GUSTATORY SWEATING AFTER PAROTID SURGERY

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TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

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DECLARATION

I hereby declare that this thesis contains no material which has been for the award of any other degree or diploma in any University, and that to the best of my knowledge and belief this thesis contains no material previously published or written by another person except where due reference is made in the text. I also hereby consent to allow this thesis to be available for photocopying and loan if applicable .

Greg Otto

ABSTRACT

Auriculotemporal syndrome has been recognized since 1757 and until the 1930's infection was the usual cause. Since this time parotidectomy has become the most common antecedent event. Despite numerous studies and reports in the literature there is still controversy about the aetiology of the condition, and consequently treatment remains unsatisfactory.

The thesis addresses the following areas of study:

1) Awareness of auriculotemporal syndrome and knowledge of parotid surgery amongst South Australian surgeons undertaking parotidectomy was assessed by questionnaire. Fifty-one percent of 111 surgeons surveyed replied. Of the surgeons who replied, 60% of those who regularly perform parotidectomy had a working knowledge of the condition and the average estimated incidence was 20%. Cases where auriculotemporal nerve avulsion was undertaken all developed the condition. Auriculotemporal nerve preservation and increased use of postoperative radiotherapy may have resulted in reduction of the incidence.

2) A study was carried out to assess the, incidence of auriculotemporal syndrome and other complications of parotid surgery at the Queen Elizabeth Hospital. 88 patient records were retrospectively reviewed for the 10 year period 1975 to 1985. 54 of these patients were interviewed and tested. In the interviewed cases the incidence of gustatory sweating was 59%.

Of these half were symptomatic and a quarter requested further treatment as a result of the interview.

3) Measurement of electrical resistance of the facial skin was used for the first time for the detection of auriculotemporal syndrome in 54 patients. The diagnostic range of skin resistance for the detection of gustatory sweating was 0-1.9 megaohms. The test has a sensitivity of 91% and a specificity of 100% when compared to the starch iodine test.

4) Ten patients between 1975 and 1985 had a barrier of Lyodura inserted as a prophylactic measure against the development of auriculotemporal syndrome. Six of these patients were reviewed. All six showed evidence of gustatory sweating when studied with starch iodine testing.

5) A case of auriculotemporal syndrome is reported in which interposition of a fascia lata graft was used. Early, but asymptomatic, recurrence was found after 10 months.

6) Cadaver dissections of 8 human auriculotemporal nerves were performed in order to demonstrate the anatomy of branches to the parotid gland. These mostly arose from the superficial temporal and auricular branches of the auriculotemporal nerve. They were frequently superficial and may therefore be easily damaged during parotid surgery.

7) The anatomy of rat, marmoset and human auriculotemporal nerve, facial nerve and parotid glands were compared by dissection in order to provide the foundation for an animal model of the auriculotemporal syndrome. In these areas, the anatomy of the experimental animals was similar to that of man.

8) An animal model of auriculotemporal syndrome in rats and marmoset monkeys was developed. Double retrograde neuronal labelling with the fluorescent dyes Diamidino Yellow and Fast Blue was used for the first time to demonstrate the development of abnormal neuronal projections of the otic ganglion to the skin. Abnormal neuronal connections developed after auriculotemporal nerve injury, but not after parotidectomy in these animals. However, the animal model did not reproduce the human symptoms of auriculotemporal syndrome.

In conclusion, the thesis reviews the auriculotemporal syndrome, its historical aspects, genesis, and treatment. Results of animal experiments suggest but do not prove, that the likely mechanism for the development of auriculotemporal syndrome is aberrant nerve regeneration after direct injury to the auriculotemporal nerve.

CHAPTER 1 LITERATURE REVIEW AND OBJECTIVES

1.1 AURICULOTEMPORAL SYNDROME - A REVIEW OF THE LITERATURE

1.11 DEFINITION AND TERMINOLOGY

Auriculotemporal syndrome can be defined as gustatory sweating, flushing or pain occurring in the distribution of the auriculotemporal nerve or its branches. The gustatory stimuli which best elicit the syndrome are hot, spicy or sour foods combined with masticatory movements.

Laage-Hellman (71) coined the phrase Gustatory Sweating and Flushing (G.S.F.) to describe the syndrome. This phrase is brief and provides a good description of the condition allowing, he felt, the older confusing array of names and eponyms to be dispensed with. However, in this thesis the term "auriculotemporal syndrome" will be used because of the useful anatomical connotations, and in order to give some due recognition to Lucie Frey's early work in the field. On occasions, the slightly less precise term, "facial gustatory sweating" will be employed interchangeably with the term "auriculotemporal syndrome".

1.12 HISTORICAL REVIEW

Facial gustatory sweating was first noted in 1757 by Monsieur Duphenix in a paper entitled "Observations on Fistulas of Stenon's (sic) Duct" (Appendix 1)(1). The paper gives a perspective of medical treatment in the Eighteenth Century, when suppuration was a common means of treating an

open wound, and techniques of blood letting were used to prevent swelling and oedema after injury. In terms of modern day medical practice, the patient seems fortunate to have survived not only the injuries, but also the medical treatment received. The patient concerned was a game keeper for the Duke of Chantilly, who sustained an antler injury to the left side of his face whilst hunting. The wound was quite extensive involving the masseter, the parotid gland and the orbit. It was treated by dressing and consequent suppuration. A salivary fistula developed due to division of Stenon's (sic) duct as a result of the initial injury. Primary treatment of the fistula began 2-3 months after the injury and involved the use of corks to compress the opening and encourage saliva to flow down the normal duct. The treatment caused swelling and pain in the parotid and Duphenix noted numerous beads of fluid gathering on the skin over the parotid. This occurred only when the patient ate and was said to have resulted only in slight amelioration of his symptoms. Duphenix drew the conclusion that saliva leaking through the skin under pressure had caused the appearance he observed. He proceeded to operate on the patient's fistula and in doing so he removed much of the skin over the parotid, inadvertently curing the gustatory sweating simultaneously, and providing an explanation as to why the phenomenon was not observed again in this patient. Duphenix had also been able to cure the fistula by creating a false channel into the mouth, a surgical accomplishment performed without the aid of either anaesthetic or antibiotics.

Unfortunately the patient was left with a severely deformed mouth which prevented him from playing the hunting

horn. The Duke, however, was able to design and construct a special mouthpiece for the horn and the game keeper's former ability was restored.

Thus was the first dim light shone on the subject of gustatory sweating after parotid injury. The topic was to remain clouded in controversy for the next 250 years, but two of the points Duphenix observed, that the gustatory sweating is associated with infection of the parotid region and that it effects the skin overlying the parotid, were to endure.

The condition of facial gustatory sweating was reported next in 1853 by Baillarger (2) almost 100 years later. The author noted that the subject developed bilateral facial moistness after food. The condition was seen as a sequela to bilateral parotid infection, and Baillarger, misled by the earlier interpretation of Duphenix believed this moisture to be a transudate of saliva resulting from a stricture of Stenon's duct.

There were several coeval reports of the condition by Bergounhioux, Botkin, Royer, Bouveret, Pokroffsky, Raymond (3,4,5,6,7,9) and others, and all of these cases were the result of parotitis or parotid abscess. Controversy raged between Baillarger, supported by Henle and Bernard, and Bergounhioux, regarding the nature of the facial moisture. Bergounhioux maintained that the acid reaction of the fluid made it more likely to be sweat, whereas Baillarger and the others adhered to the earlier view that it was saliva. With the passage of time, Bergounhioux was proven to be correct.

By the time that Weber (8) reported his case in 1897 it was well accepted that the fluid was sweat. Antecedent flush-

ing and diminished tactile sensation in the area were also observed. The patient had previously had bilateral parotitis and was also affected similarly on the opposite side. Weber held that the cause of this condition was entrapment of the sympathetic nerves in reactive tissue around the gland, and these nerves were irritated when the gland expanded during eating. An alternative explanation he entertained was that this phenomenon was an example of an abnormal reflex developing after illness.

Over the next 25 years there were further case reports (11-28) of similar observations. It seemed that the condition was more prevalent in Russia and Eastern Europe during this time, due to an epidemic of exanthematic fever between 1919 and 1921, which was frequently complicated by suppurative parotitis. The Russian author Trioumphoff (18) observed 14 cases. The aetiology of the condition remained unknown although there were many theories.

In 1923, a Polish neurologist, Lucie Frey, (10) (Appendix 2) gave consideration to the pathophysiology of the condition which subsequently came to bear her name. The patient she described sustained a gunshot injury to the parotid area. The wound was complicated by typhoid and typhus fevers and local suppuration. Frey noted that 2-3 months after the patient had recovered from these illnesses that he developed progressive gustatory sweating and flushing in the area corresponding to the distribution of the auriculotemporal nerve. In addition there was some degree of sensory loss in this area. Another doctor attempted to inject the facial nerve with alcohol in the misguided belief that this would cure the condition.

Fortunately, he missed the nerve but managed to effect a temporary cure by injecting the auriculotemporal nerve as evidenced by increased sensory loss in the appropriate distribution. These observations prompted Frey to coin the phrase "auriculotemporal syndrome" to describe the condition. She believed that it was due to exaggeration of the normal reflex of gustatory sweating, caused by irritation or entrapment of the auriculotemporal nerve in scar tissue. In order to test this hypothesis she planned to perform an operation to release the nerve, however the patient was lost to follow up before this could be done. Frey and not Weber, as stated by Turner (80), was the first person to realise the central role of the auriculotemporal nerve in the genesis of the syndrome, although the deduction was largely due to a serendipitous injection of alcohol into the auriculotemporal nerve by a third party. Understanding of cranial autonomic innervation was becoming much more complete at this time, nevertheless, in separate cases described by New (11) and Lipszat (12) a year earlier, these authors failed to make this elementary deduction.

In the late 1920's and early 1930's there were several further case reports, again mainly from eastern Europe, where typhus remained endemic. In 1932 Bassoe (29) described the first case of facial gustatory sweating following excision of a parotid tumour and from this time on with the increasing incidence of parotid surgery it became the most common antecedent event.

Up to this time there had been little attempt to quantitate the sweating phenomenon, and reports relied on visual recognition of sweating on the surface of the skin. The tech-

nique was insensitive, and has the obvious disadvantage that it is incapable of detection of variants of the condition in which sweating is minimal. Needles (30) in a case report of 1936 applied a test devised by Minor (31) in 1928. The test, using starch and iodine, allowed detection of small amounts of sweating, accurate delineation of the area involved, and a photograph could be taken as a permanent record. Although other methods for detection of sweat were tried (32-34) the extreme sensitivity of Minor's test has lead to its general acceptance as the optimal method for detecting the auriculotemporal syndrome.

The use of the starch iodine technique marked the beginning of a more scientific approach to the condition of facial gustatory sweating.

During the 1930's there were several reports of gustatory sweating occurring in regions other than the parotid area, following various pathological states and after various types of surgery. It has been noted to occur after cervical sympathectomy (35), after encephalitis (36), in connection with cervical ribs (37), with syringomyelia (38), and in the submental region after removal of cervical lymph nodes (39). In addition the related syndrome of gustatory lacrimation after facial nerve palsy was recognized first by Borograd (1928) (40) and others (41-42) and later by Ford (43) who described 4 cases in 1933 and proposed the theory of aberrant neural regeneration to explain his observations.

Urpus et al in 1934 (39) quantitated the skin temperature changes in a patient with submental gustatory sweating and flushing. With careful experiments these workers were able to

confirm and extend the somewhat patchy knowledge of the pharmacology of auriculotemporal syndrome (1.144).

In 1945 a note in the Lancet on a case of transient facial flushing after food in an infant, resulted in two replies one from F. P. Weber and another from A. D. McDwyer, suggesting that the case may have been a form of auriculotemporal syndrome perhaps resulting from a developmental abnormality.

Langenskiold (44) in a review of the literature in 1946 cited some 90 cases of facial gustatory sweating in the world literature of which 60 had been the result of local infection. He discussed two cases of his own, one being a true case of auriculotemporal syndrome following parotidectomy and the other a case of cervico-facial gustatory sweating following cervical tuberculosis. The latter case responded favourably to local skin resection, and Langenskiold was able to give some insight into the aetiology of the condition using local injections of acetylcholine. Many of the difficulties experienced at this time in relation to aetiological explanations, were a result of the presence of several overlapping conditions and difficulties in the stabilization of pharmacological agents.

In 1948 Haxton (45) partly clarified these problems by differentiating between three types of pathological gustatory sweating on the basis of their causation. The classification served to separate auriculotemporal syndrome from gustatory sweating following upper limb and cervical sympathectomy. Haxton reported several cases of facial gustatory sweating following thoraco-cervical sympathectomy and noted that in the single case of auriculotemporal syndrome there was sensory loss in the area and also that the condition was not affected

by cervical sympathectomy. Interpretation of results was difficult as the patient had both auriculotemporal syndrome and cervical sympathectomy. His conclusion, that both gustatory sweating after sympathectomy and auriculotemporal syndrome were caused by local hypersensitivity to acetylcholine was therefore probably invalid.

One of the more unusual cases of local gustatory sweating was described by Mellinkoff and Mellinkoff (46) in 1950. This was the case of gustatory sweating of the left knee in an 8 month infant during breast feeding. The explanation for this unusual observation was unclear, but the authors believed that the sweat glands of the left knee were injured by excessive crawling and rendered hypersensitive to circulating acetylcholine elevated during breast feeding. There was no definite evidence at all for this theory and this unique observation is probably destined to remain unexplained.

Pffeffer and Gellis, in 1951 (47) observed auriculotemporal syndrome in a 10 year old child. They carried out careful measurements of skin temperature and were able to demonstrate by the use of local anaesthesia that the auriculotemporal nerve was the mediator of the syndrome. In addition, their retrospective survey showed the incidence of the condition to be 1 in 17 patients following parotid infection. They admitted in their discussion that despite the growing number of case reports in the literature there were no accurate estimates of the incidence of the condition and that the true aetiology remained obscure notwithstanding a multitude of theories. Interestingly, they advised that surgical intervention for sepsis in the parotid region should be minimized in order to

prevent auriculotemporal syndrome, particularly since there was still no effective treatment.

With the expansion of head and neck surgery, the auriculotemporal syndrome was noted after other procedures. Hogeman (48,49) reported its occurrence after surgery for correction of mandibular protrusion. He found symptomatic gustatory sweating in 7% of 170 patients. The syndrome appeared between 3 and 36 months after surgery, and once established was permanent. On the basis of pharmacological experiments he postulated that the syndrome resulted from injury to the auriculotemporal nerve at the level of the ramus of the mandible. He claimed to have effected a cure in two cases by resection of the auriculotemporal nerve but the follow-up period was very short. Hogeman's study (48,49), although retrospective, represented the start of a more systematic approach to the problem and attempts to incorporate some of the previous, albeit disjointed, understanding of the syndrome.

Tarlov and Hertz (51) reported a case of gustatory sweating in the distribution of the supra-orbital nerve which was cured by division of the nerve. The observation prompted Coldwater (50) to apply the same principle to treatment of the auriculotemporal syndrome. The idea was not new, having been applied some 30 years earlier (19) with apparent success but abandoned due to the high risk of facial nerve damage. Coldwater made a point of resection of the facial anastomotic branches which he believed to carry the autonomic fibre responsible for the syndrome. He gave no good evidence for this stance, and later work (52) suggested that the supposition was not correct.

In 1953 Dey (53) described an unusual variant of auriculotemporal syndrome. A child, aged 22 months had been noted to have gustatory flushing and sweating since 7 months of age. Dey believed this to be a congenital lesion, however it could equally have been due to a traumatic forceps delivery which could have resulted in auriculotemporal nerve injury.

In the ensuing 3 years there were further case reports (54, 55, 56) of which two cases (56) were treated with partial success by intracranial division of the glossopharyngeal nerve. The authors also recorded the effects of various pharmacological manipulations on auriculotemporal syndrome (1. 144).

As the number of operations for parotid tumour increased so did the frequency of reports of series and post-operative complications (57-68 and others). In these series, which were retrospective and incomplete, the incidence of facial gustatory sweating varied from 5% to 30% (69). The studies relied on patient questioning rather than objective methods of detecting the condition, and because of differing operative techniques involved, were not readily comparable. Whilst these studies added little to the understanding of auriculotemporal syndrome, it became apparent that gustatory sweating, rather than being a rarity, was a common event after parotid surgery and was therefore of considerable clinical significance. Redon (69) in a large personal series of 450 obtained an incidence of gustatory sweating of 25% and was prompted to state that gustatory sweating was the only disturbing consequence of superficial parotidectomy. Hamilton Bailey (60) stated that

Frey's Syndrome was to be more feared than facial palsy due to the pain and embarrassment the former caused.

In 1957 and 1958 Laage-Hellman of Sweden produced a series of papers on the topic of gustatory sweating following parotid surgery (70, 71, 72, 73). Together these papers represent the largest systematic study of the condition in the literature.

In the first of these papers (70) a prospective study was undertaken of 123 patients who had undergone either subtotal, superficial or partial parotidectomy at least 8 months previously. 100% of these patients had some degree of auriculotemporal syndrome as detected by the Minor Starch Iodine test. Sixty percent of patients were aware of their symptoms and 12% were distressed by them. Laage-Hellman was the first to examine patients preoperatively for the presence of the condition reasoning that the perhaps the underlying glandular pathology may have been the initiating factor. In the large range of pathological conditions he examined he was unable to demonstrate any case of pre-existing auriculotemporal syndrome. He was also able to show that in cases where more glandular tissue was resected the severity of the condition was increased. Auriculotemporal syndrome was present after complete parotidectomy, a fact which cast doubt on some of the older theories involving local acetylcholine release.

In order to explain the condition Laage-Hellman postulated that severed parasympathetic fibres were growing directly from the cut surface of the parotid gland into the cutaneous sweat glands. This study may have been open to observer bias and some of the conclusions, in particular those

relating to the amount of parotid resected, were not quantitatively based.

A longitudinal study by Laage-Hellman clearly demonstrated the time-sequence of development of the auriculotemporal syndrome. Although the experimental design was loose in that not all patients were seen and tested in the first weeks, a trend was unmistakable: there was a latent period of at least 5 weeks before development of the condition, after which the sweating gradually worsened, extending in a concentric fashion to the surrounding skin. After 1 year all 57 patients in the series were positive. This information added support to aberrant regeneration theories of development of auriculotemporal syndrome and certainly cast doubt on some of the earlier observations in which the condition occurred only days after the injury or operation (38,45). Since most of these early observations were made retrospectively by the patients it is likely that they were inaccurate.

In a small number of patients Laage-Hellman (72) studied the effects of and differences between thermal chemical and gustatory stimuli before and after the development of auriculotemporal syndrome. He was able to show that prior to development of the syndrome, sweat glands were insensitive to both heat and parasympathomimetics. After the auriculotemporal syndrome developed there was some return of thermal response in sweat glands not responsive to gustatory stimuli, and hypersensitivity to parasympathomimetics in sweat glands responsive to gustatory stimuli. These results confirmed the observations of earlier investigators (44,48,49,56) and implied that the

hypersensitivity is a phenomenon secondary to reinnervation and not a primary response.

In the final paper of the series Laage-Hellman (73) reviewed the modes of treatment available for auriculotemporal syndrome and reported the successful use of scopolamine bromide cream in a small number of patients for the control of symptoms.

This series of papers thus embodies a minor scientific revolution. By careful study of auriculotemporal syndrome Laage-Hellman was able to disentangle much of the confusion that had been created by two hundred years of anecdotal reporting on this subject - a notable accomplishment indeed.

Shortly after these publications, Glaister et al (74), demonstrated, in an elegant series of experiments, not only gustatory sweating, but also the previously unrecognized phenomenon of thermal salivation. This was observed by accurate measurements of salivary flow rates while heating the patient. The observation increased the growing weight of evidence that aberrant neural regeneration was responsible for the development of gustatory sweating.

In addition, Herxheimer (75) and later Ashby (76) reported gustatory pilomotion in addition to sweating and flushing as a complication of cervical sympathectomy. Ashby (76) credits the first observation of this phenomenon to Herxheimer but this may be incorrect. Careful reading of Frey's original article (10, Appendix 2) reveals that she observed piloerection in her patient. She attributed the occurrence to the so called "sympathetic reverberation" effect and noted that the skin of the neck was in a constant state of piloerection but

failed to observe any gustatory influence. Her patient also had a Horner's Syndrome on the affected side, and so perhaps there was an element of sympathetic injury with the initial wound.

The American reports on the subject of facial gustatory sweating lagged behind the European and Scandinavian reports, because most of these case reports were not in English and so awareness of the condition was slow to penetrate to the American medical community. Hemmenway noted this in his publication on the subject in 1960 (77) in which he reported two cases of the syndrome, and made the earliest suggestion that division of Jacobson's nerve may relieve symptoms. There were a number of cases (79) and series (80,81) reported in the American Surgical and Dermatological literature of the early sixties. There was confirmation (82,83) of Hogeman's earlier observation (48,49) that the condition occurs after mandibular surgery. On the whole these reports added no new knowledge to the subject of facial gustatory sweating.

The British Otorhinolaryngologist Golding-Wood was the first to apply (84) the technique of tympanic neurectomy in the treatment of facial gustatory sweating. He used this operation successfully in three patients with auriculotemporal syndrome, but did not acknowledge the earlier suggestion for such use of the procedure by Hemmenway (77). The omission was pointed out 5 years later by the American surgeon Hunt (85) in a case report of similar treatment.

Golding-Wood found it necessary to combine tympanic neurectomy with section of the chorda tympani for complete cure in 2 of his patients. The fact that the chorda tympani

may provide some parasympathetic fibres to the parotid was first mooted by Reichert in 1933 (87). Further indirect confirmation of this view came from Gardiner (56) who observed incomplete cure of the condition by intracranial section of the glossopharyngeal nerve thus implying that alternate pathways exist. Although the literature remained divided on the issue, it became clear that the tympanic plexus represented the major preganglionic pathway to the parotid.

