THE PROVISION OF SPACE FOR IMPLANTABLE PROSTHETIC LUNGS: A Feasibility Study

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D E C L A R A T I O N

I declare that the work described in this thesis has been done and the thesis composed by myself. I declare further that there is no collaborative work herein and that no part of the subject matter of this thesis has been included in a thesis already approved for a degree in this or another University.

Date: 10th Dec. 1971 Signed: J. L. Wosornu.

J. L. WOSORNU.

CONTENTS

		Page
PREFACE	-	1
	- Acknowledgements	3
CHAPTER I	- INTRODUCTION	
	A. THE NATURE OF THE ENQUIRY	5
	B. REVIEW OF THE LITERATURE	6
	1. Static Prostheses	6
	2. Prosthetic Organs	9
	3. Long-term Extracorporeal Blood Gas Exchange	12
	4. The Feasibility of Implanting Prosthetic Lungs	14
	C. GENERAL DISCUSSION OF THE PROBLEMS	16
CHAPTER II	- THE TECHNICAL EXPLORATION OF THE EFFECT OF SILICONE 'SKIN' ON THE PLEURAL MEMBRANE IN DOGS	21
	Introduction	21
	Materials and Methods	21
	Postoperative Observations	23
	Results	24
	Discussion on Silicone 'skin' as the New Lining for the Pleural Cavity: Tentative Conclusions	31

Page

CHAPTER III - AUTOGENOUS SKIN AS THE NEW LINING FOR THE PLEURAL CAVITY 33

Introduction 33

Materials and Methods 34

Observations and Tentative Conclusions: The Basis of Subsequent Studies 39

CHAPTER IV - THE INVESTIGATION

THE CREATION OF A SKIN-LINED AND EXTERIORISED HEMITHORAX: An Experimental Model for the Provision of Space for Implantable Prosthetic Lungs 42

PART I

Introduction 42

Materials and Methods 48

A. Operative Techniques 48

B. Observations on the Closed Skin-lined Hemithorax 58

C. Making a Permanent Stoma into the Skin-lined Hemithorax: Operative Technique 59

D. Observations on the Skin-lined Hemithorax After the Creation of the Permanent Stoma 61

RESULTS 65

The Operation of Intrapleural Skin Grafting

1. General Progress 65

2. Size of Cavity 65

Page

3. The X-ray Demonstrations of the Cavity Before and After Creation of the Stoma 67

4. Effect of the Closed Skin-lined Pleural Cavity on Body Weight 70

5. Pleural Pressure Before and After Creation of the Stoma 72

6. The Skin-lined Hemithorax as an Open Ventilated Gas Cavity 74

(i) Spirometry 74

(ii) Arterial pH, PO_2, and PCO_2 76

DISCUSSION OF THE ABOVE RESULTS 77

CONCLUSIONS 80

PART II OF THE INVESTIGATION 82

Materials and Methods 82

A. Operative Techniques 83

B. Observations on the Pigs with the Skin-lined Hemithorax Closed 84

C. Opening the Skin-lined Hemithorax to the Exterior and Observations 85

RESULTS 90

1. General Progress 90

2. Body Weight 90

3. Pleural Pressure in the Closed Skin-lined Hemithorax 90

4. X-ray Demonstrations of the Skin-lined Hemithorax Before and After the Thoracostomy 91

Page

5. Vital Functions Before and Two Hours After Opening the Skin-lined Hemithorax to the Exterior 95

6. The Skin-lined Hemihtorax as a Ventilated Gas Cavity 97

DISCUSSION OF THE ABOVE RESULTS 99

CHAPTER V - GENERAL DISCUSSION OF RESULTS 101

SUMMARY - 105

REFERENCES - 110

APPENDIX

1. Excised Free Skin Grafts from 30 Consecutive Rats 117

2. Width of Skin-lined Hemithorax of Rats from 30 Serial Chest X-ray Films 118

3. Weight of 30 Rats During First Four Weeks After Intrapleural Skin Grafting 119

4. Weight of Ten Unoperated Rats Kept Under Identical Conditions 120

5. Pleural Pressure in Ten Normal Rats 121

6. Pleural Pressure in the Open Skin-lined Hemithorax of 15 Rats 122

7. Pressure in the Closed Skin-lined Hemithorax of 15 Rats 123

8. Minute-Ventilation in 30 Rats with Open Skin-lined Hemithorax 124

9. Minute-Ventilation in 12 Normal Rats 125

		Page
10.	Arterial pH, PO_2, and PCO_2 in 10 Normal Rats	126
11.	Arterial pH, PO_2, and PCO_2 in Rats with Skin-lined Hemithorax Open for 24 Hours	127
12.	Volume of Skin-lined Hemithorax at Four Weeks in 15 Rats	128
13.	Weight of Six Pigs with Intrapleural Skin Grafts	129
14.	Pleural Pressure in Normal Pleura and in Closed Skin-lined Hemithorax in Five Pigs	130
15.	Heart Rate, Rate of Respiration, Arterial pH, PO_2, and PCO_2 in Four Pigs Before and Two Hours After Opening the Skin-lined Hemithorax to the Exterior	131
16.	Body Weight of Pigs and Volume of Skin-lined Hemithorax Five Weeks After Intrapleural Skin Grafting	
17.	Ventilation in the Normal Hemithorax and in the Skin-lined Hemithorax of Four Pigs	133

LIST OF FIGURES

			Page
Figure	1.	Diagram Showing a Concept of an Implantable Membrane Lung	15
	2.	Sample of Silicone 'Skin' (Dacron-backed Silicone Rubber Membrane)	20
	3.	Effect of Silicone 'Skin' on the Pleural Membrane of a Dog (Photograph)	25
	4.	Photomicrograph of a Specimen taken from the Pleural Surface of the Diaphragm which had Fused with Silicone 'Skin'	27
	5.	Photograph Showing Three Patches of Free Skin Grafts which have 'taken' on the Pleura of a Dog: The Basis of Subsequent Studies	38
	6.	Drawing Showing a Concept of a Rat with the Left Hemithorax Lined with Skin and Open to the Exterior: An Experimental Model for the Provision of Space for Implantable Prosthetic Lungs	41
	7.	Drawings Showing the Rationale Behind the Approach Employed to Transform the Left Pleural Cavity into a Postpneumonectomy Skin-lined Hemithorax	45
	8.	Drawing of the System Employed to Administer Anaesthesia to the Rats in this Study	47
	9.	Drawings of Skin Capsule to be Grafted into the Pleural Cavity of a Rat	50
	10.	Photograph Showing Operating Table, Rat and Instruments all in Readiness for the Thoracotomy and Intrapleural Skin Grafting	52
	11.	Drawing of the Thoracotomy and Intrapleural Skin Grafting in the Rat	53

Figure		Page
12-14.	Photographs Showing Operative Technique of Intrapleural Skin Grafting in the Rat	55-57
15.	(i) X-ray Films of a Rat with the Closed Skin-lined Hemithorax Outlined with Hypaque at Weeks One and Four (ii) The Growth Curve of the Skin-lined Hemithorax in Rats	64.
16.	(i) Photograph of a Rat Four Weeks After Intrapleural Skin Grafting and (ii) its Chest X-ray Film	66
	(iii) Transverse Section through the Chest of the 320g Rat Shown in Fig. 16(i)	67
17.	X-ray Demonstration of the Skin-lined Hemithorax Before and After Creation of the Stoma	68
18.	X-ray Film of a Rat Four Months After Intrapleural Skin Grafting Showing a Stable Preparation	68
19.	The Growth Curve of Rats with Intrapleural Skin Grafts over the First Four Weeks	69
20.	Tracings of Pleural Pressure from the Skin-lined Pleural Cavity Before and After Creation of the Permanent Stoma in Rats	71
21.	Spirometric Tracings from the Trachea and the Skin-lined Hemithorax of a Rat	73
22.	Drawing of a Pig with the Left Hemithorax Transformed into a Skin-lined Cavity which is Open to the Exterior	81
23.	A General View of the Operating Theatre During Studies on the Open Skin-lined Hemithorax and its Effects on Cardio-Respiratory Function in a Pig	87

Page

Figure

24-26. X-ray Demonstrations of the Skin-lined Hemithorax in Pigs Before and After Thoracostomy 91-93

27. Tracings of the Electrocardiogram and Intra-arterial Pressure Before and After opening the Skin-lined Hemithorax to the Exterior 94

28. Spirometric Tracings from the Trachea and the Skin-lined Hemithorax of a Pig 96

LIST OF TABLES

			Page
Table	1.	Effect of Implanting Silicone 'skin' into the Fresh Postpneumonectomy Space of Two Dogs: Body Weight and Volume of Chest Aspirate	28
	2.	Effect of Implanting Silicone 'Skin' into the Nitrogen-treated Postpneumonectomy Space of a Dog: Volume of Chest Aspirate Before and After the Implantation	29
	3.	Effect of Implanting Silicone 'Skin' into the Nitrogen-treated Postpneumonectomy Space of a Dog: Body Weight Before and After the Implantation	30
	4.	Transverse Diameter of the Closed Skin-lined Pleural Cavity in Rats for the First Four Weeks After Intrapleural Skin Grafting	65
	5.	Comparison of the Weekly Weight Gained by Unoperated Rats with that Gained by the Test Rats	70
	6.	Comparison of Normal Pleural Pressure with the Pressure in the Open Skin-lined Hemithorax in Rats	72
	7.	Comparison of Ventilation in the Normal Hemithorax with Ventilation in the Skin-lined Hemithorax in Rats	73
	8.	Comparison of Ventilation in Unoperated Rats with Ventilation in the Normal Hemithorax of the Test Rats	75
	9.	Comparison Between Arterial pH, PO_2, and PCO_2 in Unoperated Rats and in the Test Rats	76
	10.	Comparison of Heart Rate, Rate of Respiration, Mean Arterial Pressure, and Arterial pH, PO_2, and PCO_2 Before and Two Hours After Opening the Skin-lined Hemithorax to the Exterior in Four Pigs	95

Page

Table 11. Comparison Between Ventilation in the Normal and in the Skin-lined Hemithorax of Pigs 97

12. Correlations Between (i) Body Weight/Tidal Air, (ii) Tidal Air/Rate of Respiration (Normal Hemithorax), (iii) Tidal Air/Tidal Air (The Two Halves of the Chest), and (iv) Total Capacity/Tidal Air (Skin-lined Hemithorax Only) in Four Pigs 98

PREFACE

The aim of the work described in this thesis was to see whether it was possible to reline and exteriorise the pleural cavity and to determine whether an animal can ventilate such a cavity as a result of natural respiration. These two problems had to be solved if implantable prosthetic lungs are to become feasible in the future.

A series of experiments were performed on 16 dogs, 200 rats, and six pigs. First the effect of a plastic fabric on the pleural membrane was explored in five dogs. Unfortunately, the fabric provoked much pleural effusion followed by empyema. Those parts of the chest wall (including the diaphragm) which did fuse with the fabric became rigid plaques. Therefore, the use of this material was abandoned.

Next, skin was tested as the new pleural lining and found satisfactory. Experiments in rats showed that a readily reproducible technique could transform the left hemithorax into a stable skin-lined cavity which could be opened to atmospheric pressure without embarrassing breathing in the right lung, and the animal could ventilate the cavity via a separate opening directly through the chest wall.

Experiments on six pigs demonstrated that these results could also be obtained in larger animals.

The skin-lined hemithorax in the rats and pigs experimented on was poorly ventilated when compared with the normal hemithorax. Therefore, additional devices for ventilation must be provided for a prosthetic lung implanted in this cavity. However, much work remains to be done on this model before it becomes workable.

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The Royal Postgraduate Medical School provided a stimulating atmosphere and I thank the aurtorities for all the amenities so freely available. Facilities and equipment were kindly put at my disposal. Dr J.M.B. Hughes lent me his miniature Krogh spirometer and Dr B.J.B. Grant helped me to set it up; Professor Dollery let me make use of his pig sties.

When I started the work in January 1970, I was on Study Leave from the University of Ghana Medical School and I held a Smith and Nephew Surgical Fellowship for that year. When my time ran out, Professors Welbourn and Melrose generously obtained an extension for

one more year. Many others played their part including a delegation of Professors Bentall, Calnan, and Melrose who met Professor A.A. Kwapong, Vice Chancellor of the University of Ghana, who finally approved the arrangement. All these moves would have come to naught but for the uncommon gesture of goodwill from one man: Mr Terry Verma. He went to Ghana that I might stay in London and finish the work. The debt of gratitude I owe him I now acknowledge with humility.

Last but not least, I thank my wife, Vivian, for secretarial assistance and Dr Hugh Clegg for reading the draft.

CHAPTER I

INTRODUCTION

A: NATURE OF THE ENQUIRY

Knowledge and techniques in medicine and surgery have reached the point that replacement of organs which formerly seemed impossible, has today become a reality. The progress in organ replacement has taken two directions. One has led to transplantation of viable organs from one person to another; the other has led to implantation of prosthetic, functioning organs composed entirely of non-living and inert materials. Although problems have arisen in the development of prosthetic organs, the difficulties are not insurmountable. The search is challenging and must continue (Bodell, Head, Head, and Formolo 1965).

In general, implantable prosthetic organs present two separate problems. One is the construction or engineering of the device itself. The other is the interaction at the boundary or boundaries between the host and the implanted prosthetic organ. Implantable prosthetic lungs present at least two such boundaries. One which may be described as "internal" is the boundary between circulating blood and the perfused prosthetic lung. The other or "external" is the boundary between the delicate pleural membrane and the foreign body, i.e. the implantable

prosthetic lung, permanently in contact with it. It is this second boundary which is the special concern for this investigation which began in January 1970 in an attempt to answer four questions.

1. Anatomically, is it practicable to change the normal pleura into a tougher lining in such a way that in the conscious animal the pleural cavity can be brought into direct and constant contact with the exterior? It was reasoned that the pleural cavity, thus relined and duly exteriorised could be employed to house a prosthetic lung safely and permanently. 2. By which route might the implanted prosthetic lung receive air?

3. Functionally, can the animal ventilate such a cavity with natural breathing? 4. Could it achieve adequate ventilation or would the implanted prosthetic lung need additional devices to boost its ventilation?

B: REVIEW OF THE LITERATURE

1. Static Prostheses

Internal appliances of various kinds have been used widely in orthopoedic surgery for years, and much research has been applied in evolving metals which neither corode nor cause harmful reaction in the living tissues in which they are embedded. Examples of such inert

metals and alloys are the special steel (18/8 SM_o), the chrome-cobalt alloy (vitallium) and titanium (Adams 1957).

Metals, however, are not of great value to those who are in need of soft tissue substitutes, and until recently there was no soft tissue substitute suitable for implantation. However, a whole new field of materials became available with the advent of three new plastics: Teflon* (Fluon*), Dacron* (Terylene*), and the Silicones. (*Trade name, E.I. du Pont de Nemours and Company, Wilmington; *Trade name, Imperial Chemical Industries Ltd., London.)

Teflon is a polymer of tetrafluoro-ethylene and Dacron is a polymer of polyethylene terepthalate. In soft tissue surgery, they are employed mostly after weaving into various textiles or matting into felt (Velour). Silicone, on the other hand, is a generic term covering a wide variety of materials. The silicones used most widely in medicine are the polymers known as the polydimethyl siloxanes; they are fluids of varying viscosity which are used as fluid or as rubber.

Teflon, Dacron, and the medical grade silicones produce minimal tissue reaction and they change little after implantation (Leininger, Mirkovitch, Peters, and Hawks 1964). Teflon and Dacron have been used as artificial stroma for the ingrowth of tissues and their widest application has been in cardio-vascular surgery where they have been employed to construct vascular prostheses (Fry, De Weese, Kraft, and

Ernst 1964), and as sewing rings for artificial heart valves (Starr and Edwards 1961). Dacron velour has also been used for "artificial skin" (Hall, Liotta, and de Bakey 1966) and for permitting the attachment of artificial limbs through skin directly into bone (Hall, Eppright, Engen, and Liotta 1967).

The silicones, however, have enjoyed the widest application as implant materials, particularly medical grade silicone rubber which is probably the most extensively used implant today. The following examples show the range of this application: hydrocephalus valves which serve to drain CSF from the brain into the blood stream (Nulsen and Spitz 1952); as prosthetic finger joints (Calnan 1971); as the ball in the cage-and-ball type of prosthetic heart valves (Starr and Edwards 1961); the covering for the wires of implanted cardiac pacemakers (Chardack, Gage, and Greatbatch 1960, Kantrowitz 1964); and as peritoneal-atrial shunt for the treatment of intractable ascites (Hyde and Eiseman 1966).

Many other areas of the body have seen Teflon, Dacron, and silicone rubber implants. Examples are "bile ducts, testicles, tear ducts, stapes, mandible, trachea, oesophagus, dura mater, ureter, urethra, coatings for cranial aneurysms, hernial reinforcements and tendons. The past has seen the successful development of static implants and the future will see further sophistication of these, and

also the development of dynamic devices such as implantable hearts, kidneys, muscles, and lungs. The technology for some of these new developments is either here now or is on the horizon and it is the fortunate lot of future bioengineers, chemists, and physicians to develop them" (Braley 1970).

2. Prosthetic Organs

Although many prosthetic organs have been described, it is generally agreed that some are at the earliest experimental stages of development, for example, artificial skin (Hall et al 1965), a wearable artificial kidney (Blaney, Linden, and Sparks 1966), a prosthetic urethral sphincter (Haygood and Derrick 1972), a prosthetic bladder (Stanley, Feminella, and Priestly 1971), and an implantable prosthetic anal sphincter (Kantrowitz, Affold, and Hardenberg 1971). At the other end of the spectrum are prosthetic organs which are established firmly in clinical practice for example the artificial kidney.

There is a middle category to which belong prosthetic hearts, the prosthetic gut, and prosthetic lungs. Research into the development of these prosthetic organs has become so active that recently the work has reached the stage of clinical application.

Kolff and his colleagues (1962) obtained encouraging results with prosthetic hearts as did Liotta, Hall, Cooley, and De Bakey (1964). In 1963, Liotta and his colleagues anatomically incorporated a booster

heart in one patient although, at that period in time, the step was probably premature. Atsumi and Sakurai (1970) have reviewed the development, types, and present status of prosthetic hearts, and Klain and his colleagues (1971) concluded rightly that to achieve 100 hour survival with a total mechanical heart, workers in this field must re-examine the interplay between the animal and the prosthetic heart.

Scribner and his colleagues (1970) have devised artificial gut to provide life-sustaining parenteral nutrition and have used the device on patients with chronic bowel disease in a manner similar to the use of home dialysis to maintain patients with chronic renal disease. Atkins and his colleagues (1970) described technical improvements in the device with which they maintained parenteral feeding in six outpatients for up to two months. Five patients benefitted markedly; one died with yeast septicaemia.

Although the principle of the prosthetic lung is as old as heart-lung machines, prosthetic lungs employed for long-term perfusion are recent innovations. J.H. Gibbon Jr. (1937) who published a paper on the artificial maintenance of the circulation during experimental occlusion of the pulmonary artery, is usually regarded as the doyen of workers in this field (Melrose 1956). Since then operations within the chambers of the heart have become commonplace and most are possible because of heart-lung machines (artificial oxygenators) of which there

are many varieties for example rotating disc oxygenator (Melrose 1952). In the design of oxygenators, the most vexed question remains the choice of method for gas exchange and there has been a general leaning towards the principle of imitation of the normal pulmonary anatomy where the blood is separated from the gas by a thin membrane (Melrose 1958).

Membrane blood oxygenators (membrane lungs) were conceived in the early 1950's by Kolff when he noted that oxygenation as well as dialysis occured in artificial kidneys and the first membrane oxygenator was described by Clowes, Hopkins, and Neville (1956). Since that time, many devices have been proposed by others including Melrose, Bramson, Osborn, and Gerbode (1958), Crescensi and his colleagues (1959), Kylstra, Moulopoulos, and Kolff (1961), Marx, Baldwin, and Miller (1962), Kolobow and Bowman (1963), Bodell and his colleagues (1963), Crystal and his colleagues (1964), Bramson and his colleagues (1965), Peirce (1966), Ratan and his colleagues (1967), Lande, Edwards, and their colleagues (1970), Dutton and his colleagues (1971), Murphy, Norris, and Martin (1971), and Melrose and his colleagues (1971). The common objective of these workers is to improve the efficiency of the membrane lung, and to make it practical for clinical use in organ perfusion and open-heart surgery in small infants as well as in adults. To protect patients while interfering little with the development and marketing of the membrane lungs, the American Society for Artificial Internal Organs

formed a Subcommittee for gas exchangers under the chairmanship of Peirce (1971). The Subcommittee has since published a short report as guidance for developers and manufacturers of membrane lungs intended ultimately for clinical use.

3. Long-term Extra-corporeal Blood Gas Exchange

Long-term extra-corporeal blood gas exchange is at present the level of application of the membrane lung which is nearest to the goal of an implantable prosthetic lung. Recent reports are as follows. Hill, Bramson and their colleagues (1969) reported experimental (and clinical) experiences with prolonged oxygenation and assisted circulation. The aims of the experimental study were to see if in fact prolonged oxygenation produced severe pathological changes in 14 dogs and if the membrane lung would function effectively for long periods of time. The duration of the oxygenation varied from six to 36 hours. The variables which they measured were haemolysis, blood gas tension, serum electrolytes, plasma proteins, blood sugar, and platelets; pulmonary compliance, lung morphology, and the mortality of the procedure were also recorded. They concluded that prolonged oxygenation, i.e. up to 36 hours continuously, can be performed with minimal damage to blood and no pathological effects on the body or lungs. These observations have been confirmed by others including Lande and his colleagues (1969), Lande, Edwards, and their colleagues (1970), and Timmons, Lindsey, and Woolverton (1970).

Noteworthy experimental work on prolonged extra-corporeal blood gas exchange comes from Kolobow and his colleagues (1968, 1969, and 1971), who have persistently pursued the design, manufacture, and use of a small membrane lung with which they are able to sustain lambs for long periods of time. In the first report (1968) they described partial extra-corporeal gas exchange in alert newborn lambs with a membrane lung perfused via an arterio-venous shunt for periods up to 96 hours. A year later, they reported high survival and minimal blood damage in lambs exposed to continuous veno-venous perfusion and membrane blood gas exchange for periods up to a week, and in 1971 they extended the period of the procedure up to 16 days. (Eighteen lambs were perfused for a total of 116 days ranging from 2-16 days.)

Clinically the membrane lung has been employed in an attempt to salvage terminal cases of cardio-respiratory insufficiency. Hill and his colleagues (1969) kept five patients alive for up to 24 hours; and, in 1971 they managed to keep another six patients going for periods ranging from 12 hours to 6½ days. Lande, Edwards, and their colleagues (1970) reported 20 patients on whom long-term extra-corporeal circulation was maintained up to 72 hours. Dorson and his colleagues (1970) reported the response of five infants in the terminal stages of respiratory distress syndrome in whom the perfusion period varied from 5-12 hours. A 10-day and a four-day perfusion in human infants have also

been reported (White 1970 and Kennedy 1971). As with all innovations, though, the patients in whom the procedure was used were moribund and they all died eventually. However, these initial reports are promising and Melrose (1970) and Kolff (1970) are persuaded that the future lies with membrane lungs.

4. The Feasibility of Implanting Prosthetic Lungs

The subject is recent and the literature is scanty. Although implantable prosthetic lungs have not yet been made, Bodell and his colleagues (1965) showed that it was feasible to implant prosthetic lungs, but only in short-lived experiments. They grafted 10 ten-foot lengths of Teflon between the pulmonary artery and left atrium in seven sheep and three dogs. Each graft contained 10 ten-foot silicone capillary tubes. They arranged the system in such a way that blood under the normal pulmonary arterial pressure perfused the silicone tubes while pressurised oxygen flowed around them. There was a rise in arterial oxygen tension and a fall in arterial carbon dioxide tension when both blood and pressurised oxygen were allowed to flow simultaneously through the system. They concluded that, "The artificial lung has potential as a respiratory booster for patients with diffuse pulmonary disease. Development of larger models might lead to replacement of one or both lungs".

