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Experimental tracheal homografting* **

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THE management of patients with stenosis of the cervical trachea remains a difficult clinical problem. During the last decade, the two main aetiological factors have been the steady increase in Road Traffic Accidents and the ever increasing need for prolonged tracheal intubation. Looper (1938) pointed out that infection was being replaced by trauma as a main cause of laryngotracheal stenosis. The incidence of stenosis following tracheostomy with positive pressure ventilation has been reported as high as 20% (Pearson, *et al.*, 1968).

It is now generally agreed that sleeve resection of the damaged segment of the trachea, followed by end-to-end anastomosis without tension, offers the best prognosis. Grillo (1972) has shown that in this way it is possible to resect up to 10 rings of the cervical trachea without resorting to intrapleural dissection. However, this method is limited in its application, and occasionally, the need arises for an alternative method of reconstruction of long segments of trachea. Experimental and clinical attempts to reconstruct the supporting rigid airway have been generally unsuccessful. A variety of autologous grafts, including fascia lata, peritoneum, periosteum, bone, cartilage and dermis have been used with varying degrees of success to reconstruct partial defects of the tracheal wall. The real problem arises when complete circumferential replacement of the trachea is indicated and, as yet, there is no satisfactory solution. A wide variety of allo-

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graft material has been employed in attempts to maintain a rigid wall, but success has been inconsistent because of strictures, leaks and infections. Wykoff (1973) reported his experiences with segmental tracheal prosthetic replacement in a large series of dog experiments using a variety of materials. There were no successful long-term results; most of the animals had developed severe airway obstruction within six months of surgery. Failure was attributed to infection, displacement of the prosthesis, central stenosis secondary to marked fibrosis and proliferative granulation tissue.

The cervical airway must be able to survive many insults, including flexion, compression, tension and torsion. It is also subjected to negative pressures within, alternating with abrupt changes of negative and positive pressure during coughing and sneezing. Respiratory infections are frequent and occasionally severe. It is hardly surprising that, under these circumstances, no implant, regardless of how inert it may be, can have adequate biological stability and an acceptable probability of permanent tolerance. Belsey (1950) described the essential characteristics of a reconstructed airway as follows:—

1. Lateral rigidity.
2. Longitudinal elasticity and flexibility.
3. An adequate and airtight lumen.
4. An uninterrupted lining of ciliated columnar epithelium.

Subsequent experience has shown the latter to be less important than was formerly thought, whilst a combination of rigidity and flexibility is difficult to meet.

The results of circumferential replacement of the trachea by means of homografts has generally been disappointing.

The main obstacle to long-term success in tracheal transplantation has been failure to prevent stenosis of the homograft segment. Alonso, *et al.* (1972) experienced similar failures and, encouraged by the results of cricord arch transplantation (Delahunty, *et al.*, 1970), reported his experiences with homotransplantation of the anterior two-thirds of the tracheal circumference. In this way, he was able to avoid the problems of concentric scarring and devascularization, but the problem of inadequate structural support remained. It is reasonable to suppose that a tracheal homograft will function as an ideal replacement for extensive segmental resections of the trachea, provided that the problem of late stenosis can be prevented. We have, therefore, set out to reconsider the problem of total tracheal homotransplantation.

Materials

A total of 32 cats were used in the following tracheal transplantation procedures. Three main categories were employed:— see Table I.

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TABLE I.

TRACHEAL HOMOTRANSPLANTATION

1	Autograpfts:
2	Homografts without stent:
3	Homografts with stenting:
	a) Short segments 4– 6 rings:
	b) Long segments 10–12 rings:
	c) Long segments 10–12 rings: with immunosuppression:

Procedure

General anaesthesia was employed and pairs of cats of approximately matching size were operated upon simultaneously.

In the autograft group an entire segment of trachea, containing four cartilaginous arches was removed and immediately replaced. In the homograft series the tracheas were exchanged between the pairs of animals. After preparing the neck, the trachea was exposed through a vertical mid-line incision, from the larynx to the suprasternal notch. The trachae was then mobilized circumferentially in the region of the graft, and care was taken to identify and preserve the recurrent laryngeal nerves. In groups 2 and 3a a complete segment of trachea containing four to six cartilaginous rings was removed and the defect bridged with a homograft of similar dimensions. In groups 3b and 3c a longer segment of trachea containing ten to twelve cartilaginous rings, which represents approximately 80% of the cervical trachea in the cat was removed and replaced with a matching homograft. In the cases where a Silastic stent was employed, it was positioned to project by at least 1 cm beyond each anastomotic line. The animals were sacrificed, if they developed signs of severe airway impairment or respiratory distress. All post-mortem specimens were examined and photographed, before being submitted to histological examination. The surviving animals were assessed at varying intervals by means of plain x-rays and contrast laryngo-tracheography. The Silastic stents were removed bronchoscopically.

Results

Overall, four animals died as a direct result of the surgical procedure. These deaths all occurred in our initial series of experiments, and all the animals were of small stature. These experiences, therefore, prompted us to select the larger animals with better surgical tolerance. Following this, there was only one operative death.