Spiro and Martin (89) in a retrospective review of a 127 patients found gustatory sweating in 59% of patients, and concluded that there was a higher incidence of the condition in patients who sustained some degree of facial neurapraxia. Although the study was incomplete the observation is an interesting and unique one. In addition the authors reported for the first time, the development of gustatory sweating after radical neck dissection. These observations were subsequently confirmed by McGibbon and Parletta (92) who felt that the phenomenon was largely restricted to the distribution of the greater auricular nerve in patients who had excision of the lower pole of the parotid. Again the authors presented no conclusive evidence to support their statements and their survey was carried out in retrospect by mail so their conclusions may be open to question.

In 1969 (90) and again in 1974 (91) gustatory sweating in the auriculotemporal nerve distribution was reported after mandibular fracture. Neither author seemed to be aware of the earlier work of Hogeman. (48)

Throughout the sixties and seventies isolated case reports of auriculotemporal syndrome were published

(97,98,99,100). The cases from India (97,99) appeared to have no causation and were thought without unequivocal evidence to be congenital. This seems unlikely, as birth injuries were not taken into consideration. Balfour (98), in a review of the world paediatric cases of auriculotemporal syndrome, suggested that they were all the result of forceps injury to the auriculotemporal nerve at the time of delivery.

Gordon (100) noted that the area affected by gustatory sweating overlapped the area of distribution of the contralateral greater auricular nerve in over half of his cases. The validity of his conclusion that the greater auricular nerve is involved in this condition, depended on the bilateral symmetry of nerve distribution on the face.

Boddie at al (102) described a case of gustatory rhinorrhea following parotid surgery and believed this to be a variant of gustatory sweating. This unusual case remains an isolated observation and is difficult to explain physiologically.

The main interest of investigators in the late seventies and early eighties was treatment of auriculotemporal syndrome. Prophylactic measures were suggested (103,104,105,106), there was increasing use of tympanic neurectomy (109), alternative local surgical measures were tried (107,108), and alternative medical treatments were assessed (110,111).

Case and series reports continued to appear into the eighties (112,113), including a report from China in 1984 (114) which dealt with prevention of gustatory sweating after parotid surgery by the use of muscle barriers.

1.13 NEUROANATOMY

1.131 HISTORY

The anatomists of the nineteenth century described the innervation of parotid gland in great detail (115). In 1877 Gray's Anatomy (116) gave a description of the otic ganglion and assumed its function to be connected with the sympathetic nervous system. It was not until 1897 when Weigner (117) produced a detailed description of the otic ganglion and its connections, that the pathway of secretomotor fibre to the parotid became understood. In the same year, however, Weber (8) in a paper on gustatory sweating could not explain its occurrence and stated that little was known of cranial sympathetic and parasympathetic innervation.

The Seventeenth Edition (1909) of Gray's Anatomy (118) described the otic ganglion connections to the glossopharyngeal and auriculotemporal nerves, but their parasympathetic function was ill-defined. However, by the time Lucie Frey described her case of "Le Syndrome Du Nerf Auriculotemporal" in 1923 (10) the pathway was firmly established. Frey gave credit to Muller for its elucidation, although this is doubtful in view of the many earlier descriptions (118, 119).

1.132 NORMAL INNERVATION OF THE PAROTID

The normal innervation of the parotid gland is now fairly well understood and widely accepted as summarized in Figure 1.

Primary neurones have their cell bodies in the Inferior Salivatory Nucleus of the brain stem. The fibres join the glossopharyngeal nerve and run in the nerve for a short distance until branching off with the tympanic nerve (Jacobson's Nerve). The nerve enters the temporal bone through a canalicu-

lus between jugular and internal carotid and gains the middle ear cavity to run on the broad promontory of bone overlying the cochlea. With the sympathetic nerves from the internal carotid a small plexus known as the tympanic plexus is formed. The plexus supplies the local area with sympathetic innervation via its branches and gives off the lesser superficial petrosal nerve. The nerve follows the canal of the same name to reach the otic ganglion. The otic ganglion is a minute ganglion which is attached to the mandibular division of the trigeminal nerve immediately below the foramen ovale. The parasympathetic root of the ganglion is the lesser superficial petrosal nerve and its sympathetic root is derived from the sympathetic plexus surrounding the middle meningeal artery. The parasympathetic fibres relay in the ganglion but the sympathetics do not. There are several branches. A communicating branch to the auriculotemporal nerve conveys the sympathetic and parasympathetic nerves destined to supply the parotid gland blood vessels and glandular elements respectively. The parasympathetic fibres are mainly secretomotor to the parotid acini but are also vasodilator to glandular blood vessels and motor to smooth muscle of the ducts and glandular myoepithelial cells (121). The sympathetic fibres are mainly vasomotor and sensory but may also have a role in control of glandular secretion. There are twigs connecting the ganglion to the chorda tympani and the nerve of the pterygoid canal. There are motor branches to the tensor tympani and tensor palati muscles but these are fibres of transition and do not synapse in the ganglion.

Thus, the secretomotor fibres of the parotid join the auriculotemporal nerve and travel with the nerve in its course deep to lateral pterygoid muscle on the surface of tensor palati. The nerve passes between the mandible and the sphenomandibular ligament, and at this level develops a spray of 4-5 branches of approximately equal size (120). These branches comprise 2-3 communicating branches to the facial nerve, branches to the external auditory meatus, an anterior auricular branch, and a superficial temporal branch which supplies sensation to the skin of the temporal region. There are also numerous interconnections of the auriculotemporal nerve to the greater auricular nerve (89).

The manner of distribution of parotid secretomotor fibres is variable. There is a small constant branch from the main trunk of the auriculotemporal nerve which supplies the deep lobe of the parotid. Other, more variable branches arise from the superficial temporal branch and from the facial communicating branches (120). Reissner (122) observed that glandular branches to the parotid may arise from the auricular branches of the auriculotemporal nerve and also from the facial nerve itself as it courses through the parotid gland. These fibres presumably join the facial nerve via the communicating branches and are thereby distributed throughout the parotid.

The intra-glandular distribution of secretomotor fibres is ill-defined, however it seems that there may be a dual innervation of parotid acini by sympathetic and parasympathetic nerves (123, 130, 131, 132). The nerves form a delicate beaded plexus surrounding the parotid acini. The sympathetic nerves largely supply the glandular blood vessels as do, to a

much lesser extent, the parasympathetic nerves which are vasodilator. In general, parasympathetic nerves are cholinergic and sympathetics are adrenergic. Exceptions to this rule are that sympathetic innervation of sweat glands and possibly sympathetic vasodilator fibres are cholinergic.

There is little doubt that the auriculotemporal nerve is the common pathway for the sympathetic and parasympathetic innervation of the parotid. As early as 1914 Aigrot (124) was able to demonstrate the complete cessation of secretion of the parotid by section of the auriculotemporal nerve. These observations were reinforced by Reissner (122) who routinely sectioned the auriculotemporal nerve in parotidectomy in order to reduce salivary fistula formation. Genis-Galvez (123) was able to observe almost complete atrophy of the parotid acini nerve plexuses 15 days after auriculotemporal nerve section in the cat.

1.133 CONTROVERSIES RELATING TO PAROTID INNERVATION

A number of issues concerning parotid innervation remain unresolved.

Firstly, Genis-Galvez et al (123) were unable to achieve complete atrophy of nerves in the parotid gland with auriculotemporal nerve section, suggesting that there could be alternative minor pathways.

Secondly, Reichert and Poth (87) have noted that there was recovery of function in salivary glands 3-4 months after complete intracranial section of the glossopharyngeal nerve in man. They suggested that there was an alternative pathway for preganglionic secretomotor fibres to the parotid via the facial nerve and chorda tympani to the otic ganglion. However,

an alternative explanation could be that the intact sympathetic nerves take over a secretory function. In the three cases these authors presented it was impossible to make this distinction. Further contributory evidence to the existence of alternative pathways of parotid secretory innervation comes from Gardiner and McCubbin (56) who noted only partial alleviation of facial gustatory sweating by intracranial section of the glossopharyngeal nerve. In addition, many authors (88, 93, 94, 95, 101) have noted that a slight degree of gustatory sweating persists after interruption of the tympanic plexus, and Golding-Wood (84) noted that division of the chorda tympani, in addition to tympanic neurectomy, could relieve residual gustatory sweating. On the other hand Ross (93) in an intraoperative study of the function of the tympanic plexus in both normal patients and patients with Frey's Syndrome gave a convincing demonstration that the chorda tympani played no role in either the production of saliva or the production of gustatory sweating. Intraoperative electrical stimulation of the tympanic plexus and the chorda tympani was used. Stimulation of the tympanic plexus resulted in a large salivary flow in normal patients or gustatory sweating in patients with Frey's syndrome, whereas stimulation of the chorda tympani evoked no such responses. Wallenborn (125) was able to induce complete parotid atrophy in rabbits after tympanic neurectomy, again supporting the view that the tympanic plexus is the sole pathway of parotid preganglionic parasympathetics.

Amidst these conflicting data the truth can best be approximated by stating that there are almost certainly variable

preganglionic pathways for parasympathetic innervation of the parotid either via the chorda tympani or via a branch from the geniculate ganglion to the lesser superficial petrosal nerve or from the greater superficial petrosal nerve to the lesser (88,96) (Figure 2). The failure of tympanic neurectomy may be related to the presence of these alternative pathways or as suggested by Ross (93) due to incomplete resection.

The third area of controversy regarding the normal anatomy relates to the number and function of the anastomotic branches from the auriculotemporal nerve to the facial nerve. The number of such branches varies from 1 to 4 to a "subtle plexus" (52,120,122,). Their function is largely conjectural. Baumel (52) summarizes their possible functions as follows :

1) The communicating rami may occur to facilitate the distribution of facial nerve branches and trigeminal branches destined for the same regions.

2) The communicating rami possibly conduct proprioceptive fibres from the trigeminal nerve to the muscles of facial expression.

3) The communicating rami convey sudomotor fibres for the facial skin and secretomotor for distribution to the superficial lobe of the parotid and the glands of the buccal mucosa.

4) No nerve fibres to the facial muscles run in the communicating rami.

There is no information about the composition of these communicating branches in terms of nerve types that is sensory autonomic, or motor, but according to Baumel (52) the spectrum

of fibre size in these nerves is consistent with exteroceptive or proprioceptive afferent or alpha or gamma efferent fibres.

The final area of anatomical controversy is the mode of distribution of the autonomic fibres within the parotid gland and the morphology and function of the peri-acinar plexus. These are unknown and may be of considerable interest with regard to full understanding of post-parotidectomy gustatory sweating.

There is dispute regarding the sympathetic innervation of the parotid which is believed by some to be partly responsible for glandular innervation (128). Kuntz (130), in a series of animal experiments, has demonstrated that there was a relatively richer parasympathetic innervation of the parotid than sympathetic innervation. In addition he was able to show that sympathetic nerves supply salivary gland blood vessels only. Although the methods used suffered from a lack of specificity it seems unlikely that there is significant sympathetic innervation of salivary acini. The peri-acinar and alveolar plexuses have been identified structurally (131) but not functionally. Obviously knowledge of the detailed anatomy of the intraglandular nerve distribution of the parotid is not yet complete.

In summary, the gross details of the anatomical pathways for autonomic innervation of the parotid are well known and are depicted in Figure 1. There are, however, several areas of controversy and lacunae of knowledge which need clarification.

1.14 CLINICAL ASPECTS OF AURICULOTEMPORAL SYNDROME

1.141 GENERAL

Facial gustatory sweating can result from a number of different antecedent events and because this is an unusual condition, these causes have not been clearly distinguished in the past. The factors leading to facial gustatory sweating are listed in Table 1, in approximate chronological order of description.

There are a large variety of conditions which produce facial gustatory sweating. In the pre-antibiotic era infection was the single most common cause, either primary or secondary to local trauma or dehydration. In the 1930 's facial gustatory sweating was seen most frequently as a consequence of parotidectomy. The remaining causes are now unusual and some, such as syringomyelia, diabetes, cervical sympathectomy, radical neck dissection and encephalitis can affect nerves other than the auriculotemporal nerve. Although these latter conditions may have some aetiological similarities to the auriculotemporal syndrome they are preferably considered as a separate entity.

Additional gustatory phenomena which affect the face and other areas may be aetiologically related to auriculotemporal syndrome. These are listed in Table 2 and give an indication of the extent of the clinical problems caused by aberrant nerve regeneration and related gustatory symptoms. These variants are included for completeness, and will not be considered further.

TABLE 1 CLINICAL ANTECEDENTS OF FACIAL GUSTATORY SWEATING WITH THE DESCRIBING AUTHOR IN APPROXIMATE CHRONOLOGICAL ORDER.

CAUSE	YEAR	AUTHOR	
Parotid Trauma	1757	Duphenix	(1)
Parotid Abscess	1853	Baillarger	(2)
Suppurative Lymphadenitis	1897	Weber	(8)
Familial	1909	Wende	(128)
Gunshot Wound and Infection	1923	Frey	(10)
Syringomyelia	1929	Kaminsky	(42)
Parotidectomy	1932	Bassoe	(29)
Cervical Sympathectomy	1936	Wilson	(38)
Encephalitis	1938	Vamos	(36)
Pnemococcal Parotitis	1940	Payne	(129)
Mandibular Osteotomy	1951	Hogeman	(48)
Physiological	1954	Lee	(126)
Radical Neck Dissection	1967	Spiro	(89)
Mandibular Fracture	1969	Martis	(90)
Forceps Injury at Birth	1970	Balfour	(98)
Diabetes	1973	Watkins	(127)
Post Herpetic	1987	Drummond	(136)

TABLE 2 UNUSUAL GUSTATORY PHENOMENA INDIRECTLY RELATED TO AURICULOTEMPORAL SYNDROME.

Gustatory Rhinorrhea	1976	Boddie	(102)
After Subclavian Endarterectomy	1963	Sutton	(86)
After Thoracoplasty	1958	Herxheimer	(75)
Chorda Tympani Syndrome	1956	Young	(55)
Gustatory Sweating of the Left Knee	1950	Mellinkoff	(46)
Emotional Hyperhidrosis of the Forehead	1947	Tarlov	(51)
After Nasal Operations	1936	Andre-Thomas	(15)
Submental Gustatory Sweating	1934	Urpus	(39)
Gustatory Lacrimation	1928	Bogorad	(40)
Olefactory Sweating	1909	Wende	(128)

1.142 THE CLINICAL MANIFESTATIONS OF AURICULOTEMPORAL SYNDROME

There are numerous detailed descriptions of the clinical features of the auriculotemporal syndrome to be found in the literature (8, 10, 44, 47, 48, 70, 133, 134, 135 and others).

The condition generally consists of sweating or flushing in the cutaneous distribution of the auriculotemporal nerve or the greater auricular nerve, or both. These features are provoked particularly by eating hot, spicy, dry, or sour foods. Symptoms develop after a delay of 30 to 40 seconds. The subject may first notice a warming of the affected area followed by profuse tiny droplets of sweat forming on the skin. Occasionally sweating may precede flushing. Laage-Hellman (70) noted that 90% of patients demonstrated both symptoms, in 8% of patients was sweating alone noted, and in just 2% was flushing noted solely. The sweating may be so profuse as to cause a stream of fluid to run down the neck or

to drip from the face, during most meals, thus causing considerable embarrassment to the patient. These severe cases probably led earlier investigators to wrongly assume that the fluid was saliva (1,2), an error which is sometimes still made (77,79,80,133, 2.2321). In addition, two other symptoms may be observed. There may be pain perceived as a deep boring ache or a burning sensation (95) in front of the tragus, and possibly referred to the temple (133). The pain may occasionally be severe (47). Sometimes the phenomenon of piloerection associated with eating may be observed, as reported by Frey (10), Herxheimer (77) and Scouteris (112) but this is unusual, probably because of the difficulty of observing the occurrence on the facial skin.

Vaughan (17) documented an unusual manner of presentation of facial gustatory sweating. His case report of 1925 concerns a patient who some time after a left parotid abscess presented with unilateral teeth erosion and facial gustatory sweating on the left. On further investigation it was found that the left parotid produced no saliva at all accounting for the severe left sided caries. This phenomenon has not been noted in any subsequent case of auriculotemporal syndrome.

Facial gustatory sweating may be reproduced by gustatory stimuli alone or by using vinegar or lemon on the posterior portion of the tongue (glossopharyngeal nerve territory), and can be accentuated by masticatory movements. Masticatory movements themselves or chewing on bland substances usually fail to induce the symptom (8,47,129,134).

The area affected is variable and ranges from a small area anterior to the tragus, to an area which includes the whole distribution of the auriculotemporal nerve (Figure 3).

On occasion skin posterior or inferior to the ear is affected. Some authors (70, 92, 100) believe that the greater auricular nerve is involved in the production of gustatory sweating and accounts for the skin affected below the ear. Laage-Hellman (70) noted that 70% of 123 patients were affected by gustatory sweating in the cutaneous region corresponding to the anatomical distribution of both nerves, whilst 20% occurred in the auriculotemporal nerve distribution only, and the remaining 10% in the distribution of the greater auricular nerve. The fact that there is cross-innervation between the auriculotemporal nerve and the greater auricular nerve may help to explain its apparently frequent involvement in the condition. The evidence presented is indirect and does not discount that variant distributions of the auriculotemporal nerve may exist to account for the findings. The distribution of the nerves was assumed to be identical to that described in the standard anatomical texts, no attempt being made to define it in individual patients.

Physical examination of patients with established auriculotemporal gustatory sweating may reveal impaired or even heightened sensation in the area concerned. There are normal pupillary reactions and there may be some clinical evidence of parotid atrophy on the affected side. Gustatory sweating can usually be demonstrated using the Minor starch iodine test (31) to delineate the area involved. Gustatory flushing can frequently be observed visually. Some authors

(39, 47, 134, 136) have measured skin surface temperature changes using thermocouples, and have documented increases in skin temperature of 2-3 degrees Celsius with gustatory flushing, followed by a drop in skin temperature due to evaporation of the sweat produced by the gustatory stimulus. More recently Drummond (136) has used thermography to document areas of gustatory flushing.

Thermal sweating in the area affected by gustatory sweating is commonly reduced (16, 35, 38, 48, 49, 72, 74, 134). Those sweat glands which respond to heat in skin affected by gustatory sweating are not stimulated by acetylcholine or other cholinergic drugs, and are thus are different from the sweat glands responding to gustatory stimuli (72). Glaister et al (74) were able to demonstrate the occurrence of thermal salivation in patients with auriculotemporal syndrome.

1.143 THE EPIDEMIOLOGY OF AURICULOTEMPORAL SYNDROME

The frequency of occurrence of auriculotemporal syndrome after parotidectomy varies depending on the diligence with which it is sought and the time of the study after operation. It was once thought to be a rare condition (85) but since the large series published by Laage-Hellman in the mid-fifties (70, 71, 72, 73), it has generally been accepted that the condition is a common complication of parotid surgery.

Table 3 summarises the frequency of observation of auriculotemporal syndrome after parotid surgery. Only three authors have attempted to study both symptomatic and asymptomatic patients (70, 105, 110), and when this is done virtually all the patients demonstrate the condition. Laage-Hellman was able to detect gustatory sweating or flushing, or

both, in 98% of his patients. These results must, however, be interpreted with a degree of caution because the sensitivity of the Minor starch iodine test is such that in hot environments a small amount of thermal sweating may be mistaken for gustatory sweating unless both sides of the face are tested simultaneously and evaluated by an independent observer.

TABLE 3 THE INCIDENCE OF SYMPTOMATIC AURICULOTEMPORAL SYNDROME AFTER PAROTIDECTOMY. THE NUMBER IN BRACKETS INDICATES THE COMBINED INCIDENCE OF SYMPTOMATIC AND ASYMPTOMATIC CASES.

AUTHOR	YEAR	CASES	PERCENTAGE
Redon	1952	450	25
Kidd	1955	45	23
Laage-Hellman	1955	95	30
Laage-Hellman	1957	123	63 (98)
Glaister	1958	16	63
Morfit	1961	100	54
Blumfield	1967	25	52
Spiro	1967	165	59
Kidd	1969	105	22
Kornblut	1973	70	38 (96)
Gordon	1976	55	34
Hays	1978	129	54 (94)
Hays	1982	140	60
Langdon	1984	61	13

In overall terms, approximately 60% of patients have symptomatic gustatory sweating after parotidectomy. The figures quoted in Table 3 vary considerably, due to incompleteness of testing and also because many of the surveys

from which they were derived were done by telephone or mail or were retrospective and thus were subject to large errors (94,103,111,113). Of the symptomatic patients approximately 10% (70,88) to 25% (111) are sufficiently embarrassed by their symptoms to request further treatment other than simple local measures.

Laage-Hellman (70) noted that 80% of patients requesting further treatment were males, whereas Morfit (81) found that women were bothered more often by this problem and more frequently requested further treatment. The reason for this difference is not apparent although Laage-Hellman states that "intellectuals" and "the upper class" are more sensitive in this respect. It seems likely that socio-economic factors play a role in the motivation of patients to present with auriculotemporal syndrome.

The severity of symptoms varies. Hays (110), in a rather incomplete survey of 129 post-parotidectomy patients, noted that 20% of subjects had severe symptoms (more than 3 facial wipes per meal). Those with combined radical neck dissection and parotidectomy were twice as likely to have severe gustatory sweating, although the numbers were small. As expected, those with severe symptoms were more likely to demand further treatment. Laage-Hellman (70) found that 21% of patients had severe sweating, 50% moderate sweating and 25 % mild sweating on objective testing. Interestingly, he found that in the asymptomatic patients there was a slightly higher incidence of mild (37%) and moderate (60%) sweating and a correspondingly lower incidence of severe sweating (2%), but these asymptomatic patients certainly did not all exhibit mild

sweating. Laage-Hellman (70) also raised the point that gustatory sweating only occurred after each meal in 50% of patients. In the remaining 50% the symptom occurred sporadically. This may explain why some patients with severe objective sweating do not notice the problem. Thus there was no direct correlation between the severity of sweating and the presence of symptoms. This observation certainly gives one cause to doubt the validity of the retrospective telephone and letter studies on the subject.