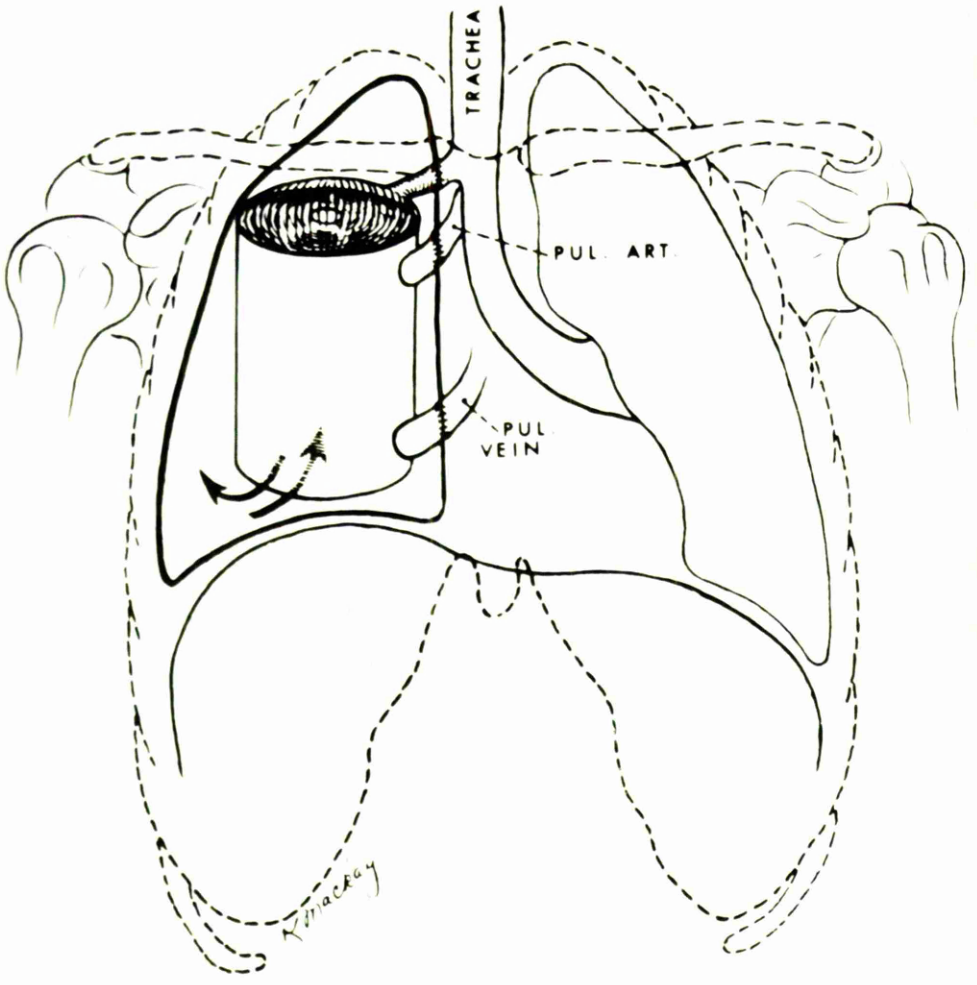
(over)

Fig. 1

A Concept of an Implantable Membrane Lung

(by E. Peirce, II 1966)

"Preliminary drawing for an implantable membrane lung composed of ultrathin silicone membrane. Details of possible air and blood manifolding are shown. Except for the pressure core, the case, and the manifolds, the entire apparatus would have functional gas exchange thereby reducing size greatly. See text". Trans. Amer. Soc. Artif. Intern. Organs, 25: 334-339



In 1966 Peirce, whose contributions towards the theoretical aspects of the membrane lung have been noteworthy, suggested that ultra-thin silicone membrane could be used to construct an implantable lung for basal oxygen needs. The next year he followed this with an excellent review article entitled "The Membrane Lung, Its Excuse, Present Status and Promise". According to Peirce (1966 and 1967), a permanently implantable prosthetic lung might occupy the pleural cavity, be perfused by blood under the normal pulmonary arterial pressure and receive its gas as air from the trachea as a result of natural breathing (Fig. 1). Such a prosthetic lung, however, presents many unsolved technical problems not directly related to the material used.

The work described in this thesis is an attempt to provide possible solutions to two of these problems. To recapitulate, first there was the difficulty of making the pleural cavity equal to the task of housing safely and permanently a functioning foreign body such as an implantable prosthetic lung. Secondly, the route by which the prosthetic lung could receive air remained to be established.

C: GENERAL DISCUSSION OF THE PROBLEMS

As a possible solution to the first problem, Peirce (1966 and 1967) suggested that the pleural space must first be lined with silicone 'skin' (i.e. Dacron-backed silicone rubber membrane) and that in this

way the pleural cavity could be effectively exteriorised. He added that silicone 'skin' should be installed at a preliminary stage and a pneumonectomy be carried out at the same time. In theory this suggestion is sound because Dacron and silicone are implant materials which cause little tissue reaction (Leininger et al 1964).

Melrose (1970) agreed with Peirce that in principle the normal pleural membrane could accept silicone 'skin', but he had doubts about the practicability of this. Melrose's reservations are valid because the normal pleural membrane will react to fresh heterologous plasma with increased capillary permeability and exudation of much fluid rich in protein (Courtrice and Simmonds 1954). It was to help resolve this issue that I investigated the effect of silicone 'skin' on the pleural membrane as one of the first practical steps towards providing space for a permanently implantable prosthetic lung.

It was argued that a thicker and less vascular pleural membrane might react less violently to irritants. Tobin, Van Liew, and Rhan (1962) showed that in subcutaneous gas pockets the gas molecules acted as foreign bodies which induced the deposition of collagen fibres in a direction parallel to the walls of the cavity. In this way the lining of the cavity became thicker and progressively less vascular. It was proposed to take advantage of this observation.

On the assumption that it was possible anatomically to reline and exteriorise the pleural cavity, the next thing to consider was the type of gas cavity that would result and how it would function.

"All normally or pathologically occuring or artificially produced gas cavities in the body may be divided into four functional types: (i) closed noncollapsible, (ii) closed collapsible, (iii) open nonventilated, and (iv) open ventilated gas cavities" (Piiper 1965). For example, whereas the normal lungs are open ventilated gas cavities, normal paranasal air sinuses are open nonventilated gas cavities; the middle ear is a closed noncollapsible gas cavity, and examples of closed collapsible gas cavities are pneumothorax (closed), pneumoperitoneum, subcutaneous emphysema, artificial gas pockets, and so on.

An exteriorised pleural cavity is an open artificially produced gas cavity. Functionally, it might be ventilated or nonventilated. If it is ventilated, it might be poorly or well ventilated. This work seeks also to establish what happens in practice.

As a possible solution to the second problem, Peirce (1966 and 1967) suggested that the prosthetic lung might receive air from the trachea as a result of natural breathing. However, such an arrangement would pose serious problems related to the different compliances and airway resistance of the prosthetic lung and the natural lung on the opposite side. Hugh-Jones and his colleagues (1971) have emphasised

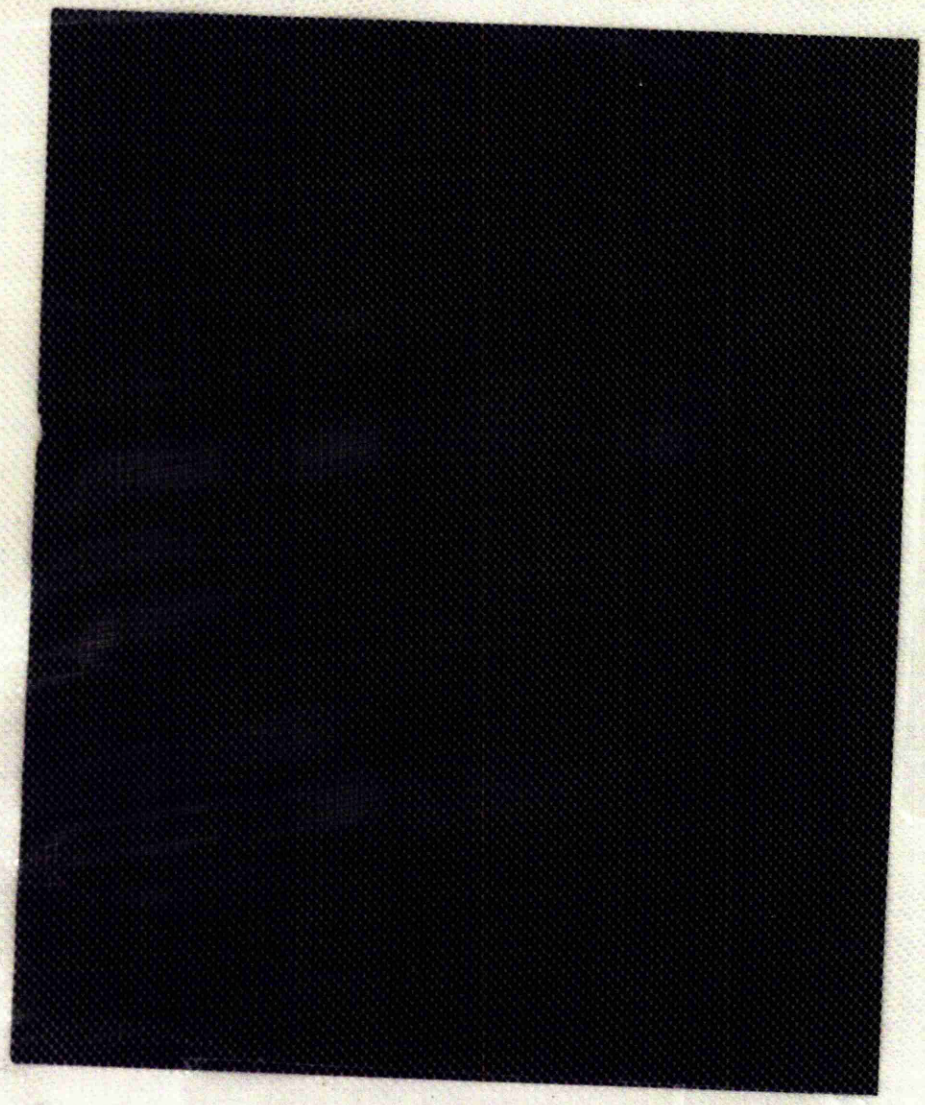
the gross imbalance between the distribution of gas and blood as a potent cause of fatal respiratory failure in lung transplantation. (Most of the inspired air goes to the original lung but most of the blood goes to the new one.)

It was reasoned that the problem might be solved if the two halves of the thorax could be so partitioned that they functioned as separate ventilating chambers with the normal lung receiving air from the trachea and the prosthetic lung receiving air independently from a separate opening directly through the chest wall. This work seeks to explore and evaluate such a possibility.

(over)

Fig. 2

Sample of Dacron-backed silicone rubber membrane (silicone 'skin') employed to test the effect of silicone 'skin' on the pleural membrane of dogs



CHAPTER II

THE TECHNICAL EXPLORATION OF THE EFFECT OF SILICONE 'SKIN' ON THE PLEURAL MEMBRANE IN DOGS

INTRODUCTION

The first practical step toward providing space for implantable prosthetic lungs was to find a suitable material with which to reline the pleural space, and the effect of silicone 'skin' was investigated. Silicone 'skin' (Dacron-backed silicone rubber membrane) was chosen to test the validity of Poiree's views.

MATERIALS AND METHODS

Five adult dogs, three mongrels and two greyhounds kept under standard laboratory conditions, were used in these initial and exploratory experiments; they weighed 18.9, 29.6, 19.4, 24.4, and 25.2 kg respectively. The silicone 'skin' employed was 30 microns thick and the average pore of the Dacron mesh was 300 microns in diameter. The sample implanted into each postpneumonectomy pleural space measured 150 x 100 mm (Fig. 2).

In a well equipped theatre all major operations were performed on dogs under general anaesthesia and with full aseptic technique.

Anaesthesia was induced by 0.5 per cent intravenous thiopentone sodium (dose: 5 mg/kg) and maintained with fluothane/air mixture (concentration of fluothane 0.5 to 1.5 per cent). The Palmer Ideal Respirator provided intermittent positive pressure ventilation through a cuffed rubber endotracheal tube. The tidal air varied between 400 and 500 ml and the rate of ventilation between 14 to 18 strokes a minute.

All five dogs had a standard left pneumonectomy, which was performed as follows. The left chest was opened through the bed of the unresected seventh rib and wound towels and rib spreaders were applied. The inferior pulmonary ligament was divided and the hilar structures were identified and dealt with individually. The pulmonary artery was dissected, isolated, and divided between two 1/0 silk ligatures and the proximal stump transfixed with 2/0 atraumatic catgut. The pulmonary veins were divided between 2/0 silk ligatures. Usually, two veins but sometimes one and sometimes three drained each lobe. Finally, the main stem bronchus was clamped and divided, a little at a time, proximal to the clamp; the stump was closed with interrupted atraumatic 3/0 silk, checked to ensure that it was airtight and then allowed to retract beneath the aortic arch. Haemostasis was satisfactory; the chest was closed in layers and water-sealed drainage established via a polythene tube introduced through a separate stab-incision.

In dogs one and two the sample of silicone 'skin' was implanted immediately after pneumonectomy - i.e., just before the chest was closed. In dogs three, four, and five implantation was delayed for five weeks.

Postoperative Observations

Two observations were of special interest in the immediate postoperative period: the volume of fluid aspirated from the chest and the weight of the dogs. The chest was aspirated continuously with an electric suction apparatus for four to six hours on day one. On days two and three, suction was applied three times a day over 30-minute periods at 10 a.m., 2 p.m., and 6 p.m. The total volume aspirated was measured and accepted as the volume for that day. The chest was aspirated on alternate days for one week and less frequently after that. The dogs were weighed once a week.

Dogs four and five died 24 hours after pneumonectomy; they were both greyhounds. In dog three the chest drain was removed on the third postoperative day and a week later 500 ml of nitrogen was introduced under X-ray control into the postpneumonectomy pleural space. This restored the mediastinum back to midline. The dog was X-rayed three weeks later and the space refilled with an additional 200 ml of nitrogen. Five weeks after the pneumonectomy the dog had a second thoracotomy

(through the bed of the sixth rib) and the sample of silicone 'skin' was implanted into the nitrogen-treated cavity. The postoperative observations were the same as before.

RESULTS

Results are available for the three mongrel dogs. Dogs one and two failed to thrive, and a mean of 680 ml of blood-stained fluid a day was aspirated from the chest (Table 1).

The experiments on dog three provided much useful information. After the standard pneumonectomy the mean chest aspirate was 17.6 ml a day (Table 2). The postpneumonectomy space containing nitrogen gas for four weeks remained free of fluid as judged by X-ray screening. The dog's weight was steady (Table 3), and at the second thoracotomy the lining of the cavity was found to be fibrous, avascular, and 2-3 mm thick. However, when silicone 'skin' was implanted into this cavity the following were observed:

i) A mean of 390 ml of blood-stained fluid a day was aspirated. This contrasted with 17.6 ml a day from the same cavity before silicone 'skin' was implanted, and it confirmed experience with normal pleural membrane, where a daily mean obtained was 680 ml (Tables 1 and 2).

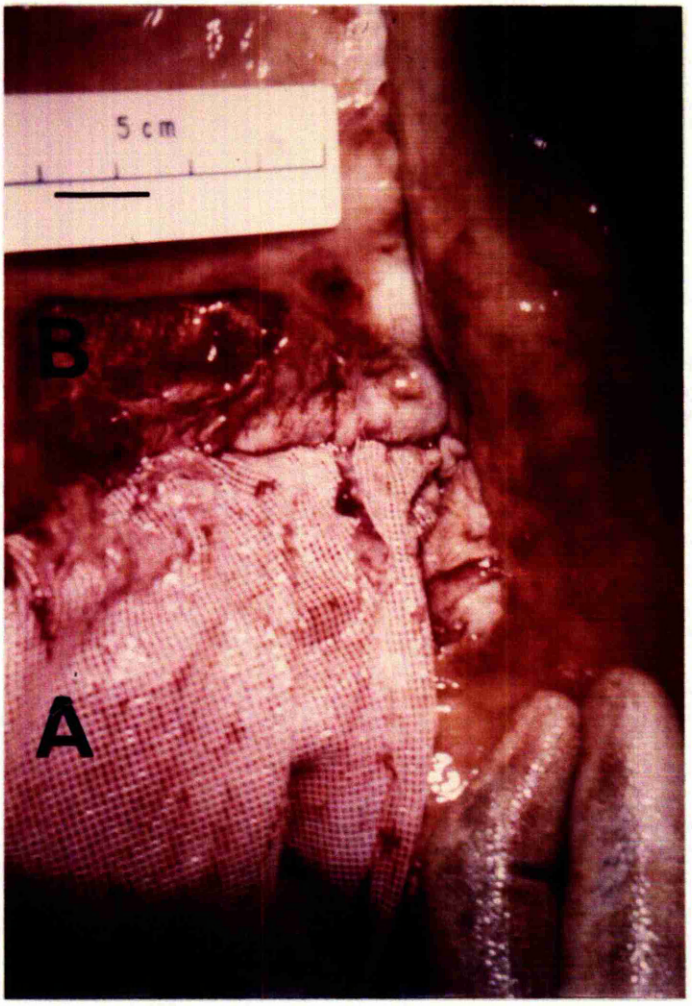
(over)

Fig. 3

The Findings in a Dog which was Killed Five Weeks after the Implantation of Silicone 'Skin' into the Postpneumonectomy Pleural Cavity

Silicone 'Skin' as the Possible New Pleural Lining

Silicone 'skin' (A) has been stripped by sharp dissection from the pleural surface of ribs six and seven leaving a raw area (B). The thickened pleura is seen (yellow) and the centimetre ruler indicates pleura to which silicone 'skin' did not adhere



ii) The dog lost 0.5 kg after standard pneumonectomy; but it lost 6 kg in the four weeks during which the postpneumonectomy pleural space contained a sample of silicone 'skin' (Table 3). Again, this confirmed experience with dogs one and two, which also failed to thrive while harbouring the implant (Table 1).

iii) The dog developed empyema.

iv) At the third thoracotomy it was impossible to remove the implanted silicone 'skin', which had adhered firmly to the chest wall and the diaphragm, and it was therefore necessary to kill the dog.

At necropsy, 700 ml of fluid was present in the left chest, and the silicone 'skin' had fused firmly, with the formation of hard fibrous plaques, with the diaphragm and the backs of ribs six and seven, the sites of two previous thoracotomies. Silicone 'skin' adhered less firmly into the costovertebral groove, and elsewhere in the chest cavity not at all (Fig. 3). Figure 4 shows the photomicrograph of Dacron fibres embedded in young fibrous tissue: the specimen was taken from the pleural surface of the diaphragm.

Fig. 4

Photomicrograph of specimen taken from the pleural surface of the diaphragm of a dog into whose chest Silicone 'skin' (Dacron-backed silicone membrane) had been implanted for five weeks. It shows the Dacron fibres (arrowed) in the middle of the field; top right hand corner shows much granulating tissue and elsewhere young connective tissue (H and E x 150).

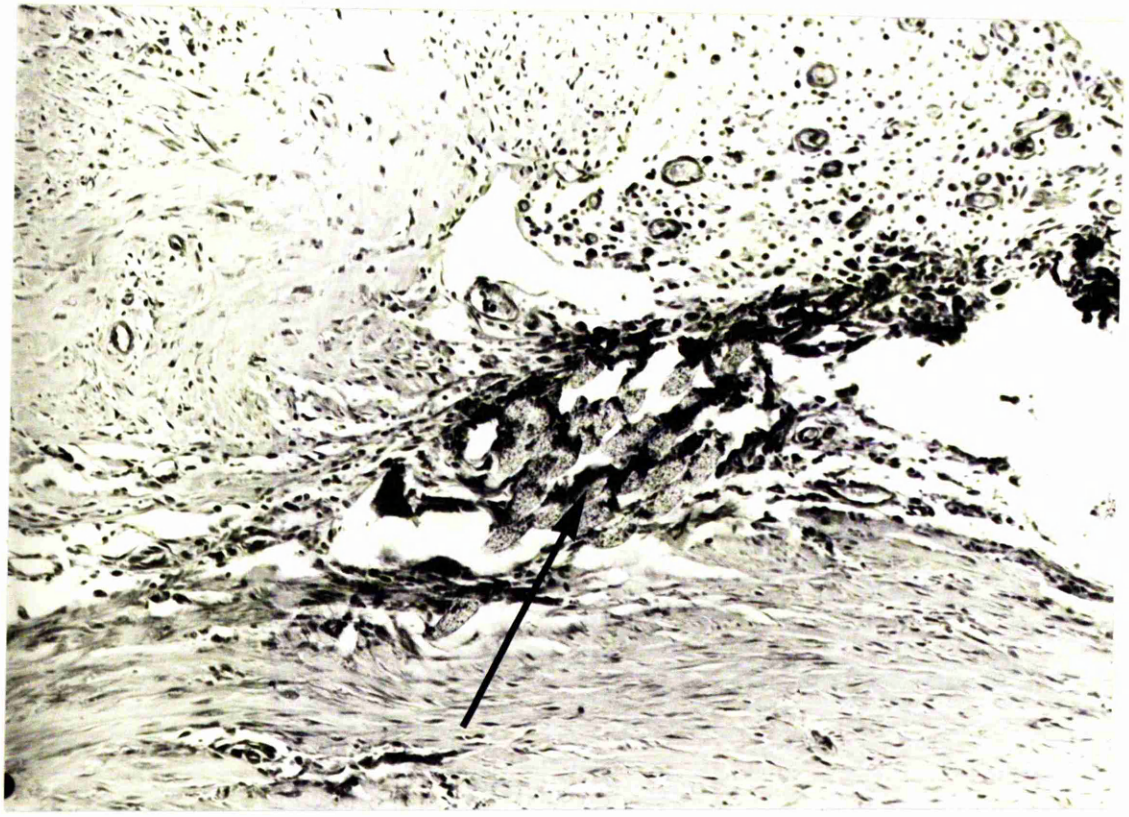


Table 1

Effect of Implanting Silicone 'Skin' into the Fresh Postpneumonectomy Space of Two Dogs

Bodyweight and Volume of Chest Aspirate

	Dog One		Dog Two	
	Weight in kg	Vol. (ml.) of Chest Aspirate	Weight in kg	Vol. (ml.) of Chest Aspirate
Day 0	18.9	...	29.6	...
1		120		150
2		225		350
3		295		600
6	18.0	600	27.6	2,000*
8		600		
11		650	Mean	775
15	17.3	700		
16		800		
20	16.5	1,755*		
	Mean	638		

* Dog Killed

Table 2

Effect of Implanting Silicone 'Skin' into the Nitrogen-treated Postpneumonectomy Space of a Dog

Volume of Chest Aspirate Before and After the Implantation

	Vol (ml) of Fluid	
	Before	After
Day 1	3	460*
2	25	110
3	25+	450
4		700
6		600
8		210
10		200
Mean	17.6	390

* Drainage tube removed electively three days after pneumonectomy.

+ Five Weeks postpneumonectomy; space kept open with refills of nitrogen gas; it remained free of fluid as judged by X-ray screening.

Table 3

Effect of Implanting Silicone 'Skin' into the Nitrogen-treated Postpneumonectomy Space of a Dog

Bodyweight Before and After the Implantation

		Weight (kg)	
		Before	After
Week	0	19.4	20.4**
	1	19.0	20.0
	2	18.9	19.2
	3	19.6	18.0
	4	20.2	16.2
	5**	20.4	16.0†
	6	....	16.0
	7	....	15.2
	8	....	14.4

* First thoracotomy, left pneumonectomy performed.

** Five weeks postpneumonectomy, space kept open with refills of nitrogen gas. Second thoracotomy: sample of silicone 'skin' implanted.

† Empyema drained.

DISCUSSION ON SILICONE 'SKIN' AS THE NEW LINING FOR THE PLEURAL CAVITY: TENTATIVE CONCLUSIONS

The initial experiments in the present study showed that in three dogs silicone 'skin' provoked much pleural effusion which needed protracted chest drainage: one dog developed an empyema. This was contrary to what one would expect from Peirce's assumptions and confirmed Melrose's opinion.

In this one dog the parts of the chest wall (including the diaphragm) which did fuse inseparably with silicone 'skin' and thereby gave the required result became stiff: histological examination of a specimen from the surface of the diaphragm showed the Dacron fibres embedded in fibrous tissue. About this, Braley (1970) has stated that although it gives the sensation of softness Dacron is not a soft implant material. The tissue which grows into the interstices of Dacron becomes fibrous tissue, which in time will shrink and harden, so that the ultimate effect is one of stiff scar tissue. Because of this Dacron cannot be used where permanent softness is needed.

It is therefore tentatively concluded that although it was technically possible to get the pleural surfaces to fuse with silicone 'skin' the resultant chest wall would be so stiff that an animal would be unable to ventilate it as a result of normal breathing.

The two practical difficulties met with were much pleural effusion (which needed protracted chest drainage) and infection. These observations were equally valid for the other plastic fabrics in current use, namely Teflon and Velour (Dacron or Teflon). It was therefore considered unjustified to pursue further this line of enquiry. Rather, a fundamentally different material was sought as the new lining for the pleural cavity, and the use of autogenous skin for this purpose was investigated.

CHAPTER III

AUTOGENOUS SKIN AS THE NEW LINING FOR THE PLEURAL CAVITY: THE BASIS OF SUBSEQUENT STUDIES

INTRODUCTION

The ultimate objective of using autogenous skin was the possibility that a skin-lined hemithorax could be opened directly to atmospheric pressure without embarrassing breathing in the contralateral lung. Skin, the natural covering of the body, also lines most body cavities which are naturally open to the outside for example the oral cavity, the nostrils, the outer ear, and so on. It seemed reasonable, therefore, to reline the pleural cavity with skin before exteriorising it.

