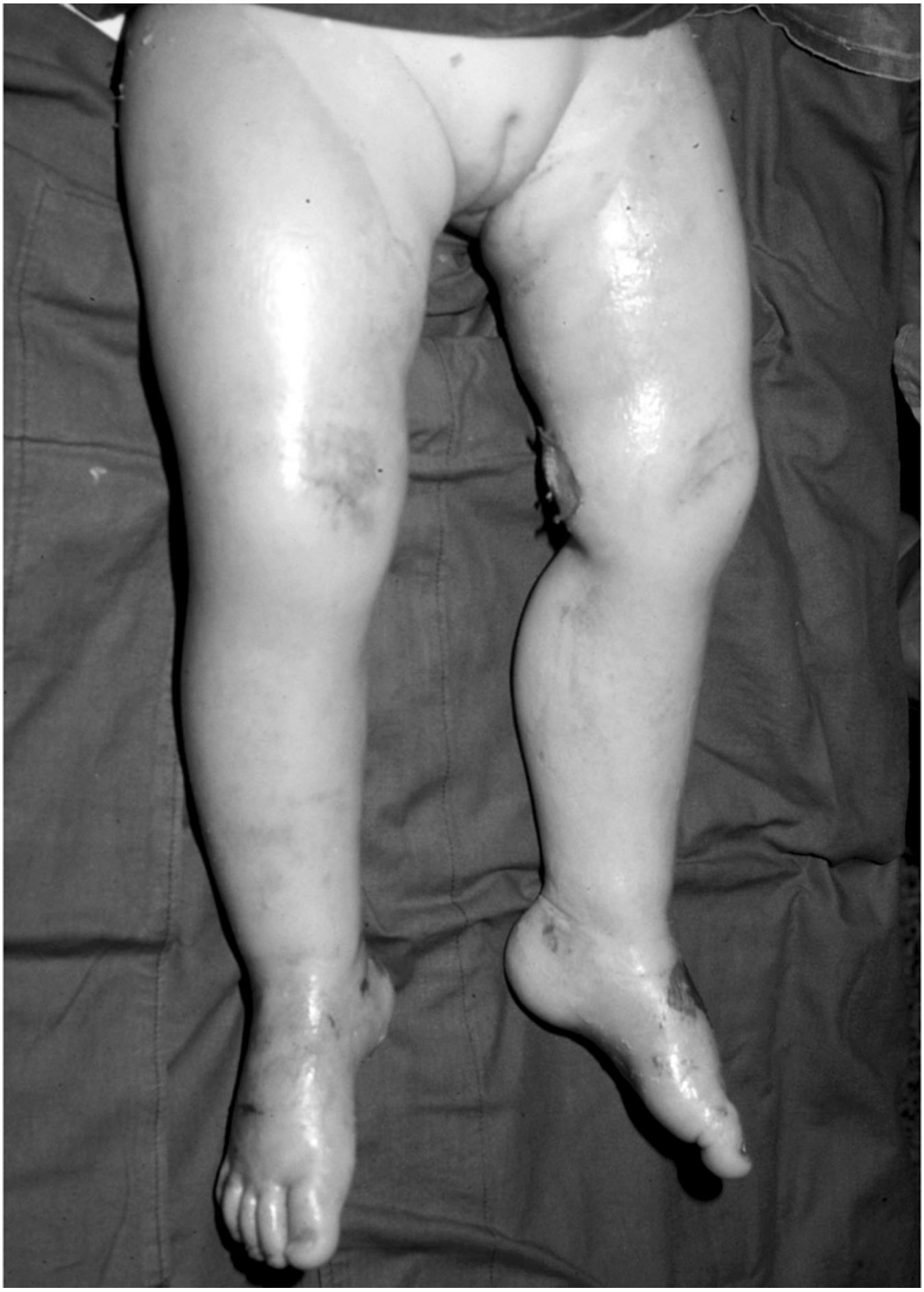


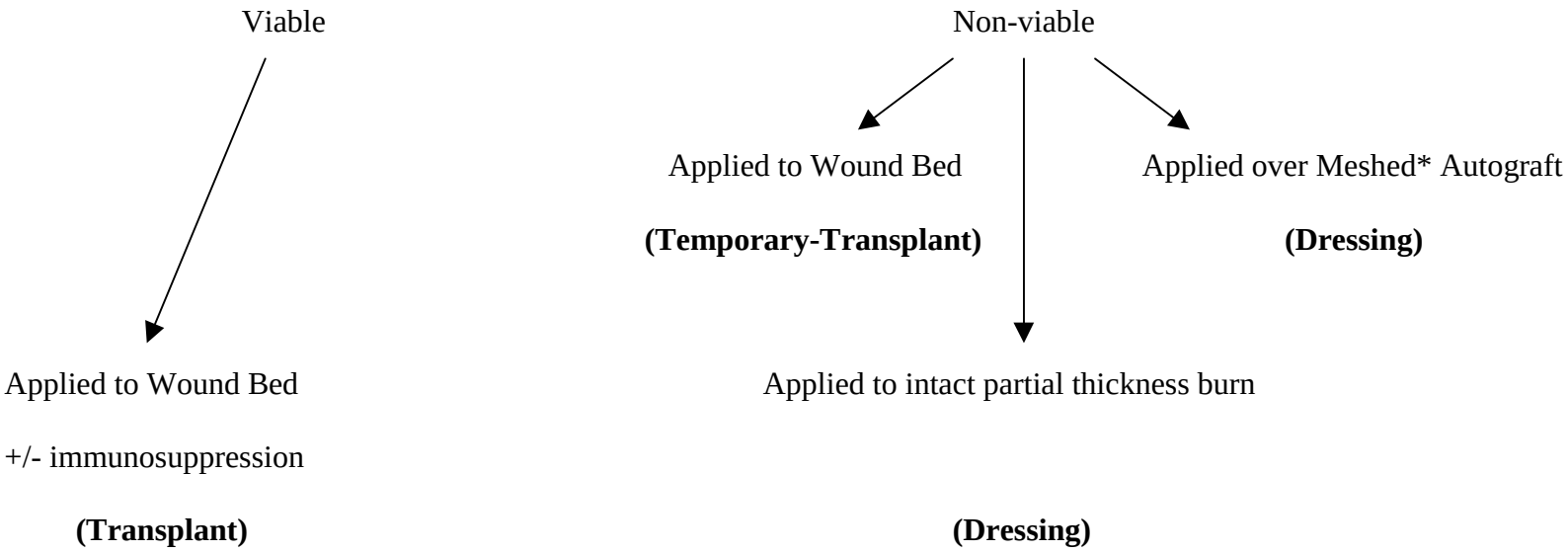
Figure 2a







Allogenic Skin



* If mesh ratio small enough for interstices to re-epithelializa before temporary 'take' of allograft i.e. <1:3.

Figure 3