Facial gustatory sweating has an equal sex distribution (70,100) although Laage-Hellman observed that males were more likely to develop objectively severe gustatory sweating (42%) than females (10%). He speculated that this reflects a denser distribution of facial sweat glands in the male.

The age distribution of auriculotemporal syndrome has only been recorded twice in the literature (70,100), the latter with a limited number of patients. There seemed to be no definite age preference with the distribution following the incidence of the commonest parotid tumour (pleomorphic adenoma) (60). Because of the higher incidence of malignant tumours in the elderly, and the concomitant use of local radiotherapy, the aged have a slightly lower incidence of auriculotemporal syndrome (70). The observation may also be related to poorer nerve regeneration powers in the older age groups.

Several authors have attempted to correlate the development of auriculotemporal syndrome with the parotid pathology (70,89,100,101,106,113). No definite correlation has been be demonstrated, although Langdon (113) noted that

auriculotemporal syndrome rarely, if ever, occurs after surgery for Sjogrens Syndrome or chronic infection. These observations are in disagreement with those of Laage-Hellman (70) and probably reflect the fact that Langdon's series was small and incomplete. In a larger series Spiro (89) commented that parotidectomy for inflammatory conditions of the parotid resulted in an increased frequency of gustatory sweating when compared to parotidectomy for tumours.

It seems likely that the amount of parotid gland resected has a bearing on the development of auriculotemporal syndrome. Laage-Hellman (70) first noted that partial conservative parotidectomy gave rise to auriculotemporal syndrome less frequently and less severely than superficial parotidectomy or subtotal parotidectomy. Spiro (89) in a series of 165 patients observed gustatory sweating in 33% of patients following tumour enucleation, in 60% of patients after superficial parotidectomy and in 84% after total parotidectomy. He also found that facial nerve neurapraxia or sacrifice was associated with a 70% incidence of development of auriculotemporal syndrome, but no direct causality could be established. These observations have been confirmed by other authors (100, 106, 107, 110), and have resulted in the general belief that the amount of parotid resected is a major factor in the development of auriculotemporal syndrome. This theory, however, has never been investigated systematically.

Generally, the onset of auriculotemporal syndrome tends to be delayed, and is quite variable. In the early literature, auriculotemporal syndrome was noticed as soon as 1 or 2 days after the injury (11, 16, 35, 38, 45, 50,). Unfortunately, none of

these reports are objective, and are based largely on patient observation. In addition none of these authors undertook preoperative testing to rule out pre-existing gustatory sweating. The aetiological theories based on these early observations must be treated with circumspection.

Laage-Hellman (70) is the only author to have made preoperative comparisons using the Minor starch iodine test, in order to confirm that facial gustatory sweating seen after parotid surgery was not pre-existing.

Table 4 provides a summary of the estimates of the time of onset of auriculotemporal syndrome : there is a wide scatter, ranging from days, to more than 5 years. The scatter is most probably caused by a combination of the unreliability of patient reporting and approximations made in medical recording of the data.

The only study to address the problem systematically is that of Laage-Hellman (71). In a longitudinal study of 57 post-parotidectomy patients it was found that the median time for development of the condition was 8 weeks, with a range of 5 weeks to 30 weeks. Laage-Hellman was also able to observe that gustatory flushing sometimes preceded the development of gustatory sweating by several weeks. Turner et al (80) noted that flushing may precede sweating by months or years, but these observations were largely subjective. The only factors that could be identified to influence the development of auriculotemporal syndrome were, firstly, that the development was delayed for up to a year or more if postoperative radiotherapy was given; and secondly, that the condition

developed more rapidly in children attributable to a higher rate of juvenile nerve regeneration.

Because of the progressive development of gustatory sweating some patients may not notice their symptoms until the involved area becomes large enough for the resulting gustatory sweating to become conspicuous. This may explain some of the variability in the literature regarding the time of onset of facial gustatory sweating. Skin flap thickness may also play a role in the timing of the onset of gustatory sweating (103) with thick flaps resulting in delayed onset. The auriculotemporal syndrome, once it has developed is permanent, and although spontaneous resolution has occasionally been reported (18) the accuracy of these reports is doubtful. Baillarger (2) documented a case which remained unchanged for nearly 70 years. Payne (13) described a case in which symptoms were present for some 30 years and Freedberg for 25 years (135). There are numerous other examples of patients whose long-term symptoms of facial gustatory sweating remained unchanged (30, 35, 44, 47, 56, 98, 99).

1.144 PHARMACOLOGICAL MANIPULATION OF THE AURICULOTEMPORAL SYNDROME

The effects of diverse pharmacological agents on the clinical manifestations of auriculotemporal syndrome has lead to greater understanding of the afferent and efferent nervous pathways involved, the aetiology, and treatment of the syndrome.

TABLE 4 THE ONSET OF AURICULOTEMPORAL SYNDROME BY AUTHOR AND YEAR

AUTHOR	YEAR	ONSET
Duphenix	1757	6 weeks
New	1922	Immediately
Frey	1923	1 month
Bassoe	1932	4 months
Bassoe	1932	36 months
Needles	1934	6 months
Urpus	1934	12 months
List	1938	Immediately
Payne	1940	4 months
Langenskiold	1946	1-24 months
Karnosh	1946	7-24 months
Freedberg	1948	2-12 months
Dey	1950	7 months
Pffeffer	1951	18 months
Coldwater	1951	1-2 days
Goatcher	1954	6 months
Laage-Hellman	1958	1-9months
Hemmenway	1960	18 months
Turner	1960	2-18 months
Morfit	1961	3-12 months
Chisa	1964	4 months
Hunt	1966	8 months
Smith	1970	11 months
Storrs	1974	48 months
Langdon	1984	3-60 months
Sui	1984	3-6 months

Frey (10) was the first to study the effects of various pharmacological agents on facial gustatory sweating. She found that atropine temporarily abolished the syndrome as did alcohol injection of the auriculotemporal nerve. Pilocarpine

caused sweating in the affected area which was further enhanced by eating. Adrenalin had little effect. Many authors have subsequently confirmed and extended these observations (30, 35, 38, 39, 44, 45, 47, 48, 49, 50, 72, 77, 133, 134). The agents and their effects are summarised in Table 5.

In essence, the anticholinergic agents suppress the appearance of gustatory sweating while the parasympathomimetic drugs accentuate the condition. The results of local nerve blockade serve to confirm the afferent and efferent neural pathways involved. Indeed, pharmacological responses of sweat glands demonstrating gustatory sweating are much the same as for normal sweat glands (150). Aetiological theories must satisfactorily explain these pharmacological and physiological observations.

1.15 AETIOLOGICAL THEORIES OF AURICULOTEMPORAL SYNDROME

Early authors in the field such as Duphenix (1) attributed the condition to blockage of Stenon's duct (sic) and consequent exudation of saliva through the skin. This theory fell into disrepute as soon as it was realized that the fluid was sweat not saliva (3). Weber (8) felt that the condition was due to irritation of the cervical sympathetic nerves by scar tissue, but his explanation was hampered by lack of complete clinical, anatomical and physiological knowledge of gustatory sweating. With the growth of knowledge in these areas in the first half of the twentieth century, aetiological theories became almost as numerous as authors on the subject (44).

TABLE 5 THE EFFECTS OF CERTAIN PHARMACOLOGICAL AGENTS ON THE MANIFESTATION OF AURICULOTEMPORAL SYNDROME.

TEST	EFFECT
Local anaesthesia of the auriculotemporal nerve	Abolishes syndrome in the distribution of the nerve
Local blockade of the superior cervical ganglion	No effect
Local blockade of the lingual nerve	Abolishes syndrome by gustatory stimulation on the affected side
Local blockade of the tympanic plexus	Abolishes the syndrome
Subcutaneous Atropine Subcutaneous Pilocarpine	Abolishes the syndrome Provokes the syndrome with heightened gustatory response
Intradermal Acetylcholine	Sweating around wheal in affected area; no sweat in normal skin
Intradermal Carbachol	Sweating around wheal in affected area ;no sweat in normal skin
Intravenous Acetyl methylcholine	Increased sensitivity of sweat glands in abnormal area
Intradermal Adrenalin	Blanching in the area of flushing; no effect on sweating

Any theory of aetiology of auriculotemporal syndrome must be capable of explaining the following basic observations :

1. There is usually a degree of impaired sensation in the distribution of the auriculotemporal nerve.
2. There is increased sweat gland sensitivity to parasympathomimetic drugs in the affected area.
3. There is reduced thermal sweating in the affected area.
4. Thermal salivation can be demonstrated.
5. There is reduced salivary flow on the affected side.
6. The onset of the syndrome is delayed for at least eight weeks.
7. Cervical sympathetic blockade does not influence the condition.
8. Gustatory flushing occurs in addition to sweating in many cases.
9. The syndrome occurs in the vicinity of nerves which contain true secretory and vasodilator fibres to the parotid.

Dating from the initial report of Frey (10) there was general agreement that auriculotemporal syndrome was mediated via a reflex arc the afferent limb of which involved gustatory stimuli in the posterior portion of the tongue, and the efferent limb being identical to that for production of saliva from the parotid. This notion explains the observed effects of nerve section and nerve blockade and fits well with the observed delay of 20-30 seconds from the stimulus to the observation of gustatory sweating, such a delay being

consistent with the reflex arc proposed. The controversy arose from attempts to explain how facial sweat glands come to be connected to this reflex arc. The main theories on this point are collected in Table 6.

These remained a source of great dispute until the careful and complete studies of Laage-Hellman (70, 71, 72, 73) gave sufficient clarity to the clinical, physiological and pharmacological details of auriculotemporal syndrome so as to leave only one viable theory. He believed that the theory of misdirected nerve regeneration (Ford) is the only theory capable of accounting for all the observations.

The theory of misdirected nerve regeneration holds that parasympathetic fibres running in the auriculotemporal nerve destined to provide secretomotor innervation to the parotid and sympathetic fibres to the skin are injured, and in the process of regeneration, cross-innervation occurs. This results in skin sweat glands and vessels becoming functionally innervated by secretomotor fibres originally destined for the parotid (Figure 4). Thus a new reflex arc of gustatory sweating is established.

The only phenomenon which is difficult to explain by this theory is sweat gland hypersensitivity to acetylcholine. However Laage-Hellman noted that neither normal sweat glands nor denervated sweat glands respond to this chemical stimulation. He postulated that the newly innervated sweat gland show an increased response to acetylcholine. Ashby (76) suggested that perhaps there is a lower threshold due to altered neural tone in the renervating nerve fibres. Furthermore Ashby (76) and others (56) have confirmed the

observation that denervated sweat glands do not become hypersensitive to acetylcholine.

Many authors prior to Laage-Hellman subscribed to the theory of aberrant nerve regeneration (15, 43, 45, 48, 49, 56, 129, 133 and others). Subsequently, almost all agreed that the aberrant nerve regeneration theory is the most likely explanation for the occurrence of auriculotemporal and other related syndromes (77, 82, 84, 85, 89, 91, 94, 106, 110, 112, 113, 114, 135, 137, and others).

There is abundant evidence as to the physiological feasibility of this proposal. The innervation of sweat glands whilst anatomically sympathetic is functionally cholinergic.

TABLE 6 AETIOLOGICAL THEORIES OF AURICULOTEMPORAL SYNDROME AND THEIR ORIGINATORS.

AUTHOR	YEAR	THEORY
Frey	1923	Auriculotemporal nerve irritation
Ford	1933	Aberrant Regeneration
Vamos	1938	Exaggeration of a normal reflex by release from inhibitory factors
Peet	1938	Diffusion of acetylcholine
Freedberg	1946	Denervation Hypersensitivity
Chorobski	1951	Transaxonal Excitation

Parotid parasympathetic innervation is also cholinergic (89,110,113,137), and so, theoretically, there is no incompatibility of neurotransmitter if aberrant regeneration should occur. Dale (138), showed that one cholinergic fibre could functionally replace another, and Murray and Thompson (139) showed that vagal fibres could reinnervate the denervated superior cervical ganglion of the cat by a process of vigorous collateral sprouting. Ford (43) had documented sympathetic reinnervation in man some 20 years earlier. Further, Langley and Anderson (141) in 1904 had found in animal experiments that autonomous nerves after cross-union could grow into each other's supply area and form functional synaptic contact with the end-organs.

The theory of aberrant nerve regeneration, whilst it explains all the known facts relating to auriculotemporal syndrome, and is entirely possible from the point of view of the physiology of autonomic nerve regeneration, has never been tested objectively in humans or animals.

There are at least two further areas which remain unclear. Firstly, while gustatory sweating has been studied extensively, gustatory flushing has not. Laage-Hellman (72) felt that the same mechanism was responsible for both phenomena: that is, parasympathetic parotid secretomotor or sympathetic parotid vasodilator fibres come to reinnervate skin blood vessels. Storrs (91), the only other author to consider this problem, raised the objection that subcutaneous blood vessels are innervated by the sympathetic adrenergic system, and thus it was unlikely that they could form a functional synapse with a misdirected cholinergic fibres.

Storrs theorized that perhaps normal cutaneous blood vessels had a dual adrenergic (vasoconstrictor) and cholinergic innervation (vasodilator), the latter of which could be theoretically reinnervated by parotid parasympathetic vasodilator fibres. Alternatively, he felt that there may be a kinin or neurotransmitter released by the abnormally innervated sweat glands which would result in direct dilatory stimulation of local arterioles. No experimental work has yet been done to clarify this point.

The second area which remains obscure is the level at which the aberrant reinnervation takes place. The confusion has arisen because of the need to explain the observation that frequently the greater auricular nerve and the auriculotemporal nerves appear to be involved in gustatory phenomena.

The first possible explanation for this is that the auriculotemporal nerve simply has an abnormal distribution in these cases and that the injury to the auriculotemporal nerve occurs at a level where the skin sympathetic supply and the parotid secretomotor supply coexist (43, 77, 90, 96, 98, 112, 129, 140). Further, others invoke the anastamotic connections between the auriculotemporal nerve and the facial nerve (48, 50, 81) or the greater auricular nerve (56, 74, 83, 89, 91), to explain gustatory phenomena outside the distribution of the auriculotemporal nerve. The implication is that the auriculotemporal nerve is injured in a position where both parasympathetic and sympathetic fibres coexist, and the regenerating fibres reach the skin-effector organs by way of these communicating branches. Thus skin in the distribution of

the greater auricular nerve or buccal nerve could be affected. This explanation probably has the widest literature support and most easily accounts for all of the clinical observations on gustatory phenomena, however no definite evidence for this line of reasoning exists.

The second explanation for the occurrence of gustatory sweating outside the distribution of the auriculotemporal nerve was first advanced by Karnosh (133). It supposes that the severed parasympathetic parotid fibres after parotidectomy regrow directly into the skin sweat glands overlying the parotid or into severed branches of the greater auricular or auriculotemporal nerves. This theory has found favour with many authors (88, 92, 100, 103, 105, 107, 108, 142) including Laage-Hellman (70). It has formed the basis for the use of "barrier techniques" for treatment (107, 108) and prevention (103, 105, 114). The explanation is quite plausible, but tends to lose credibility because of the failure of some of these "barrier techniques" (105, 106).

Although the general mechanism of development of auriculotemporal syndrome is almost certainly by cross-innervation after nerve damage, the exact details of this process are not clear. Improvement of understanding in this area would potentially be of great benefit in development of better treatment of the condition.

1.16 TREATMENT OF POST-PAROTIDECTOMY GUSTATORY SWEATING

The effective treatment of facial gustatory sweating remains a challenge. Although the course of parotid secretomotor fibres has been interrupted surgically at every conceivable point from the brain stem to the skin and many

pharmacological agents have been employed there is no universally effective means to control this condition. Fortunately, for most patients a simple explanation is sufficient treatment;, however, 10-25% of patients, in whom the symptoms are severe, require further treatment (70,80,111). Correct selection of treatment can be a frustrating exercise for both patient and doctor.

The earliest form of treatment for gustatory sweating was carried out almost inadvertently by Duphenix (1) when he excised the affected skin. This seemed to control the problem but the consequent facial scarring and deformity has precluded the use of the technique in others, with the exception that it has been used successfully by Langenskiold (46) for the treatment of limited areas in unobtrusive locations.

Lucie Frey (10) was the first to suggest the alcohol injection or surgical division of the auriculotemporal nerve for control of symptoms. This suggestion has been applied by several authors (19,22,48,49,50,57,73). The effectiveness of the therapy is difficult to assess as series were limited to 2 or 3 patients, but overall it seems that 50% gain complete relief from their symptoms and the remainder obtain partial improvement. None have been followed for any longer than 1 year so the long term results are not known. Some have reported recurrence after 6- 12 months (74,83,107). Coldwater (50) and Hogeman (48,49) have emphasized the need to divide all the facial-auriculotemporal nerve intercommunications for complete success. These branches can be quite variable (120) and failure to divide them may account for the partial successes and recurrences. Occasionally the auriculotemporal

nerve has been avulsed routinely at parotidectomy as a prophylactic measure, without consistent success (40, 57, 74, 113, 122).

The likely reason for the lack of success with auriculotemporal nerve ablation is an anatomical one. The auriculotemporal nerve divides into 4 or 5 branches in the dense parotid capsule at the level of the mandible and thus simple avulsion is unlikely to result in division of all of the anastamotic branches. In addition there may be more than one branch of the nerve supplying the skin (74). An additional disadvantage of this technique is that there is some risk of damage to the facial nerve particularly in patients who have had a previous parotidectomy (50, 77, 80, 88, 91, 142). The alternative approach of complete division of the auriculotemporal nerve at the level of the mandible is a technically difficult task and leaves the patient with a large area of anaesthetic skin which may sometimes become hyper-aesthetic or painful. For these reasons ablation of the auriculotemporal nerve has not been a widely employed treatment modality.

The use of local irradiation was first proposed by Needles (30) but his patient did not complete the course of treatment. The principal of the treatment is to destroy the local sweat glands by irradiation. Local complications of irradiation also occur, such as dry mouth and skin changes. However, it is certainly effective, as noted by Laage-Hellman (70) in patients who had local radiotherapy for other reasons. The treatment has recently been used with some success in a patient with severe intractable symptoms bilaterally (104).

Most authors believe this to be too drastic a step for a benign condition (74, 81, 83, 88, 108).

Gardiner (56) is the only author to advocate the use of intracranial division of the glossopharyngeal nerve in cases of facial gustatory sweating. He performed this on two occasions. One patient was completely cured while the other had residual but much ameliorated symptoms. The explanation for the incomplete cure probably lies in the fact that a proportion of parotid secretomotor innervation is of seventh nerve origin as proposed by Reichert and Poth (87). Again, most subsequent investigators agree that open craniotomy is too extreme a measure for treatment of facial gustatory sweating (74, 81, 83, 88, 91, 108, 135, and others).

Sessions (107) and Wallis (108) have made use of the interposition of free fascial grafts between the skin and the surface of the parotid gland to treat auriculotemporal syndrome. The principle of treatment is to disrupt the sweat gland innervation to the affected skin and to insert an anatomical barrier to the regrowth of nerves. The authors have claimed some early success with this method in a very limited number of patients. There is of course attendant risk of damage to the facial nerve with this procedure (106).

The technique of tympanic neurectomy (Figure 5) was initially described by Lempert in 1946 (78) for the treatment of tinnitus. Hemmenway (77) suggested its use in the treatment of auriculotemporal syndrome but neither of his two patients with the condition accepted treatment. Golding-Wood (84) applied this modality independently in 1962 to 3 patients. In one patient he achieved complete relief of symptoms and the

other two gained partial benefit which was further improved by division of the chorda tympani in the middle ear. The treatment has been used subsequently by several investigators (85, 88, 93, 94, 95, 96, 101, 109, 135, 142, 143, 144) in small series with variable results. The results are presented in Table 7.

All patients after tympanic neurectomy initially obtain immediate and complete relief from symptoms. Recurrence becomes apparent within 1 to 8 weeks of operation (88, 93, 109), when an altered or reduced sweating pattern may be noted.

Some workers put the success rate of tympanic neurectomy at 80-90% (96, 110). This estimate includes those who are symptomatically improved but not cured, and still have small residual areas of sweating. The rate of cure of symptoms as seen in Table 7 is 58%, and even this figure is probably an overestimate, as several patients were only followed for a short time. When all patients were studied carefully with the starch iodine test 80-90% were found to have residual gustatory sweating (93, 135). However, most of these were asymptomatic because of the small area of skin involved.

The failure of tympanic neurectomy to completely abolish facial gustatory sweating is due to two factors. Firstly, there are probably alternate pathways for parasympathetic innervation of the parotid (88, 93, 96, 109, 110, 135, 142). These include anastamotic fibres between the otic ganglion and the chorda tympani and between the greater and lesser superficial petrosal nerves (Figure 2). Division of the chorda tympani combined with tympanic neurectomy has been used by some (84, 144) with improved effect but has the disadvantage of creating severe xerostomia. Secondly, success must vary with

the skill and experience of the surgeon as there is a hypotympanic branch of the tympanic plexus which is often missed, but can be divided later if recurrence occurs (109) (Figure 5).

Although tympanic neurectomy does not effect a complete cure in all patients, it is a relatively harmless procedure which can be performed under local anaesthetic. Hearing is not affected (95,109) and the only complications reported are tympanic perforation and otitis media (109,110).