The experiments described in this section were performed in an attempt to answer three questions. First, would skin grafts 'take' on the normal pleural surfaces? Secondly, could the damaging effect of shed hair and squames in the free pleural cavity be prevented by grafting closed capsules of skin into the cavity? Thirdly, could one adopt two techniques used by plastic surgeons to provide skin cover for extensive surfaces: the use of postage stamp grafts, and the technique of fenestration described by Feller and Hill (1965)? (The use of skin homografts was considered unwise as it would introduce another complex variable.)

MATERIALS AND METHODS

Eleven adult mongrel dogs which weighed 25.6 ± 1.2 kg were employed. As already described in the previous chapter, all operations were performed with the dogs under general anaesthesia and with full aseptic techniques.

A: Taking the Graft

Two different techniques were employed to obtain free skin grafts: complete excision of full thickness skin followed by defatting with a scalpel, and the use of a Humby knife. This determined the area of skin prepared. Hair was removed with an electric hair clipper and a razor blade was used for a closer shave. The shaved area was scrubbed thoroughly with a 2.5 per cent solution of chlorhexidine in water and washed down with normal saline.

In the first nine dogs the back was prepared and a rectangular piece of full thickness skin was excised; it measured about 150 x 100 mm. The raw area was covered with warm saline packs to control bleeding (diathermy was employed occasionally) and the skin wound closed. The free graft was pinned onto a piece of cork and defatted in the usual way.

(In the last two dogs both shoulders and both gluteal regions were prepared in anticipation for taking split-skin grafts with the Humby knife. But I found this technique difficult in both dogs, because I never managed to obtain sufficiently broad sheets of skin

without cutting down deeply into muscle. These two dogs were therefore eliminated from the study.)

The nine dogs were divided into three groups of four, three, and two, and the skin grafts were shaped in three different ways. In the first group (Nos. 6-9) the grafts were cut into 20 x 80 mm flat rectangular pieces suitable for use of onlay grafts.

In the second and third groups the skin grafts were sutured with 2/0 silk into capsules which were turned inside out so that the hair-bearing surfaces were enclosed. In group two (dogs 10-12) the skin capsules were closed completely. They measured 60 x 60 mm, 90 x 30 mm, and 120 x 100 mm; they were kept flat and roughly rectangular in shape with a framework of thin stainless-steel wire.

The technique for increasing autograft coverage (Feller and Hill 1965) was used in dogs 13 and 14 (group three). The technique consisted of slitting the free skin graft in many places; each slit was about 15 mm long and the spaces between them about 25 mm. In this way the skin graft could be stretched to cover more surface area. To keep the skin capsules stretched they were filled with silicone membrane to measure 80 x 60 x 60 mm. (The sample of silicone employed was 75 microns thick, 300 mm wide, and 4,500 mm long.)

B: Applying the Skin Grafts

1. In group one (dogs 6-9) median sternotomy was chosen. With the dog placed on its back, its front paws were held forward and the front of the chest prepared and draped. The skin incision was made co-extensive with the sternum. A cutting diathermy was used to separate the apposed medial borders of pectoralis major muscles. Anterior perforating branches of intercostal vessels were also diathermised. The sternum was split with a sharp pair of 15 cm long two-bladed secateurs. (A Gigli saw was unsuitable because the sternum was too narrow; an electric saw was tried but found too risky, because the sternum had a sharp central ridge off which the saw slipped repeatedly and dangerously.) The cartilage of the manubrium was split to get a wide exposure although it meant poor wound healing afterwards. Two pairs of rib spreaders and wound towels were applied and the chest was opened widely.

In dog six both halves of the chest cavity were used. On the right side the parietal pleura was stripped off ribs five to nine and off the diaphragm. (On the ribs, the pleura stripped readily but not on the diaphragm.) Oozing from the raw area was controlled with warm saline packs. The left half of the chest was left undisturbed. The strips of onlay skin grafts were sutured with interrupted 2/0 catgut to pericardium, mediastinum, rib cage, aorta, oesophagus, and diaphragm. Both lungs were expanded fully at regular intervals during the operation.

Dogs seven and eight had similar operations except that only the left pleural cavity was employed; the right was not interfered with. In these three dogs, then, the lungs remained in situ to provide external compression for the onlay skin grafts.

In dog nine, however, the left lung was removed before the grafts were sutured on to the structures listed, so that in this dog the skin grafts had no external compression.

Two chest plastic drains were inserted and brought out through separate stab incisions. The intrathoracic parts of the drainage tubes were sutured loosely with catgut into the costo-sternal groove anteriorly to keep them away from the skin grafts. The wound was closed carefully in layers, as follows: interrupted horizontal mattress sutures of silk to costal cartilages, two layers of continuous silk to muscle, followed by interrupted nylon to skin. The drains were connected via a Y-piece of firm plastic tube sealed underwater, and suction at between -3 and -5 mm Hg was applied.

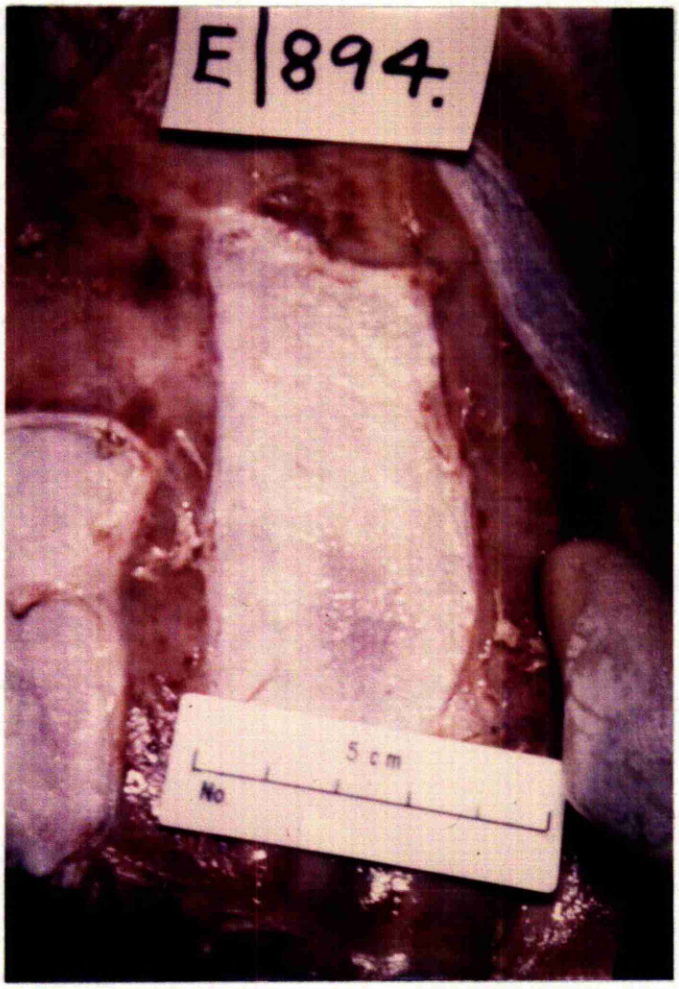
2. In groups two and three the skin capsules were implanted into the normal left pleural cavity. Thoracotomy was performed through the bed of the unresected seventh rib; the lung was not removed. As already described, the chest was closed carefully in layers and a water-sealed drain established.

(over)

Fig. 5

The Basis of Subsequent Studies:
Autogenous Skin as the New
Pleural Lining Showing

Three patches of free skin grafts have 'taken' on the unstripped pleura. The cut edges of ribs, three below and one at the extreme top left hand corner, are also seen. The central patch of skin measured 8 x 3 cm. The dog was killed four weeks after the strips of onlay skin grafts were sutured onto the normal pleura on the ribs.



3. After operation, the dogs received daily intramuscular injections of one mega unit crystalline penicillin and one gramme streptomycin for five days; the chest drains were removed on the third day and the dogs were killed in the fourth week.

OBSERVATIONS AND TENTATIVE CONCLUSIONS:
THE BASIS OF SUBSEQUENT STUDIES

In group one all the onlay grafts 'took', and Fig. 5 shows an example of skin growing on the normal pleural surfaces of the rib cage. Adhesions had formed in dogs six to eight between the grafts and the lungs. In dog nine, which had prior pneumonectomy, the pleural cavity contained over 1,200 ml of blood-stained fluid.

In group two the closed skin capsules 'took' on the normal surrounding structures: lung and rib cage. There was minimal fluid in the free pleural cavity. However, blood-stained fluid had gathered in the lumen of the skin capsules; it amounted to 15, 20, and 25 ml in the three dogs. In group three, however, the fenestrated skin capsules were found embedded in thick fibrous exudate with about two litres of fluid in the free pleural cavity.

These observations agreed with the following statement: "Free skin grafts 'take' on any living tissue except cortical bone: they will 'take' on fat, fascia, muscle, tendon, periosteum, marrow, dura

mater, artery, nerve, and bowel; but there are obvious disadvantages in using free grafts in some of these sites" (Jackson 1967).

Four tentative conclusions were drawn. First, free skin grafts would 'take' on the pleural surfaces whether stripped or not. Secondly, the skin could be applied as onlay grafts or, preferrably, as skin capsules in which the hair-bearing surfaces had been enclosed. Thirdly, skin capsules grafted into the normal pleural cavity were associated with haemorrhagic pleural effusion. Fourthly, when the capsules were fenestrated the fluid escaped into the free pleural cavity; however, when the capsules were closed the fluid accumulated in and remained confined within their lumen.

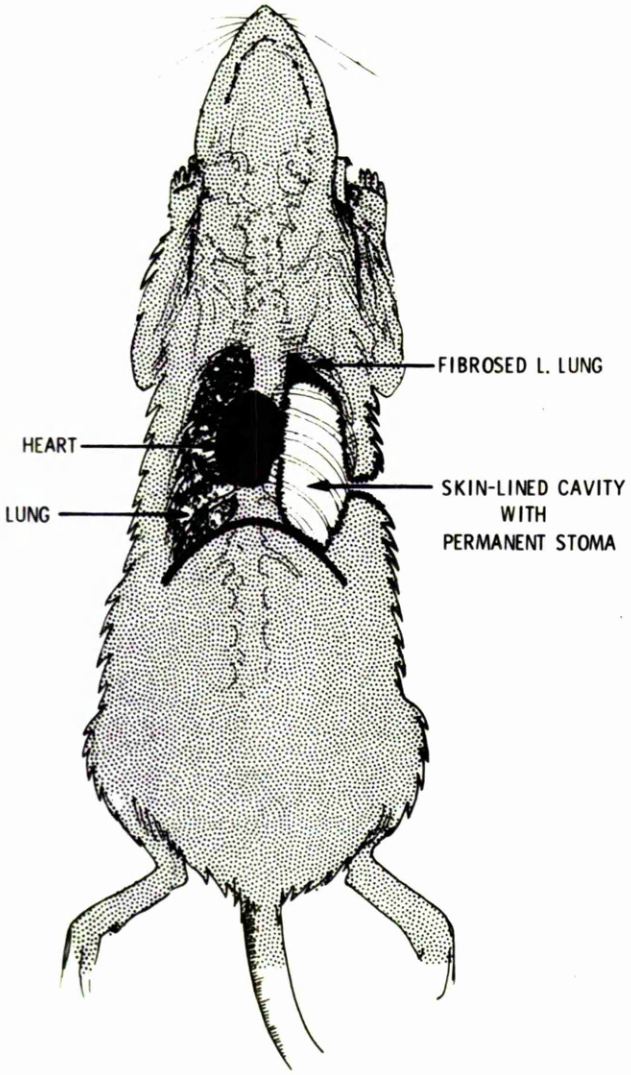
These tentative conclusions were accepted as the basis of subsequent studies.

(over)

Fig. 6

The Skin-lined Hemithorax Rat Preparation

The left hemithorax has been changed into a stable skin-lined gas cavity, which can be opened to the exterior without embarrassing respiration in the contralateral lung. The experimental preparation is presented as a model for providing space for implantable prosthetic lungs.



CHAPTER IV

THE INVESTIGATION

THE CREATION OF A SKIN-LINED AND EXTERIORISED HEMITHORAX: An Experimental Model for the Provision of Space for Implantable Prosthetic Lungs

PART I

INTRODUCTION

The aim of this part of the work was threefold. First, to attempt to transform the hemithorax into a skin-lined cavity. Secondly, to investigate the possibility that the skin-lined hemithorax could be opened directly to the exterior without embarrassing respiration in the contralateral lung (Fig. 6). Thirdly, to see whether the animal could ventilate such a cavity as a result of normal breathing.

Three points were considered. First, if the pleural cavity were lined with skin instead of the normal pleural membrane it might become equal to the task of housing an implantable prosthetic lung. Secondly, if the skin-lined hemithorax could be opened directly to the air outside without embarrassing respiration in the remaining lung the thorax could be changed into two separate ventilating chambers which received air from independent openings, with the air inspired through

the trachea ventilating the normal lung only. (This arrangement would eliminate the problems of ventilation imbalance which usually accompanies lung replacement, whereby most of the inspired air follows the line of least resistance into the less rigid of the two lungs.) Thirdly, a quantitative assessment of ventilation in the skin-lined hemithorax would answer the question whether additional devices for ventilation would be needed for implantable prosthetic lungs.

The provision of space for implantable prosthetic lungs had to be investigated in a suitable laboratory animal to establish the general principles, to define the difficulties, and to make observations that might be applied to man.

The experimental animal chosen first was the rat for two reasons. First, the rat had much loose skin relative to the size of its body, so that, if required, much autogenous skin graft would be obtained readily. Secondly, being a small animal the rat needed little supervision and a large series could be rapidly built up.

From previous relevant work on rats, two things became clear. 'Specific pathogen-free' (SPF) colonies must be used because they were free, at least initially, of endemic chronic respiratory disease from which other rat colonies suffer. (It is a chronic peribronchitis with increased number of goblet cells, increased bronchial secretion, lymphoid hyperplasia, and peribronchial lung damage (King and Bell 1966).)

Rats delivered by Caesarean section and reared under sterile conditions are not free from all bacteria, but do not suffer from the specific endemic respiratory disease probably caused by a pleuropneumonia-like organism. Binns, Clark, and Healey (1971) have found it important to use healthy, SPF rats for studies of lung physiology.

Secondly, it was necessary to use a simple and safe method of anaesthesia for rats intended to recover after chest surgery. Rats' chests could be opened and the animal kept alive for up to two hours by giving direct intratracheal anaesthesia, but this procedure was suitable for short-lived experiments only, because tracheostomies in the rat could not be closed again (Griffith and Farris 1942). Initial experiments in six rats confirmed this. Kluge and Tveten (1968) had been able to accomplish this.

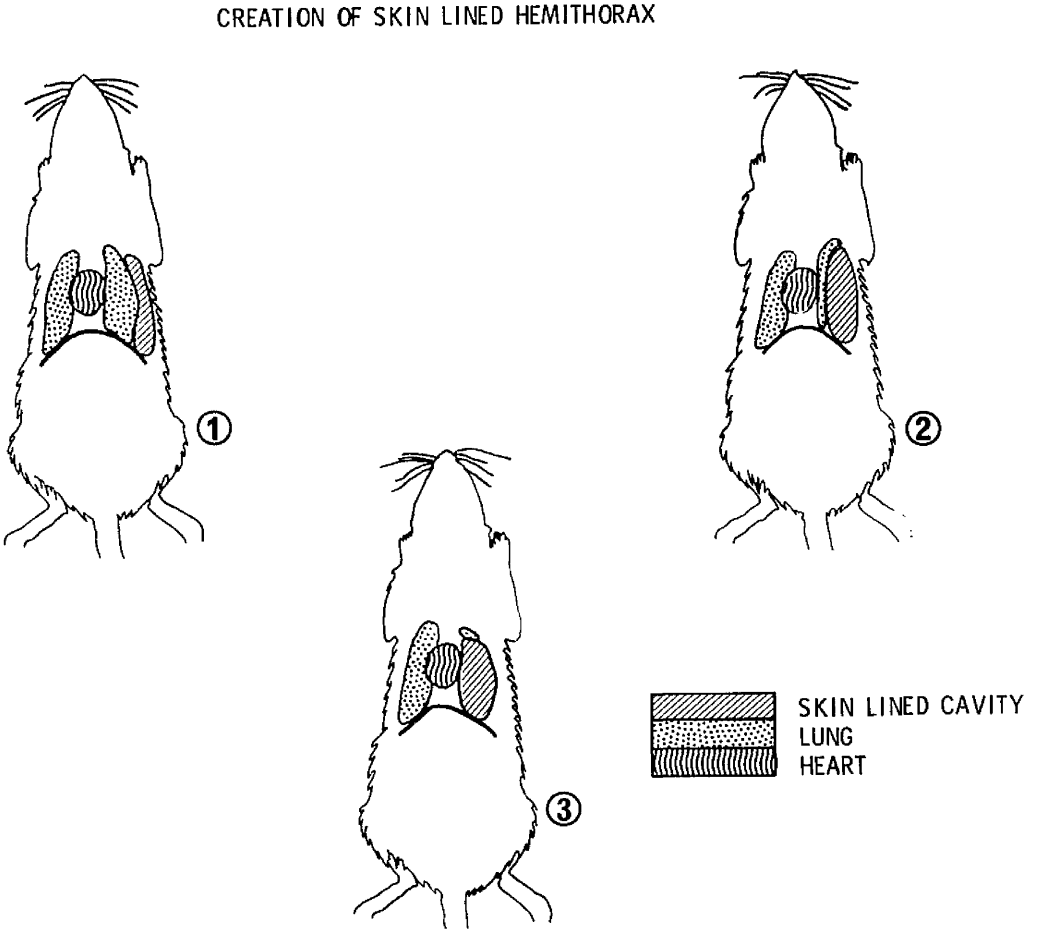
In my investigations the rat was anaesthetised but not intubated, the chest was opened, the skin capsule was implanted into the normal pleural space, and the chest closed again. It was thought that if the chest was opened for but a short time and the investigator was quick in operation, the rats should survive the thoracotomy. In this way the frustrations of direct intratracheal anaesthesia in rats could be circumvented. With this approach, 150 out of 168 (89.3 per cent) survived the thoracotomy ($P < 0.001$).

(over)

Fig. 7

Rationale Behind the Approach Employed to Transform the Left Pleural Cavity into a Postpneumonectomy Skin-lined Hemithorax

1. A closed skin capsule has been grafted into the left normal pleural cavity. 2. The skin capsule enlarged as fluid accumulated in it. 3. It occupied the left hemithorax displacing the ipsilateral lung. At a later stage the skin-lined hemithorax could be opened to the exterior through a permanent thoracostomy.



At this stage there were three things to be done. The first was to attempt to transform the hemithorax of rats into skin-lined cavities. Secondly, it had to be discovered whether the skin-lined hemithorax could be exposed to the outside air without embarrassing respiration in the contralateral lung. The third aim was to see whether the rats could ventilate the skin-lined hemithorax during natural breathing.

The rationale behind the approach employed in this study was as follows (Fig. 7). If a thin sheet of skin was sutured into a closed capsule and grafted into the normal pleural space, the graft would 'take' on the surrounding structures. The skin would form a closed cavity in which fluid would accumulate. The cavity would expand to occupy the hemithorax displacing the lung on the same side. If the pressure in the cavity was sufficiently high for a long enough time, the ipsilateral lung would undergo compression atrophy and, "autopneumonectomy" be the result. If the heart and the contralateral lung continued to function normally the animal would survive in the absence of unexpected complications.

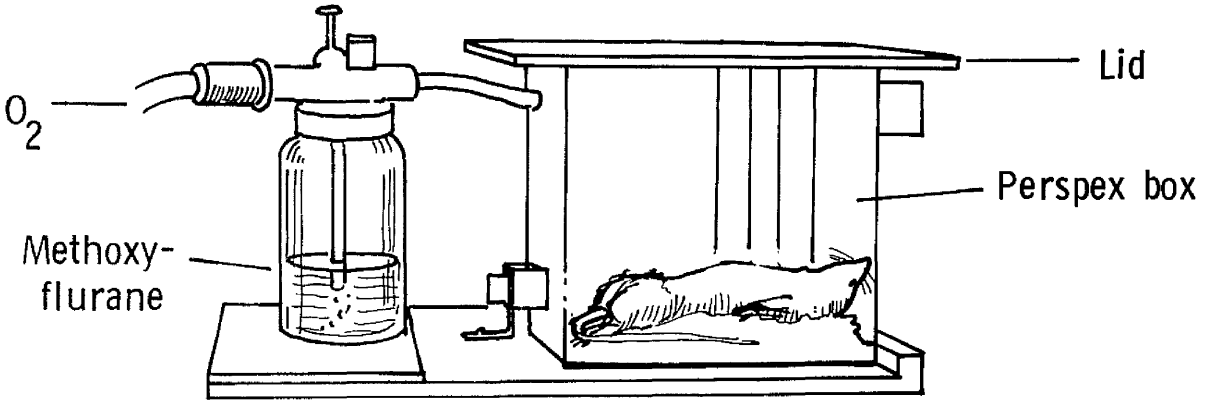
The skin-lined pleural cavity could then be opened to the exterior and a permanent thoracostomy be established. If the animal survived this stage, the result would be what was required - namely, a rat whose postpneumonectomy hemithorax was lined with skin grafts

(over)

Fig. 8

The system employed to administer anaesthesia to the rats in this study. It shows from left to right, oxygen, which was bubbled through a glass jar containing methoxyflurane. The gas mixture was led into a perspex box, 200 mm cube, into which the rat was placed; the lid of the box was not fixed.

ANAESTHESIA



and open to the exterior without embarrassing respiration in the lung on the opposite side.

MATERIALS AND METHODS

A: OPERATIVE TECHNIQUES

1. Intrapleural Skin Grafting in Rats

Male albino Wistar SPF rats (purchased from Carworth, Hutingdon) were used. Their mean initial weight was 240 ± 30g. They were kept under standard laboratory conditions in large cages each of which housed a maximum of five.

All operations were performed under general anaesthesia in a fully equipped theatre; however, for rat operations, the gloves, gowns, drapes, and instruments used were clean, not sterile.

Anaesthesia and Preparing the Skin for Grafting

The anaesthetic employed was methoxyflurane ("Penthrane") in oxygen. A glass jar containing methoxyflurane was connected to an open perspex box which measured 200 mm cube. When oxygen was bubbled at the flow rate of one to two litres a minute through the methoxyflurane and the box was closed with a lid (Fig. 8) the concentration of methoxyflurane was sufficient to anaesthetise a 250g rat in five to eight minutes. The chest and lumbar region of the rat were shaved

closely with an electric hair clipper, and loose hair was removed with a moist swab; antiseptic solutions were not employed. This procedure usually took about five minutes, and rats which had regained consciousness were put back into the anaesthetic box for a further five minutes.

An elliptical piece of full-thickness skin was excised as a free graft from the back of the rat. With the anaesthetised rat in the prone position a transverse fold of skin centred over the middle third of the ribcage was held up and excised with a pair of 5" Mayo scissors. Bleeding was slight. (Thirty consecutive grafts taken in this manner were measured and weighed: Appendix 1.) The defect was closed easily by primary suture without tension with interrupted 2/0 silk. Because the left chest was to be opened shortly, only the right half of the wound was closed; meantime, one suture held together the left half of the skin wound. The rat was then returned to the open perspex box, with the methoxyflurane turned off.

The skin was pinned onto a piece of cork, and defatted in the usual way with a No. 22 Swan Morton blade mounted on a No. 3 Bard Parker handle, as described in the last chapter. It was then folded on itself with the hair-bearing surface outside and 35 x 20 mm rectangular piece cut out.