Reference to table II shows that there were no long-term survivors in the autograft group.

In group 2, a total of ten cats underwent resection of a four-to-six ring segment of trachea, which was replaced by means of a homograft. A Silastic stent support was not employed and the results are summarized in table III.

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TABLE II.

AUTOGRAFT WITH 4–6 RINGS

Cat Number	Survival time in weeks	Cause of Death
1	8	Sacrificed Airway obstruction
2	2	Airway obstruction Stenosis Bronchopneumonia
3	Expired during surgery	
4	1	Infection

TABLE III.

HOMOGRAFTS WITHOUT STENT—4–6 RINGS

Cat	Survival Time (weeks)	Cause of Death
5	24	Sacrificed, marked stenosis, respiratory distress
6	10	Sacrificed, respiratory distress
7	5	Airway obstruction, marked stenosis
8	2	Airway obstruction, marked stenosis
9	1	Infection, bronchopneumonia
10	4	Airway obstruction, stenosis, bronchopneumonia
11	$2\frac{1}{2}$	Infection (peritracheal abscess), bronchopneumonia
12 13 14	Expired during Surgery	

The longest survivor was sacrificed at six months with symptoms of airway obstruction. (Fig. 1).

The average survival time in this group was five weeks. In those cases where no stent support was used, clinical observation demonstrated marked stridor in the early post-operative days. This usually disappeared within a week and can be attributed to a combination of post-operative oedema and the valve-like action of the grafted segment, which was noted to collapse on inspiration. In group 3 we performed a homograft replacement using a Silastic stent support. The results are summarized in table IV.

In this series of experiments the most difficult technical problem was satisfactory fixation of the stent. Seven of the animals from this group died between ten days and three weeks post-operatively as a result of the premature loss of the stent. The two survivors had their stents removed bronchoscopically at four to nine weeks post-operatively. An adequate airway could be demonstrated radiologically three months after removal of the stent (Fig. 2).

Both these animals remain alive and well without any signs of airway

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FIG. 1.
Airway at 4 months—no stent.

TABLE IV

HOMOGRAFTS WITH STENT—GROUP A—4–6 RINGS

Cat	Survival Time (weeks)	Cause of Death
15	2½	Slipped stent, stenosis, bronchopneumonia
16	Alive and well 26 weeks	Stent removed 9 weeks
17	1½	Slipped stent, stenosis, bronchopneumonia
18	2½	Slipped stent, respiratory distress
19	1½	Slipped stent caused acute obstruction
20	2½	Slipped stent, marked stenosis, bronchopneumonia
21	2	Acute obstruction, slipped stent due to stenosis
22	Alive and well 24 weeks	Stent removed 4 weeks
23	3	Slipped stent, marked stenosis
24	Expired postoperatively	Respiratory arrest

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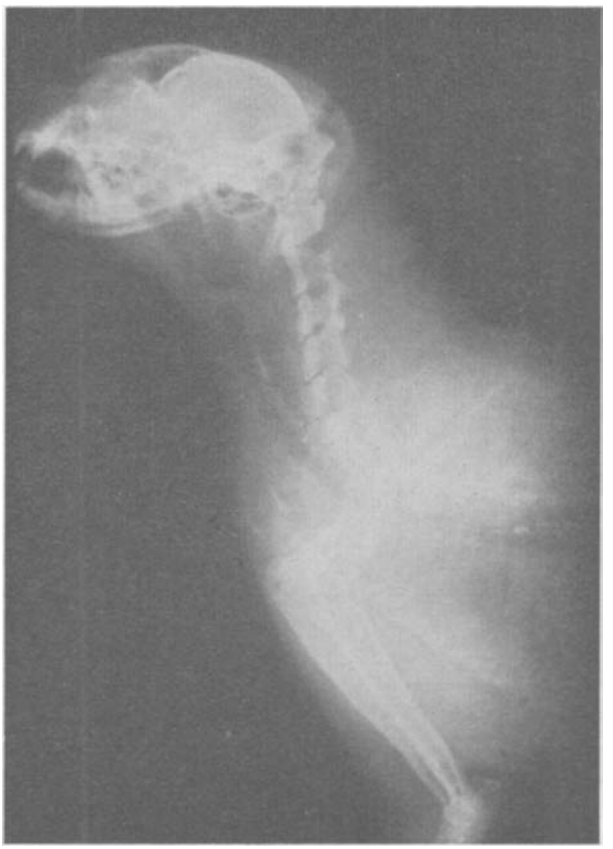


FIG. 2.
Airway at 3 months, following removal of stent.

obstruction. In this group of animals there were no problems with local infection, which is in marked contrast to those undergoing long resections, the results of which are summarized in table V.

The longest survivor expired following removal of the stent. Bronchoscopically there was no evidence of stenosis and the epithelium appeared to be quite healthy, but on removing the stent, the grafted segment was seen to collapse on inspiration (Fig. 3).

One other animal died from acute airway obstruction after losing the stent. The remaining two developed marked infection, peritracheal abscess and necrosis of the graft.