TABLE 7 RECORDED RESULTS OF TYMPANIC NEURECTOMY

AUTHOR	YEAR	NUMBER	%ASYMPTOMATIC	%POSITIVE STARCH IODINE	FOLLOW-UP
Golding-Wood	1961	3	66	NA	2 years
Rumball	1964	3	66	NA	36 months
Hunt	1966	1	100	100	1 year
Holloway	1967	1	0	100	6 weeks
Blumfield	1967	4	0	100	18 months
Dishloeck	1968	1	100	0	18 months
Ross	1969	5	40	80	1 year
Smith	1970	1	100	100	4 months
Friedman	1974	4	100	50	2 year
Edison	1974	1	100	0	2 days
Sessions	1979	2	0	100	6 months
Harrison	1979	17	53	NA	2 months
TOTAL		43	58	NA	

Attempts have been made to prevent the development of auriculotemporal syndrome. Most of these prophylactic attempts are based on the aetiological assumption that severed secretomotor nerve fibres in the parotid gland grow to directly innervate sweat glands of the skin. Apart from auriculotemporal nerve avulsion discussed previously, the techniques involve placement of various "barriers" between the skin and cut parotid surface at the time of the initial operation (Figure 6). The "barriers" consist of either sternomastoid muscle flaps (105,106), fascial flaps of varying origins (114), and more recently freeze-dried cadaver dura or silastic sheets (104). Kornblut (105,106) was unable to show a reduction in the incidence of gustatory sweating with the use of sternomastoid flaps. Sui (114) claimed to reduce the incidence of auriculotemporal syndrome from 57% in a control group to 20% by insertion of autologous fascia.

Singleton (103) in a study of 164 post-parotidectomy patients claimed that those in whom thin skin flaps were raised over the parotid had a 6 times higher incidence of gustatory sweating than those with thick skin flaps. He suggested that only thick skin flaps should be used in parotidectomy.

The weaknesses of both these studies (103,114) are that the follow-up period was short and that no objective means of detecting sweating were employed. Their conclusions are thus open to question.

The role of the prophylactic measures currently used for prevention of auriculotemporal syndrome remains uncertain.

Pharmacological agents have been used with some success in the treatment of auriculotemporal syndrome. Systemic agents such as atropine or other anticholinergic drugs have been tried (10, 49, 110, 111, 127, 133, 145) but the high dosage required for complete effect results in unacceptable side effects (73, 145).

Locally applied substances have been employed to control symptoms since Trioumphoff (18) reported that mud-baths provided lasting symptomatic relief. Other agents such as formalin, potassium permanganate, ammonia and aluminium salts (73, 111) have also been tried but these compounds need to be applied regularly through the day to prevent gustatory sweating. Aluminium salts, such as those found in proprietary-line antiperspirants, are still in use for temporary control of the condition, but meet with limited patient acceptance (110, 111).

Laage-Hellman (73) was the first to use locally applied preparations containing the anticholinergic drug scopolamine hydrobromide. He used 1-3% concentration of the drug in cream and applied it to the affected area. He found that one treatment resulted in lasting inhibition of gustatory sweating for up to 8 days. Females obtained a better effect, in general, than males and almost all patients reported dryness of the mouth as a side-effect. The other important side-effects were blurred vision, eye dryness, and a significant incidence of skin sensitization (83). Acute angle glaucoma may be precipitated in patients with a shallow anterior chamber (111) and other systemic effects may occur such as tachycardia, psychosis and acute urinary retention. These

disadvantages lead Hays (110,111) to evaluate the agent glycopyrrolate, a quaternary ammonium salt, in a double blind placebo controlled trial with scopolamine in order to compare the effectiveness of these compounds in the control of gustatory sweating. He found that glycopyrrolate in concentrations of 0.5% to 1% was effective for 4 or 5 days and was without systemic side-effects. Scopolamine in concentrations of 0.25% to 3% was equally effective but there was considerable dose variation between individuals and the treatment was poorly tolerated due to side-effects. Placebo was without effect.

Locally applied anticholinergic drugs therefore provide a useful adjunct to the treatment of auriculotemporal syndrome particularly for patients in whom other treatment modalities have failed, or in those who do not want further surgery. Unfortunately topical anticholinergic agents are not presently available in Australia. The only form of local therapy available in this country for gustatory sweating is the application of aluminium-containing anti-perspirants, which are of limited value. Chisa (83) suggested the use of topical local anaesthetic (xylocaine) on the tongue and buccal mucosa to prevent the gustatory symptoms. His suggestion has never been followed and seems unlikely to meet with much success.

The treatment of gustatory flushing per se has rarely been addressed. Flushing, however is sometimes the predominant symptom (48,70,91,136) particularly in young female patients. Laage-Hellman (71) commented that flushing was probably the response of blood vessels to the same aetiological mechanism, and both flushing and sweating are usually abolished by local

anaesthesia of the auriculotemporal nerve (47,48,49,77,134). This has only been studied objectively by Pffeffer (47) who was able to show that the skin temperature rise seen in an area affected by gustatory flushing was abolished by auriculotemporal nerve block. Some investigators specifically mention that flushing as well as sweating is abolished by tympanic neurectomy (95,101). The use of topical anticholinergic agents certainly diminishes the occurrence of flushing (73,111) but a slightly higher concentration of drug is required for complete control.

It seems likely that when gustatory flushing is the predominant symptom, successful control can be achieved with the same treatment modalities as for gustatory sweating.

From the preceding discussion it is apparent that there is no universally effective means of treating auriculotemporal syndrome. Further progress in this area must await more detailed knowledge of the aetiology of the condition.

1.2 RESEARCH OBJECTIVES

The present research addresses the unresolved aspects of the auriculotemporal syndrome, in the hope that optimal treatment modalities can be discovered and applied.

The aims of the study are as follows:

1. To obtain data of clinical experiences with auriculotemporal syndrome and parotid surgery in South Australia, and assess awareness of the condition amongst surgeons as well as its incidence and treatment by surgeons.

2. To study the following areas of clinical controversy: the incidence of auriculotemporal syndrome, and other complications; the influence of tumour pathology; the treatment of auriculotemporal syndrome; the effect of tumour size or type on the development of auriculotemporal syndrome; the usefulness of "barrier methods" for prevention of the condition; the effect of development of other complications of parotid surgery on the development of the syndrome; the case-notes of a series of patients who have undergone parotidectomy over the last 10 years at the Queen Elizabeth Hospital will be examined.

3. To test the efficacy of a new method, measurement of skin electrical resistance, in the detection of facial gustatory sweating.

4. To study in the rat, marmoset, and human, the comparative anatomy and histology of auriculotemporal nerve, facial nerve, otic ganglion and parotid gland in order to facilitate the development of an animal model of auriculotemporal syndrome.

5. To propose and investigate an animal model of auriculotemporal syndrome in order to evaluate the role of neuronal mechanisms in the aetiology of the condition.

CHAPTER 2 CLINICAL STUDIES OF POST-PAROTIDECTOMY GUSTATORY SWEATING

2.1 LOCAL SURGICAL ATTITUDES TO PAROTID SURGERY

2.11 INTRODUCTION

It is difficult to assess awareness and attitudes concerning a rare surgical subject amongst practicing surgeons, nevertheless it is an important objective, because such information has implications for both undergraduate and post-graduate medical education and provides an indirect gauge as to the true magnitude of a given problem. The level of knowledge on a given subject directly reflects the ability of specific literature on that subject to reach the practicing surgeon, and the motivation of the surgeon to keep up with recent advances. Motivation is proportional to the clinical relevance of a problem as it is thus largely determined by patient demands. This is especially true in the relatively esoteric area of gustatory sweating. Faced with an ever-expanding medical knowledge base, most surgeons are likely to know little of such esoteric issues unless they pose a real clinical problem. Therefore, assessment of surgical awareness of this condition will provide an indirect estimate of the clinical significance of the problem in the surgical community.

Generally speaking, the main means of evaluating the extent of surgical knowledge of a particular topic is by reviewing the literature of the subject. However, as a means

of assessing the extent of such knowledge in the practicing surgeon this suffers from two main disadvantages. Firstly, few are able to read all of the available literature on a given subject, and secondly, the literature is written largely by individuals with specific expertise in the given area. These two factors will tend to give a false impression of the depth and breadth of knowledge of any singular subject in the general surgical community if such an assessment is based on literature review alone.

The surgical literature does not adequately represent that wealth of anecdotal information which constitutes the surgical experience of any given surgeon. It was hoped that in attempting to access this type of information by questionnaire, new insights and different perspectives would be gained into the problem of facial gustatory sweating. Furthermore, insight into quality of parotid surgery in South Australia may be obtained by comparison of local operation and complication rates to those of other centres.

Thus, in order to assess surgical knowledge of gustatory sweating after parotidectomy, to define any local preferences of operative techniques in parotidectomy, to gauge the extent of the problem of auriculotemporal syndrome and it's modes of treatment in practice, and to attempt to assess quality of parotid surgery, a questionnaire was distributed amongst surgeons practicing in South Australia.

2.12 METHODS

The names and addresses of all surgeons likely to be involved in parotid surgery, were obtained from the Register of the Medical Board of South Australia (146). The list

included the names of all registered Otorhinolaryngologists, Plastic Surgeons and General Surgeons. All those who had died, retired, no longer practised surgery, who were involved in unrelated sub-specialty practice, or were resident interstate or overseas were excluded. Each was then sent a letter and questionnaire (Appendix 3.1 and 3.2). The questionnaires were anonymous and consisted of six parts. Those not performing parotid surgery were asked to complete only parts 1 and 2 which dealt with age, specialty, work load and knowledge of auriculotemporal syndrome.

The remaining four parts dealt with surgical techniques in parotidectomy, common pathology encountered, post-operative treatment and complications including the incidence and treatment of gustatory sweating.

The questionnaires were sent out once only, with no reminders, and the replies of the respondents were tabulated. Statistical analysis of the data so obtained was felt to be inappropriate.

2.13 RESULTS

2.131 GENERAL

A total of 111 letters were sent comprising 16 to Plastic Surgeons, 26 to Otorhinolaryngologists and 69 to General Surgeons. 58 replies were received (51.5%). Table 8 shows the distribution of replies between the specialties, with the mean age of respondent and mean annual estimated number of major operations. The incidence of replies was equal in the three groups tested.

TABLE 8 PAROTID SURGERY SURVEY SPECIALTY BY NUMBER REPLYING, MEAN AGE AND NUMBER OF ANNUAL OPERATIONS.

SPECIALTY	REPLIES	MEAN AGE	ANNUAL OPERATIONS
Plastics	8	44.5	510
Otorhinolaryngology	12	49.9	620
General Surgery	38	50.5	380

Of those replying 30 indicated that they were involved in parotid surgery (51%). Table 9 displays the distribution between the specialties of surgeons performing parotidectomy.

TABLE 9 RATE OF PAROTIDECTOMY AS A FUNCTION OF SURGICAL SPECIALTY.

SPECIALTY	TOTAL	PAROTIDS/YEAR		MAJOR OPERATIONS/PAROTID
		Superficial	Total	
Plastic Surgery	2	2.5	0	200
Otorhinolaryngology	5	3.2	.8	180
General Surgery	23	3.0	.09	140

Of the surgeons responding to the questionnaire who did not perform parotid surgery 78% had little or no knowledge of the auriculotemporal syndrome, its incidence or its treatment. Of the 4 non-parotidectomists who indicated the incidence of the condition, the mean estimated incidence was 15%. Table 10 summarizes these responses.

TABLE 10 KNOWLEDGE OF AURICULOTEMPORAL SYNDROME-RESPONSES OF SURGEONS NOT PERFORMING IN PAROTIDECTOMY (N=28).

QUESTION	DON' T KNOW	INCORRECT	CORRECT
Incidence	20	8	0
Symptoms	22	0	6
Treatment	22	2	4

These figures contrast markedly with those from surgeons regularly involved in parotid surgery. In this group 60% of responders had a good knowledge of symptoms and treatment. Whilst 80% of surgeons replying were prepared to state an incidence, the average estimated incidence was only 20%, with only 1 reply in the generally accepted range of 50-100%. These results are displayed in Table 11.

The remaining data from surgeons performing parotidectomy is collated in Tables 12 and 13. Where applicable the median values and ranges are quoted. Otherwise the values obtained are expressed as a percentage of the total number responding to a particular question.

TABLE 11 KNOWLEDGE OF AURICULOTEMPORAL SYNDROME-RESPONSES OF SURGEONS PERFORMING IN PAROTIDECTOMY (N=28)

QUESTION	DON'T KNOW	INCORRECT	CORRECT
Incidence	6	22	2
Symptoms	9	3	18
Treatment	10	1	19

Technically, 93% of responding surgeons commence dissection of the facial nerve posteriorly with just 7% preferring to start anteriorly. Only 53% make routine use of a nerve stimulator, 66% customarily preserve both the auriculotemporal and greater auricular nerves, and 83% routinely use diathermy on the parotid gland surface.

The most common pathological diagnoses encountered in the series and the general post-operative radiotherapy practices are grouped in Table 12. Table 13 details the medians and ranges reported for follow up and surgical complications of parotidectomy. Although the ranges are large, most of the responses are in fact clustered close to the medians quoted unless otherwise stated.

TABLE 12 COMMONEST PATHOLOGIES ENCOUNTERED AND POST OPERATIVE RADIOTHERAPY PRACTICES OF SURGEONS PERFORMING PAROTIDECTOMY

COMMONEST BENIGN PATHOLOGY	
Pleomorphic Adenoma	86%
Adenolymphoma	14%
COMMONEST MALIGNANT PATHOLOGY	
Metastatic Carcinoma	41%
Mucoepidermoid Carcinoma	30%
Adenocarcinoma	20%
Others	9%
USE OF RADIOTHERAPY	
Completely resected Malignant disease	
Used	40%
Variable	15%
Not Used	45%
Incompletely resected Malignant Disease	
Used	85%
Variable	15%
Not Used	0%
Incompletely resected Benign Disease	
Used	25%
Variable	8%
Not Used	67%
Recurrent Benign Disease	
Used	20%
Variable	8%
Not Used	72%

TABLE 13 FOLLOW UP DURATION AND COMPLICATION RATES AFTER PAROTID SURGERY. * = BIMODAL DISTRIBUTIONS WITH A SECOND PEAK AT THE UPPER RANGE EXTREMES.

	MEDIAN	RANGE
DURATION OF FOLLOW UP		
Benign	6 months	1-60 months
Malignant	80 months	24months-lifetime*
COMPLICATIONS		
Salivary Fistula	5%	0-40%
Wound Breakdown	0%	0-20%
Permanent Facial Paralysis		
Benign	0%	0-25%
Malignant	20%	0-90%
Transient Facial Paralysis		
Benign	30%	0-100%
Malignant	50%	0-100%
Facial Dysthesia	5%	0-50%
Ear Numbness	50%	0-100%*
Numbness of Face	0%	0-100%
Local Recurrence		
Benign	0%	0-25%
Malignant	30%	0-100%

2.132 AURICULOTEMPORAL SYNDROME

Most surgeons (83%) do not use any method of prophylaxis against the development of gustatory sweating. Of the five who had used a prophylactic technique, two practised auriculotemporal nerve avulsion, and the remaining 3 used various barrier techniques. Of the two surgeons using

auriculotemporal nerve avulsion one had abandoned the technique due to the occurrence of severe gustatory sweating in several of his cases.

Of those surgeons performing parotidectomy, 33% had observed no cases of gustatory sweating. The median number of cases of gustatory sweating seen was 3 cases per surgeon with a range of 2 to 55. The surgeons noting gustatory sweating tended to have a slightly higher mean age (52) and a slightly increased incidence of parotidectomy (3.5 per year) when compared with the group as a whole. There were no other factors which could be unequivocally identified as being associated with the development of gustatory sweating.

In total there were 108 cases of auriculotemporal syndrome observed by the respondents. Of these 20 (18%) obtained further treatment. The only type of treatment which was carried out was tympanic neurectomy which was claimed to be completely successful in 70% of patients and partially successful in the remainder.

2.2 POST PAROTIDECTOMY AURICULOTEMPORAL SYNDROME

2.21 INTRODUCTION

The incidence of auriculotemporal syndrome after parotid surgery varies quite widely (1.143 Table 3) from 13% (113) to 100% (70). It is difficult to understand the influences responsible for the observed differences. Clearly factors such as operator skill, anatomical variation, response to injury, surgical technique and others, must be important, as they could potentially modify the regenerative process leading to the development of auriculotemporal syndrome. These factors

could be expected to vary from hospital to hospital and so account for changes in incidence of the condition. Although some of the factors possibly involved in the development of auriculotemporal syndrome have been put forward such as skin flap thickness (103), facial nerve neurapraxia (89), the amount of parotid gland resected (100,106,107), age (70), few, if any, of these factors have been confirmed or are generally accepted (1.15). The influence of other local complications has not been studied. Parotid tumour pathology does not seem to have a bearing on the development of auriculotemporal syndrome. The results of barrier techniques used (104,105,106,114) for the prevention of post-parotidectomy gustatory sweating are conflicting (1.16).

Some of the variation noted in the estimates of incidence of gustatory sweating in the literature can be accounted for by incomplete testing of patients, but even when this component was corrected, for considerable differences were still apparent.

The standard method for detection of facial gustatory sweating is the Minor starch iodine test (31) (1.1). This test has the advantages that it is inexpensive, extremely sensitive, and allows quantification and photographic documentation of the areas involved. The disadvantages are that it is messy, takes several minutes and cannot be used on patients with iodine sensitivity. Other techniques for detection of sweat are available. Most of these require the area to be painted with a substance which changes colour on contact with moisture (32,33,34,146,147).

The electrical resistance of the skin depends largely on the state of hydration of the skin which is in turn dependent on sweating (149, 150, 151). Sweating of the skin depends on many factors such as local heat, emotional factors, waking state, innervation and others (150). Denervation of the sweat glands of the skin by sympathectomy (150, 152) or interruption of the sensory supply (149, 154, 156) causes a large increase in the electrical resistance of the skin. These facts were used by Haxton (155) to observe regeneration of the sympathetic nervous system after sympathectomy. More recently Wilson (151, 156) applied the technique of measurement of skin resistance to evaluation of nerve injuries. He devised a simple instrument (151) to perform skin resistance measurements. Whilst this instrument did not provide quantitative estimates of skin resistance, it gave reproducible readings and was sufficiently sensitive to allow diagnosis of digital nerve injury and to follow re-activation of sweat glands consequent upon sensory reinnervation of the finger as healing progressed.

It is proposed to use the technique of skin resistance measurement in the detection of auriculotemporal syndrome. If facial gustatory sweating were present, in comparison to the normal side of the face, there would be a fall (as opposed to the rise induced by sensory nerve injury) in skin resistance with gustatory stimulation.

Therefore, in order to determine the incidence of the condition and related factors which may be important in the development of gustatory sweating, a study was made of all patients who had undergone parotidectomy at the Queen

Elizabeth Hospital over the last ten years. Furthermore, the ability of skin resistance measurement to detect the condition, and the usefulness of prophylactic barrier techniques, were assessed in these patients.

2.22 METHODS

2.221 PATIENT SELECTION

The case-notes for all patients in whom a tissue type of "salivary gland" was recorded in the computer data-base of the Pathology Department between the years 1975 and 1985 were obtained and reviewed. Those who did not have parotidectomy were excluded from the study.

2.222 SURVEY OF PAROTID SURGERY

The following data were extracted from the case-notes of patients who had undergone parotid surgery in the ten years 1975 to 1985 :

Name and Address of Patient
Age of patient
Sex of patient
Patient still alive
Side of lesion
Date of operation
Operator
Use of Lyodura
Pathology
Tumour size
Complications
Auriculotemporal syndrome
Radiotherapy Usage

Tumour size was assessed by the pathologists in all cases and recorded as 3 dimensions in the histopathology report. The product of the dimensions was used as an estimate of tumour volume.

The results were then tabulated. No statistical analysis was performed. Due to small numbers survival figures for malignant disease were not adjusted for age-specific life expectancy.

2.223 AURICULOTEMPORAL SYNDROME - A CASE FOLLOW-UP STUDY

The approval of the Queen Elizabeth Hospital ethics committee was obtained for this study. (Appendix 3.3 and 3.4)

Attempts were made to contact by mail all those patients whose case-notes were surveyed and were still alive. A copy of the letter sent to each patient is reproduced in Appendix 3.5. The patients who replied were given an out-patient appointment. Those who did not reply were sent a second letter (Appendix 3.6). For those who still did not reply, or whose letter was returned "not at this address", the address was checked in the telephone book and personal contact was made by telephone. Every attempt was made to ensure that follow-up was as complete as possible.

The patients attending the outpatient clinic were asked to sign a consent form (Appendix 3.7), after detailed explanation of the tests involved. They were then questioned, in a standard manner, regarding allergy to iodine, presence of general symptoms, and presence of specific symptoms related to gustatory sweating (Appendix 3.8). In addition, the patients were asked about the presence of facial or ear numbness, the function of the facial nerve was tested, and the cosmetic

acceptability of the scar was assessed. Next the Minor starch iodine test was performed (2.2221) on both sides of the face and the result recorded. Finally, one week later, each subject was assessed for signs of iodine sensitivity, and skin resistance measurements were made (2.2222) on each side of the face before and after maximal gustatory stimulus and the result recorded. In order to test whether age, sex, tumour type, complication type, correlated with the development of gustatory sweating, multiple linear regression and logistic regression analysis of the data was performed using the Epilogue Statistical Package (165). Where tests of kurtosis and skewness (158) showed this to be appropriate the Student t-test was applied using the Statistics package for a Hewlett-Packard HP 97 Calculator (159). The nonparametric Chi-Square test of statistical significance was applied in circumstances when the t-test was considered to be inappropriate (160,161).

The normal range of facial skin resistance was defined as mean value plus or minus two standard deviations. Using the starch iodine test as reference standard the sensitivity and specificity of the skin resistance in detection of gustatory sweating was calculated. In general a p-value of less than 0.05 was taken to indicate statistical significance.

2.2231 THE MINOR STARCH IODINE TEST

The method used was essentially that described by Minor (31). In females cosmetics were first removed if necessary using soap and water. The tests were carried out in an air-conditioned room maintained at 25 degrees after the patients had been allowed 30 minutes to equilibrate.