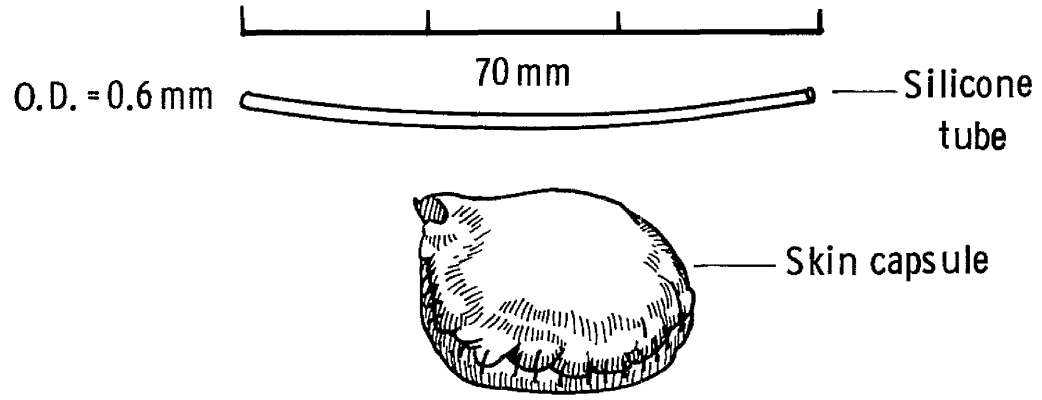
Two of the three free edges were sutured together with 2/0 atraumatic silk on a taper-cut needle. A pair of artery forceps was introduced through the third and still open edge and used to turn the

(over)

Fig. 9

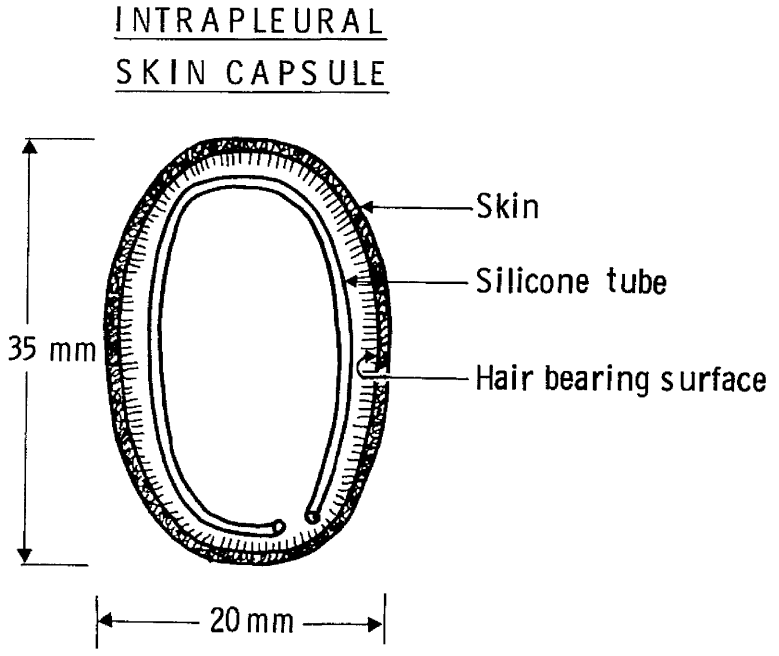
(i) Drawing of a completed specimen of skin capsule and a sample of silicone tube with which the capsule was splinted to give it a roughly rectangular shape. (ii) Diagram of a sagittal section through the skin capsule.

(i)



SKIN CAPSULE + SILICONE TUBE

(ii)



specimen inside out so that the hair-bearing surface now faced inside; a piece of soft silicone capillary tube (70 mm long and 0.6 mm external diameter) was inserted into the capsule to splint it and to give it an approximately rectangular shape. This edge was then sutured together. In this manner the hair-bearing surface was completely isolated (Fig. 9). To end the preparation the specimen was wrapped in a moist swab and laid aside.

Left Thoracotomy and Implantation of the Skin Capsule into the Normal Pleural Space

The rat, anaesthetised but not intubated, was placed on its right side on the operating table with its head pointing away from the seated investigator; the single skin suture had been removed to re-open the skin incision (Fig. 10). The thin latissimus dorsi muscle was divided transversely. By beginning this incision from the posterior edge of the muscle, the correct layer was identified readily when the shining aponeurosis of the erector spinae muscle was seen. The intercostal muscles were divided in the direction of their fibres down to but not through the pleura. The seventh or eighth intercostal space was chosen usually and a muscle incision 15-20 mm long was adequate.

The capsule of skin was held ready with a pair of mosquito artery forceps, and at the right level of analgesia (i.e. the corneal reflex had just returned) the exposed parietal pleura was incised and

Fig. 10

Operative Technique of Intrapleural Skin Grafting in Rats

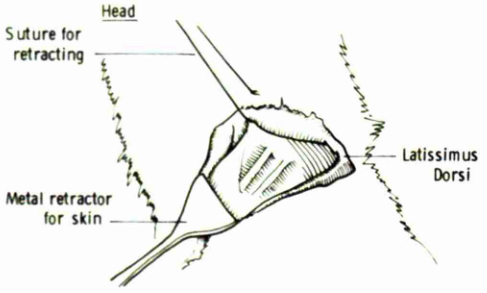
All is ready for the thoracotomy and implantation of the skin bag, which is shown held in a pair of artery forceps. The rat, anaesthetised but not intubated, is placed in the left-chest-up position. The skin incision has been re-opened and a silk suture (which appears in all subsequent photographs) acts as a self-retaining retractor. The instruments used are also shown. They are, left to right, a needle, two pairs of dissecting forceps, a scalpel, a pair of 5" sharp pointed Nelson's scissors, a needle holder, and a 10 ml syringe.

(over)

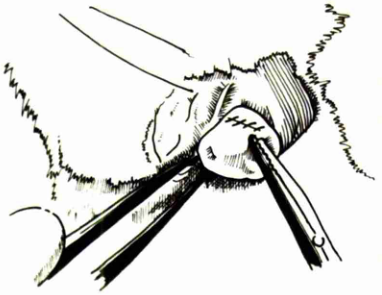
Fig. 11

Operative technique of intrapleural skin grafting in rats. The stage of thoracotomy has been reached. These diagrams were drawn from the photographs shown in the next three pages of illustration.

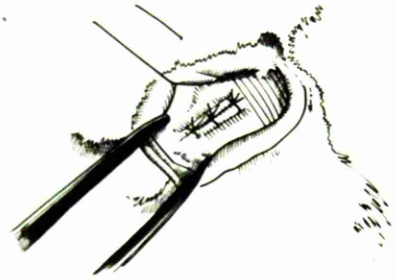
STEPS IN INTRAPLEURAL SKIN GRAFTING



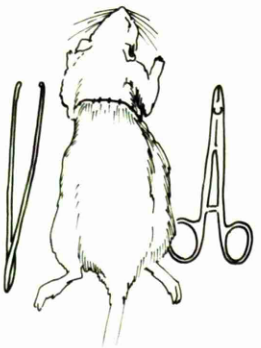
1. INTERCOSTAL SPACE EXPOSED



2. IMPLANTING SKIN CAPSULE INTO PLEURAL SPACE



3. CLOSURE: PERICOSTAL SUTURES IN PLACE



4. CLOSURE: FINAL APPEARANCE NO CHEST DRAIN

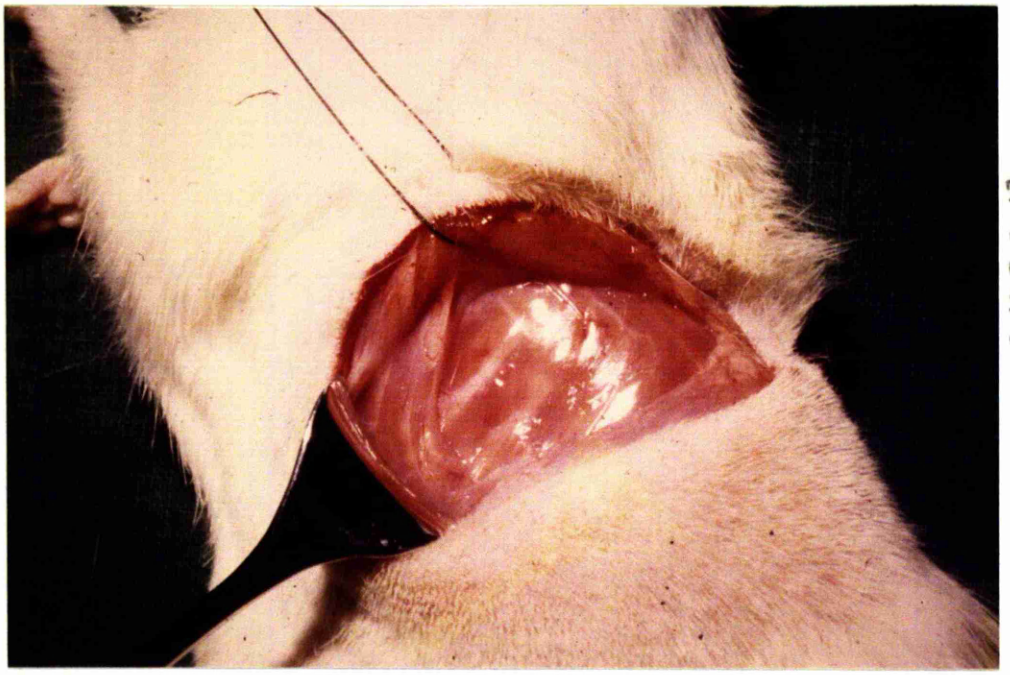
the capsule of skin implanted inside the normal pleural space. The first pericostal suture was placed in the middle of the incision and tied to control the open pneumothorax. Figure 11 shows the essential steps in the operation. (It was drawn from the photographs shown in Figs. 12 to 14.)

It usually took under 90 seconds to open the parietal pleura, implant the skin capsule inside the pleural space, and tie the first vital pericostal suture.

The chest was then closed carefully in layers, without drainage, with two additional interrupted pericostal sutures and continuous sutures to muscle; 2/0 atraumatic silk on taper-cut needle was used; skin was closed with interrupted 2/0 silk. To end the operation the wound was sprayed with Nobecutane and, the rat, now breathing vigorously, was returned into the perspex box.

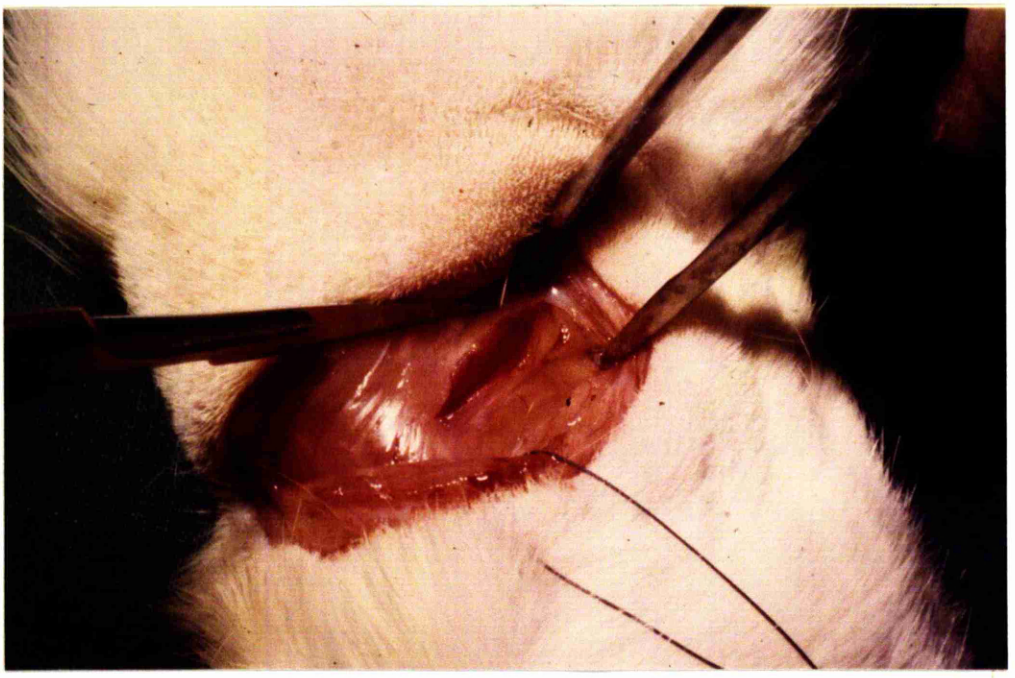
Fig. 12

Operative Technique of Intrapleural Skin Grafting in Rats



(i)

The intercostal spaces 7-9 are exposed. A retractor is in the medial end of the wound.

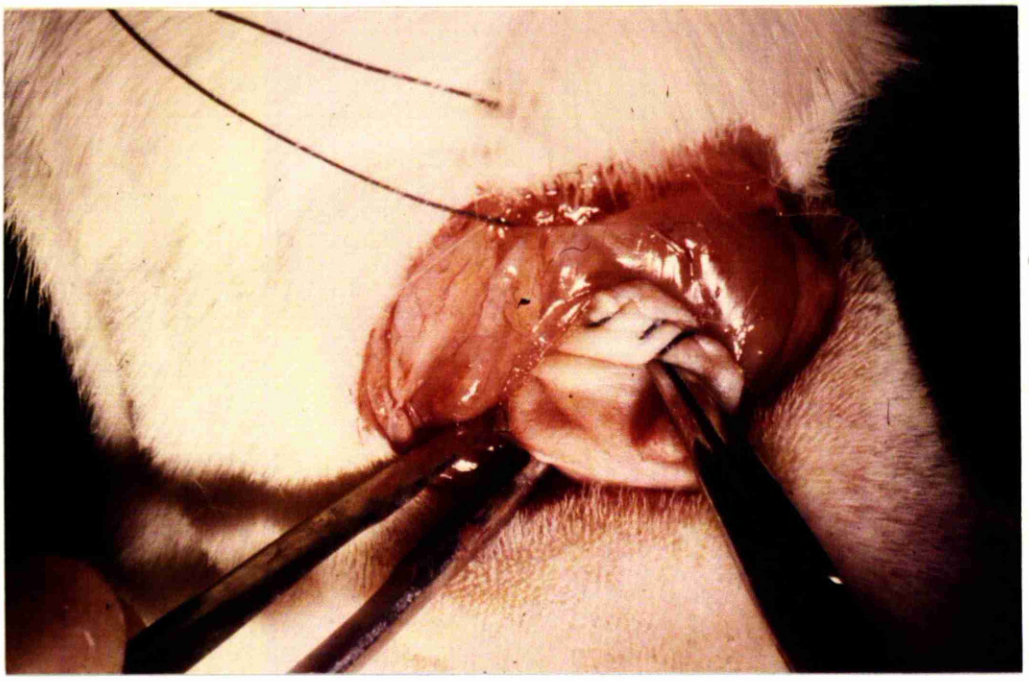


(ii)

The muscles in the 8th intercostal space are incised down to but not through the parietal pleura. The dissecting forceps and scalpel are also shown.

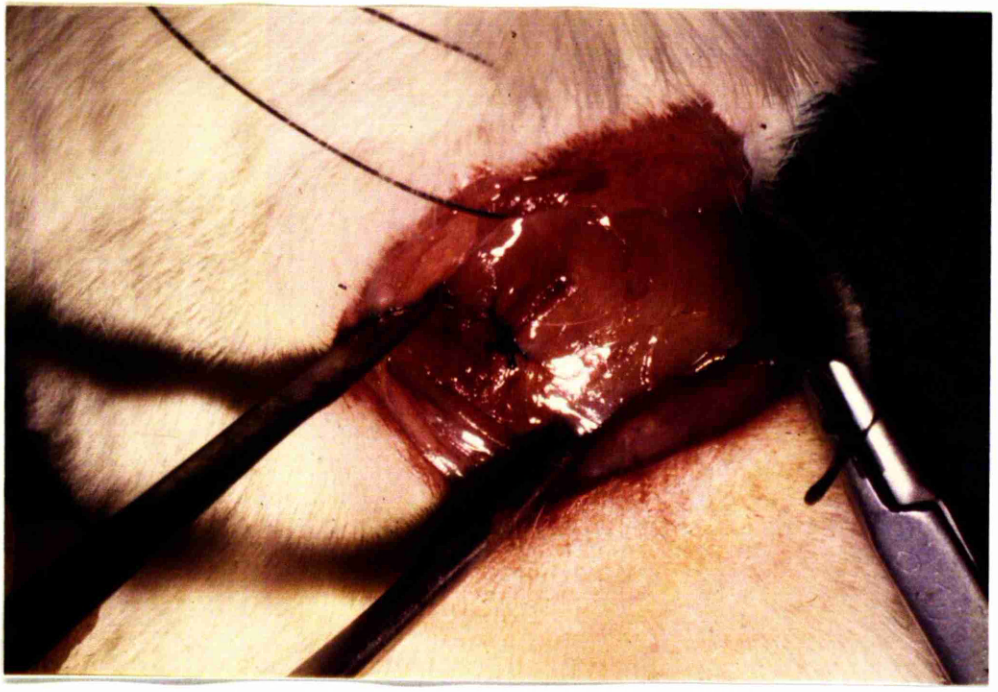
Fig. 13

Operative Technique of Intrapleural Skin Grafting in Rats



(i)

The bag of skin is being implanted into the left normal pleural cavity using a pair of artery forceps and dissecting forceps.



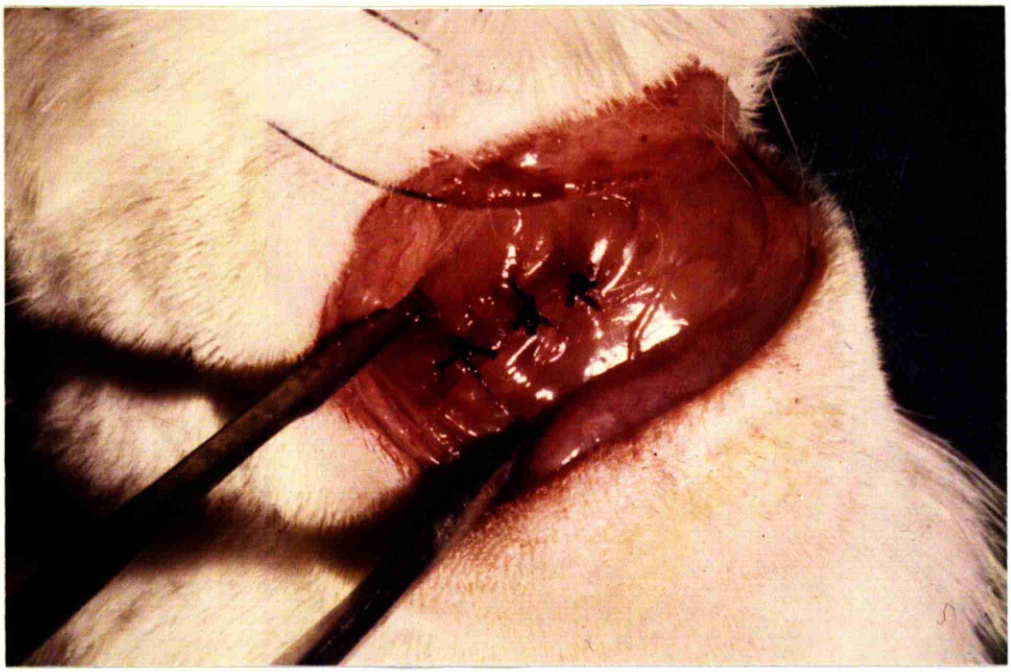
(ii)

Closure

The first and vital pericostal suture has been placed and tied.

Fig. 14

Closure



(i)

Two additional pericostal sutures have been placed and tied.

(ii)

The Operation has Ended

The wound has been sutured carefully; interrupted black silk to skin. The needle holder and the pair of dissecting forceps are also shown.

B: OBSERVATIONS ON THE CLOSED SKIN-LINED HEMITHORAX

A total of 168 rats had the operation of intrapleural skin grafting. Their general progress was observed and the operative mortality recorded. Three special observations were made: the skin-lined hemithorax was demonstrated by X-ray examination and by transverse sections; the pressure inside the cavity was measured and compared with the normal pleural pressure; and the animals were weighed once a week.

1. Chest X-ray Examination

The rats were divided into three main groups. In group one (30 rats), serial chest X-ray films were taken once a week for four weeks. The rats were anaesthetised as already described and one ml 45 per cent hypaque (Sodium Diatrizoate, B.P.) was injected into the skin-lined hemithorax under X-ray control. The transverse diameters of the cavities were measured from the X-ray films, corrected for magnification, and plotted against time.

2. Body Weight

The 30 rats (group one above) and ten unoperated rats were weighed once a week for four weeks.

3. Measurements of Pleural Pressure: Group Two

The pressures in the pleural cavities, both the skin-lined and the normal (right) pleura, were measured with a strain gauge manometer and recorder (Emma: S.E. Laboratories, Type SE 4912 and Type SE 3006).

One end of the rigid nylon catheter (40 cm long and 1.0 mm internal diameter) was connected to the manometer and the other end fitted with a hypodermic needle (18 gauge) and both filled with water. The needle was then introduced into the pleural cavities in the region of the inferior angle of the scapula. The pressure measurements were made in 15 other rats (group two) at week four.

4. Other Observations

The 30 rats (group one) at week four were killed and sectioned transversely. The 15 rats (group two) and seven others were observed for up to eight months to ascertain their natural fate.

C: MAKING A PERMANENT STOMA INTO THE SKIN-LINED HEMITHORAX: OPERATIVE TECHNIQUE

The skin-lined hemithorax was opened to the exterior and sutured to skin thereby creating a permanent stoma directly through the chest wall. The rat was anaesthetised as before with methoxyflurane except that anaesthesia took longer, 10 to 15 minutes, to induce, and supplementary anaesthesia was required; this was provided with an open mask system. The face of the rat was kept at the mouth of a small beaker containing a piece of absorbent cotton wool soaked in methoxyflurane.

The operation consisted of the following steps. With the rat supine a disc of skin (about 10 mm in diameter) centred 15 to 20 mm above and lateral to the xiphoid process was excised. The pectoral muscles were incised transversely to expose the intercostal spaces. It was observed that they were wider than normal (because of the underlying high pressure cavity), and for the same reason the intercostal muscles were stretched out and thin. The intercostal muscles were carefully incised with a sharp-pointed scalpel (No. 11 Swan Morton blade mounted on a No. 2 Bard Parker handle) until the pearly-white wall of the skin-lined cavity was exposed. A disc of this skin, about 5 mm in diameter, was excised and fluid under pressure was allowed to escape. With interrupted 2/0 atraumatic silk on a taper-cut needle, the edges of the skin lining the cavity were sutured to skin covering the chest wall to establish skin-to-skin stoma. The silicone capillary tube (with which the original capsule was splinted) and the silk sutures on the edges of the capsule were removed. Finally, the hemithorax was irrigated with warm water and the animal returned into its cage.

This operation was performed on 75 rats (group three), which consisted of 65 other rats at week four and ten out of the 15 from group two at week sixteen.

D: OBSERVATIONS OF THE SKIN-LINED HEMITHORAX AFTER CREATION OF THE PERMANENT STOMA

1. X-ray Demonstration

The rats were screened by X-rays after creation of the permanent stoma. (It was observed that there was no paradoxical respiration and that both halves of the diaphragm moved normally.) Chest X-ray films were taken.

2. Arterial pH, PO_2, and PCO_2 were measured with the Radiometer Type BMS/3.

The sample was obtained from the exposed abdominal aorta in ten rats in which the skin-lined hemithorax had been opened to atmospheric pressure for 24 hours. They were anaesthetised with intraperitoneal sodium pentobarbitone (2 mg/100g). Ten unoperated rats were used as controls. With a heparinised syringe two to three ml of blood was withdrawn slowly, care being taken to exclude air bubbles; the estimations were made immediately afterwards.

3. Measurements of Pleural Pressure

The pressure in the open skin-lined hemithorax was measured in ten test rats. A nylon connecting piece (30 mm long, internal diameter 3.5 mm) was wedged firmly into the stoma to ensure an airtight fit, and connected to the manometer; oesophageal pressure was measured simultaneously with a second open-ended catheter. The pressures were recorded for several minutes.

4. Volume of the Skin-lined Hemithorax

Four weeks after the intrapleural skin grafting the remaining 15 rats (group four) were killed and the volume of the closed skin-lined hemithorax measured directly by emptying its contents of straw coloured fluid into a graduated cylinder.

5. Measurements of Ventilation

The ventilation per minute in the normal and the skin-lined hemithorax was measured separately. This was possible because the two halves of the thorax now functioned simultaneously as separate ventilating chambers, with the normal hemithorax receiving air through the trachea, and the skin-lined hemithorax receiving air independently through the newly created opening in the chest wall.

Thirty test rats of mean weight 356.8 ± 20.1g were used together with 12 normal SPF rats of mean weight 394.3 ± 40.4g as controls. The skin-lined hemithorax had been opened to the exterior for 24 hours. A miniature Krogh spirometer was employed; the maximum capacity of the air chamber was 25 ml. The output signal from the spirometer, a displacement transducer, was passed through a transducer converter into a direct current amplifier (Type SE 905) and recorded on an ultra-violet recorder (Type SE 3005). Linear calibration was achieved readily.

Tracheostomy

The rats were anaesthetised with intraperitoneal pentobarbitone (2 mg/100g). A vertical mid-line skin incision was made in front of the neck. The rat's well developed pair of submandibular salivary glands with embedded lymph nodes were reflected upwards to expose the strap muscles, and the trachea was exposed by separating these muscles in the mid-line. The exposed trachea was cannulated with a 30 mm long metal cannula (14 gauge) tied firmly in position. The stoma in the chest wall was fitted with a nylon connection piece, as already described; again an airtight fit was ensured.

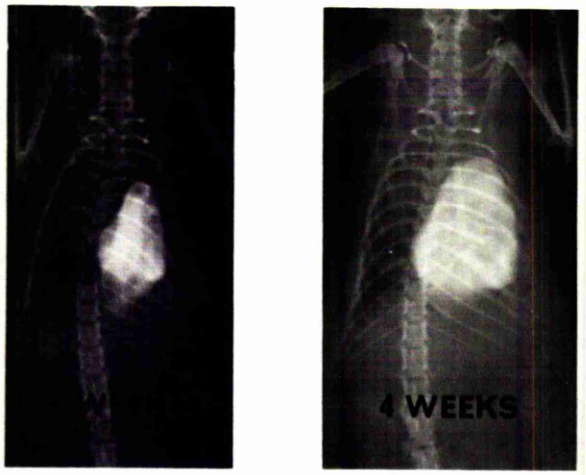
Before the tidal air was recorded, the rats were allowed five to ten minutes to adapt to the tracheal cannula. The tidal air of the skin-lined hemithorax was recorded first. Recordings from the tracheal cannula were made continuously for between 30-60 seconds, because the system was closed and contained no agent to remove carbon dioxide. Three separate readings were made and the mean accepted as the true tidal air and rate of respiration.