The animals in group C underwent similar extensive resections, but also received immunosuppressive therapy with deposteroid. The results are summarized in table VI.

All the animals in this group progressed well in the early stages and

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TABLE V

HOMOGRAFTS WITH STENT—GROUP B—10–12 RINGS

Cat	Survival Time in weeks	Cause of Death
25	4	Infection (Peritracheal abscess) No stenosis
26	5	Tracheal collapse following removal of stent
27	4	Infection Necrosis of graft
28	3	Acute airway obstruction due to slipped stent

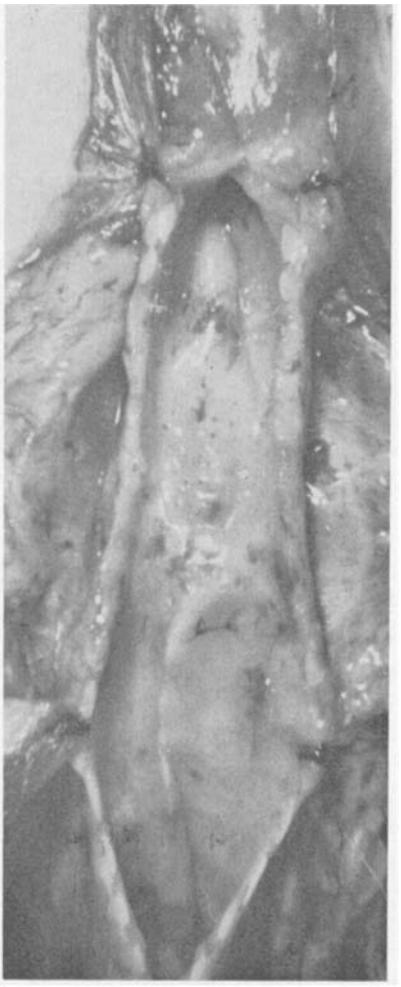


FIG. 3.
Post mortem specimen showing lack of cartilaginous support.

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TABLE VI.

HOMOGRAFTS WITH STENT—GROUP C—10–12 RINGS WITH DEPOMEDRONE

Cat	Survival Time in weeks	Cause of Death
29	4½	Slipped stent Acute airway obstruction due to marked stenosis
30	10	Erosion by stent Tracheal fistula
32	4	Tracheal collapse, following removal of stent

there was only one death due to premature loss of the stent. Two animals developed tracheal fistulae due to erosion of the subglottis by the stent.

Pathology

Gross examination of the autopsy specimens consistently showed marked shrinkage and softening of the homograft segment. All those specimens which had not been supported by a stent showed marked stenosis at the centre of the graft and, in some cases, the airway was narrowed to one or two millimetres. Granulation tissue developed to a marked degree and was very evident at two to three weeks. In one case, marked stenosis developed at ten days (Fig. 4). Microscopic examination of the tissues shows adequate vascularization of the donor tissue in most cases, but there is a dense lymphocytic infiltration with varying degrees of necrosis and resorption of transplanted cartilage. At ten days resorption and repair are well under way and, in some cases, stenosis of the segment is evident. There is marked proliferation of granulation tissue and in those cases where a stent was not employed stenosis is very evident at two to three weeks. In the cases where a stent was employed early stenosis has been avoided, but the problems of lack of rigidity remains due to resorption of cartilage. In the autograft specimens resorption and necrosis of cartilage is much less marked, as is the inflammatory response and subsequent development of granulation tissue. In those animals receiving steroids, the inflammatory reaction, dissolution of cartilage and granulation tissue formation are all delayed, but in the late specimens, the lack of support remains.

Summary

Several factors seem to have an influence upon the fate of the homotransplanted tracheal segments. Such factors are:—

1. The width of the transplant compared with that of the host animal.
2. The length of the transplant.
3. Possible infection or haematoma.
4. Surgical technique.
5. The histological compatibility of the two animals.

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FIG. 4.
Marked stenosis at 10 days post-operatively.

Refinements in surgical technique and elimination of infection can lead to a successful outcome with regard to transplantation of short segments of trachea containing up to six rings of cartilage. We have been unable to define the optimum time for stent removal, but, in cats, a period of six to eight weeks would appear to be sufficient. A longer period invites complications due to ulceration of tissue by the stent. The shorter the transplanted segment, the better are its chances of survival. Certain experts in the field of tissue transplantation have rather optimistically recommended the laryngotracheal structures as potentially ideal homograft material. This opinion is based on the unique property possessed by cartilage of not provoking an immune response when transplanted allogenically. However, the trachea must be considered as a composite graft, and the potential antigenicity of the surrounding soft tissues may have been under-estimated. The dissolution of cartilage so consistently observed in these experiments can probably be explained on a vascular

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basis, but it is possible that the phagocytosis in the tracheal cartilaginous arches of the graft is a rejection phenomenon and that its elimination or suppression may extend the survival time of the graft.

It can be seen that in our present state of knowledge, this form of surgery is still in its infancy, and the prospect of laryngeal transplantation is still far away.

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