A solution of alcoholic iodine (Iodine 3 grams, castor oil 20 grams, made up to 200 ml. with absolute alcohol.) was applied to both sides of the face in a symmetrical fashion from the hairline superiorly, to the ramus of the mandible inferiorly, to the tragus of the ear posteriorly and behind the ear, and to the anterior limit of the zygomatic arch anteriorly (Figure 7). The area was then allowed to dry and dusted lightly with starch powder (Figure 7). The patient was given a slice of fresh lemon to induce maximal gustatory stimulation. The two sides of the face were compared after 3 minutes. The test was performed in a blinded fashion without knowledge of which was the operated side, except where scaring made this apparent. When there was an obvious difference between the two sides the test was considered positive (Figure 7). If the difference between the sides was equivocal the number of active sweat glands was counted on each side and the test was deemed positive if there were 4 times as many active sweat glands on the affected side when compared to the normal side.

At the completion of the test the iodine solution was removed using a solution of 5 grams per 100 mls of sodium thiosulphate.

2.2232 SKIN RESISTANCE MEASUREMENTS.

Skin resistance measurements were made using an instrument made in the Queen Elizabeth Hospital department of Bio-medical Engineering, to the specifications of Swain et al (151). The electrical resistance was measured between two silver electrodes fixed 1 cm. apart. The probe (Figure 8) is activated by a spring loaded micro-switch adjusted to be

actuated by a pressure of 3 N or more. After 30 seconds the reading was held on the LED read-out. This allowed measurements to be made at constant time and at a minimum skin pressure. The time of 30 seconds was chosen because experimentation with the instrument showed that this was the maximum time required to achieve a stable reading. The instrument provided a read-out of skin resistance of between 0 and 12 megaohms and measured resistance at constant current of 0.1 microamperes and displayed on an LED read-out (Figure 8). The device could be reset by a switch on the transducer thus enabling the next reading to be taken. Swain (151) investigated the effects of diurnal variation, common skin contaminants, hydration of the skin, changes in electrode separation, area and composition, and changes in measuring current, on the performance of the instrument, and found that there was minimal variation in the measured resistance. Although this instrument was incapable of giving absolute values for skin resistance it provided a reproducible measurement of a quantity bearing a constant relationship to the true skin resistance and was capable of detecting changes in skin resistance caused by changes in surface sweating. In the present context the device was used to detect reduction in skin resistance due to gustatory sweating. Clearly, measurement of absolute values for skin resistance was not necessary, provided reproducible relative values were obtained from each patient on each side of the face before and after maximal gustatory stimulus. In order to achieve this each patient's face was washed with soap and water and allowed to dry for 3 minutes. The probe was placed 1cm. anterior to the

tragus of the ear (Figure 9). The skin resistance was measured three times on each side of the face. Maximal gustatory simulation was achieved by asking the patient to chew a slice of fresh lemon for 30 seconds. The skin resistance measurements were then repeated three times on each side of the face. The normal range for facial skin resistance was defined and the sensitivity and specificity of this test was determined in comparison to the starch iodine test (2.222).

2.2233 THE USE OF LYODURA

In an endeavour to prevent the development of post-parotidectomy gustatory sweating a layer of freeze dried irradiated cadaveric dura (Lyodura TM B. Braun Melsungen AG) was inserted between the skin and cut surface of the parotid gland (Figure 6) in 10 of the patients between 1975 and 1985. This procedure was carried out with the informed consent of the patients concerned.

Firstly, a standard superficial parotidectomy was carried out. At the conclusion of the operation careful parotid gland haemostasis was achieved. Then a piece of Lyodura was cut to shape, making certain that the whole surface of the gland would be covered. The Lyodura was then carefully sutured around the margins to the subcutaneous fascia using interrupted catgut sutures. The skin was then closed in the usual manner, ensuring that the presence of the barrier of Lyodura had not resulted in any cosmetic deformity of the face. In June 1987 (157) there was a report of the transmission of Creutzfeldt-Jakob disease by batch number 2105 of Lyodura. Since that time the use of Lyodura for the above

purpose has been abandoned at the Queen Elizabeth Hospital, in favour of autologous tissues, such as fascia lata.

2.23 RESULTS

2.231 PAROTID SURGERY AT THE QUEEN ELIZABETH HOSPITAL 1975-1985

2.2311 GENERAL

There was a total of 88 superficial parotidectomies performed at the Queen Elizabeth Hospital between 1975 and 1985. Of these 44 were performed on males and an equal number on females. The mean age of this group of patients was 54 years. The median case-note follow-up time was 4 months (range 1-96 months). Fourteen of the 88 patients had died. The additional data collected for this group of patients is presented in Table 14.

TABLE 14 DATA FOR PAROTID SURGERY DERIVED FROM A RETROSPECTIVE CASE-NOTE SURVEY.

Total Patients	88
Mean Age	54 years
Alive	74
Tumour size (mls.)	23.7 ± 1.7
Lyodura Used	10
Radiotherapy Used	16
Consultant Surgeon	68
Registrar Surgeon	20
Complications	50
Pathology Benign	72
Pathology Malignant	16

TABLE 15 PATHOLOGICAL DIAGNOSES ENCOUNTERED IN THE COURSE OF PAROTID GLAND SURGERY 1975-1985 AT THE QUEEN ELIZABETH HOSPITAL. WHERE NUMBERS WERE TOO SMALL TO BE MEANINGFUL THE AGE RANGE, MEDIAN AGE OR SEX RATIO WAS OMITTED.

DIAGNOSIS	NUMBER(%)	M: F	AGE RANGE	MEDIAN
A) BENIGN	54 (62)	26: 29	16-77	53
Pleomorphic adenoma	39 (44)	16: 23	16-67	50
Adenolymphoma	10 (12)	6: 4	57-77	65
Oncocytic Adenoma	2 (2.2)	-	-	-
Cyst	1 (1.1)	-	-	-
Lipoma	1 (1.1)	-	-	-
Haemangioma	1 (1.1)	-	-	-
B) MALIGNANT	17 (19)	11: 6	21-86	60
Mucoepidermoid	6 (7)	4: 2	21-67	46
Epidermoid	3 (3.4)	-	-	-
Anaplastic	5 (6)	3: 2	57-86	74
Metastatic	2 (2.2)	-	-	-
Acinic Cell	1 (1.1)	-	-	-
C) INFLAMMATORY	14 (16)	5: 9	46-87	60
Mickulicz	6 (7)	3: 3	-	-
Sialadenitis	4 (5)	-	-	-
Abscess	1 (1.1)	-	-	-
Sarcoid	1 (1.1)	-	-	-
Parotitis	2 (2.2)	-	-	-
D) NORMAL	3 (3.4)	-	-	-

2.2312 PATHOLOGICAL DIAGNOSES

The pathological diagnoses encountered in the course of superficial parotidectomy can be divided into three main groups. Benign tumours make up 62% of the total, malignant tumours 18% and inflammatory conditions 16%. The parotid gland appeared histologically normal in 4% of cases. Of those patients who had malignant tumours 6 had died of their disease while 2 died of unrelated causes. The median survival from time of diagnosis for those patients who died of their disease was 24 months (range 10-54 months). Of those patients surviving at the end of 1985 the median survival time was 74 months (range 60-106 months). The rate of usage of radiotherapy was the same for those who survived and those who did not (75%). The overall 5 year survival rate for malignant disease of the parotid was 50%, however anaplastic carcinoma had a poorer prognosis (20% five year survival, median life expectancy after diagnosis for those dying of disease 16 months) than mucoepidermoid lesions (66% five year survival, median life expectancy after diagnosis for those dying of disease 30 months). No statistical analysis was attempted in view of the small numbers.

The details of the remainder of the pathological findings, age ranges and medians are tabulated in Table 15.

The sex distribution of parotid lesions was relatively even except for the diagnosis of pleomorphic adenoma where women were slightly over-represented (23: 16 F: M).

2.2313 COMPLICATIONS

The complications encountered following parotid surgery in the retrospective survey of the case-notes are listed in Table 16.

TABLE 16 THE COMPLICATIONS AND COMPLICATION RATES OBSERVED FOLLOWING PAROTID SURGERY.

Facial Neurapraxia	29	33%
Salivary Fistula	5	6%
Facial Paralysis	3	4% (One Complete)
Infection	1	1%
Frey's Syndrome	2	2%
Haematoma	4	5%
Incomplete Excision	3	4%
Local Recurrence	3	4%

The overall complication rate was 57%. However, the cases of facial neurapraxia can be omitted, as they all resolved with time. This reduces the complication rate to a more acceptable 24%. It is to be noted that the incidence of auriculotemporal syndrome determined in this retrospective study was very low.

2.232 AURICULOTEMPORAL SYNDROME - A CASE FOLLOW-UP STUDY

2.2321 GENERAL

Of the 88 patients included in the case-notes review study, 14 had died, leaving a total of 74 patients who were still alive. These patients were contacted by mail. A total of 20 subjects could not be followed up for various reasons (Table 17), leaving 54 patients who consented to undergo testing. Amongst these patients women were slightly over-represented (M: F 20: 34). This is probably because females are

still more likely to be at home than men, and were thus more easily accessible for out-patient appointments.

TABLE 17 PATIENTS REVIEWED IN CASE FOLLOW-UP STUDY

88 CASES TOTAL	
14	Died
7	Moved Interstate
4	Uncontactable
3	Refused
6	Missed Appointment
54	TOTAL TESTED

Those patients listed in Table 17 as "missed appointment" should probably be considered as "refusals" since most missed their appointments on 4 or more occasions, and it became obvious that, although they agreed to participate over the telephone, they never really intended to come.

In the course of reviewing the patients several additional complications were noted. These are listed in Table 18.

One patient complained of facial flushing with meals but did not have gustatory sweating either subjectively or on testing. Flushing could be demonstrated with gustatory stimulation in the distribution of the auriculotemporal nerve.

TABLE 18 ADDITIONAL COMPLICATIONS NOTED IN CASE FOLLOW-UP STUDY.

Minor Facial Nerve Palsies	5
Local Recurrence	4
Cosmetically Unacceptable Scar	6
Greater Auricular Nerve Neuroma	1
Superficial Venous Thrombosis	1
Xerostomia	1

Two patients with auriculotemporal syndrome had been misdiagnosed as having salivary fistulas and underwent fruitless surgical exploration, in one case on two separate occasions. Their symptoms continued unabated.

A third patient with auriculotemporal syndrome was treated for several months for what was incorrectly diagnosed as a chronic otitis externa.

Six patients noticed pain in lateral aspect of the face with meals. Five of these patients had demonstrable gustatory sweating and the sixth had gustatory flushing.

The incidence of auriculotemporal syndrome as detected by starch iodine testing was 59% (32 patients). If the patients who had radiotherapy were excluded from this calculation the incidence became 64%. Of these 17 (53%) were aware of their symptoms (10 females, 7 males) and 6 (19%) were so severely distressed by their symptoms as to request further treatment (4 females, 2 males). The main cause for their distress was

embarrassment when eating with other people. Those requesting further treatment were referred back to their original clinic.

Table 19 lists further results of the case follow-up study.

Complications refer to only the local complications of parotid surgery such as facial nerve palsy, haematoma, wound infection, and salivary fistulas. Patients who had radiotherapy were excluded for the purposes of statistical comparison.

Multiple linear regression analysis was performed in order to detect whether any specific diagnosis was more likely to be associated with auriculotemporal syndrome. No pathological diagnosis carried any increased incidence of gustatory sweating, a finding noted by others (70, 89, 100, 101).

2.2322 SKIN RESISTANCE MEASUREMENT

The measurements of facial resistance before gustatory stimulation were approximately normally distributed (skewness .016, kurtosis 3.25) about a mean of 6.42 Megaohms ± 2.01. There was no significant difference between the sides of the face before gustatory stimulation to paired t-test. There was no difference in skin resistance before and after maximal gustatory stimulus on the non-operated side of the face (mean 6.75 Megaohms, ± 2.4).

TABLE 19 FREQUENCY OF OCCURRENCE OF CERTAIN PARAMETERS FOR THOSE WHO DEVELOPED GUSTATORY SWEATING AND THOSE WHO DID NOT. * = SIGNIFICANT DIFFERENCE TO CHI-SQUARED TEST P<.05. ** = SIGNIFICANT DIFFERENCE TO STUDENT T-TEST, P<.05.

PARAMETER		GUSTATORY SWEATING	NO GUSTATORY SWEATING	
TOTAL		32	22	
Mean Age(years)		53	50	
Sex	M	10	10	
	F	22	12	
Symptomatic		17	-	
	M	7		
	F	10		
Side	R	11	12	
	L	21	10	
Complications	TOTAL	19	5	*
Facial Nerve Damage		17	5	
Salivary Fistula		2	0	
Ear Numbness		20	7	*
Pathology				
	Benign	32	18	
	Malignant	0	4	*
Operator				
	Registrar	8	6	
	Consultant	24	16	
Radiotherapy		0	4	*
Lyodura		6	0	*
Tumour Volume (mls.)		31.9	17.6	**

There was no difference in skin resistance on the operated side of the face before and after gustatory stimulation in patients who had a negative starch iodine test

(mean 6.1 Megaohms, ± 2.2). In those patients who had a positive starch iodine test the measurements of facial resistance were distributed, in a slightly skewed fashion, about a mean of 0.76 megaohms, ± 0.5.

The difference between the means of facial resistance for patients with and patients without gustatory sweating was statistically significant to t-test ($p<.001$).

Using this data the normal range for facial resistance was defined as the mean plus or minus two standard deviations to give a 97.5% confidence interval. Thus the normal range for facial skin resistance was 2.0 to 11.0 megaohms. The diagnostic range for facial gustatory sweating was set at 0-1.9 megaohms.

Using these ranges the test has a sensitivity of 94% and a specificity of 100% when compared to the Starch iodine test for the detection of facial gustatory sweating. The positive predictive value of the test is 100% and the negative predictive value is 92%. The results are summarized in Table 20.

TABLE 20 NUMERICAL RESULTS OF THE COMPARISON BETWEEN SKIN RESISTANCE METHOD AND STARCH IODINE METHOD FOR DETECTION OF GUSTATORY SWEATING.

Skin Resistance Result	Starch Iodine Result		Total
	Positive	Negative	
Positive	30	0	30
Negative	2	22	24
Total	32	22	54

The two false negatives for skin resistance measurements arose because the small patch of involved skin was outside the area in which the probe was placed. Neither patient was symptomatic.

2.2323 THE USE OF LYODURA

Ten patients had a layer of Lyodura inserted between the skin and the cut parotid surface at the time of the original parotidectomy as prophylaxis against the development of auriculotemporal syndrome. Of these, six were available for review.

These patients all had positive starch iodine tests (Table 19). The incidence of gustatory sweating was significantly higher in this group of patients than in the remainder of the case-note follow-up series (Chi-Squared test $p<.05$).

Two of the six were symptomatic, and one had severe enough symptoms to request further treatment. The numbers were too small to allow a valid statistical analysis.

2.2324 TREATMENT

Six patients in the group of 54 (11%) requested further treatment for facial gustatory sweating. These were referred to their parent clinic for treatment as seen fit by the consultant surgeon in charge.

The treatment modalities offered to the patients are summarized in Table 21.

TABLE 21 TREATMENT OF SYMPTOMATIC GUSTATORY SWEATING

Local Antiperspirants	3
Tympanic Neurectomy	1
Irradiation	1
Fascia Lata Barrier	1

Patients using local Antiperspirants (20% Aluminium Chloride in alcohol) obtained good control of symptoms for 8-12 hours with a single application. This was sufficient to allow the patient to enjoy a meal without embarrassment.

The patient who underwent tympanic neurectomy has been asymptomatic for the last 6 months, although she has not been formally re-evaluated by starch iodine testing.

There were a further two patients amongst the case-notes reviewed who had undergone tympanic neurectomy prior to the study. One patient, who was not available for review, had the procedure performed for chronic sialadenitis. The other patient, who was reviewed, had the procedure performed for auriculotemporal syndrome, and was found to have had recurrence of her symptoms after about 8 months, with a strongly positive starch iodine test.

One patient had facial irradiation in order to control the problem. This was only contemplated after other means had failed. The patient unfortunately had bilateral parotidectomies and bilateral severe gustatory sweating as a result. In addition he had a bilateral hearing problem

requiring hearing aids. Tympanic neurectomy was thus contraindicated. The gustatory sweating, in addition to causing extreme embarrassment, was causing hearing aid malfunction due to a build up of moisture. Attempts were made to insert a silastic barrier between the parotid and the skin, but this failed due to local sepsis, and the graft had to be removed. As a last resort a course of superficial irradiation was arranged and was partially effective in relieving his symptoms (104).

The final patient in the treated group elected to undergo insertion of a fascial barrier. This case forms the basis of a more detailed report (2.3).

2.3 THE AURICULOTEMPORAL SYNDROME - A CASE STUDY

2.31 INTRODUCTION

The technique of insertion of a barrier between the parotid gland surface has been used both for prophylaxis (104, 105, 106, 114) and for treatment of auriculotemporal syndrome (107, 108). Sessions (107) claimed good short term results with this technique in the treatment of two patients with recurrent gustatory sweating after tympanic neurectomy.

The method is based on the assumption that the auriculotemporal syndrome is caused by direct reinnervation of skin sweat glands by nerve fibres growing from the transected parotid surface (Figure 6). Division of these fibres and insertion of a fascial barrier beneath the skin is held to prevent further regrowth of parotid nerve fibres. There is a certain element of risk to the facial nerve inherent in the

technique as the nerve lies immediately beneath the skin after superficial parotidectomy, and may be difficult to define by dissection due to the presence of scar tissue.

The weaknesses of the technique are twofold. Firstly, if the above aetiological theory is incorrect then late recurrence may be expected as the aberrant nerve connections are re-established. Secondly the success of the technique is dependent on the long-term stability of the barrier used. Should the integrity of the avascular sheet of fascia deteriorate over time then again late recurrence would be expected. Although auriculotemporal syndrome usually develops after 2 or 3 months (72) it can be delayed for two years or more (113), and so in order to adequately assess the efficacy of the barrier techniques at least five years of follow-up would be necessary.

2.32 CASE REPORT

Mrs. J.S was a 77 year old widow who lived alone. She had a past history of right menisectomy in 1956, bilateral oophorectomy 1953, anterior repair of a cystocele 1966 and a crush fracture of T8 in 1976. Apart from some mild arthritis in her right knee she was in good health. In 1983 she was referred to a general surgeon by her local doctor for evaluation of a mass in the left parotid which had been present and slowly growing for the previous 15 months. Clinical examination at that time revealed a lesion in the lower pole of the left parotid gland, suspicious of a pleomorphic adenoma. This suspicion was confirmed by needle aspiration cytology. On 18/03/83 a left superficial parotidectomy was performed. Histopathological examination of

the resected tissue revealed a completely excised pleomorphic adenoma. She made an uneventful recovery except for a minor wound collection of serous fluid which required drainage on two occasions. Six months after the operation she noticed a small amount of fluid dripping down her face with meals, but did not report this at her follow-up outpatient visits. She was discharged from the clinic after one and a half years.

Mrs. J.S. agreed to participate in the follow-up survey of parotid surgery and was seen on 12/6/86. She had marked gustatory sweating as demonstrated by the starch iodine test (Figure 10) and was complaining bitterly of her problem which had progressively worsened. Apart from embarrassing sweating during meals she also noted sweating on the left side of the face whilst singing in the church choir which she found especially annoying. She was referred to her general surgeon for treatment. He decided to use the fascial interposition method of Sessions (107). The operation was performed on 24/02/87.

2.33 METHOD

The method used was essentially that of Sessions (107). After the routine preoperative workup the area of the face was carefully mapped using starch iodine test (Figure 11). Under general anaesthetic a skin flap was mobilized beyond the limits of the area affected, with careful attention to preservation of the superficially located facial nerve (Figure 11). Skin biopsies of the affected area were taken. Next a 6 cm. by 8 cm. patch of fascia lata was harvested from the patients left thigh using a lateral incision (Figure 12). The fascia was cut to size making certain that it would cover the

whole area involved in gustatory sweating, with particular attention to the area close to and behind the ear. The graft was then sutured into position using chromic cat gut sutures (Figure 12). The wounds were closed with interrupted 4/0 nylon sutures.

Mrs. J.S. made an uneventful recovery with full function of the facial nerve.

2.34 RESULTS

The skin biopsies of the area affected by gustatory sweating were examined histopathologically and there was no detectable abnormality in the number or morphology of the sweat glands of the area.

The wound healed without scar and the patient remained asymptomatic.

Mrs. J.S. was reviewed weekly for 4 weeks, monthly for the following 3 months and finally at 10 months. The Starch Iodine test was performed on each occasion. This remained negative until the 10 month follow-up. On this occasion a small area of gustatory sweating was present anterior to the tragus (Figure 13). The patient remains unaware of this and is delighted with the results of her surgery thus far.

2.4 DISCUSSION

The research reported in this Chapter is based on retrospective studies, case reports, case follow-up studies and questionnaire. It is accepted that these are weak study designs (162), but it was necessary to employ these techniques because of the relative rarity of parotid gland surgery and because of the constraints of time. Powerful experimental

designs such as randomized prospective trials, cohort studies, and case control studies comprise less than 40% of the medical literature over the last 40 years (162). The frequency of weaker study designs such as cross-sectional studies and case reports is over 50% and increasing. Many factors (162) influence these observations, such as editorial policy of medical journals, the high cost of prospective and cohort studies in terms of time and money, and the strong political pressures on academics and clinicians to publish papers, and others. These attitudes tend to increase the quantity of medical research at the expense of quality. In the long term they can only impede and confound the acquisition of knowledge unless appropriate interpretation is made.

Results of clinical studies are notoriously difficult to interpret and have a high incidence of type I and type II errors (160) for reasons related to study design, (162) completeness, and inappropriate application of the statistical method (163). With the weaker study designs employed in the clinical studies reported in this thesis there is a high likelihood that the results are not complete. It is therefore important to apply statistical tests only when appropriate and to interpret the results with caution in order to avoid these interpretational errors.