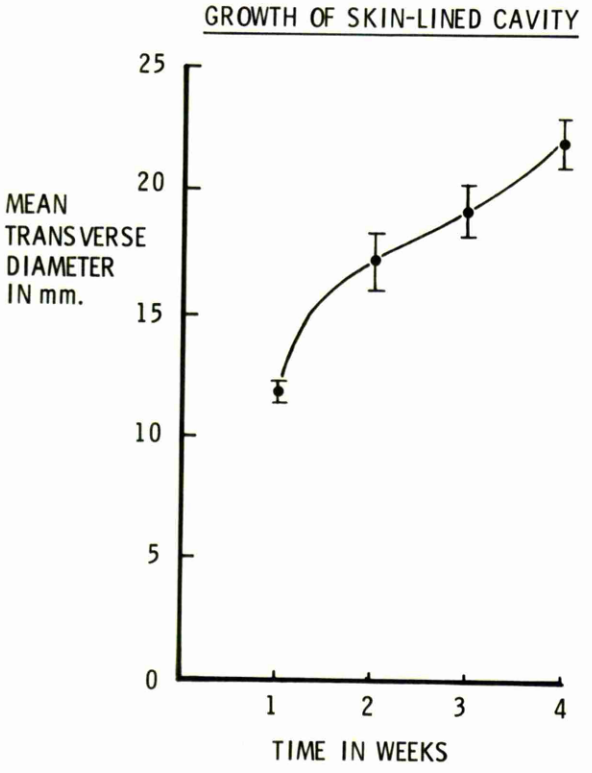
(over)

Fig. 15

(i) Two examples of rats with the skin-lined cavity in the left pleura outlined with one ml of hypaque. The X-ray film on the left was taken at the end of one week, the X-ray film on the right at the end of four weeks; the cavity had enlarged. From a series of such X-ray films, the transverse diameter of the cavity was measured, corrected for magnification, and plotted against time (ii).

(i) (ii)





R E S U L T S

A: THE OPERATION OF INTRAPLEURAL SKIN GRAFTING

1. General Progress

A total of 168 rats had the operation. Although they were anaesthetised but not intubated, 150 (89.3 per cent) survived the procedure ($P < 0.001$). Of these, 132 (88 per cent) survived the next four weeks ($P < 0.001$).

2. Size of Cavity

The implanted skin capsule enlarged to occupy the left hemithorax in the rats. Figure 15(i) shows the chest X-ray film of one rat taken at the end of weeks one and four. Table 4 summarises the sizes of the cavities in relation to time in weeks. These results are expressed graphically in Fig. 15(ii).

Table 4 (Appendix 2)

	Transverse Diameter (mm) of Skin-lined Pleural Cavity (Mean ± S.E.M.) N = 30
Week No. 1	11.9 ± 2
2	17.2 ± 3
3	19.2 ± 2
4	22.1 ± 2

(over)

Fig. 16

(i) The rat shown in this photograph had intrapleural skin grafting four weeks ago. It looks well (weight 320g), the wound had healed and its hair had regrown.

(ii) Chest X-ray films (antero-posterior and lateral films) of the rat above. The left hemithorax is a skin-lined cavity outlined with one ml of hypaque.

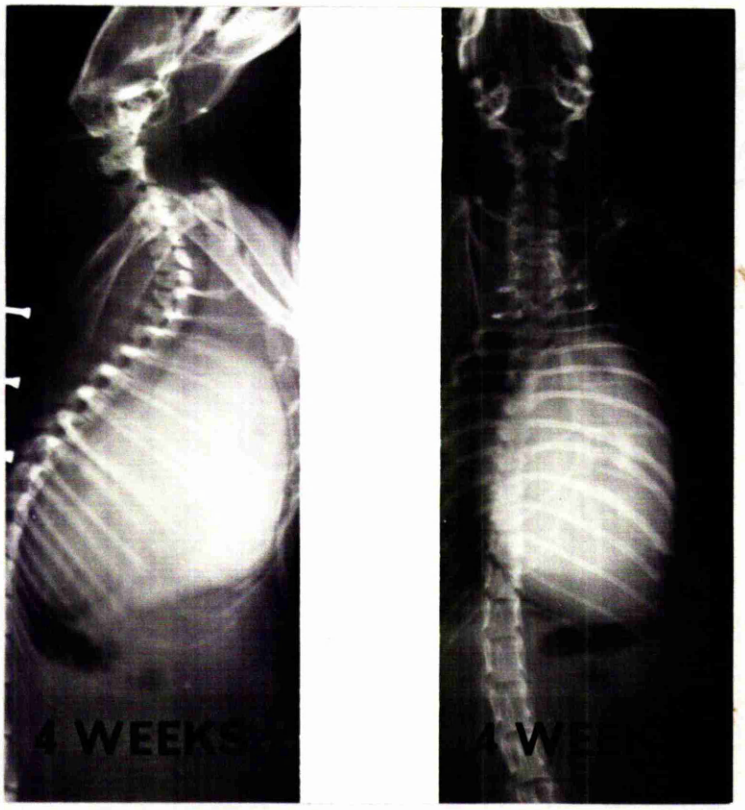
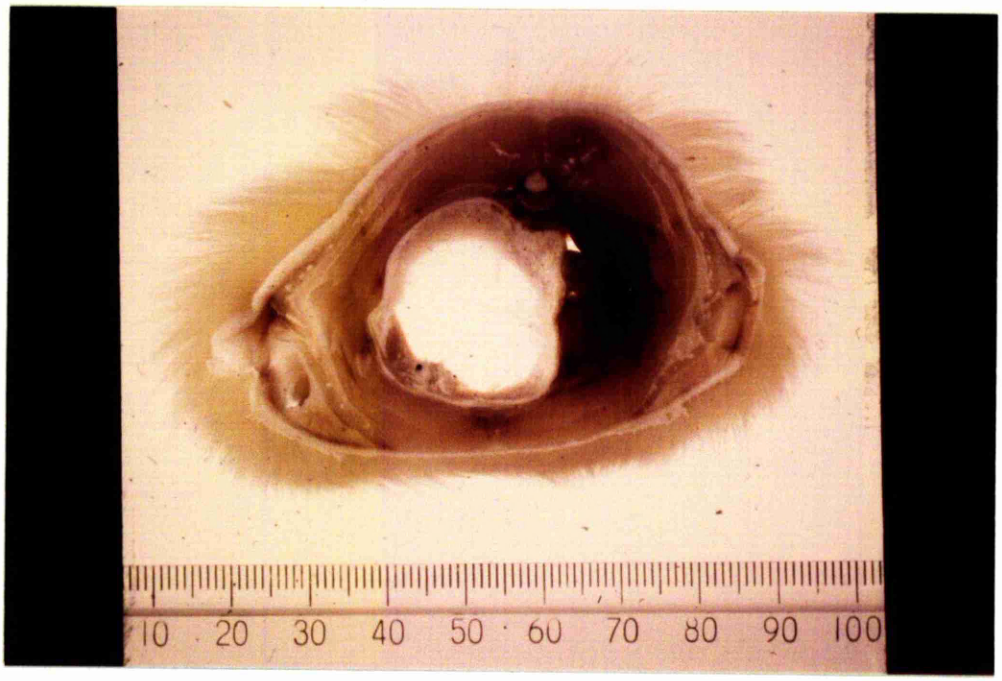


Figure 16(i) shows a rat four weeks after the operation of intra-pleural skin grafting; Fig. 16(ii) its chest X-ray film; and Fig. 16(iii) shows the transverse section through its chest.

Fig. 16(iii)

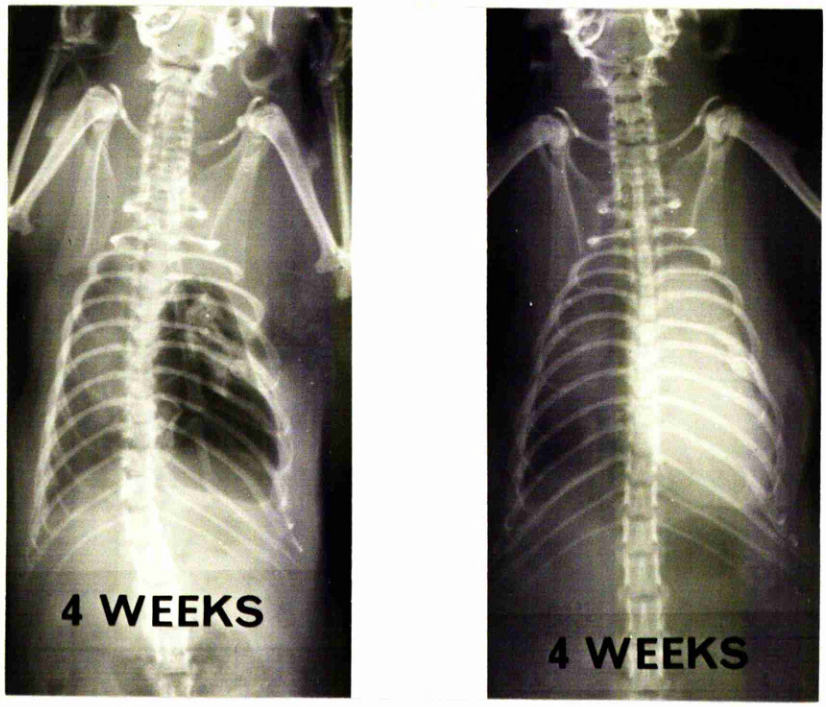
Transverse section through the chest of the 320g rat, Fig. 16(i), showing here the left hemithorax lined with skin.



3. The X-ray Demonstrations of the Cavity Before and After Creation of the Stoma (Fig. 17).

Fig. 17

X-ray film of a rat before and after creation of stoma taken four weeks after intrapleural skin grafting. The X-ray film on the right shows the skin-lined hemithorax, closed and outlined with hypaque. The X-ray film on the left is the same cavity open to atmospheric pressure. It is now an open skin-lined hemithorax.



Beyond the fourth week, the preparation became stable (Fig. 18).

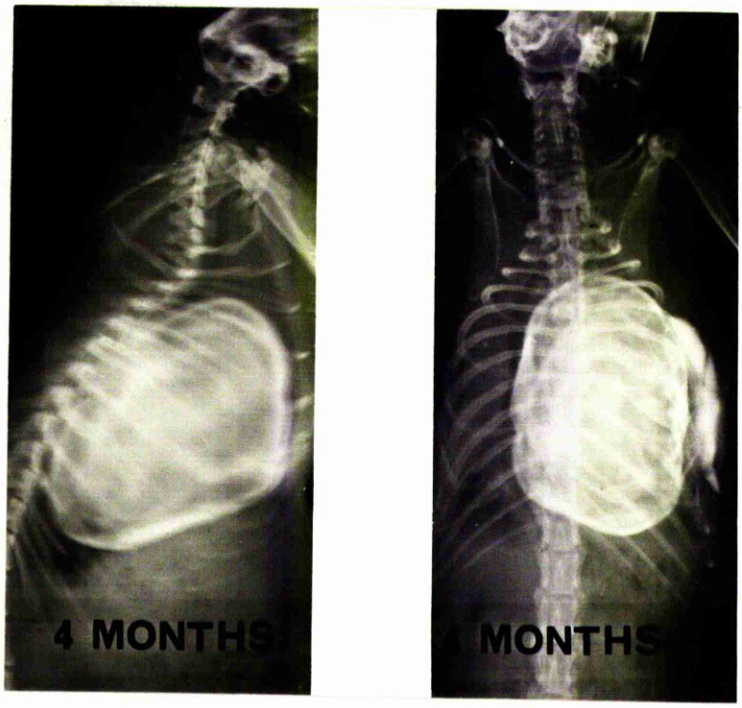


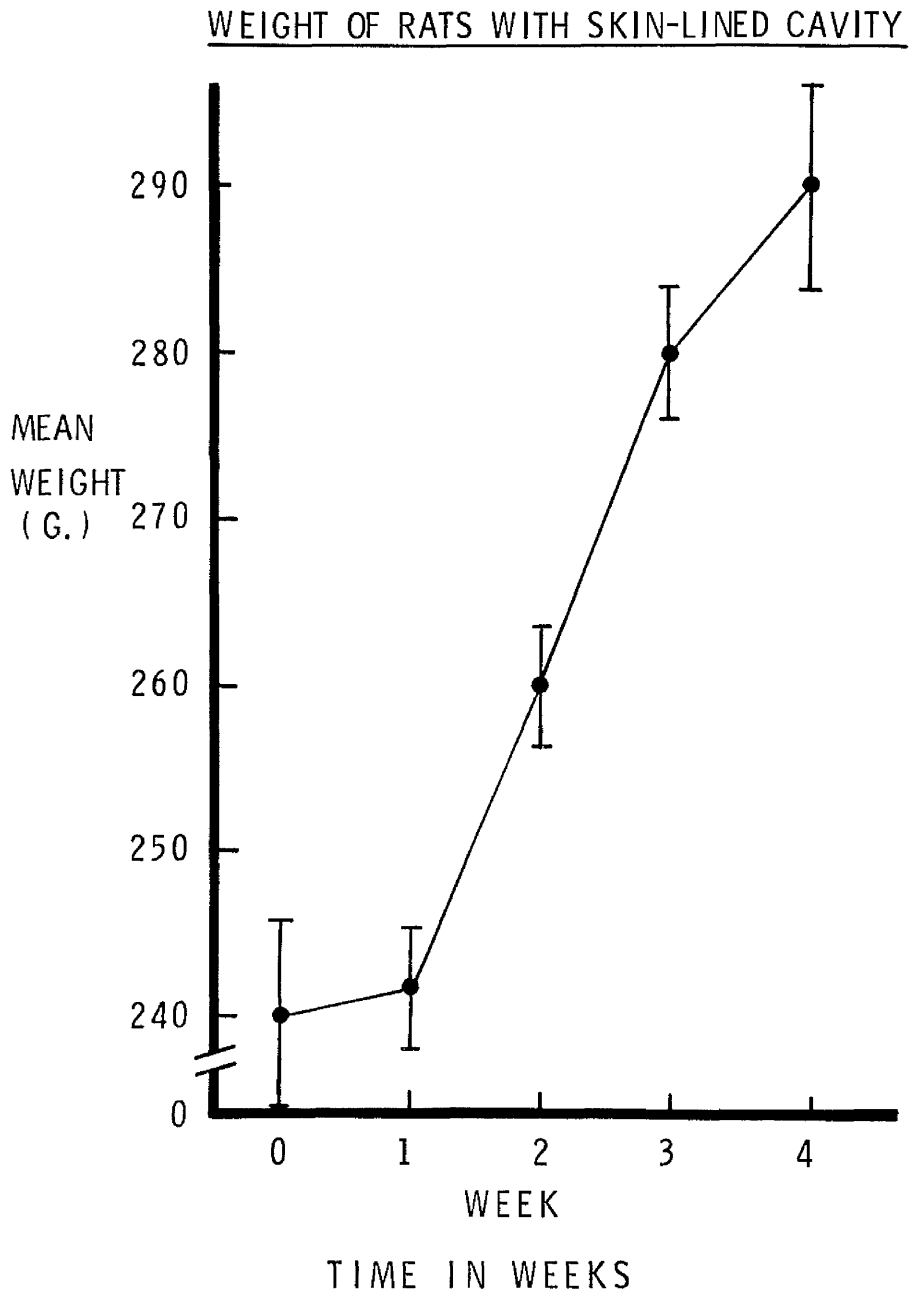
Fig. 18

X-ray film of a rat four months after intrapleural skin grafting, showing the left hemithorax, now a skin-lined cavity, outlined with hypaque.

(over)

Fig. 19 (Appendix 3)

Thirty rats (group one) were weighed once a week for four weeks after the operation of intrapleural skin grafting. The points on the graph represent Mean ± S.E.M.



Twenty-two rats were observed beyond four weeks: ten were used at four months for ventilation studies, five died between six and seven months, and seven were alive at the end of eight months.

4. Effect of the Closed Skin-lined Pleural Cavity on Body Weight

At the end of the first two weeks the unoperated rats gained significantly more weight than the test rats. However, beyond the second week the test rats were also thriving (Fig. 19). Table 5 shows the weight gained by the two groups, and tests of significance between the differences.

Table 5 (Appendices 3 and 4)

Week No.	Weekly Weight (g) Gained: Mean ± S.E.M.		Statistical Analyses (D.F. = 38)	
	Test Rats (n = 30)	Unoperated Rats (n = 10)	T=	P=
1	1.7 ± 3.8	22.5 ± 2.4	3.08	0.004*
2	19.2 ± 2.5	31.0 ± 2.2	2.62	0.012*
3	18.5 ± 2.9	19.5 ± 2.2	0.194	0.847+
4	9.8 ± 5.1	14.5 ± 1.2	0.528	0.601+

* Significant

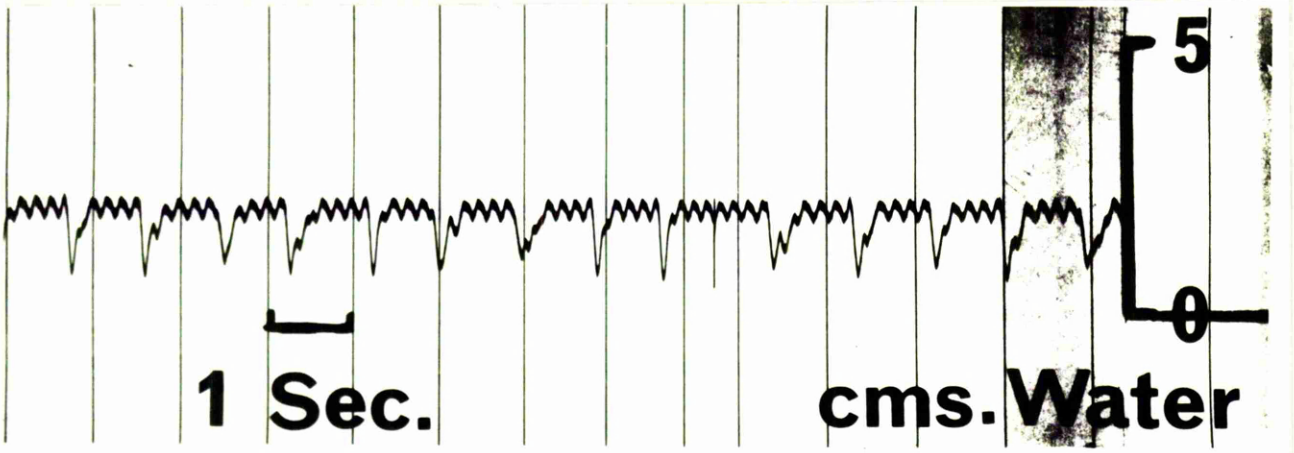
\+ Not significant

(over)

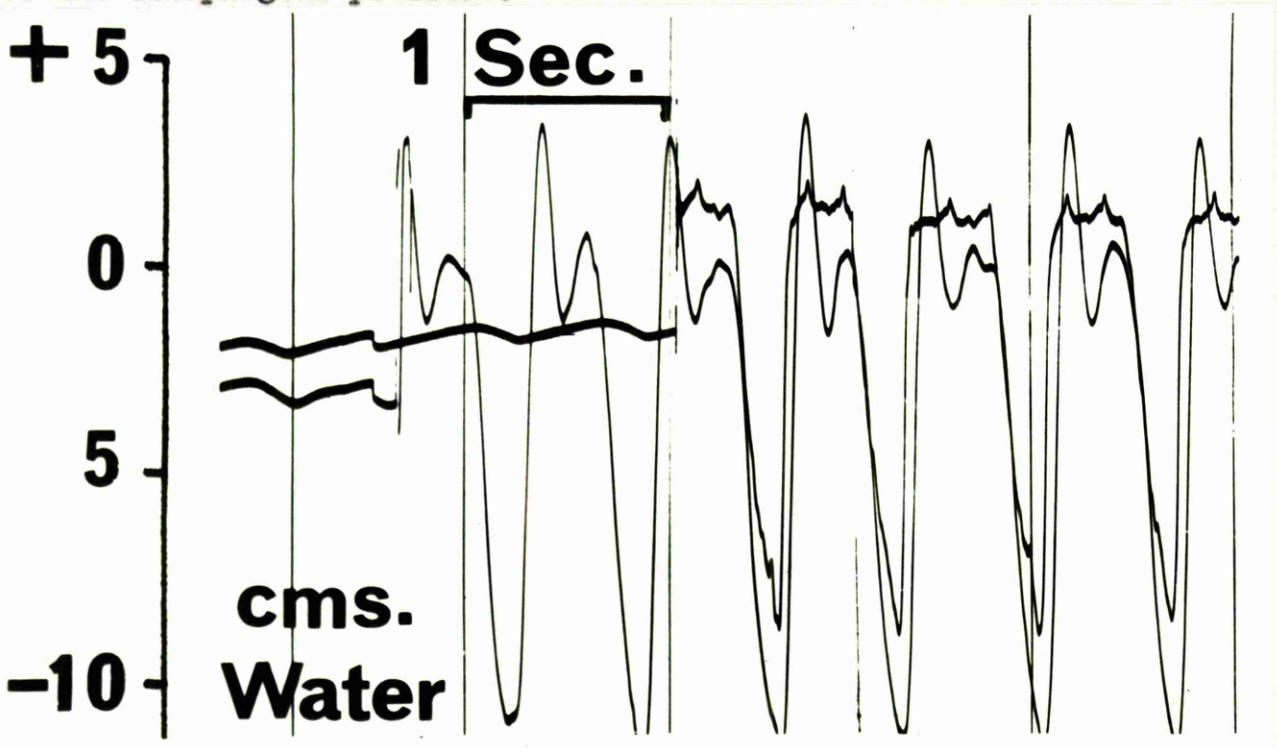
Fig. 20

Tracings of Pleural Pressure from the Skin-lined Pleural Cavity Before and After Creation of the Permanent Stoma in Rats

(i) With the cavity closed, the pressure was above atmospheric; the characteristic pause at the end of expiration in the rat is shown and, during these pauses cardiogenic oscillations were recorded.



(ii) After the creation of the stoma, the pressure, top trace, in the skin-lined hemithorax became subatmospheric. When oesophageal pressure, bottom trace, was recorded simultaneously, the pleural pressure was in phase with and similar in magnitude to the oesophageal pressure.



5. Pleural Pressure Before and After Creation of the Stoma

The mean pressure was +2.9 ± 0.6 cm H_2O in the closed skin-lined hemithorax (Fig. 20(i)). However, after creation of the stoma the pressure became -2.5 ± 0.6 cm H_2O ($P < 0.001$). With respiration the pressure in the open skin-lined cavity was subatmospheric; it was in phase with oesophageal pressure and similar to it in magnitude (Fig. 20(ii)). Table 6 shows the mean values and the tests of significance between the differences.

Table 6 (Appendices 5-7)

Comparison of Normal Pleural Pressure with the Pressure in the Skin-lined Hemithorax after Creation of the Stoma in Rats

	Pressure (cm H_2O) Mean ± S.E.M.		
	End of Expiration	End of Inspiration	Mean Pressure
Normal Pleura (n = 10)	-3.4 ± 0.2	-8.7 ± 0.5	-3.7 ± 0.2
Skin-lined Hemithorax (n = 15)	1.7 ± 0.6	-7.7 ± 1.1	-2.5 ± 0.6
Statistical Analyses (D.F. = 23)	T = 7.22	T = 0.704	T = 1.59
	$P < 0.001$*	$P = 0.489$+	$P = 0.126$+

* Significant + Not significant

(over)

Table 7 (Appendix 8)

Comparison of Ventilation in the Normal Hemithorax and in the Skin-lined Hemithorax

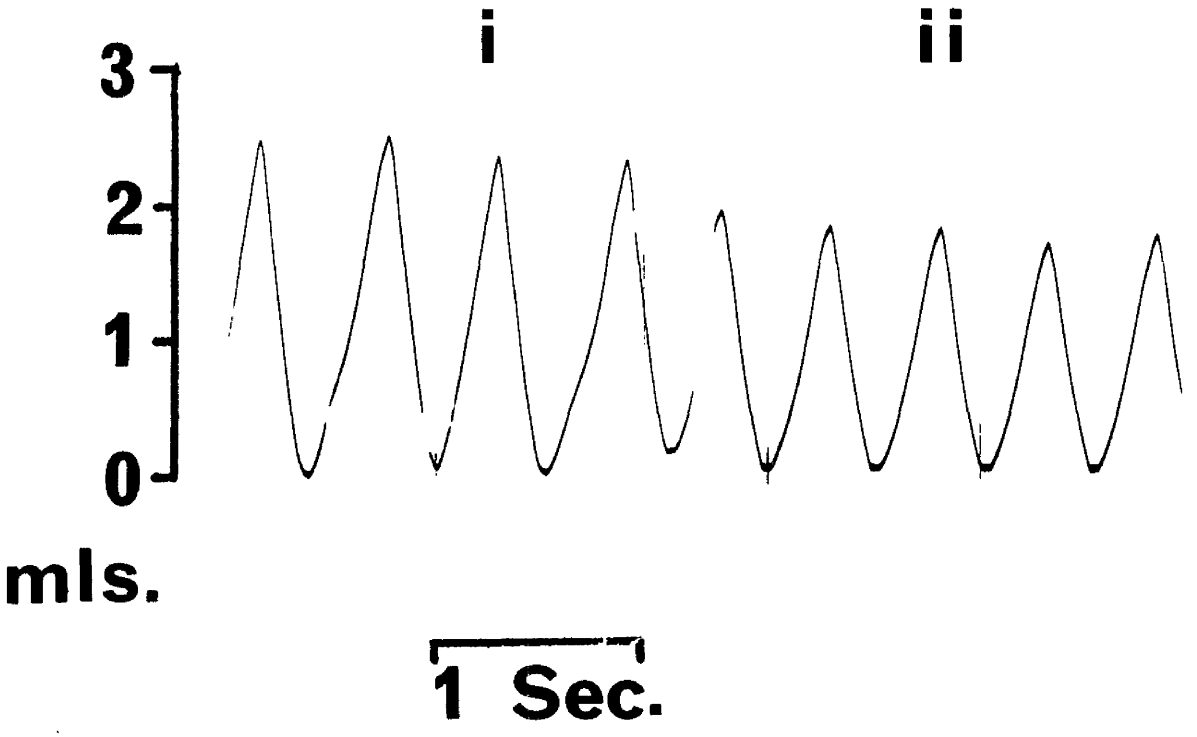
		Mean ± S.E.M. Tidal Vol (ml)	Minute Ventilation ml/kg/min
Normal Hemithorax		1.68 ± 0.04	506.1 ± 36.2
Skin-lined Hemithorax		0.93 ± 0.06	271.6 ± 24.4
Statistical Analyses	T	= 10.6	= 8.98
D.F. = 29	P	< 0.001*	< 0.001*

* Significant

(N = 30; Body Weight = 356.8g; Mean rate of respiration = 98.5/min)

Fig. 21

Spirometric tracings from a rat (320g) (i) from the tracheal cannula and (ii) from the cannula fitted to the stoma in the skin-lined hemithorax.



6. The Skin-lined Hemithorax as an Open Ventilated Gas Cavity

(i) Spirometry

Functionally, the skin-lined pleura was an open ventilated gas cavity. Figure 21 shows the spirometric tracings from a test rat. In these rats the two halves of the chest functioned as separate ventilating chambers, with the normal (right) half receiving air from the trachea and the left skin-lined half receiving air independently from an opening in the chest wall. Two ventilation variables measured were tidal volume and rate of respiration. The minute-ventilation and hence the minute-ventilation per kilogram of body weight were calculated from the results. The four sets of values obtained were compared as follows. Ventilation in the skin-lined hemithorax was compared with the normal right lung, which in turn was compared with that of unoperated rats.

In the test rats the mean tidal volume in the normal hemithorax was 1.7 ± 0.04 ml as compared with 0.9 ± 0.07 ml in the skin-lined hemithorax; and the respective minute-ventilations (tidal volume x rate of respiration) were 506.1 ± 36.2 ml/kg/min and 271.6 ± 24.4 ml/kg/min; the differences are significant (Table 7).

The rate of respiration in the unoperated rats (78/min) was slower than the 98.5/min in the test rats, and their respective tidal volumes were 1.9 ml and 1.7 ml. The differences are significant (Table 8).

However, the minute-ventilation in the unoperated rats (407 ± 50.5 ml/kg/min) was not significantly different from the value obtained for the normal hemithorax in the test rats (Table 8).

Table 8 (Appendices 8 and 9)

Comparison of Ventilation in Unoperated Rats and in the Normal Hemithorax of Test Rats

		Mean ± S.E.M.			
		Rate of Respiration per min	Tidal Vol (ml)	Weight (g)	Minute Ventilation ml/kg/min
Unoperated Rats (12)		76.1 ± 5.3	1.94 ± 0.12	394.3 ± 40.44	407.0 ± 50.4
Normal Hemithorax Test Rats (30)		98.5 ± 4.3	1.68 ± 0.04	356.8 ± 20.11	506.1 ± 36.2
Statistical Analyses (D.F. = 40)	T	= 2.96	= 2.59	= 0.923	= 1.51
	P	= 0.005*	= 0.013*	= 0.361+	= 0.139+

* Significant

\+ Not significant

(ii) Arterial pH, PO_2 and PCO_2

The means of the arterial pH, PO_2, and PCO_2 in the test rats were similar to those in the unoperated rats (Table 9).

Table 9 (Appendices 10 and 11)

Comparison Between Arterial pH, PO_2, and PCO_2 in Unoperated Rats and in Test Rats

		Mean ± S.E.M.		
		pH	PO_2 mm Hg	PCO_2 mm Hg
Unoperated Rats (10)		7.349 ± 0.015	80.18 ± 2.77	38.24 ± 0.94
Test Rats (10)		7.355 ± 0.017	77.03 ± 2.65	38.41 ± 2.41
Statistical Analyses (D.F. = 18)	T	= 0.258	= 0.822	= 0.066
	P	= 0.799$^+$	= 0.422$^+$	= 0.948$^+$

$^+$ Not significant

(iii) Volume of the Skin-lined Hemithorax

Four weeks after intrapleural skin grafting the mean volume of the skin-lined hemithorax was 7.4 ± 0.3 ml in rats of mean weight 298.3 ± 9g (Appendix 12).

DISCUSSION OF THE ABOVE RESULTS

The experiments described above have confirmed the rationale behind the approach employed in this study.

To recapitulate, thin autogenous skin was sutured into closed capsules and implanted into the normal left pleural space of 150 SPF rats of which 132 survived the next four weeks. The skin graft 'took' on the surrounding structures, formed a closed cavity in which fluid accumulated, and the cavity expended to displace the ipsilateral lung (Figs. 15-18). The left hemithorax could be transformed into a closed postpneumonectomy skin-lined cavity in most SPF rats (88 per cent; $P < 0.001$).

The greatest change in the size of the skin-lined cavity occurred between the first and second weeks (Fig. 15(iii)), and by the end of the second week the cavity was already occupying the left hemithorax. Thereafter the rats thrived and the size of the cavity kept pace with their natural growth (Figs. 16(i), 16(ii), 18, and 19). This suggests that there was no advantage in observing the rats much beyond two weeks.

The mean pressure in the closed skin-lined hemithorax was $+2.9 \pm 0.6$ cm H_2O; it was significantly higher than the mean pleural pressure of -3.4 ± 0.4 cm H_2O in the normal rat ($P << 0.001$). The ipsilateral lung underwent compression atrophy (Fig. 16(iii)).

In 59 out of 75 rats (78.7 per cent) the skin-lined hemithorax was opened successfully to the exterior and the opening was sutured to skin ($P < 0.001$). After creation of the permanent stoma, the mean pressure in the skin-lined hemithorax was -2.5 ± 0.6 cm H_2O, and with respiration was in phase with oesophageal pressure and similar to it in magnitude ($P = 0.1$; Table 6 and Fig. 20(ii)).

In rats with a skin-lined hemithorax, therefore, the two halves of the chest behaved as separate ventilating cavities in phase. The normal hemithorax received air normally through the trachea and the skin-lined hemithorax received air from an independent opening directly through the chest wall.

In this investigation the results obtained for the mean tidal volume (1.9 ml) and the mean rate of respiration (78/min) for unoperated rats agreed closely with those reported by others (Crosfill and Widdicombe 1961, King 1966, Binns *et al* 1971, and McIntyre 1971). Therefore, the results obtained for the test rats might be compared with those for the unoperated rats, since the experimental conditions were identical.

The test rats breathed significantly more rapidly than normal rats ($P = 0.005$) and there was also a significant difference between their tidal volumes ($P = 0.01$). However, there was no significant difference between their minute-ventilations ($P = 0.1$; Table 8).

This suggested that the test rats achieved normal ventilation by means of a compensatory increase in the rate of respiration.

King and Bell (1966) found the mean arterial oxygenation in 35 normal SPF rats was 89.3 ± 2.9 S.D. and they commented also on the well-known difficulty in obtaining arterial blood samples from unanaesthetised rats. In this study, the test rats maintained normal arterial pH, PO_2, and PCO_2 - a further indication that, under basal conditions, the respiration was adequate in the lung on the opposite side.

The volume of the skin-lined hemithorax (7.4 ml) was a direct measure of the total capacity of the cavity as a ventilating chamber in 298g rats; it compared with the functional residual capacity of 1.55 ml in 250g rats (Crosfill and Widdicombe 1961).

CONCLUSIONS

Three conclusions may be drawn. First, a readily reproducible technique has been developed for transforming the left hemithorax of rats into stable skin-lined cavities. Secondly, the cavities can be opened to the exterior without embarrassing respiration in the lung on the opposite side. Thirdly, as a functional gas cavity the skin-lined hemithorax is poorly ventilated.

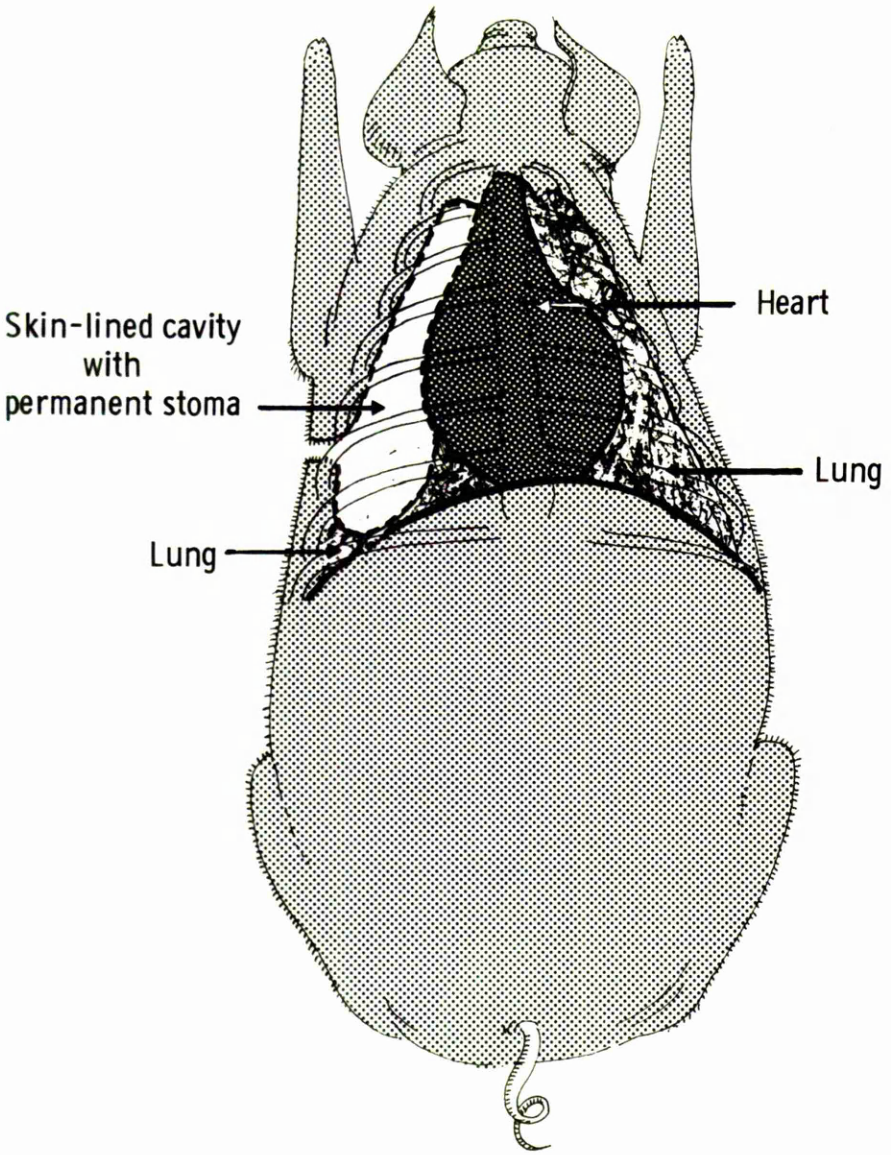
This experimental preparation was put forward as a model for the provision of space for implanting a prosthetic lung, which needed, however, additional devices to boost ventilation.

A final series of experiments were performed in six pigs to investigate whether these conclusions were valid for larger animals also. Pigs were chosen because they were larger animals whose physiological similarity to man was generally recognised.

(over)

Fig. 22

A pig with the left hemithorax transformed into a skin-lined cavity which is open to the exterior. The drawing was based on chest X-ray films (Fig. 25).



THE INVESTIGATION

PART II

A series of experiments identical in design to those described in the rats were carried out on six pigs.

MATERIALS AND METHODS

Six pigs (four male and two female) were used. They were mixed Lanrace strain of mean initial weight 16.0 ± 1.6 kg. They were kept under standard laboratory conditions in sties made of reinforced asbestos and fitted with infra-red lamps so that temperatures of 30°C could be reached - an important consideration in the immediate postoperative period. They were fed once a day with 2 kg of concentrated pig food (purchased from Spillers, London) and the drinking water was replenished as required.

Under general anaesthesia, the six pigs had autogenous skin bags grafted into the normal left pleural space. Anaesthesia was induced by halothane/air mixture with the technique described recently by Singh, Elliot, and Melrose (1971). After the induction, the pigs were intubated and anaesthesia was maintained with positive pressure ventilation by the Palmer Ideal Respirator as described earlier (Chapter II).

A: OPERATIVE TECHNIQUES

Both shoulders and both gluteal regions were prepared carefully for use as donor sites as in the dog experiments (Chapter II), except that the electric hair clipper alone ensured a close shave. After surgical towelling, thin split skin grafts (Thiersch grafts) were taken from the four sites with a standard Humby knife. This procedure was straightforward because the pigs, unlike the dogs, had firm and relatively thick skin. The broad sheets of skin were sewn together with 2/0 atraumatic silk. The skin bags were then turned inside out so that the hair-bearing surfaces were enclosed completely, as in the rat experiments. A piece of silicone tube, 40 cm long (outer diameter = 3 mm) was used as internal splint to give a roughly rectangular shape to the completed skin bag. The individual initial weights of the animals and sizes of skin bags were as follows:

	Initial Body Weight (kg)	Size of Skin Bag (mm)
Pig No. 1	21.3	125 x 125
2	18.2	163 x 75
3	18.2	180 x 85
4	12.7	138 x 113
5	10.9	138 x 76
6	14.3	125 x 75

With the left chest uppermost, the thorax was opened through the bed of the unresected fifth rib. Bleeding was slight. The bag of skin was laid inside the normal pleural space care being taken to ensure that it reached the apex. The lungs were expanded and the chest was closed carefully in layers, without drainage. During the closure, the lungs were inflated repeatedly. At the end of the operation, five mega units of crystalline penicillin were given by intramuscular injection, the chest wound and donor sites were sprayed with Nobecutane, and the pigs were returned into the warm sty.

Their postoperative recovery was remarkably swift and uneventful. Intramuscular crystalline penicillin was repeated for the next five days (dose: one mega unit once a day). The pigs required hardly any supervision, and the fact that the chest was closed without drainage insured against accidents usually associated with chest drains in experimental animals. The day after the operation they resumed normal feeding.

B: OBSERVATIONS ON THE PIGS WITH THE SKIN-LINED HEMITHORAX CLOSED

Their general progress was observed and they were weighed once a week; the skin-lined hemithorax was demonstrated radiologically; and the pressure inside the cavity was measured and compared with the normal pleural pressure.

1. Body Weight

The six pigs were weighed once a week for the next three weeks.

2. Chest Radiographs

Under X-ray control, 20 ml of 45 per cent hypaque was injected into the skin-lined hemithorax on the 10th postoperative day in the first three pigs and chest X-ray films were taken. The procedure was repeated in the third week on all six pigs. On each occasion light general anaesthesia without intubation was employed. At the end of the third week, one pig was killed and sectioned transversely; five pigs remained for subsequent studies.

3. Pressure in the Pleural Cavity

The pressure in the pleural cavities were measured in the five pigs with similar instruments and techniques already described in the rat experiments.

C: OPENING THE SKIN-LINED HEMITHORAX TO THE EXTERIOR

The skin-lined hemithorax was opened to the exterior five weeks after intrapleural skin grafting. The pigs were anaesthetised, and were intubated as a precaution against protracted periods of breath holding. Anaesthesia was induced with a halothane/air mixture and supplemented

with intravenous pentobarbitone (dose: 10 mg/kg body weight). (Attempts at intubation failed in pig No. 4 and it died shortly after induction of anaesthesia.)

The following observations were made on the remaining four pigs before and after opening the skin-lined hemithorax to the exterior. The pigs were in the lateral position, left chest uppermost.

1. Monitoring

The systemic blood pressure and electrocardiogram were monitored and displayed continuously on the oscilloscope of a six channel recorder (Emma: S.E. Laboratories). A branch of the superficial femoral artery was exposed in the right groin and cannulated to obtain direct measurements of intra-arterial blood pressure. After the pig had been breathing air spontaneously for ten minutes, and the blood pressure and electrocardiogram had become stable as judged from the oscilloscope, recordings were made for three minutes. Arterial blood sample was then taken in a 5 ml heparinised syringe, care being taken to exclude air bubbles, and pH, PO_2, and PCO_2 were measured directly with the Radiometer Type BMS/3.

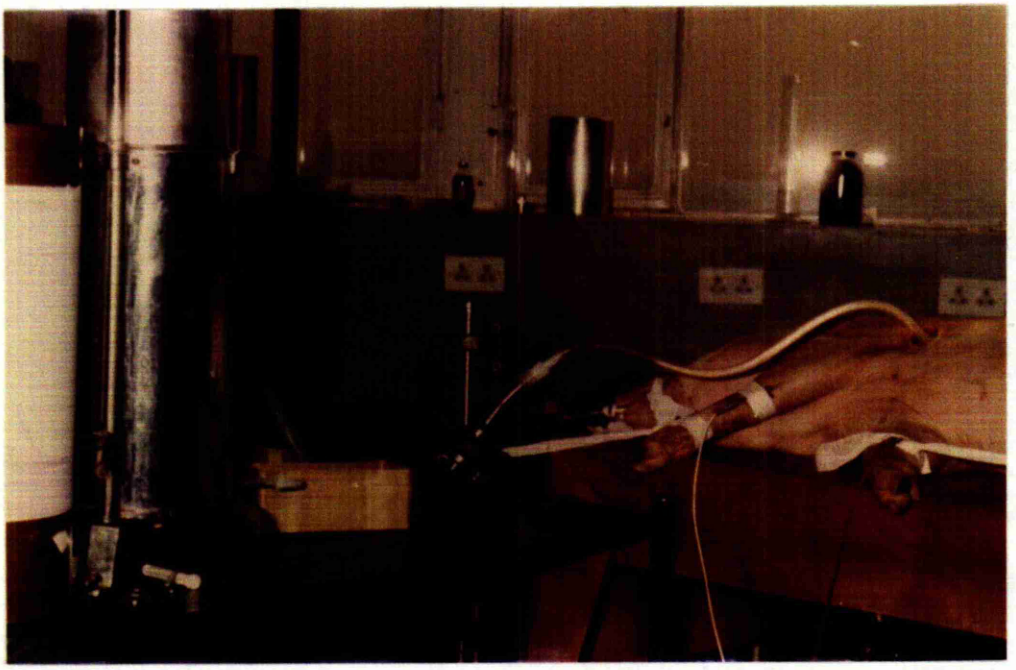
2. Spirometry

The tidal air from the trachea was next measured with a Benedit-Roche spirometer and the tracing was recorded on a rotating drum with a direct recording pen.

(over)

Fig. 23

A general view of the operating room during studies on the open skin-lined hemithorax and its effect on cardio-respiratory function of a pig. It shows, from left to right, the spirometer, the large bore tubes connecting it to the pig via (i) the cannula leading into the skin-lined hemithorax (centre of the picture) and (ii) the endotracheal tube. Two of the (hypodermic) leads of the electrocardiogram are shown secured by tape to the fore limbs. (Out of the picture are the pig's hind limbs with the arterial line, and the six channel electronic recorder.)



3. The skin-lined hemithorax was next opened to the exterior.

Operative Procedure

A disc of skin about 4 cm in diameter was excised from the fourth left intercostal space about 10 cm from the sternum. The intercostal muscles were excised, a little at a time, until the thick, pearly-white, skin-reinforced parietal pleura was exposed over an area of about 30 x 20 mm. A disc of this skin was then excised; it measured about 15 mm in diameter. The fluid in the skin-lined hemithorax was aspirated and its volume measured. The pig breathed spontaneously during the procedure.

4. Spirometry on the Skin-lined Hemithorax

After the cavity had been opened to the exterior, a nylon tube (4 cm long, internal diameter = 15 mm) was wedged firmly into the stoma in the chest wall and connected to the spirometer (Fig. 23). The tidal air from the skin-lined hemithorax was recorded.

5. Repeat Measurements

After the anaesthetised pig had been breathing air spontaneously for two hours with the skin-lined hemithorax opened to the exterior the following variables were recorded again: systemic blood pressure, electrocardiogram, and arterial pH, PO_2, and PCO_2. Thus paired data were obtained on the four pigs: data before and after opening the skin-lined hemithorax to the exterior.

6. Chest Radiographs

After the arterial cannula and the leads of the electrocardiogram were removed, the pigs were screened radiologically and spot X-ray films of the chest were taken.

The investigations ended with the taking of these chest X-ray films. All the pigs but one were killed immediately thereafter. (By this time, i.e. five weeks after intrapleural skin grafting, the pigs had grown so large (mean weight 37.5 ± 2.5 kg) that they would wreck the sties if confined any longer.) The remaining pig (No. 3) recovered fully and thrived further; it was killed four months later.

RESULTS

PART II

1. General Progress

All six pigs survived the operation of intrapleural skin grafting ($0.012 < P < 0.016$). Their postoperative recovery was remarkably swift and uneventful and five remained alive and well for the next five weeks. (One was killed electively three weeks after the operation.)

2. Body Weight (Appendix 13)

The six pigs thrived and doubled their mean initial weight over the observation period of three weeks as shown below.

	Mean ± S.E.M.
Initial Weight	16.0 ± 1.6 kg
Weight at the end of three weeks	32.4 ± 2.6 kg
Weight gained in three weeks	16.4 ± 1.5 kg

3. Pleural Pressure in the Closed Skin-lined Hemithorax (Appendix 14)

Paired data are available for five pigs. The normal mean pleural pressure was -4.8 ± 0.4 cm H_2O; in the closed skin-lined hemithorax, the mean pressure was 1.3 ± 0.3 cm H_2O ($P < 0.001$).

4. X-ray Demonstrations of the Skin-lined Hemithorax Before and After the Thoracostomy (Figs. 24-26).

Fig 24

Antero-Posterior Chest X-ray Films Taken in the Third Postoperative Week (Pigs 1-3)

The skin-lined hemithorax was outlined with 20 ml of 45 per cent hypaque. Fluid accumulated in and had remained confined to the closed skin-lined cavity, the left lung bases being remarkably clear on the X-ray films. The cavities became nearly co-extensive with the hemithorax. The shape, however, varied from pig to pig. Mediastinal shift was moderate and the right lung fields were normal.

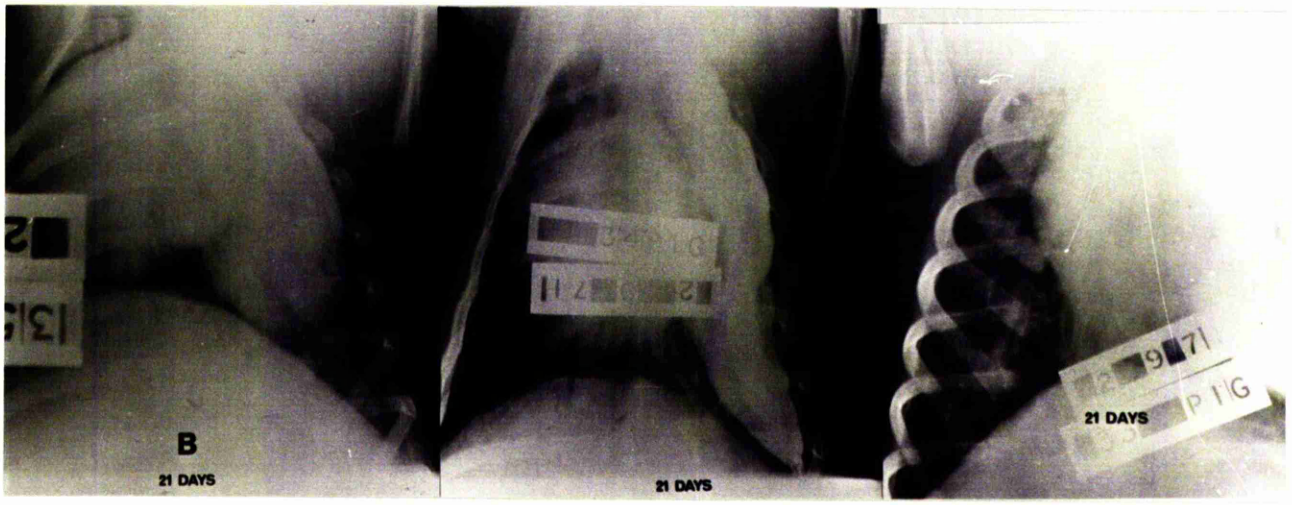


Fig. 25

Antero-Posterior Chest X-ray Films of Pig No. 3
Before and After Opening the Skin-lined
Hemithorax to the Exterior

In the X-ray film, B, the closed skin-lined hemithorax was outlined with 20 ml of hypaque at three weeks. Two weeks later, the cavity was opened to the exterior. The intrapleural skin graft had closely reproduced the contours of the left hemithorax and the right lung field remained normal on both X-ray films.