There are several limitations inherent in the survey of local surgical knowledge and attitudes (2.1). Firstly there was a disappointing 51.5% response rate to the questionnaire. The likely reasons for the lack of response are numerous and include; time constraints, inability to readily access the required data, embarrassment over poor results, concern over

confidentiality, incorrect addresses, and many others. The 51.5% response limits the validity of any conclusions about global attitudes to and experience of South Australian surgeons with auriculotemporal syndrome because the results are incomplete and therefore likely to be skewed.

The second area of weakness in the study is inherent in the design of the questionnaire. The questions, by design, were open and at times vague and tended to invite a guess where the answer is not known. The intention of conducting the questionnaire was to obtain general basic information rather than obtaining specific data. This approach necessarily limited validity and consistency of answers but may have made the questionnaire easier to answer and less threatening than a structured format. It was anticipated that the format used would also aid the flow of anecdotal information about auriculotemporal syndrome.

The third area of weakness is that statistical tests can not be used to analyze this incomplete and subjective data. Figures quoted are thus, approximations and differences observed can only be regarded in general terms.

Despite the shortcomings of the study some interesting trends may be observed. Overall, the specialty surgeons tend to be younger and busier than the generalists amongst responders. Nevertheless parotidectomy is still largely the province of general surgeons who by weight of numbers perform the bulk of these operations. This is a surprising conclusion in view of the fact that there has recently been a trend towards the performance of head and neck surgery only by specialist head and neck units comprising ENT and Plastic

Surgeons, rather than by general surgeons. Perhaps the older general surgeons have tended to retain this element of practice and as the average age of general surgeons becomes lower, so will the incidence of parotidectomy by this group. This possible explanation is supported by the observation that the general surgeons responding to the questionnaire had a higher average age than the other specialist groups. It was not possible to analyze the age related data in any more detail because of the small numbers involved in each group.

Surgeons who perform parotidectomy perform about 3 of these procedures each year. It is interesting to speculate whether this level of operating is necessary or sufficient for an individual to maintain the surgical skills necessary to perform the operation safely. The observation that the complication rates are much the same in the case-note review study (2.2) as those seen elsewhere for this type of surgery, attests to the fact that an average of three parotid operations per year is sufficient to maintain the necessary skills. A meaningful answer to this question of quality assurance, however, could only be obtained by a more careful and complete prospective audit of parotid surgery. This is the only valid means by which comparison may be made between individual surgeons, between surgical units or within and between countries. Because of the comparative rarity of parotid surgery, such audits could only be effectively performed by maintenance of individual computerized data bases by each surgeon. Because of the political implications of quality assurance in surgery, such audits should become a priority of the relevant medical authorities.

Surgeons regularly involved in parotid surgery, unlike those who rarely perform parotidectomy, have a good general knowledge of the condition and its treatment, but grossly underestimated its incidence. Most authors (70,89,105,110) would agree that the incidence for symptomatic gustatory sweating after parotid surgery is 40-60%. There are at least two possible explanations for this discrepancy. Firstly, it is possible that the condition is not recognized by the surgeon either due to lack of knowledge, or due to the condition developing after the patient has been discharged from follow-up. The median follow-up time was only 6 months for benign disease whereas auriculotemporal syndrome may develop up to 3 years post-operatively (Table 4).

Secondly, it is possible that there is a genuinely lower incidence of this condition in South Australia perhaps due to surgical practices. The only techniques likely to influence the development of gustatory sweating are the use of radiotherapy, preservation of the auriculotemporal nerve, and the use of prophylactic surgical techniques. Very few surgeons responding to the questionnaire used such prophylactic techniques in parotidectomy. However, there seems to be a generally increased usage of radiotherapy for malignant tumours and incompletely resected benign tumours, in comparison to other series (164). Most South Australian surgeons also indicated that they routinely preserve the auriculotemporal nerve. Assuming that the aberrant regeneration theory of development of auriculotemporal syndrome is the correct explanation, it may be that by

rigorous and careful preservation of the auriculotemporal nerve, the development of gustatory sweating can be prevented.

Further indirect support for this contention comes from the observation made by a surgeon who performed auriculotemporal nerve avulsion in an attempt to prevent development of the condition. The surgeon was forced to abandon the technique because of the development of auriculotemporal syndrome in several of his patients. The only means of clarifying the situation would be to assess the true incidence of these variables in a more complete study.

From a technical angle most responding surgeons commenced their dissection of the facial nerve posteriorly as in the classical descriptions of the operation (57, 58, 59, 60, 64, 122). The use of diathermy and nerve stimulators was common in parotid surgery in South Australia. It is therefore unlikely that either of these techniques play a role in the development of auriculotemporal syndrome, particularly since, in historical terms, the rate of occurrence of the condition has not changed since the use of these modalities has become widespread.

The incidence of benign and malignant tumours parallelled that seen in other series (164, 166, 167).

The rates of various complications had large ranges probably as a result of "educated guesses", nevertheless the median values agreed with estimates of complications reported by others (164, 168). Salivary fistulas, wound infection, permanent facial paralysis and local recurrence of benign tumours were all rare, whereas permanent and transient facial

nerve injury and local recurrence were more common after excision of a malignant tumour.

Gustatory sweating was very rarely seen as a complication requiring further treatment, and infrequently seen as a complication in general. This, in itself, may add to the impression that auriculotemporal syndrome is less prevalent in South Australia than elsewhere. Experience with the treatment of the condition, because of its comparative rarity, was limited in this series to twenty patients, all of whom had tympanic neurectomy. The claimed success rate of this treatment was 70% which compares favourably with the 80-90% success rate documented elsewhere (96,110).

The results of the retrospective case-note study (2.222) also have limitations in their interpretive value. Although the group of patients studied was a complete representation of those who had undergone parotidectomy in period 1975 to 1985, the data was collected retrospectively and therefore is inevitably incomplete. The case-notes were often incomplete, pages were missing, data was not recorded to any plan, and information was recorded by many different individuals with varying methods. These factors combined to limit the type of information collected and to restrict the extent and validity of conclusions.

An example of this effect is the observation that the incidence auriculotemporal syndrome was noted to be 2% in the retrospective study. From the case-note review study the incidence was much higher than this, being closer to 60%.

The same lack of accuracy must apply to other retrospectively collected data, such as complication rates,

tumour size and whether the patient is still alive, and so these must be interpreted with caution.

Absolute data, however, such as age and sex of patient, use of Lyodura or radiotherapy, surgeon, and pathological diagnoses are likely to be much more accurately recorded and therefore more reliable.

The mean age of patients presenting for parotid surgery was 54 years, with an equal sex distribution, which compares favourably with other series (167).

Radiotherapy at the Queen Elizabeth Hospital was used almost exclusively for malignant disease even when the tumour was reported as completely excised. It was occasionally used for locally recurrent benign and malignant tumours. These practices differ from the clinical practices of the South Australian surgeons responding to the questionnaire, who stated that they used radiotherapy much more frequently in these situations. It is possible that the disparity is simply due to inaccuracy of response to the questionnaire. Alternatively, if the differences are real, it may be that they reflect variation between hospital and private medical practice.

Consultants performed many more parotidectomies than registrars in this series. An increased rate of complication and therefore higher incidence of auriculotemporal syndrome may have been expected with the lesser experience of the registrar operator. This was not the case as complication rates were the same for both groups. The probable reason for the observation is that the registrars who did parotidectomies were in their post-fellowship years and thus quite experienced

and in addition all were closely supervised by a senior surgeon.

The ratio of benign to malignant disease in the study was 3 to 1, a figure which is comparable to most other series (164, 169, 170, 171). In addition, the distribution of histological diagnoses was similar to that seen elsewhere in the world. The observation that females are more frequently afflicted with parotid tumours than men was less apparent in this series than elsewhere (169) although, for pleomorphic adenomas women were affected more often than men. The remaining figures were too small to allow meaningful comparisons with other series.

The five year survival rate for malignant disease, overall, was 50%, much as reported elsewhere (169, 172, 173). The observation that anaplastic carcinomas have a poorer prognosis than mucoepidermoid tumours is confirmed by the data of Kirklin (172), who found that patients with undifferentiated tumours had a 32% five-year survival, and those with mucoepidermoid tumours had an 83% five-year survival.

The rates of complication reported here were again largely in agreement with the literature (167, 168, 170, 171). Toyara et al (170) reported a 41% incidence of transient facial palsy after parotidectomy which is similar to the 33% incidence noted here.

Permanent facial nerve damage occurred in 4% of patients which concurs with the data of Powell (168).

As has been already alluded to, the incidence of auriculotemporal syndrome is lower in the case-note review

study (2%) than that generally reported in the literature. This probably is due to a combination of factors including the retrospective design of the study and the short median follow-up time of 4 months given that auriculotemporal syndrome has a lag period of 8 months or more to its development. The use of prophylactic techniques are unlikely to have influenced this figure as they were only employed in 12% of patients and did not result in a diminished occurrence of the condition anyway (vide infra).

The prospectively collected data which forms the basis of the case-note follow-up study (2.232) is, in general, much more reliable than that of the retrospective studies.

The major disadvantage of this study is that follow-up could not be complete despite the most strenuous efforts. The overall follow-up rate excluding those who had died was 73%, which is probably enough to allow meaningful conclusions to be drawn (174).

The incidence of auriculotemporal syndrome in the group tested was 59%, or slightly higher (64%) if patients who had radiotherapy were excluded. The rate is lower than that reported in series in which all patients were tested by the starch iodine test (70,105,106,110), where the incidence approached 100%. The reason for this difference was not readily apparent, but it seemed unlikely to have resulted from either radiotherapy practices or the use of barrier methods of prevention. The latter technique resulted in a statistically significant increase in the incidence of the condition.

In this series, the only identifiable events which were associated with the development of auriculotemporal syndrome

in a statistically significant manner were the occurrence of complications, the complaint of ear numbness and the removal of a large tumour. Perhaps the occurrence of a complication can be regarded as measure of the operative care or skill of the surgeon. Thus a more skillful surgeon would be less likely to inadvertently damage the auriculotemporal nerve by traction or other means. Numbness of the ear can occur as a result of injury of either the auricular branch of the auriculotemporal nerve or the greater auricular nerve. As such it may be considered to act as a marker for auriculotemporal nerve damage and thus auriculotemporal syndrome.

Tumour volume was significantly greater in those patients at the Queen Elizabeth Hospital who developed auriculotemporal syndrome than those that did not. Whilst it is accepted that the measurement of tumour size in this study was performed by many different pathologists and could be subject to error, the observation confirms the sentiments of other authors (70, 89, 100, 106, 107, 110), who failed to measure tumour size. The explanations for the observation are not entirely clear, but it is possible that the resection of a larger tumour may give more opportunity for direct or indirect damage to the auriculotemporal nerve, or alternatively may provide a larger surface of transected parotid tissue resulting in an increased chance of direct innervation of sweat glands by salivary secretomotor fibres.

Another possibility to explain the reduced incidence of gustatory sweating in this series, is that perhaps parotid lesions are operated on earlier at the Queen Elizabeth Hospital, resulting in smaller resected tumours and a

consequent reduction in the development of gustatory sweating. This speculation is difficult to confirm or refute as there is no information in the literature regarding the distribution of sizes of resected tumours at other centres, and so, in this regard, there is no basis for comparison.

The fact that patients having radiotherapy had a statistically significant lower rate of development of auriculotemporal syndrome confirms the earlier observations of Needles (30) and Laage-Hellman (70).

The prophylactic manoeuvre of insertion of Lyodura between the parotid gland and the skin was not effective in preventing auriculotemporal syndrome, and in fact resulted in a significantly increased incidence of the condition. There did not seem to be any difference in the percentage of patients who were symptomatic (31% in the "no Lyodura" group and 33% in the "Lyodura" group), but the numbers were too small to allow valid comparisons to be made. The reasons for the apparent failure of this technique are unknown. Perhaps the nerves penetrate the Lyodura barrier, or perhaps the Lyodura is reabsorbed over a few months due to local inflammatory reaction or rejection. The manufacturer's product information sheet for Lyodura states that rejection does not occur due to the processing of the material which renders it antigen free. Lyodura is stable for many years when used in the cranial cavity as a dural patch (Personal communication). Reabsorption of this substance in the parotid region has not been studied, but seems unlikely.

An alternative explanation of the failure of the barrier technique may lie in the level at which the reinnervation

causing auriculotemporal syndrome might occur. If damage to the auriculotemporal nerve itself were the cause of the syndrome, rather than direct regrowth of cut parotid nerves into the skin, a barrier between the skin and parotid would be ineffectual as cross-innervation would still occur within the nerve at the point of injury. If this hypothesis is correct these observations would provide indirect evidence to support the belief that direct auriculotemporal nerve damage is necessary for development of the condition.

In addition to the lower overall incidence of auriculotemporal syndrome in the series the percentage of symptomatic patients (33%), and patients demanding further treatment (11%) were less than other reported series (111, Table 3, 1.143). Presumably this reduction simply parallels the reduced overall occurrence of the condition.

The prospective study disclosed several additional complications which increased the complication rates. The composite result is recorded in Table 22, and underscores the fact that retrospective studies tend to underestimate the frequencies of many parameters.

The true facial palsy rate of 10% is probably higher than that seen in most reported series (168,169). The incidences of greater auricular neuroma, superficial venous thrombosis and xerostomia are not reported elsewhere.

The scar has seldom proved to be a problem in the past (168), but in this series it was unacceptable to the patient in 6% of cases. It is unlikely that the quality of the scar has been adequately assessed previously.

TABLE 22 OVERALL COMPLICATION RATE DERIVED BY COMBINATION OF THE CASE FOLLOW-UP AND CASE-NOTE REVIEW STUDIES .

Facial Palsy	10%
Cosmetically unacceptable scar	7%
Local Recurrence	9%
Superficial Venous Thrombosis	1%
Greater Auricular Neuroma	1%
Xerostomia	1%

The local recurrence rate of 9% is still substantially less than recorded recurrence rates for parotid tumours. Beahrs (171) recorded an average recurrence rate of 51% for malignant tumours whereas the recurrence rate for benign tumours is reported as 1-2% (164,168). In the current series the early recurrences were all due to malignant disease, while half of the late recurrences were for pleomorphic adenoma. Thus, the recurrence rate for pleomorphic adenoma is 5% whereas that for malignant growths is 27%. The latter is still reduced in comparison to literature estimates, as a probable consequence of the frequent use of radiotherapy for malignant parotid disease at the Queen Elizabeth Hospital, or possibly related to earlier presentation of these tumours.

The estimation of skin resistance proved to be a useful means of detecting gustatory sweating. The test has high rate of specificity and sensitivity. The few false negatives that occurred were in asymptomatic patients and occurred due to

patchy distribution of gustatory sweating. The main forms of bias to which the experimental design is open are diagnostic-review bias and test-review bias (175). The former can be avoided if the diagnosis of gustatory sweating is made before the skin resistance measurements, as was the case in this study. Test-review bias is best minimized by reading the test result in a manner blind to both the diagnosis and the operated side. It is best accomplished by incorporating a third party to interpret the test result in isolation. In the current study this method could not be employed, and instead the two tests were performed a week apart with the patients in random order and without specific knowledge of the operated side. Five or six patients were seen each week and test-review bias was thus minimized.

In order that the skin resistance test could be used as a screening test the diagnostic range could be broadened to 0-3.0 megaohms. This would result in reduction of the specificity of the test to 91% with 100% sensitivity, thus providing a useful screening test (175). Because the specificity would be reduced the starch iodine test could then be used to detect the false positive patients. The skin electrical resistance therefore is a potentially useful screening test for the detection of facial gustatory sweating.

It is interesting to note that prior to gustatory stimulus there was no difference in skin resistance between the two sides of the face. This is somewhat surprising in view of the evidence that thermal sweating is reduced in an area of skin affected by gustatory sweating (16, 35, 48, 449, 72, 74, 134). It is most likely that the instrument was not sensitive enough

to detect small differences in thermal sweating at room temperature. It is possible that by exposing the patient to a warm environment, differences in thermal sweating may be detected by measurement of skin resistance, possibly making gustatory stimulation unnecessary for diagnosis of auriculotemporal syndrome with this technique. Further study would be necessary to validate this speculation.

The treatment of cases of established gustatory sweating in this series was limited to six severely symptomatic patients. Local antiperspirants were adequate in half of the patients. The remainder have had some early benefit from tympanic neurectomy, fascial interposition and radiotherapy.

The case study of the patient treated for auriculotemporal syndrome by fascial interposition shows how useful and successful this form of treatment can be, at least in the short term. Surprisingly, there were no technical difficulties experienced with the facial nerve. At 10 months the starch iodine test was only faintly positive and the patient remained asymptomatic.

It is difficult to understand why this technique may succeed whereas barrier methods of prophylaxis fail. The first point to make is that it is not possible to decide on the success or failure of homologous fascial interposition on the basis of short term follow-up of one case. Secondly, there is some evidence of recurrence at 10 months and this may, in time worsen and become symptomatic. Thirdly, it may be that fascia lata and Lyodura have differing stabilities and other properties when inserted under the facial skin. Finally, it is possible that established auriculotemporal syndrome can be

treated by disconnection of the sweat glands and fascial interposition only when the exact extent of the area involved by gustatory sweating is defined by preoperative testing. If direct reinnervation of the skin sweat glands by parotid secretomotor fibres were the mechanism for development of auriculotemporal syndrome then both techniques would be expected to succeed. Therefore, the observation that the fascial interposition seems to be successful only after the syndrome has developed, provides some indirect evidence that direct auriculotemporal nerve damage is the mechanism of development of facial gustatory sweating, although there are other possible explanations.

In summary, the following conclusions can be drawn on the basis of these clinical studies.

Firstly, that at the Queen Elizabeth Hospital, although there was much the same incidence of other complications of parotid surgery, and much the same spectrum of parotid disease as seen elsewhere, the incidence of gustatory sweating detected with starch iodine testing seemed to be reduced. The reasons for this were not clear from the study, but it is possible that the auriculotemporal nerve was injured less often.

Secondly, that the removal of larger tumours was associated with an increased incidence of gustatory sweating.

Thirdly, that retrospective studies lead to underestimation of complication rates.

Fourthly, that skin resistance measurement was a useful and simple screening test for gustatory sweating.

Fifthly, that Lyodural layer interposition has little value as a prophylactic measure, but fascia lata autograft may have a role in the treatment of established gustatory sweating.

And finally, while the surgical technique, pathology and complication rates for parotid surgery in South Australia are similar to other centres there appears to be a reduced incidence of auriculotemporal syndrome. It was not possible to correlate definitely the development of the condition with any local surgical techniques, other than to suggest that an apparent increase in use of postoperative radiotherapy and careful preservation of the auriculotemporal nerve both may play a role. Prospective audit is necessary for substantiation of the trends observed.

CHAPTER 3 AURICULOTEMPORAL SYNDROME - COMPARATIVE ANATOMY

3.1 HUMAN ANATOMY

3.11 INTRODUCTION

The gross human anatomy applicable to the area of the parotid, the auriculotemporal nerve, the facial nerve, and the otic ganglion, has been extensively described in the standard anatomical texts and are summarised in 1.13. The intention is not to restate these observations but rather to investigate some of the detailed anatomy of the human auriculotemporal nerve. This has already been described to a large extent by Baumel et al (120) and Wegener (117). The typical auriculotemporal nerve arises by two roots from the mandibular nerve. The roots embrace the middle meningeal artery. After a short trunk a spray of branches develops. Usually there are six such branches which are named. These are; two communicating rami to the facial nerve, two branches to the external auditory meatus, the anterior auricular ramus and the superficial temporal ramus. The auriculotemporal nerve divides into these branches just before it pierces the dense parotid fascia. The branches to the parotid gland may arise from many different regions of the nerve.

The issue of exactly where the branches supplying the parotid gland spring from is crucial to the understanding of the aetiology of the auriculotemporal syndrome. Clearly if direct injury of the nerve is to play a major role in the

development of the syndrome it is only injury of the nerve in the region where both parotid secretomotor fibres and sudomotor fibres to the skin coexist that is important. It is therefore necessary to know at what level both these sets of fibres coexist in order to assess the likelihood that nerve damage during parotidectomy could feasibly result in auriculotemporal syndrome. Should all the fibres innervating the parotid arise from the auriculotemporal nerve at a level deep to the gland, nerve damage resulting in aberrant regeneration would be unlikely to occur during superficial parotidectomy. On the other hand, if parotid secretomotor fibres were given off by the auriculotemporal nerve at very superficial levels nerve damage during parotid surgery, and consequent development of auriculotemporal syndrome, would be much more feasible.

Baumel described parotid rami as numerous inconstant twigs given off from the main trunk of the auriculotemporal nerve, the superficial temporal ramus and the facial communicating rami. Reissner (122) extended these observations and noted that parotid rami also branch from the auricular branches of the auriculotemporal nerve, and as branches from the facial nerve itself. Neither author was able to be specific as to the exact points along the auriculotemporal nerve, and its various branches, at which the parotid rami were given off. In particular there was no information about how superficially the parotid rami might arise.

Therefore, in order to obtain some more detailed information as to exactly where along the course of the auriculotemporal nerve branches to the parotid are given off,

dissection of the nerve and the parotid gland was undertaken in human cadavers.

3.12 MATERIALS AND METHODS

Four human cadavers were obtained by permission from the Adelaide Medical School and the dissections were carried out in the Medical School dissection room. The subjects consisted of two males and two females of unknown ages. A total of 8 parotid dissections was performed in the following manner.