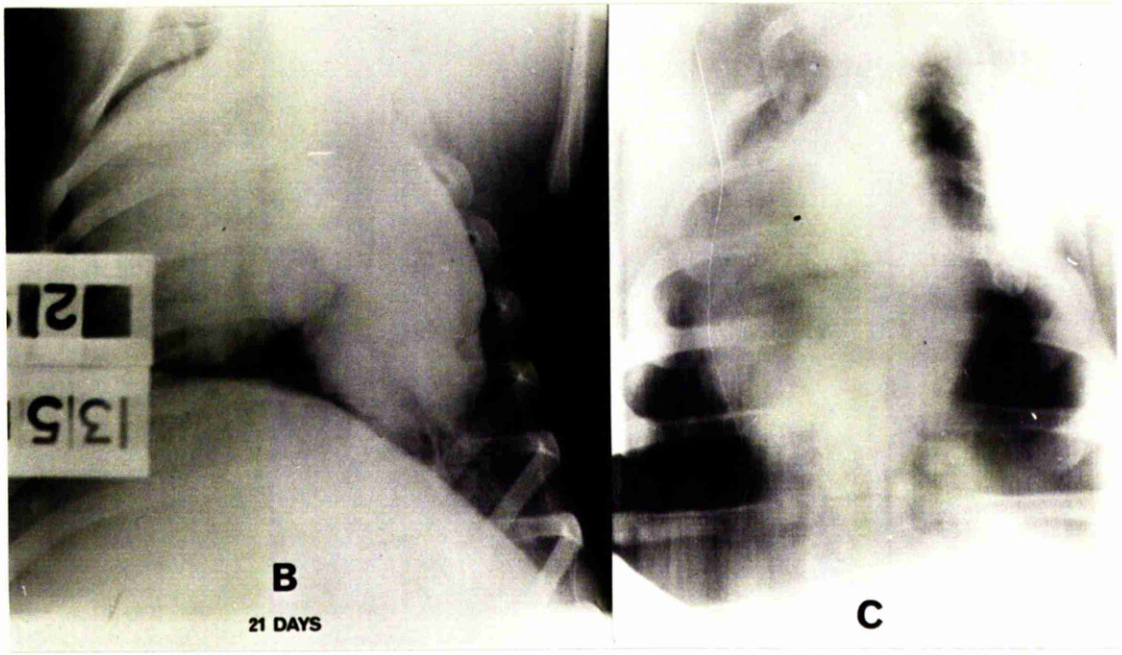
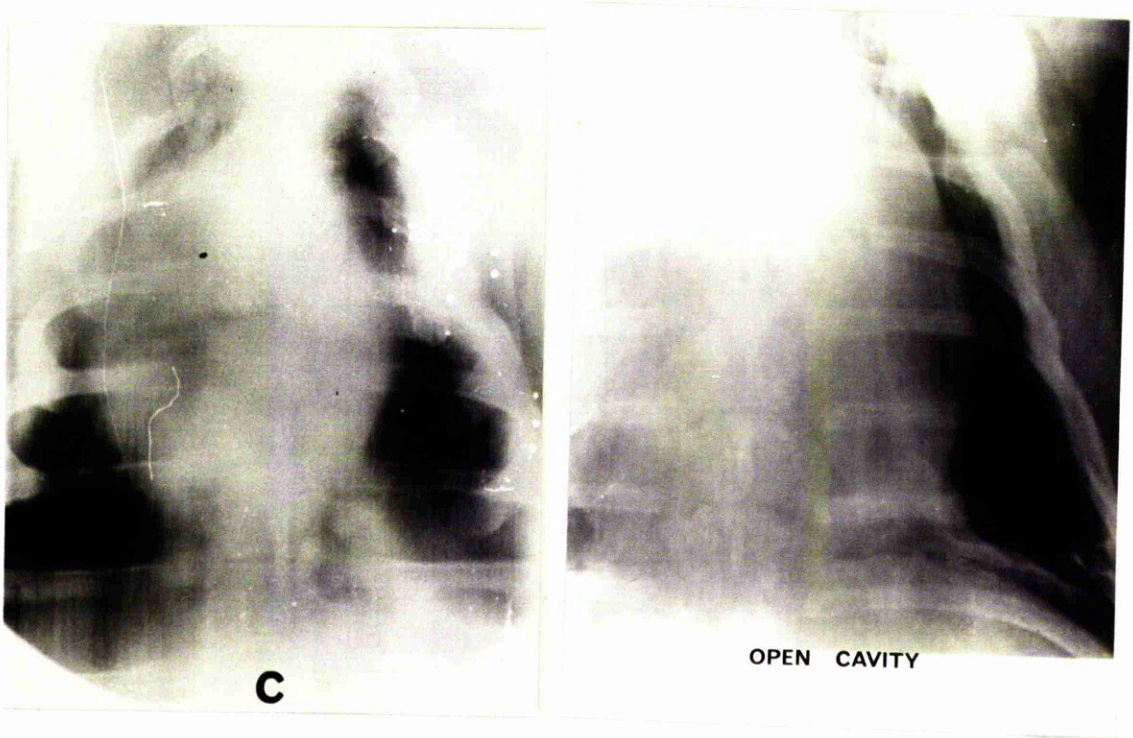


Fig. 26

Antero-Posterior Chest X-ray Films of Pig Nos. 3 and 6
Taken Five Weeks After Intrapleural Skin Grafting

The skin-lined hemithorax (left) had been opened to the exterior. The X-ray film on the left (Pig No. 3) was taken in inspiration: both halves of the thorax filled well with air. In the X-ray film on the right (Pig No. 6), the silicone tube with which the implanted skin capsule was splinted (five weeks earlier) can be seen. The close reproduction of the contour of the left hemithorax on both X-ray films was noteworthy.



(over)

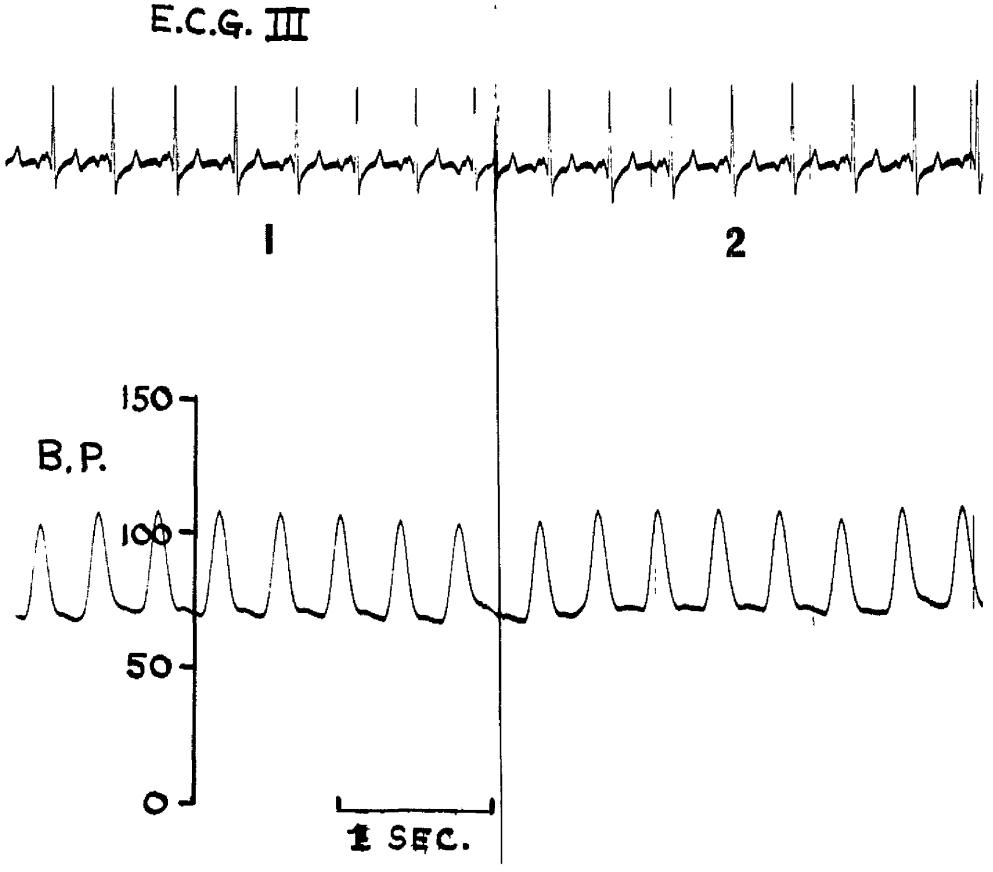
Fig. 27

Tracings of electrocardiogram and intra-arterial pressure (i) before and (ii) two hours after opening the skin-lined hemithorax to the exterior (Pig No. 5).

(i) Heart Rate = 150/min, Blood Pressure = 110/70 mm Hg

(ii) " " = 150/min, " " = 115/75 mm Hg

(i) (ii)



5. Vital Functions Before and Two Hours After Opening the Skin-lined Hemithorax to the Exterior

Cardiac rhythm and rate of respiration remained unchanged (Fig. 27). Table 10 shows paired data on the four pigs. Mean arterial pressure, arterial pH and PCO_2 remained unchanged; however, the rise in heart rate and fall in arterial PO_2 were significant.

Table 10 (Appendix 15)

Comparison of Heart Rate, Rate of Respiration, Mean Arterial Pressure, and Arterial pH, PO_2, and PCO_2 (A) Before and (B) Two Hours After Opening the Skin-lined Hemithorax to the Exterior in Four Pigs (Paired Data)

		Mean Arterial Pressure (mm Hg)	Rate/min		Arterial*		
			Heart	Respiration	pH	PO_2	PCO_2
Mean ± S.E.M.	A	70 ± 4	150 ± 7	31.7 ± 6.5	7.346 ± 0.009	78.2 ± 6.4	45.7 ± 1.8
	B	73 ± 5	158 ± 5	39.0 ± 4.2	7.316 ± 0.023	57.4 ± 2.8	45.3 ± 3.3
Statistical Analyses (D.F. = 3)	T =	1.00	3.00	0.844	1.04	5.24	0.103
	P =	0.39*	0.05*	0.46*	0.38*	0.014*	0.92*

* Pigs breathing air; * Significant; * Not significant

(over)

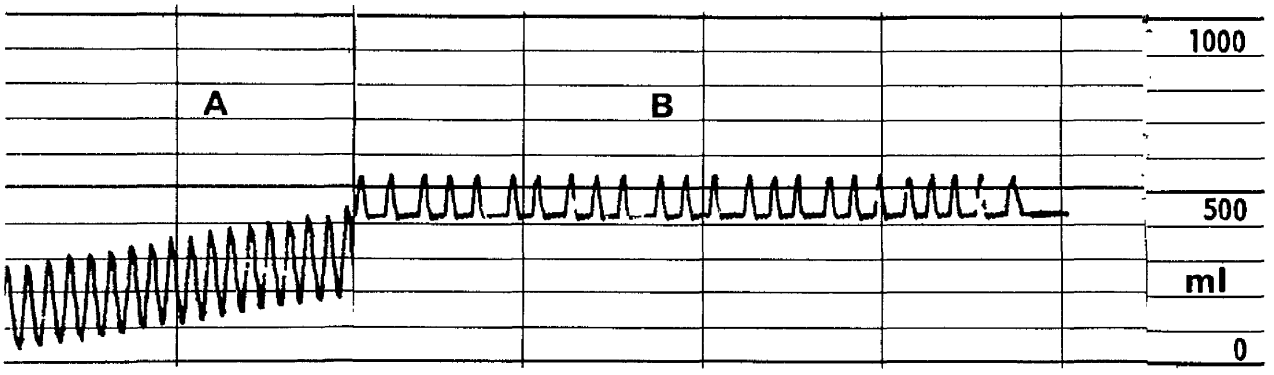
Fig. 28

Spirometric Tracings of Pig No. 3

(Chest X-ray Films: Figs. 24-26)

Tidal air in (A) normal hemithorax and (B) skin-lined hemithorax. Body weight = 41.4 kg; speed of kymograph = 128 mm/min; inspiration (↑).

	A	B
Rate of respiration/min	48	31
Tidal air (ml; STP)	96.6	49.2
Minute-ventilation (ml/kg/min)	112	72.3
Total capacity	...	230 ml



A B

6. The Skin-lined Hemithorax as a Ventilated Gas Cavity (Fig. 28).

(i) The mean volume of the skin-lined hemithorax was 276 ± 20 ml five weeks after intrapleural skin grafting. (Appendix 16).

(ii) The mean tidal volume in the normal hemithorax was 82 ± 11 ml; it was 47 ± 8 ml in the skin-lined hemithorax (P = 0.005). The respective minute-ventilations were 85 ± 10 ml/kg/min and 49 ± 9 ml/kg/min (P < 0.001; Table 11). The volumes were corrected to STP.

Table 11 (Appendix 17)

Comparison Between Ventilation in the Normal and in the Skin-lined Hemithorax

(N = 4 (paired data); Mean weight = 37.5 ± 2.5 kg; Mean rate of respiration = 39 ± 4/min.)

	Mean ± S.E.M.		Statistical Analyses (D.F. = 3)	
	Normal Hemithorax	Skin-lined Hemithorax	T =	P
Tidal Volume (ml)	82.2 ± 11.1	47.4 ± 8.3	7.40	= 0.005*
Minute-ventilation (ml/kg/min)	85.1 ± 9.5	49.3 ± 9.3	40.3	< 0.001*

* Significant

(iii.) In the normal hemithorax, there was good correlation between body weight and tidal air ($r = 0.96$), and there was negative correlation between tidal air and rate of respiration ($r = -0.21$); the correlation between the two halves of the chest was also good ($r = 0.92$). However, there was poor correlation between the total capacity of the skin-lined hemithorax and its tidal air ($r = 0.47$; Table 12).

Table 12

Correlations Between (i) Body Weight/Tidal Air; (ii) Tidal Air/Rate of Respiration (Normal Hemithorax); (iii) Tidal Air/Tidal Air (Two Halves of Chest); and (iv) Total Capacity/Tidal Air (Skin-lined Hemithorax Only)

($N = 4$, $D.F. = 2$)

		Regression Equation	r	P
Normal Hemithorax	Body Weight (x) Tidal Air (y)	$y = 3.48x - 46.1$	0.962	0.019*
	Rate of Respiration (x) Tidal Air (y)	$y = -0.554x + 104$	-0.211	0.39*
	Tidal Air (x) Tidal Air in Skin-lined Hemithorax (y)	$y = 0.689x - 9.28$	0.921	0.039*
Skin-lined Hemithorax	Total Capacity (x) Tidal Air (y)	$y = 0.180x - 0.919$	0.472	0.26*

*Significant; *Not significant

DISCUSSION OF THE ABOVE RESULTS

The experiments described above show that the conclusions drawn from the experiments on rats (Page 80) are valid also for larger animals such as pigs. All six pigs survived the operation of intrapleural skin grafting and thrived ($P < 0.016$). The skin grafts 'took' and the cavities expanded to occupy the left hemithorax and reproduced its contour (Figs. 24-26). The mean pressure in the closed skin-lined hemithorax was 1.3 ± 0.3 cm above atmospheric ($P < 0.001$), and the ipsilateral lung underwent compression atrophy (X-ray film: Fig. 26).

In four out of four pigs the skin-lined hemithorax was opened successfully to the exterior and the two halves of the chest behaved as separate ventilating chambers in phase as in the rats. The normal hemithorax received air normally through the trachea and the skin-lined hemithorax received air from an independent opening directly through the chest wall. Cardiac rhythm, rate of respiration, arterial blood pressure, and arterial pH and PCO_2 remained unchanged. However, the rise in the heart rate was significant at the five per cent level and the fall in arterial PO_2 was significant at the one per cent level. There was no obvious explanation for the last observation although it is noteworthy that pig No. 3, which was preserved, recovered fully.

The good and positive correlation which was obtained between body weight and the tidal air in the normal hemithorax is a normal finding (Table 12). Therefore the results obtained for the skin-lined hemithorax might be compared with the normal hemithorax since the experimental conditions were identical. (Indeed, there was good correlation between the tidal volumes in the two halves of the chest (Table 12).)

Functionally, the skin-lined hemithorax was an open ventilated gas cavity which the pigs could ventilate with normal breathing as did the rats. However, the cavities were poorly ventilated; the mean minute-ventilation was about half (57.7 per cent) of the mean value obtained for the normal hemithorax. (Table 11).

CHAPTER V

GENERAL DISCUSSION OF RESULTS

The work described in this thesis has been an attempt to provide possible solutions to four problems which had to be solved if implantable prosthetic lungs are to become feasible in the future. To recapitulate: first, there was the difficulty of making the pleural cavity equal to the task of housing safely a functioning foreign body such as an implantable prosthetic lung. Secondly, the route by which the prosthetic lung could receive air remained to be established. On the assumption that it was possible anatomically to reline and exteriorise the pleural cavity, the third and fourth things to consider were the type of gas cavity that would result and whether it would function adequately.

The possible solution to the first problem which Peirce (1966 and 1967) had suggested did not work. He suggested that the pleural cavity could be lined with silicone 'skin' and that in this way the cavity would be effectively exteriorised. Unfortunately, initial experiments in the present study showed that in dogs silicone 'skin' provoked much pleural effusion which needed protracted drainage. In one dog the effusion became infected. Parts of the chest wall, including the diaphragm, fused inseparably with silicone 'skin' and gave the required result, but developed into hard plaques.

Although it gives the sensation of softness, Dacron is not a soft implant material. It cannot be used where permanent softness is needed because the tissue which grows into the interstices of Dacron is fibrous and contracts with time to become hard and fixed (Braley 1970).

The results of the initial experiments in the present study confirmed this observation. It was therefore tentatively concluded that, although it was possible to get fusion between silicone 'skin' and the pleural surfaces, the resultant chest wall became so rigid that the animal could not ventilate it with natural breathing. The practical difficulties will be much pleural effusion and infection. These observations which confirmed the reservations made by Melrose (1970), are equally valid for other implantable fabrics such as Teflon and Velour. However, they could be employed if the required space for implantable prosthetic lungs is a cavity with rigid fixed walls, the above practical difficulties being borne in mind.

The matter was pursued further and it was found that one solution lay in the use of skin grafts. A series of experiments in eleven dogs showed that free skin grafts would 'take' on the normal pleural surfaces even when the skin was sutured into capsules in which the hair-bearing surfaces were enclosed. When implanted into the pleural space, the skin capsules were associated with pleural effusion which accumulated

in and remained confined to the lumen of the capsules provided they had been completely closed initially. These observations were accepted as the basis of subsequent studies.

An experimental preparation was required in which the pleural space was lined fully with skin grafts so that the cavity was effectively exteriorised. A readily reproducible technique was developed for doing this in a series of experiments in rats, and the skin-lined hemithorax was put forward as a cavity which could house a prosthetic lung.

The route by which the prosthetic lung would receive air was next established when the skin-lined hemithorax was opened directly to the exterior without embarrassing respiration in the contralateral lung. Thus, in this experimental preparation, the two halves of the chest behaved as separate ventilating chambers in phase. The normal hemithorax received air through the trachea and the skin-lined hemithorax received air from an independent opening in the chest wall.

The answer to the third question was that the skin-lined hemithorax appeared to function as an open ventilated gas cavity. Spirometric studies were therefore performed on it to answer the fourth question which was this: could the animal achieve adequate ventilation or would the implanted prosthetic lung need additional devices to boost its ventilation?

It was found that tidal volume and minute-ventilation in the skin-lined hemithorax were about half of the normal hemithorax ($P < 0.001$). It was concluded that as a gas cavity, the skin-lined hemithorax was poorly ventilated.

A final series of experiments performed on six pigs showed that these conclusions were valid for larger animals also. All six pigs survived the operation of intrapleural skin grafting ($P < 0.016$). They thrived and doubled their mean initial weight within three weeks. The skin capsule enlarged and occupied the left hemithorax and reproduced its contour remarkably closely. The skin-lined hemithorax was opened to the exterior without embarrassing cardio-respiratory function in the four pigs in which paired data were complete. The functions monitored were intra-arterial pressure, electrocardiogram, and arterial pH, PO_2, and PCO_2. Spirometry showed that, functionally, the skin-lined hemithorax was a poorly ventilated gas cavity compared with the normal hemithorax. It was concluded that an implantable prosthetic lung would need additional devices to boost its ventilation.

SUMMARY

1. When the function of a vital organ such as the kidney, heart, or lung is severely impaired, the crippling of the patient has until recently been accepted as the inevitable consequence. However, today the diseased organ can in some patients be replaced surgically with much improvement in health, either by transplantation of a normal organ or by implantation of an artificial organ.

2. Bodell and his colleagues (1965) showed that it was feasible to implant prosthetic lungs, but only in shortlived experiments. However, they concluded that the prosthetic lung could be improved and that the development of larger models could lead to the replacement of one or both lungs.

3. Peirce (1966 and 1967) suggested that permanent prosthetic lungs could occupy the pleural space and receive gas as air from the trachea as a result of normal breathing. However, the pleural cavity must first be made equal to the task of housing safely a functioning foreign body such as an implantable prosthetic lung. In other words, a special place must be provided for it.

4. The observations recorded here have been made to see whether this is feasible.

5. To provide this special place, the pleural cavity must be relined and exteriorised effectively. Peirce (1966 and 1967) suggested silicone 'skin' as the new pleural lining which might be installed as a preliminary stage, together with pneumonectomy. However, Melrose (1970) had doubts about the feasibility of this.

6. In the present study, therefore, I first investigated the effect of silicone 'skin' on the pleural membrane of five dogs. The pleural membrane did not readily accept silicone 'skin', which provoked much pleural effusion followed by empyema after a protracted chest drainage.

7. The required result was obtained when some parts of the chest wall, including the diaphragm, fused inseparably with silicone 'skin'. But histological examination showed that the parts became rigid through the formation of scar tissue.

8. Dacron is not a soft implant material although it gives the sensation of softness. It cannot be used where permanent softness is needed, because the tissue which grows into the interstices of Dacron is fibrous and contracts with time to become hard and fixed. These remarks apply equally to Teflon, Velour, and other implantable artificial fabrics available at present (Braley 1970).

9. Therefore, if the pleural cavity were lined completely with silicone 'skin' and then exteriorised, the result would be an open nonventilated gas cavity with rigid walls which would not be ventilated with natural respiratory movements.

10. A different lining for the pleural cavity was sought in the use of autogenous skin grafts.

11. From a series of experiments in eleven dogs, four tentative conclusions were drawn. First, free skin grafts would 'take' on normal pleural surfaces. Secondly, the skin grafts could be applied as capsules in which the hair-bearing surfaces had been enclosed. Thirdly, skin capsules grafted into the normal pleural space were associated with pleural effusion. Fourthly, when the capsules were closed the fluid accumulated in and remained confined to their lumen. The tentative conclusions were accepted as the basis of further studies.

12. It was shown to be possible to transform the hemithorax of a rat into a stable skin-lined cavity which could be opened to the outside air without embarrassing respiration in the remaining lung. The two halves of the thorax were demonstrated to function as separate ventilating chambers in phase; the normal hemithorax received air normally from the trachea, and the skin-lined hemithorax received air independently from a separate opening directly through the chest wall.

13. But the skin-lined hemithorax was a poorly ventilated gas cavity compared with the normal hemithorax. Its tidal volume and its minute-ventilation (tidal volume x rate of respiration) were about half of normal.

14. The rate of respiration was significantly higher and the tidal volume was significantly lower in the test rats compared with unoperated rats. However, there were no significant difference between their minute-ventilations. This suggested that the test rats achieved adequate ventilation by means of compensatory increase in the rate of respiration because of their smaller tidal volumes.

15. From these series of experiments in the rats it was concluded that a readily reproducible technique had been developed for transforming the hemithorax into a stable skin-lined cavity which could be opened to atmospheric pressure without embarrassing respiration in the contralateral lung. The experimental preparation is presented as a model for providing space for permanent implantable prosthetic lungs. However, the animal could not adequately ventilate such a lung as a result of natural breathing because, functionally, the skin-lined hemithorax was a poorly ventilated gas cavity.