Initially a skin flap was removed from the side of the face as shown in Figure 14. The parotid gland was then freed from the underlying tissue and reflected posteriorly to expose the ramus of the mandible. Next the mandibular ramus was removed and the auriculotemporal nerve exposed by blunt dissection (Figure 15). The terminal branches of the auriculotemporal and facial nerves were freed from the parotid gland by gentle blunt dissection. Photographic records were made of the dissections and of the fine parotid rami arising from the auriculotemporal branches. A Pentax Super A camera equipped with dental close-up lenses and a ring flash unit was used. After some experimentation the correct exposure was found to be obtained with a shutter speed of 1/125 th. of a second and an aperture of f16. Fuji 100 ISO colour film was used. Magnification varied from 1/2 to 1 1/2 times depending on the lens combination used.

3.13 RESULTS

The dissections were hampered to some extent by the tough fibrous nature of the parotid gland. The results are tabulated in Table 23.

The auriculotemporal nerve was seen to arise from two roots of variable length in all eight dissections. Invariably there was a branch to the deep lobe of the parotid from the trunk (Figure 15). At the level of the mandibular ramus the auriculotemporal nerve divided into 6-8 terminal branches which were approximately equal in size. At the point of branching because of the multiple nerve branches present the auriculotemporal nerve trunk became extremely adherent to the dense capsule surrounding the parotid and was relatively fixed by this structure. The branches comprised 2-4 facial communicating branches, 2-3 auricular branches, and 1-2 superficial temporal branches. These were difficult to demonstrate photographically. In one of the subjects the facial communicating branches were so numerous that they formed a plexus of fine branches. This variation was not observed in any of the other cadavers.

TABLE 23 AURICULOTEMPORAL NERVE BRANCHES OBSERVED IN EIGHT CADAVER DISSECTIONS. P, PLEXUS OF NERVE BRANCHES; *, PAROTID BRANCHES PRESENT.

				AURICULOTEMPORAL NERVE BRANCHES		
CADAVER	SIDE	ROOTS	TRUNK	COMMUNICATING BRANCHES	AURICULAR BRANCHES	SUPERFICIAL TEMPORAL BRANCHES
1	R	2	1 *	2	3 *	2*
1	L	2	1 *	3	2	2 *
2	R	2	1 *	P	2 *	2 *
2	L	2	1 *	P	3 *	1 *
3	R	2	1 *	4	2 *	1 *
3	L	2	1 *	3	2 *	1
4	R	2	1 *	3	2 *	1 *
4	L	2	1 *	4	2 *	2 *

No communicating branches from the auriculotemporal nerve to the greater auricular nerve were observed.

Multiple fine branches of the superficial temporal and auricular branches of the auriculotemporal nerve could be identified (Figure 16). These fine branches seemed to provide parotid innervation and were present in very superficial locations. They appeared to sprout from these auriculotemporal nerve branches throughout their courses within the parotid gland. No definite evidence of parotid innervation could be detected from either the facial nerve or the communicating rami of the auriculotemporal nerve.

3.2 ANIMAL ANATOMY

3.21 INTRODUCTION

A detailed understanding of animal head and neck anatomy is a fundamental prerequisite for establishment of an animal model of auriculotemporal syndrome. One needs to know where the parotid gland is situated and its relationship to the facial nerve in order to facilitate parotidectomy and any other procedure which may be part of the animal preparation. The parotid parasympathetic and sympathetic nerve supplies, the animal-equivalent of the otic ganglion, and the auriculotemporal nerve, its course and relational anatomy, must be defined if extrapolation from the model to the human situation is to have any validity.

The two animal species utilized in these studies were the laboratory rat (Rattus rattus strain Sprague-Dawley) and the common marmoset (Callithrix jacchus) bred at the Queen Elizabeth Hospital Animal House.

Little is written in the literature of detailed head and neck anatomy of these animals. Rowett's booklet (176) "Dissection Guides - The Rat" devotes only 1 or 2 pages to detail of neck anatomy, and almost nothing to the anatomy of the head. Marmoset anatomy is less well documented - there being no dissection manuals or other guides for this species. As a starting point some basic anatomical information for this small primate can probably be extrapolated from human anatomy of the area. **Thus with a minimum of background information rat and marmoset head and neck dissections were undertaken.**

In order to assist in identification of structures and ganglia in particular, the technique of retrograde neuronal labelling was employed. The technique involves injection of the end organ or tissue with a substance which diffuses into local axons and is transported by retrograde axonal flow to the cell body of the axon. The rate of retrograde axonal flow is 70-220 mm. per day (177,178). The technique was first developed using substances such as Horse Radish Peroxidase (178), Bovine Serum Albumin (179), labelled Tetanus Toxoid (180), labelled Adenosine (181), and others. These techniques were time consuming and demanding. Kuypers et al (182,183,184) were the first to use retrograde neuronal transport of fluorescent substances such as bisbenzimide, propidium iodide, Evans Blue or primuline to label cell bodies of axons thus facilitating mapping of the nervous system. These workers also pioneered the technique of double retrograde neuronal labelling with fluorescent substances to enable neurones with multiple projections to different areas to be identified. Several other substances capable of undergoing retrograde

axonal transport were described (185, 186, 187, 188). These are fluorescent dyes and two of them have the properties of specific transport over long distances (186), long term stability (188) and slow migration out of the cell (187). The dyes are Fast Blue (Diamidino compound 253/50 (186)) and Diamidino Yellow Dihydrochloride (187). The former agent is a cytoplasmic label with bright blue fluorescence, and the latter is a nuclear label which produces a golden yellow colour. Both substances fluoresce when illuminated with light in the near-UV spectrum wavelength 370 nm (186, 187), and so both substances can be identified with a single observation at this wavelength when present within a cell, enabling double labelling of cells to be accurately detected.

The single retrograde label Fast Blue was used in combination with dissection to facilitate the localization of the otic ganglia in the experimental animals.

3.22 METHODS

3.221 GENERAL

The following experiments were carried out with the approval of the Queen Elizabeth Hospital Animal Ethics Committee (Appendix 4.1 and 4.2).

10 rats and 6 marmosets of either sex were used in these anatomical dissections. The marmosets, because of the high cost of the animals, were same animals used for the experiments reported in Chapter 4. Each animal was killed with an overdose of pentobarbitone (60 mg.) and then exsanguinated by cardiac puncture, to promote easy dissection of the head and neck region.

Cardiac puncture was performed with the animal supine. A 16 gauge needle mounted on a twenty ml. syringe was introduced under the xiphisternum, angled upwards, slightly to the left, and slightly dorsally and inserted to the full 2 inches. The heart was stabilized in the thorax by gentle transverse pressure with the finger and thumb of the other hand. The needle could be felt entering the heart as it developed a strong bouncing motion. 15 to 20 mls of blood could usually be easily withdrawn with occasional minor adjustments of the position of the needle tip.

Dissection was performed using a dissecting microscope when necessary. A midline skin incision was made from the sternal notch to the mandible and skin flaps reflected laterally. The submandibular gland and adjacent lymph nodes were removed to expose the strap muscles of the neck. The strap muscles were divided longitudinally at their origins and reflected, thus exposing the neurovascular bundles. The tendon of the digastric muscle was then divided and the medial pterygoid muscle detached from its origin medially and removed, exposing the mandibular branch of the trigeminal nerve. Careful dissection was required in order to avoid the nearby retromandibular vein. Removal of a portion of the mandible and the stylomandibular ligament allowed exposure of the auriculotemporal nerve throughout its length. The facial nerve was exposed from the stylomastoid foramen to the masseter muscle by division of the parotid between the deep and superficial lobes where necessary. The branches of the auriculotemporal nerve were dissected and displayed.

All sections to be examined by light microscopy were first placed in phosphate buffered formalin (10% formaldehyde in 130 mM phosphate buffer pH 7.0). The tissue was sectioned and stained with haematoxylin and eosin by routine methods used in the Histopathology Department of the Queen Elizabeth Hospital. The sections were then examined using an Olympus light microscope, fitted with a PM 10-A camera to allow photomicrographs to be made if required. Fuji 100 ISO colour slide film was used throughout.

Dissections were performed with the aid of a Zeiss operating microscope fitted with zoom capability and a 12.5 X objective lenses providing magnification of 10 to 20 times. A Zeiss Ikon camera was also fitted via a 50% beam splitter. Photographic records of the dissections were made after some initial experimentation using this system. The best images were produced using Fuji colour slide film ISO 400 at a shutter speed of 1/125 th and f 44 with the aid of a Nikon ring-flash unit attached to the microscope. The anatomical descriptions below refer to the animal lying in the supine position with the neck extended unless otherwise specified.

3.222 FAST BLUE LABELLING OF THE OTIC GANGLION

At least 48 hours prior to dissection each animal underwent a general anaesthetic (for details of anaesthetic see 4.22). The dye Fast Blue was obtained from Dr. Illing (Dr. Illing GmbH and Co KG Makromolekulare und Pharmazeutische Chemie Postfach 1150 D-6114 Gross-Umstadt).

A small skin incision was made and Fast Blue (0.5mg in 0.5 ml. water) was injected under vision into each parotid with multiple passes of a 25 gauge needle mounted on a 0.5 ml

syringe. This quantity of Fast Blue was chosen because in preliminary tests it was found to give consistent labelling and the quantity of fluid injected was sufficient to distend the parotid capsule without spillage of the dye into surrounding tissues. The animals were allowed to recover and fed a normal diet for two days. They were then killed and dissected in the manner described above.

Structures removed for examination by fluorescent microscopy were treated in the following manner. After rapid dissection and removal of the structure it was mounted on a microneedle to facilitate handling. The tissue was then immersed in formalin phosphate buffer for 1 hour (12% formaldehyde in 130 mM phosphate buffer at pH 7.4), to provide enhancement of fluorescence (182), and to minimize diffusion of the dye out of the cells (185). The sample was then dehydrated in sucrose phosphate buffer for half an hour (10% sucrose in 130 mM phosphate buffer at ph 7.4). Specimens were next immersed in Tissue-Tek mounting medium, frozen at -20 degrees C and rapidly sectioned at 7 microns using an Ames Cryostat. Each 7th section was collected and mounted on an albuminized slide and stored at room temperature in the dark without coverslips. The sections were examined using a Leitz-Wetzlar Dark field Transmitted Light Fluorescent microscope using transmission filter UG1 Red Suppression Filter BG38 and Suppression Filter K 430. This gave illumination of the specimen with light of wavelength 360 nm corresponding to the absorption peaks of both Fast Blue and Diamidino Yellow (186, 187). The number of labelled and unlabelled cells could be counted visually using the highpower 40X objective, and

expressed as a ratio of cells per high power field (X400). The microscope was equipped with a beam splitter and a Leica M1 camera to allow photographic records to be made. This was done using Fuji 100 ISO colour slide film exposed manually for a period of 90 seconds.

3.223 AURICULOTEMPORAL NERVE LIGATION IN THE RAT

Four rats were subjected to the following experiment. Under general anaesthetic a transverse skin incision was made at the level of the angle of the mandible (Figure 17). Lateral to the posterior facial vein and anterior to the submandibular gland the dissection was deepened with scissors until the medial pterygoid muscle was encountered. The posterior border of the muscle was bluntly dissected away from the surrounding tissues with the aid of the dissecting microscope. At the posterior border the incision was deepened further until the retromandibular vein was visualized. Gentle dissection anterior to the vein usually revealed the auriculotemporal nerve lying on the lateral pterygoid muscle (Figure 18). The chorda tympani could usually be seen crossing the nerve medially. A 10-0 Prolene tie was then applied to the auriculotemporal nerve just lateral to the chorda tympani. The opposite side was sham operated, that is the auriculotemporal nerve was exposed but not ligated. All animals then received an injection of .05 mg. of Fast Blue in 0.5 ml. in each parotid, as described above (3.222). 48 hours later the animals were killed (3.222) and the auriculotemporal nerves and otic ganglia removed for fluorescent microscopy. Prior to fluorescent microscopy the tissue was treated exactly as described above (3.222).

3.3 RESULTS

3.31 AURICULOTEMPORAL NERVE

3.311 RAT

In the subsequent figures the rat is positioned supine with neck extended and viewed from above. The head of the animal is beyond the top of the illustration.

The rat auriculotemporal nerve (Figures 19 to 22) arose from the posterior part of the mandibular division of the trigeminal nerve as it left the foramen ovale. In all the rats the nerve had two roots (one large and one small) which joined immediately but could be traced along the nerve. The auriculotemporal nerve was crossed by a bony ridge which obliquely bisects the foramen ovale. A constant large vein ran medial to this ridge and drained into the large adjacent venous plexus of the base of the skull. The nerve ran posteriorly almost parallel to the ridge, then curved gently laterally on the surface of the lateral pterygoid muscle. It was invariably crossed by the chorda tympani and by two constant branches of the large retromandibular vein. The more medial of these veins crossed ventrally (dorsally in 3/10 animals), and the more lateral crossed dorsally (ventrally in 2/10 animals), although this is variable. Finally the auriculotemporal nerve was invariably crossed by the stylomandibular muscle and ran between the parotid and the ramus of the mandible. Medially, the posterior relation of the nerve was the retromandibular vein and the temporal bone but more laterally the posterior relation was the deep lobe and then the superficial lobe of the parotid. The auriculotemporal nerve had several branches. Early in its course it gave short

motor branches to the medial pterygoid muscle and received branches from the otic ganglion. There was a constant branch to the deep lobe of the parotid which arose just lateral to the second venous crossing. As the nerve approached the superficial lobe of the parotid it always fragmented into a spray of equal branches. In general there were seven branches: there were 4 (4/10 animals) or 5 (6/10 animals) branches which each communicated with a major branch of the facial nerve; there was a single superficial temporal branch which divided into multiple branches to supply the skin of the temple and preauricular area and there were 1 (8/10 animals) or 2 (2/10 animals) auricular branches which supplied the skin of the external auditory meatus. Branches apparently supplying the parotid gland arose from the superficial temporal branches, the auricular branch and from the facial nerve branches in all animals.

3.312 MARMOSET

The anatomy of the auriculotemporal nerve of the marmoset was very similar to that of the rat. The major difference being that because of the difference in facial structure between the two animals, the marmoset foramen ovale was much more deeply placed. The auriculotemporal nerve of the marmoset arose from the posterior portion of the mandibular division of the trigeminal nerve as a single trunk. It was also crossed invariably by the chorda tympani (Figure 23) early in its course and gave motor branches to the medial pterygoid muscle. The vein which formed its posterior relation for most of its length was small and had no branches. A single branch of the nerve always supplied the deep lobe of the parotid and the

nerve was crossed by a ligamentous structure before running between the mandible and the parotid gland. As it entered the parotid capsule the nerve fragmented (Figure 24) in a similar pattern to that seen in the rat with 4 (2/6 animals) or 5 (4/6 animals) branches to the facial nerve, and a single superficial temporal branch in all cases, which appeared to give rise to the auricular branch. Branches apparently supplying the parotid gland could be seen arising only from the superficial temporal branch where ever this was in contact with the gland (Figure 25). Unfortunately the photographic records of this dissection were technically poor.

3.32 THE PAROTID GLAND

3.321 RAT

The parotid gland of all the rats examined consisted of superficial and deep lobes (Figures 21 and 26) which were completely separated by the facial nerve trunk. The deep lobe was cream in colour, had a granular appearance and was roughly pyramidal in shape. Its average weight was 110 milligrams (± 20 mg., N=10). The lobe was the immediate anterior relation of the bony part of the external auditory canal. Anteriorly lay the auriculotemporal nerve, retromandibular vein and the lateral pterygoid muscle. Medially it was in contact with the posterior belly of the digastric, and laterally with the main trunk of the facial nerve. A large vein crossed its ventral surface (Figure 19) and drained into the external jugular which lay laterally.

The superficial lobe of the parotid had an average weight of 470 milligrams (± 40 mg., N=10), and was softer in consistency than the deep lobe. It was a flattened structure

and lay immediately deep to the skin. Anteriorly it was in contact with the extra-orbital lachrymal gland above. Its upper border was grooved by the cartilaginous part of the external auditory meatus. The gland extended as far as the tragus of the ear anteriorly. Posteriorly it was limited by the sternomastoid muscle and the inferior auricular muscle covered the posterior portion of the superficial surface of the gland. Medially it was constantly related inferiorly to the facial nerve trunk and the facial artery and vein, and to the masseter muscle above. The nerves closely related to the gland were the auriculotemporal nerve and branches anteriorly and medially, the facial nerve trunk medially, and the branches to the auricular muscles posterio-medially. The auricular muscle branches were the only branches of the facial nerve to arise from the intra-parotid course of the nerve in the rat. The branch largely supplied the inferior auricular muscle overlying the parotid. A standard haematoxylin and eosin section of the superficial lobe of the parotid is displayed in Figure 27.

In all animals, the parotid duct coursed anteriorly from the midpoint of the anterior border of the gland.

The facial nerve (Figure 26) left the skull via the stylomandibular foramen and was closely related to the sternomastoid and posterior belly of the digastric. The branches to the auricular muscles arose and travelled cephalad deep to the parotid just before the nerve trunk crossed the external auditory canal at the junction between the bony and the cartilaginous portions. At this point it was crossed by a large branch of the facial artery and vein. With the exception

of the branch to the auricular muscles, the facial nerve never formed branches in its course deep to the lower pole of the superficial lobe of the parotid. The nerve formed its major branches deep to the extra-orbital lachrymal gland. As previously described the facial nerve in the rat received multiple branches from the communicating rami of the auriculotemporal nerve.

3.322 MARMOSET

The parotid of the marmoset weighed on average 510 milligrams (N=4). It did not separate readily into superficial and deep lobes. The gland was always situated subcutaneously and anterior to the tragus of the ear and extended to the angle of the mandible and posteriorly to the sternomastoid. The small inferior auricular muscle overlay the posterior part of the surface of the parotid. The gland occupied a wedge-shaped space, the anterior wall of which was made up of the masseter superficially and the posterior borders of the pterygoid muscles and the auriculotemporal nerve, at a deeper level. The retromandibular vein was small or nonexistent in all animals. The posterior wall of the space consisted of the sternomastoid muscle and the bony and cartilaginous portions of the external auditory canal. Within the gland ran the facial nerve and blood vessels, and the parotid duct arose from the lower third of the anterior border of the gland. The appearances of the marmoset parotid stained with haematoxylin and eosin are presented in Figure 28.

The facial nerve in the marmoset left the skull by way of the stylomastoid foramen and came into immediate close relationship with the cartilaginous portion of the external

auditory meatus. It then entered the lower pole of the parotid. The branches to the auricular muscles were given off prior to entry into the parotid. Within the parotid gland the nerve divided into upper and lower divisions. Each received a contribution from the auriculotemporal nerve. The facial nerve then left the anterior border of the parotid and the remaining branches formed. In the marmoset the facial nerve was thus mainly related to the lower pole of the parotid gland.

3.33 THE OTIC GANGLION

3.331 RAT

The otic ganglion of the rat was always situated just medial to the ridge of bone under which the mandibular nerve emerged. It occupied the posterior portion of a small fossa formed by the ridge and the sphenoid bone. The ganglion was about 1mm. by 1mm. by .5mm. in size and nearby ran a large invariable branch of the retromandibular vein and laterally a small artery (Figure 29 and 30). The ganglion had at least 6 branches (Figure 31), but these were too small to trace to their origins, although there was always one constant large branch to the auriculotemporal nerve.

Haematoxylin and eosin sections of a typical otic ganglion is displayed in Figure 32. In comparison to red blood cells (7 Microns) the neuronal cells are approximately 20 to 40 microns in diameter with nuclei 10-12 microns in diameter.

3.3311 FAST BLUE LABELLING

Injection of the parotid gland with Fast Blue, 2 days prior to dissection (as described in Method 3.222), resulted in labelling of the otic ganglion cells with bright blue fluorescence. A typical labelled otic ganglion is displayed in

Figure 33. The mean labelling rate obtained with the technique was 18.5 (± 5, (10 animals 200 highpower fields counted)) cells per highpower field. There was a mean total of 59.9 (± 8, (10 animals, 200 highpower fields)) cells per highpower field, giving a Fast Blue labelling rate of about 31%.

After ligation of the auriculotemporal nerve (3.223) the following results were obtained. The control otic ganglia were labelled at the mean rate of 18 (± 2.5,(40 highpower fields)) cells per highpower field. On the side of the auriculotemporal nerve ligation the mean labelling rate was 0.05 (± .05 (40 highpower fields)) cells per highpower field, a statistically significant difference to t-testing ($p<.0001$). Figure 34 depicts the accumulation of fluorescent dye in the auriculotemporal nerve proximal to the point of ligation.

3.332 MARMOSET

The otic ganglion of the marmoset was invariably situated in close relationship to the posterior part of the mandibular nerve. Thus it was almost adjacent to the origin of the auriculotemporal nerve. In order to expose the ganglion the posterior edge of the foramen ovale was removed (Figure 35). The ganglion was approximately 1mm. by .5mm by .5mm. in size and a representative haematoxylin and eosin section is displayed in Figure 36. The apparent size of the ganglial cells is 20-40 microns in diameter with a 7-10 micron nucleus. The sizes were estimated in comparison to red blood cells.

The otic ganglion was closely applied to the auriculotemporal nerve and so no definite branches could be detected.

3.3321 FAST BLUE LABELLING

Injection of the marmoset parotid gland with Fast Blue 48 hours prior to dissection (3.222) resulted in labelling of the otic ganglion cells with bright blue fluorescence of Fast Blue (Figure 37). The mean labelling rate of the animals studied was 13 (± 4,(6 animals, 60 high power fields)) cells per highpower field. The mean number of cells per high-powered field was 43.2 (± 5, (6 animals, 60 high-powered fields)), giving an average labelling rate of 30%.

The auriculotemporal nerve ligation experiment could not be performed in marmosets due to the cost of the animals.

3.34 THE SUPERIOR CERVICAL GANGLION

3.341 RAT

The superior cervical ganglion of the rat was easily located. It was situated on the medial side of the bifurcation of the common carotid artery in all animals examined. The sympathetic cord could clearly be seen attached to the ganglion, which was a spindle shaped yellowish structure roughly 5 mm. by 1mm. by 1 mm. in size. From its upper pole the sympathetic cord could be seen continuing into the head. The usual posterio-lateral relation of the ganglion was the vagus nerve to which there appeared to be fine connections. The immediate medial relation was invariably the oesophagus below and inferior constrictor above (Figure 38). A representative haematoxylin and eosin section of this structure is shown in Figure 39.