16. Identical experiments performed in six pigs showed that these conclusions were valid for larger mammals.

17. It is concluded finally that a readily reproducible technique had been developed for transforming the hemithorax into a skin-lined cavity which could be opened to atmospheric pressure without embarrassing the cardio-respiratory function in the animal. The conclusion is valid for small animals such as rats as well as for larger animals like pigs.

The experimental preparation is presented as a model for the provision of space for implantable prosthetic lungs. As the skin-lined hemithorax was poorly ventilated with natural breathing, two additional devices are needed, namely, a to-and-fro type of respirator and a unidirectional valve in the dependent pleural position to boost ventilation and to drain any fluid that tended to collect in the pleural space (Peirce 1966).

18. Much work remains to be done on this model before it becomes a practical proposition. Perhaps the single most important next step is to lead into the skin-lined hemithorax a vascular channel which connects the pulmonary artery and the left atrium.

19. Whether the grafted skin will assume the innervation of the parietal pleura, whether the squamous epithelium will undergo other adaption with time, and whether the animal will continue to ventilate a chamber which has unusual sensory feedback mechanisms are all matters which belong to the future.

20. I would end by quoting the following observations by Kolff (1970): "And therefore I predict that whether my contemporaries and I make an artificial heart, a better artificial kidney, better artificial valves, usable artificial eyes , a practical artificial placenta(lung) - all these will eventually be made; perhaps not by us - but that is not so important".

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APPENDIX 1

Excised Free Skin Grafts from 30 Consecutive Rats

No.	Length (mm)	Width (mm)	Wet Wt. (g)
1	80	50	11.3
2	78	60	10.7
3	85	58	14.5
4	78	56	11.2
5	75	54	10.7
6	94	54	11.4
7	95	60	10.8
8	100	50	14.8
9	90	52	11.7
10	92	53	11.0
11	83	61	11.6
12	79	58	15.4
13	82	60	14.4
14	85	58	12.1
15	100	60	12.6
16	96	61	16.1
17	97	58	15.0
18	92	60	14.6
19	82	51	12.6
20	84	52	13.8
21	90	54	12.4
22	92	54	10.7
23	85	60	12.7
24	95	62	11.8
25	96	58	14.2
26	84	54	15.3
27	87	50	16.0
28	90	58	16.1
29	100	56	14.2
30	94	54	11.8
Mean	88.7	56.3	13.1
S.D.	7.3	3.7	1.7
S.E.M.	1.3	0.7	0.3

APPENDIX 2

Width (mm) of Skin-lined Hemithorax of Rats from 30 Serial Chest X-ray Films

Rat No.	Week 1	2	3	4
1	10.1	15.4	18.3	20.4
2	11.2	17.5	17.5	18.0
3	10.8	15.8	18.5	25.1
4	12.1	18.3	20.0	24.1
5	14.2	19.1	20.4	23.3
6	11.7	17.5	21.6	22.9
7	14.2	19.1	26.6	28.3
8	12.1	20.0	20.0	20.0
9	12.4	19.0	19.5	19.5
10	10.0	14.1	14.1	18.0
11	11.3	16.2	18.4	20.0
12	11.7	19.1	19.1	20.4
13	11.3	17.9	18.0	20.0
14	12.0	14.2	16.4	20.0
15	11.7	15.0	15.8	23.3
16	12.0	18.1	20.1	21.6
17	11.3	17.8	20.4	27.5
18	10.8	14.1	19.2	20.0
19	15.8	19.6	20.0	28.3
20	11.7	19.1	26.6	26.6
21	14.2	20.1	21.6	24.0
22	8.8	13.3	13.3	16.6
23	11.7	13.0	13.3	16.3
24	11.8	20.8	24.1	24.1
25	10.0	19.0	19.1	20.0
26	11.7	15.0	16.6	20.8
27	12.5	19.0	19.1	25.1
28	11.7	16.0	16.6	21.6
29	15.0	16.2	21.6	21.6
30	12.0	19.1	21.6	22.1
Mean	11.9	17.2	19.2	22.0
S.D.	1.4	3.3	3.1	3.1
S.E.M.	0.2	0.6	0.5	0.5

APPENDIX 3

Weight (g) of 30 Rats During First Four Weeks After Intrapleural Skin Grafting

Rat No.	Week 0	1	2	3	4
1	220	260	280	295	235
2	200	235	230	285	270
3	200	200	255	270	320
4	210	245	280	290	285
5	200	220	230	245	250
6	210	210	245	260	195
7	220	250	290	290	305
8	215	240	275	305	325
9	220	260	300	310	310
10	280	250	250	250	280
11	255	250	265	300	310
12	240	245	250	295	310
13	245	250	280	300	330
14	280	255	270	300	325
15	290	260	265	255	270
16	290	265	280	280	325
17	260	250	270	270	275
18	270	240	250	275	300
19	245	230	245	265	290
20	245	250	275	260	208
21	230	215	230	235	245
22	275	280	290	300	305
23	230	220	230	250	280
24	265	270	270	300	315
25	250	250	280	305	325
26	220	205	230	250	270
27	255	260	260	290	310
28	240	240	260	290	300
29	240	235	250	285	310
30	220	220	240	265	295
Mean	240.7	242.0	260.8	279.0	289.1
S.D.	30.4	19.7	20.3	21.2	34.2
S.E.M.	5.6	3.6	3.7	3.9	6.2

APPENDIX 4

Weight (g) of Ten Unoperated Rats Kept Under Identical Conditions

Rat No.	Time in Weeks				
	0	1	2	3	4
1	245	265	290	305	320
2	230	260	280	290	315
3	205	220	260	285	300
4	200	230	265	290	310
5	240	260	285	300	315
6	210	225	260	280	300
7	200	230	270	295	305
8	210	220	250	280	295
9	260	290	315	325	335
10	240	265	300	320	330
Mean	224.0	246.5	277.5	297.0	312.5
S.D.	21.6	24.4	20.3	15.7	13.2
S.E.M.	6.8	7.7	6.4	5.0	4.2

APPENDIX 5

Pleural Pressure (cm H_2O) in Ten Normal Rats

Rat No.	End Expiration	End Inspiration	Mean Pressure
1	-2.7	- 8.2	-4.1
2	-2.7	- 8.2	-4.1
3	-4.1	-10.9	-2.7
4.	-4.1	- 8.2	-2.7
5	-2.7	- 9.5	-4.1
6	-4.1	- 6.8	-4.1
7	-4.1	- 8.2	-4.1
8	-2.7	- 9.5	-4.1
9	-2.7	- 6.8	-2.7
10	-4.1	-10.9	-4.1
Mean	-3.4	- 8.7	-3.7
S.D.	0.7	1.5	0.7
S.E.M.	0.2	0.5	0.2

APPENDIX 6

Pressure (cm H_2O) in the Open Skin-lined Hemithorax of 15 Rats

Rat No.	End Expiration	End Inspiration	Mean Pressure
1	-2.7	- 8.1	-4.1
2	+3.4	-16.3	-4.1
3	+4.1	-16.3	-4.1
4	+2.7	- 4.0	0
5	+1.4	- 6.8	+0.7
6	+3.4	- 5.4	0
7	+4.1	- 9.5	-0.7
8	+2.7	- 4.1	-1.4
9	-2.0	-10.8	-4.1
10	-0.5	- 8.0	-3.0
11	0	- 3.5	-3.0
12	+1.0	- 6.0	-4.0
13	+2.0	- 2.0	-0.5
14	+3.0	- 5.0	-2.0
15	+3.0	-10.0	-7.5
Mean	+1.7	- 7.7	-2.5
S.D.	2.1	4.3	2.2
S.E.M.	0.6	1.1	0.6

APPENDIX 7

Pressure (cm H_2O) in the Closed Skin-lined Hemithorax of 15 Rats

Rat No.	End Expiration	End Inspiration	Mean Pressure
1	+ 3.4	+0.7	+2.0
2	+ 6.8	+2.7	+4.8
3	+ 6.8	-2.7	0
4	+ 2.1	-1.4	0
5	+ 7.8	0	+4.1
6	+ 9.5	+5.4	+6.8
7	+ 6.2	-7.4	+4.1
8	+11.6	+8.8	+8.2
9	+ 3.0	+2.0	+2.5
10	+ 4.0	+3.0	+3.0
11	+ 6.0	+4.0	+4.0
12	+ 1.0	+1.0	+1.0
13	+ 1.0	+1.0	+1.0
14	+ 0.5	-1.0	0
15	+ 6.8	+2.7	+2.0
Mean	+ 5.1	+1.3	+2.9
S.D.	3.3	3.7	2.5
S.E.M.	0.9	1.0	0.6

APPENDIX 2

Minute-Ventilation (M.V.) in 30 Rats with Open Skin-lined Hemithorax

Rat No.	Wt. (g)	Resp. Rate/min	Skin-lined Hemithorax			Normal Hemithorax		
			Tidal Vol(ml)	M.V. ml/min	M.V. ml/kg/min	Tidal Vol(ml)	M.V. ml/min	M.V. ml/kg/min
1	208	72	0.6	43.2	207.6	2.0	114.0	692.3
2	250	88	0.8	70.4	281.6	1.6	140.8	563.2
3	265	108	1.0	108.0	407.5	1.9	205.2	774.3
4	280.	120	1.0	120.0	428.5	2.0	240.0	857.1
5	280	120	1.3	156.0	557.1	2.0	240.0	857.1
6	300	96	1.1	105.6	352.0	1.8	172.8	576.0
7	300	144	1.0	144.0	480.0	1.7	244.8	816.0
8	300	72	1.0	72.0	240.0	1.8	129.6	432.0
9	300	150	1.3	195.0	650.0	1.3	195.0	650.0
10	300	114	0.5	57.0	190.0	1.5	171.0	570.0
11	305	114	1.0	114.0	373.7	1.5	171.0	560.6
12	305	96	0.6	57.6	188.8	1.2	115.2	377.7
13	310	90	1.2	108.0	348.3	1.5	135.0	435.4
14	316	96	0.8	76.7	243.0	1.7	163.2	516.4
15	320	90	1.0	90.0	281.2	1.7	153.0	478.1
16	325	144	0.5	72.0	221.5	1.8	259.2	796.9
17	330	114	1.0	114.0	345.5	1.9	216.6	654.5
18	340	96	1.0	96.0	282.3	1.8	172.8	508.2
19	340	84	0.5	42.0	123.5	1.2	100.8	296.4
20	345	96	0.8	76.8	222.6	2.0	192.0	556.5
21	350	96	0.5	48.0	137.1	1.4	134.4	384.0
22	350	114	0.4	45.6	130.2	1.4	159.6	456.0
23	360	96	1.0	96.0	266.6	1.5	144.0	400.0
24	364	96	0.8	76.8	237.0	1.7	163.2	448.3
25	365	114	0.5	57.0	156.1	1.5	171.0	468.4
26	475	60	2.1	126.0	265.2	1.8	108.0	227.3
27	560	70	1.0	70.0	125.0	2.0	140.0	250.0
28	580	60	0.9	54.0	93.1	1.9	114.0	196.5
29	600	76	1.1	83.6	139.3	1.8	136.8	228.0
30	680	70	1.7	119.0	175.0	1.5	105.0	154.4
Mean	356.8	98.5	0.93	89.8	271.6	1.68	164.6	506.1
S.D.	110.0	23.5	0.37	36.3	133.8	0.24	43.5	198.2
S.E.M.	20.1	4.3	0.06	6.6	24.4	0.04	7.9	36.2

APPENDIX 9

Minute Ventilation (M.V.): 12 Normal Rats

Rat No.	Weight (g)	Tidal Vol (ml)	Resp. Rate per min	M.V. ml/min	M.V. ml/kg/min
1	233	1.6	69	96.0	412.0
2	237	1.2	72	86.4	364.5
3	265	2.3	90	207.0	781.1
4	265	1.3	90	117.0	441.5
5	268	1.7	114	193.8	723.1
6	400	2.0	84	168.0	420.0
7	416	2.3	60	138.0	336.5
8	420	2.0	55	110.0	261.9
9	480	2.1	55	115.5	240.6
10	565	2.1	90	189.0	334.5
11	580	2.3	63	144.9	249.8
12	603	2.4	80	192.0	318.4
Mean	394.3	1.94	76.1	146.5	407.0
S.D.	140.1	0.34	18.3	41.86	174.4
S.E.M.	40.4	0.12	5.3	12.09	50.4

APPENDIX 10

Arterial pH, PO_2, and PCO_2 in 10 Normal Rats

Rat No.	pH	PO_2	PCO_2
1	7.351	64.2	44.0
2	7.327	79.9	38.2
3	7.398	79.5	41.0
4	7.311	88.5	35.8
5	7.427	92.2	36.8
6	7.314	75.6	33.5
7	7.330	88.4	40.4
8	7.316	84.7	38.2
9	7.424	79.2	36.4
10	7.308	69.6	38.1
Mean	7.349	80.18	38.24
S.D.	0.048	8.8	3.0
S.E.M.	0.015	2.77	0.94

APPENDIX II

Arterial pH, PO_2, and PCO_2 in 10 Rats with Skin-lined Hemithorax Open for 24 Hours

Rat No.	pH	PO_2	PCO_2
1	7.383	79.8	40.2
2	7.422	87.5	34.4
3	7.359	88.0	33.8
4	7.248	81.0	38.6
5	7.341	79.6	37.4
6	7.366	82.6	34.2
7	7.334	66.7	32.9
8	7.407	68.3	54.4
9	7.282	66.3	48.5
10	7.404	70.5	29.7
Mean	7.355	77.03	38.41
S.D.	0.055	8.4	7.6
S.E.M.	0.017	2.65	2.43

APPENDIX 12

Volume (ml) of Skin-lined Hemithorax at Four Weeks in 15 Rats

Rat No.	Wt (g)	Vol. (ml.)
1	320	7.5
2	315	7.0
3	300	6.5
4	210	8.0
5	300	9.0
6	315	5.0
7	270	9.0
8	240	9.0
9	310	9.0
10	340	8.5
11	295	7.0
12	305	6.5
13	340	6.0
14	300	7.0
15	315	6.0
Mean	298.3	7.4
S.D.	34.8	1.3
S.E.M.	9.0	0.3

APPENDIX 13

Weight (kg) of Six Pigs with Intrapleural Skin Grafts

Pig No.	Time in Weeks 0	1	2	3	Wt. (kg) Gained in Three Weeks
1	21.4	23.6	27.3	34.5	13.1
2	18.2	23.9	28.2	37.3	19.1
3	18.6	23.6	29.1	40.0	21.4
4	12.7	17.3	23.2	29.1	16.4
5	11.1	15.5	17.7	22.3	11.2
6	14.1	21.1	23.6	31.4	17.3
Mean	16.0	20.8	24.9	32.4	16.4
S.D.	4.0	3.6	4.3	6.3	3.8
S.E.M.	1.6	1.5	1.7	2.6	1.5

APPENDIX 14

Pleural Pressure (cm H_2O) in (A) Normal Pleura (B) Closed Skin-lined Hemithorax (5* Pigs; Paired Date)

Pig No.	End of Expiration		End of Inspiration		Mean Pressure	
	A	B	A	B	A	B
2	5.0	8.0	-12.0	-10.0	-4.0	1.0
3	1.0	7.0	-15.0	- 7.0	-4.5	1.0
4	2.0	8.0	-10.5	- 8.0	-4.0	0.5
5	3.0	6.0	-10.0	- 4.0	-5.5	2.0
6	-2.0	4.0	-10.0	- 4.0	-6.0	2.0
Mean	1.8	6.6	-11.5	- 6.6	-4.8	1.3
S.D.	2.59	1.67	2.12	2.61	0.90	0.67
S.E.M.	1.16	0.75	0.94	1.17	0.40	0.30
T =	6.53		4.28		8.76	
P = (D.F. = 4)	0.003*		0.013*		0.0009*	

* Significant

* Pig No. 1 was killed electively at three weeks.

APPENDIX 15

Heart Rate, Rate of Respiration, Arterial Blood Pressure and Arterial pH, PO_2, and PCO_2 in Four* Pigs (A) Before and (B) Two Hours After Opening the Skin-Lined Hemithorax to the Exterior (Paired Data)

Pig No.	Rate/min				Arterial Blood Pressure (mm Hg)			
	Heart		Respiration		Systolic/Diastolic		Mean Pressure	
	A	B	A	B	A	B	A	B
2	170	170	25	34	90/45	100/50	60	65
3	150	150	48	31	110/70	115/75	80	85
5	130	150	18	41	110/50	90/55	70	65
6	150	160	36	50	110/50	120/50	70	75
Mean	150.0	157.5	31.7	39.0	105/53.8	106.3/57.5	70.0	72.5
S.D.	14.1	9.6	13.1	8.4	10.0/11.1	13.8/11.9	8.2	9.6
S.E.M.	7.1	4.8	6.5	4.2	5.0/5.5	6.9/5.9	4.1	4.8

Pig No.	Arterial					
	pH		PO_2		PCO_2	
	A	B	A	B	A	B
2	7.323	7.314	59.7	50.5	48.7	46.4
3	7.354	7.343	86.0	63.0	45.4	53.8
5	7.366	7.251	78.9	55.1	40.7	43.0
6	7.340	7.355	88.0	60.8	48.0	38.0
Mean	7.346	7.316	78.2	57.4	45.7	45.3
S.D.	0.018	0.046	12.9	5.6	3.6	6.6
S.E.M.	0.009	0.023	6.4	2.8	1.8	3.3

* Pig No. 1 was killed electively; No. 4 died accidentally of asphyxia (laryngeal spasm).

APPENDIX 16

Body Weight (kg) of Pigs and Volume (ml) of Skin-lined Hemithorax Five Weeks After Intrapleural Skin Grafting

Pig No.	Weight (kg)	Vol (ml)
1*	••••	•••
2	36.8	255
3	43.4	230
4	40.1	340
5	28.2	255
6	40.9	300
Mean	37.48	276.0
S.D.	5.49	43.79
S.E.M.	2.45	19.58

*Killed electively two weeks earlier

APPENDIX 17

Ventilation in (A) the Normal Hemithorax and (B) the Skin-lined Hemithorax of Four Pigs (Paired Data) The Pigs were Anaesthetised with 5% Halothane in Air

Pig No.	Weight (kg)	Rate of Respiration per minute	Tidal Vol(ml)		Minute Ventilation ml/kg/min	
			A	B	A	B
1+	....	....	....	....	....	....
2	36.8	34	91.0	55.0	84.1	50.8
3	41.4	31	96.6	49.2	72.3	36.8
4*	40.1	....	....	....	....	....
5	28.2	41	49.2	23.7	71.5	34.5
6	40.9	50	91.9	61.5	112.3	75.2
Mean	37.48	39.0	82.2	47.4	85.1	49.3
S.D.	5.49	8.4	22.1	16.6	19.1	18.7
S.E.M.	2.45	4.2	11.1	3.3	9.5	9.3

+ Killed electively two weeks earlier.

* Died accidentally of asphyxia due to laryngeal spasm.

THE PROVISION OF SPACE FOR IMPLANTABLE PROSTHETIC LUNGS: A Feasibility Study

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF MEDICINE

TO

THE UNIVERSITY OF GLASGOW

BY

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SEPARATE SUMMARY

1. Knowledge and techniques in medicine and surgery have reached the point that replacement of organs which formerly seemed impossible has today become a reality. The progress in organ replacement has taken two directions. One has led to transplantation of viable organs from one person to another; the other has led to implantation of prosthetic, functioning organs composed entirely of non-living and inert materials. Although problems have arisen in the development of prosthetic organs, the difficulties are not insurmountable. The search is challenging and must continue.

2. Bodell and his colleagues (1965) showed that it was feasible to implant prosthetic lungs, but only in shortlived experiment Peirce (1966 and 1967) described, in theory, an implantable prosthetic lung which permanently occupied the pleural cavity. This concept implies many unsolved problems and I have performed experiments designe to provide possible solutions to four of them.

3. First, there was the difficulty of making the pleural cavity equal to the task of housing safely and permanently a functioni foreign body such as implantable prosthetic lung. In other words a special place must be provided for it: the pleural cavity must be relined and exteriorised effectively. Secondly, the route by which the prosthetic lung could receive air remained to be established.

On the assumption that it was possible, anatomically, to reline and exteriorise the pleural cavity, the third thing to consider was whethe functionally, the animal could ventilate such a cavity with natural breathing; and the fourth thing was to quantify the ventilation, if an

4. The possible solution to the first problem which Peirce (1966) had suggested did not work. He suggested the pleural cavity could be lined with silicone 'skin'. Unfortunately, I found in initi experiments in five dogs that silicone 'skin' provoked much pleural effusion which needed protracted drainage. In one dog the effusion became infected. Parts of the chest wall, including the diaphragm, fused with silicone 'skin' and gave the required result, but developed into hard plaques.

5. Dacron is not a soft implant material although it gives the sensation of softness. It cannot be employed where permanent softness is needed, because the tissue which grows into the interstice of Dacron is fibrous and contracts with time to become hard and fixed. These remarks apply equally to Teflon, Velour, and other plastic fabri in current use (Braley 1970).

6. I therefore abandoned the use of plastics and sought a different lining for the pleural cavity in the use of skin grafts. From a series of experiments in 11 dogs I drew conclusions which forme

the basis of further studies. I found that free skin grafts would 'take' on normal pleural surfaces even when the skin was applied as capsules in which the hair-bearing surfaces had been enclosed. When grafted into the normal pleural space the skin capsules were associated with pleural effusion which accumulated in and remained confined to the lumen of the capsules provided they had been completely closed initiall

7. An experimental preparation was required in which the pleural space was lined fully with skin grafts so that the cavity was effectively exteriorised. A readily reproducible technique was developed for doing this in a series of experiments in rats. I grafte closed capsules of skin into the left pleural space of 150 SPF rats and 132 (88 per cent) survived the next four weeks ($P < 0.001$). In these rats the skin capsules enlarged to occupy the left hemithorax as judged by serial chest X-ray films, and the rats thrived. The skin-lined hemithorax was put forward as a cavity which could house a prosthetic lung.

8. The route by which the prosthetic lung would receive air was next established when the skin-lined hemithorax was opened to the exterior without embarrassing respiration in the lung on the opposite side. Thus 59 out of 75 rats so exposed survived ($P < 0.001$). In this experimental preparation the two halves of the chest behaved as

separate ventilating chambers in phase. The normal hemithorax received air through the trachea and the skin-lined hemithorax received air from an independent opening in the chest wall.

9. The answer to the third problem was that the rats could ventilate the skin-lined hemithorax with natural breathing. However, and as the answer to the fourth problem, the skin-lined hemithorax was a poorly ventilated gas cavity compared with the normal hemithorax. Its mean tidal air (0.93 ± 0.06 ml) and its mean minute-ventilation (271.6 ± 24.4 ml/kg/min) were about half of normal ($P < 0.001$). The arteria pH, PO_2, and PCO_2 in the test rats were not significantly different from normal.

10. I concluded from these series of experiments that a readil reproducible technique could transform the hemithorax into a stable skin-lined cavity which could be opened to the exterior without embarrassing respiration in the contralateral lung in rats.

11. I performed identical experiments in six pigs which showed that these conclusions were valid for larger animals. All six pigs survived the operation of intrapleural skin grafting, and thrived. The skin-lined hemithorax was opened safely to the exterior in four out of four pigs and the outline of the hemithorax was reproduced closely as shown by repeat chest X-ray films.

12. After creation of the thoracostomy, the mean arterial pressure, rate of respiration, electrocardiogram, arterial pH and PCO_2 remained unchanged; but there was significant rise in heart rate and a fall in arterial PO_2. In the skin-lined hemithorax, the mean tidal air (47.4 ± 8.3 ml) and the mean minute-ventilation (49.3 ± 9.3 ml/kg/min) were about half of normal ($P = 0.005$ and $P < 0.001$).

13. It is concluded finally that a readily reproducible technique has been developed for transforming the hemithorax into a skin-lined cavity which could be opened to atmospheric pressure without embarrassing the cardio-respiratory function in the animal. The conclusion is valid for small animals like rats and for larger animals like pigs. The experimental preparation is presented as a model for the provision of space for implantable prosthetic lungs. As the skin-lined hemithorax was poorly ventilated with natural breathing, two additional devices are needed, namely, a to-and-fro type of respirator and a unidirectional valve in the dependent pleural position to boost ventilation and to drain any fluid that tended to collect in the pleural space (Peirce 1966).

14. Much work remains to be done on this model before it becomes a practical proposition. Perhaps the single most important next step is to lead into the skin-lined hemithorax a vascular channel which connects the pulmonary artery and the left atrium.

15. Whether the grafted skin will assume the innervation of the parietal pleura, whether the squamous epithelium will undergo other adaption with time, and whether the animal will continue to ventilate a chamber which has unusual sensory feedback mechanisms are all matters which belong to the future.

16. I would end by quoting the following observations by Kolff (1970): "And therefore I predict that whether my contemporaries and I make an artificial heart, a better artificial kidney, better artificial valves, usable artificial eyes, a practical artificial placenta (lung) all these will eventually be made; perhaps not by us - but that is not so important".