3.342 MARMOSET

The superior cervical ganglion of the marmoset was a round yellow structure approximately 4 mm. in diameter.

Prolongations of the sympathetic chain could be seen from its upper and lower poles. Again the structure was situated on the medial side of the carotid at its bifurcation, although it was more variable in position in the marmoset compared to the rat. The ganglion was always closely related to the vagus and the oesophagus (Figure 40), but, unlike the rat, the ganglion was buried in a constant pad of yellow fat. This sometimes made localization difficult. Figure 41 depicts a representative haematoxylin and eosin section of the superior cervical ganglion of the marmoset.

3.4 DISCUSSION

The cadaver dissections performed confirmed the observations of Baumel (52,120) and Reissner (122), that secretomotor fibres to the parotid arise from the trunk of the auriculotemporal nerve, and its superficial temporal and auricular branches. The number of dissections was limited to four cadavers, because it was felt unnecessary to repeat the extensive and detailed work of these authors.

In the eight dissections no communicating branches from the auriculotemporal nerve to the greater auricular nerve could be demonstrated. There was no detectable innervation of the parotid gland from the facial communicating branches of the auriculotemporal nerve or directly from the facial nerve as claimed by others (52,89,120,122). It may be that this is the result of the small number of dissections, or perhaps these branches are so delicate as to be lost in dissection of the tough parotid parenchyma. Baumel (120) used 3% nitric acid to soften the parotid gland and facilitate dissection. In one

cadaver there were multiple intercommunicating branches between the facial nerve and the auriculotemporal nerve forming a "subtle plexus" as observed by Reissner (122). In this case the parotid gland was soft and easy to dissect. Perhaps these multiple communications are more common than believed by Baumel (122), but are not usually seen due to the difficulty of dissection of the parotid gland.

The method for demonstration of these communications could possibly be improved by the use of fresh unfixed cadavers. The parotid gland could be removed in toto with the facial and auriculotemporal nerve trunks and then subjected to digestive techniques to remove the parotid tissue. In this manner the anatomy of the connections could be studied more completely.

The function of the auriculotemporal-facial interconnections is largely unknown, but believed to be mainly proprioceptive (52). Although the function of these connections is not addressed by the current study, the dissection technique described above of removal of the whole fresh parotid gland and nerves en block, may facilitate such investigation. A method of obtaining functional information about these structures would be to apply the technique of immunofluorescence to fresh parotid gland preparations in order to detect substances such as substance P, Vasoactive Intestinal Peptide, Calcitonin Gene-Related Peptide, Tyrosine Hydroxylase, Somatostatin, Enchephalin, Neuropeptide Y and others (189,190, 191,192,193). There is evidence that some of these substances act as neurotransmitters (189,194,), have functional activity (195) and act as markers for neuronal

types (196). By this means functional information regarding this incompletely understood group of nerve interconnections could readily be obtained.

In the eight dissections the parotid innervation appeared to arise from the superficial temporal and auricular nerves, which are branches of the auriculotemporal nerve. The branches innervating the parotid arose from these nerves where they were in contact with the parotid gland and were present both at superficial levels and also deep to the gland. The auricular and the superficial temporal nerves are both related to the deep surface of the gland and its posterior margin. Thus injury of the nerve at these sites where both sudomotor and parotid secretomotor fibres coexist could potentially lead to the development of the abnormal neuronal connections resulting in auriculotemporal syndrome. This would fit in well with the observation (see 2.2) that patients with the condition have an increased incidence of ear numbness and hence have evidence of increased incidence of damage to the auricular branch of the auriculotemporal nerve.

The observation that the trunk of the auriculotemporal nerve is a relatively fixed point may also have implications for the development of auriculotemporal syndrome. The trunk is fixed by virtue of three factors. Firstly, it is in a narrow space between the mandible and the temporal bone, a factor which could make the nerve vulnerable to compression injury by local haematoma, infection or distension of the parotid capsule. Secondly, at this point the nerve breaks up into 5 or 6 major branches within the substance of the parotid gland. Any movement of the gland would thus tend to be transmitted to

the point at which the nerve divides. Thirdly, the auriculotemporal nerve tends to be fixed to the dense parotid capsule at the point of its division. Thus the auriculotemporal nerve trunk could be indirectly damaged by small movements of the parotid gland at the time of surgery, or by local infection or haematoma. This conjecture is further supported by the observations (see 2.2) that auriculotemporal syndrome is more frequent after complicated parotidectomies, and when a large tumour mass is removed. In the latter case, a larger tumour may require more vigorous retraction and parotid manipulation thus making auriculotemporal nerve injury more likely.

The human dissections presented here have established that the nerve injury necessary to produce auriculotemporal syndrome could occur even at superficial levels. The dissections also serve to emphasize the large number and superficial position of the parotid branches, an observation which is at variance with the work of Baumel (120) who believed these branches to be somewhat deeper, although describing them as numerous inconstant twigs.

The auriculotemporal nerves of the rat and the marmoset were anatomically quite similar and had several parallels to that of man. In both these animals the nerve arose by two roots from the posterior portion of the mandibular division of the trigeminal nerve. The mandibular division of the trigeminal nerve in the rat and the marmoset as in man, left the skull by way of the foramen ovale in the sphenoid bone. In the rat, the foramen was divided by an oblique spur of bone not present in man or the marmoset. In all three animals the

mandibular division was similar, with major branches comprising inferior alveolar nerve, lingual nerve, buccal nerve and auriculotemporal nerve. In the rat unlike man or marmoset, the motor innervation of the pterygoid muscles appeared to be derived from the auriculotemporal nerve trunk. The trunk of the auriculotemporal nerve in the two experimental animals was relatively long when compared to that of man (120). As in man both animals had a constant twig of innervation of the deep lobe of the parotid arising from the trunk. In all three species the auriculotemporal nerve divided into a terminal spray of branches at the posterior border of the mandible, but the number and arrangement of these branches varied. Baumel describes six branches of this nerve in man (120), comprising 2 communicating branches, 2 branches to the external auditory meatus, a branch to the anterior auricle and a superficial temporal branch. In the rat and marmoset there were usually at least 5 communicating branches to the facial nerve, one to each major branch. However, branches to the external auditory canal were less numerous than in man, there being a single branch in each animal, with that of the marmoset arising from the superficial temporal branch. Both animals possessed a single superficial temporal nerve.

The constancy of auriculotemporal-facial nerve interconnections has been confirmed in baboons (197) and in other mammals (198,199). Although the function of these connections is still unclear their role is likely to be an important one in view of their evolutionary preservation. The parotid innervation was derived from the superficial temporal and auricular branches in the rat and marmoset and was similar

in this respect to the human situation. In the experimental animals no parotid branches could be seen to arise from the communicating branches or from the facial nerve, a point which is in dispute in humans (120, 122).

The relations of the auriculotemporal nerve vary between the species. These variations are probably related to the upright stance and longitudinally compressed face of man when compared to the rat or marmoset. In man the nerve is related to the lateral pterygoid and the tensor veli palati at its origin. The upper root runs on the greater wing of the sphenoid, whilst the lower root is deeper and indented by the middle meningeal artery where it crosses the chorda tympani. The nerve then comes into contact with the medial aspect of the temporomandibular joint and runs beneath the stylomandibular ligament. At the level of terminal branching of the auriculotemporal nerve the nerve becomes closely related to the maxillary and superficial temporal arteries. The nerve is related posteriorly to the upper part of the parotid and finally emerges from behind the gland to form superficial temporal branches running with the superficial temporal vessels.

By comparison in the marmoset and rat the nerve runs its course on the lateral pterygoid muscle and is crossed by the chorda tympani. In addition in the rat and to a lesser extent in the marmoset the constant posterior relation is the pterygoid plexus of veins as well as the sphenoid. There are one or two tributaries of this vein which cross the nerve and course anteriorly in these experimental animals. The nerve is crossed by the stylomandibular ligament in both the animals

just prior to its division into terminal branches. The stylomandibular ligament is more muscular in the rat. In neither animal does the nerve come into close relationship with the maxillary artery which is a much deeper structure. In summary, the anatomy of the auriculotemporal nerve is strikingly similar in these three species.

The anatomy of the facial nerve in the rat, the marmoset and the human is similar in regard to the initial course of the nerves. The facial nerve arises from the stylomastoid foramen of the temporal bone and courses anteriorly and ventrally between the mastoid and styloid processes to cross beneath the external auditory canal at the osseo-cartilaginous junction. In the human (200) this course is short compared to the rat and marmoset. In man and marmosets there is a small posterior auricular branch of the facial nerve given off before the nerve enters the parotid. In the rat the branch leaves the facial nerve within the gland. The human facial nerve also gives off, close to the stylomastoid foramen, small branches to the digastric and stylohyoid muscles, but these branches were not apparent in either the rat or marmoset. The facial nerve of man then divides into temporomandibular and cervicofacial divisions between the deep and superficial lobes of the parotid. It gives off the remainder of its branches in this plane whilst it is deep to the gland. There are 8 recognizable patterns of division of the nerve (200).

The facial nerve of the marmoset, however, forms into two divisions within the parotid but the remaining branching does not occur until the divisions have left the anterior border of the gland. The facial nerve is related only to the lower pole

of the parotid. In the rat the facial nerve courses between the deep and superficial lobes of the parotid and does not divide until it has left the anterior border of the gland. The nerve is again only related to the lower pole of the parotid.

Thus it appears that, in relation to the facial nerve, the parotid of the rat and marmoset is "moved" posteriorly and dorsally when compared to human morphology. This would make facial nerve injury less likely during parotidectomy in these experimental animals, particularly if dissection was confined to the upper pole of the gland.

Histologically the parotid glands of man (201), the rat and the marmoset are similar. The glands are all purely serous and are composed of a number of lobules bound together by connective tissue. Each lobule is filled with tubular or saccular alveoli. The alveolar cells are filled with acidophilic zymogen granules (201) and have spherical nuclei. The different appearance of the zymogen granules between marmoset and rat is probably related to different secretion states of the parotid glands at time of death. In both rats and marmosets there can be seen multiple circular alveoli, interlobular septa and occasional ducts with characteristic cuboidal cells. There is little intraglandular infiltration of fat in the normal parotid in the two experimental animals, but the human gland is often infiltrated with adipose tissue.

Anatomically the parotids of humans, rats, and marmosets are similar. The glands have the same size, shape and location, and ductal arrangements are much the same. In marmosets and rats the parotid glands form about 0.3% of body weight. The main morphological difference lies in the fact

that the marmoset does not appear to have separate deep and superficial lobes, the distinction being made by relationship to the facial nerve. In the rat, however, there are distinct deep and superficial lobes with no apparent interconnection and completely individual gross appearance. The significance of these differences is not clear. There are no significant differences in histological appearance between the lobes.

The histology of the otic and superior cervical ganglia of man (201,202) is identical to that seen in the rat and marmoset. These ganglia are composed of cells of varying size, with a single nucleus and prominent nucleolus. The cytoplasm is basophilic and the cells tend to be triangular in shape. There are some species differences in terms of the neuronal packing of the superior cervical ganglion (203) the higher mammals showing a much higher ratio of neurones entering the ganglion to neurones leaving, implying greater amplification of sympathetic activity.

Marmoset otic ganglia tend to be flatter and smaller than those of the rat. In addition the cells are less densely packed but the neuronal size is similar.

Anatomically, the position of the otic ganglion varies between species. In the rat it occupies the medial portion of the foramen ovale in a small fossa formed by an oblique spur of bone which bisects the foramen. The otic ganglion of the marmoset is just under the posterio-medial lip of the foramen ovale closely applied to the auriculotemporal nerve. These otic ganglia are approximately the same size and in the rat there are at least six nerve connections associated with the structure.

The human otic ganglion is a reddish structure closely attached to the posterio-medial side of the mandibular branch of the trigeminal nerve. It is usually just below the foramen ovale on tensor palati and has seven nerve interconnections which are: a parasympathetic root formed by the lesser petrosal nerve, a sympathetic root from the periarterial plexus around the middle meningeal, a communicating branch to the auriculotemporal nerve, two connecting branches to the chorda tympani, and motor branches to the tensor palati and tensor tympani (202).

The technique of retrograde neuronal labelling was used to demonstrate that these ganglia are responsible for parotid innervation in both marmosets and rats. The technique is specific and reliable, provided precautions are taken to minimize diffusion of dye out of labelled cells (186). These steps included limited use of formalin fixatives and rapid dissection and low temperature tissue processing. Under these conditions there was reproducible labelling of the otic ganglion after parotid injection. Diffusion of dye within the otic ganglion did not present a problem, as there was little neuroglial labelling noted adjacent to labelled neurones. In rats about 31% of otic ganglion cells were labelled, while 30% of marmoset ganglion cells were labelled. Not all of the cells were labelled presumably because, firstly, dye did not reach all of the parotid gland, and secondly, not all otic ganglion neurones supply the parotid (120). In later experiments it was found that the labelling rate increased slightly after one week (Chapter 4) indicating a degree of diffusion of dye within and throughout the parotid in this time interval.

It could be argued that the fluorescent dye had diffused from the parotid in these experiments and had resulted in indiscriminate labelling of a local ganglion which was not, in fact, the otic. This is unlikely for several reasons. Firstly, strong anatomical data has been presented that the ganglion is the otic, in that it was intimately associated with the auriculotemporal nerve, and there were no other local ganglia of this size. Secondly, in rats the labelling of the ganglion was completely abolished by ligation of the auriculotemporal nerve and the dye could be visualized proximal to the tie. This implies that the dye labelling the otic ganglion was travelling in the auriculotemporal nerve and not attaining it by any other route, either by direct diffusion or by retrograde neuronal transport. Thirdly, preliminary experiments showed that injection of the skin in the distribution of the auriculotemporal nerve resulted in no labelling of the otic ganglion, an observation which is confirmed in later double labelling experiments (Chapter 4). Thus, the cells in the small ganglion adjacent to the auriculotemporal nerve were labelled specifically by parotid injection of axons which travel in the auriculotemporal nerve. Therefore this ganglion must be the otic ganglion. These experiments also confirm that the auriculotemporal nerve carries the parotid secretomotor fibres in the rat, as it does in man.

Although the auriculotemporal nerve ligation experiment could not be performed in marmosets, the anatomical situation is probably analogous. Collaborating evidence for this statement is gained from the observation in one marmoset that

auriculotemporal nerve injury resulted in a reduced labelling rate of the otic ganglion at one week (Chapter 4).

The anatomy of the superior cervical ganglion is identical for rats and marmosets. The ganglion lies medial to the bifurcation of the common carotid and is a spindle shaped structure. The same situation holds for man. The ganglion lies on the longus capitus muscle and is medial to the carotid division (202).

In summary, the anatomical and histological similarities of the parotid, auriculotemporal nerve, otic and superior cervical ganglia have been established between human, rat and marmoset. The similarities are such that either of these animals could be readily used as a model for study of parotid surgery and the auriculotemporal syndrome. Any model developed with these animals could, on these grounds, be validly extrapolated to man. In addition, the dye Fast Blue has been successfully used in these experimental animals to study the parasympathetic innervation of the parotid and verify the identity of the small otic ganglion.

CHAPTER 4 AN ANIMAL MODEL OF AURICULOTEMPORAL SYNDROME

4.1 INTRODUCTION

4.11 GENERAL

Animal models have been extensively used in the past in order to promote the understanding of biological aspects of human diseases and in order to assess and develop new treatment techniques. The use of animals generally allows application of techniques which it would not otherwise be possible to employ, and to scrutinize a disease state in much greater detail, with much larger numbers than would be possible in humans. This is particularly important in rare human disease states where scientific evidence may be anecdotal and conflicting.

The success of animal models relies heavily on the interspecies similarities of anatomy, biology, physiology and biochemistry. These similarities are strong throughout the order of mammals and for this reason mammals are usually chosen as an experimental animal.

Unfortunately very few human diseases occur naturally in other mammals, and so chemical, mechanical or viral means must be employed to induce of the desired disease state. Because of the artificial induction of disease, pathological responses obtained may only partially mimic human disease. In order that a model be valid, it is important to examine closely the

disease state induced in the experimental animal to ensure that it simulates all known aspects of the human disorder.

Auriculotemporal syndrome is an ideal condition to examine using an animal model. Although it is a common condition after parotidectomy the number of operations is small, so the that condition is a rare occurrence in the general population. The opportunities for study of auriculotemporal syndrome have thus been infrequent, and, with some notable exceptions (70,105,110) have consisted of anecdotal reports involving a few patients. As alluded to in earlier discussion, the paucity of studies has resulted in much confusion and controversy in the literature. Aetiological theories of auriculotemporal syndrome remain numerous and unproven. Development of better treatment modalities depends on complete and thorough understanding of the aetiology of the condition. In addition, there are many unanswered questions such as: What nerve types are involved in the genesis of the condition? Are the parasympathetic secretomotor fibres the mediators or could it be parasympathetic parotid vasodilator fibres which form aberrant connections with the sweat glands? At what level does nerve injury occur? Is crossed regeneration the correct aetiological theory? Why do barrier methods of prophylaxis fail when fascial interposition techniques for treatment of the established condition seem to succeed? Can nerve regeneration be prevented by the use of drugs or other means?

An animal model of auriculotemporal syndrome may perhaps allow identification of the aetiological mechanism of the

condition and provide answers to some of these questions: thus it was undertaken to develop such a model.

4.12 THE CHOICE OF ANIMAL

Mammals were to be used for ease of comparison at a basic level. Animal selection should also made on the basis of the similarity to mankind of attributes such as the presence of skin sweat glands, and local anatomy and neuroanatomy of the parotid. The animals need to be in ready supply, be easy to handle feed and house and be relatively inexpensive. In addition the animals need to have a life span of at least 3 months which is the time interval required for development of auriculotemporal syndrome in man (Chapter 1).

The marmoset monkey and the rat were studied (Chapter 3) and satisfy most of these criteria, in that both possess parotid glands with innervation and local anatomy similar to that of man. There were however some important differences in the occurrence and type of sweat glands between these species.

Man possesses both apocrine and eccrine sweat glands in the hairy skin (204). The apocrine glands are confined to the axilla, chest, face and perineum and are responsible for elaboration of sexual scents (207). They are probably adrenergically innervated (208), but do not produce true sweat and do not respond to pilocarpine. The eccrine glands are more widely distributed over the body (207) but are concentrated on the palms and feet. They are mostly concerned with thermoregulatory sweating, generally have cholinergic innervation (208) and are responsive to pilocarpine. There remains some controversy regarding sweat gland innervation (209). It appears that both apocrine and eccrine glands may

have both adrenergic and cholinergic innervation in man and maraques (209,210). The cholinergic innervation is more dense around eccrine glands and around apocrine ducts. It is likely that pilocarpine-activated sweat glands distributed about the face, trunk and limbs of man (35,38,211) are of the eccrine type. The type and distribution of sweat glands in maraques (210,211), Rhesus monkey (204) and man are similar, but little is written concerning marmoset monkeys.

The rat, however, like most small furred animals, has sweat glands only on the pads of the feet (148,204,205,206). There is no sweating apparatus in the hairy skin.

On these bases it was proposed to use both marmosets and rats in the development of a model of auriculotemporal syndrome. The absence of sweat glands in the rat does not detract from the use of this animal, considering that auriculotemporal syndrome can consist of flushing and piloerection in addition to sweating in man. It was intended that the use of the marmoset, a primate, would give increased validity of the model in extrapolation to the human syndrome. In the course of the experiments the presence, type, and pharmacological reactivity of marmoset facial sweat glands would also be studied.

4.13 EXPERIMENTAL INDUCTION OF AURICULOTEMPORAL SYNDROME

Earlier authors (70) suggested that aberrant neuronal regeneration was the most likely basis for the development of auriculotemporal syndrome (Chapter 1), although the mechanism was not confirmed by quantitative experiment. There is on-going conflict (1.15) about the level that such regeneration might take place, whether it be at the cut surface of the

parotid gland directly into the skin sweat glands, or at a deeper level in the auriculotemporal nerve. These alternatives have differing implications for treatment and preventative measures.

In terms of the investigating the likely aetiology and the possible levels at which nerve damage might occur, it would be appropriate to attempt to induce auriculotemporal syndrome in the experimental animals firstly, by simple parotidectomy and secondly, by direct auriculotemporal injury at a point deep to the parotid gland.

4.14 DETECTION OF AURICULOTEMPORAL SYNDROME IN EXPERIMENTAL ANIMALS

Human auriculotemporal syndrome is detected by means of sweat tests, observation of gustatory flushing or skin temperature changes and other means (Chapter 1). These methods may be applicable in animals with sweat glands. Direct observation of gustatory flushing may be possible. However all the methods are non-quantitative, may suffer from observer error and may not be reproducible.

In man, development of auriculotemporal syndrome equates to, in neurological terms, the development of abnormal neuronal projections of the otic ganglion to the skin. A technique applicable to the detection of such abnormal connections in animals, would be that of retrograde neuronal labelling using fluorescent tracers (182, 184, 185, , 187, 188, 212). This technique was discussed in Chapter 3. It is proposed to use the technique of double retrograde labelling. The otic ganglion cells supplying the parotid are labelled by injection of dye into the parotid at the start of the experiment. At the completion of the study a second dye is

injected into the skin only. The technique would allow the identification and quantitation of neurones that originally projected to the parotid, which projected to the skin after the experimental procedure. Such neurones would be the ones labelled by both dyes, that is the dye injected into the parotid initially and the dye injected into the skin at the end of the experiment. The presence of double-labelled otic ganglion neurones would establish the existence of abnormal neuronal connections from the otic ganglion to the skin and thus auriculotemporal syndrome. Cell counting techniques can be used to allow quantitation of the effect.

The fluorescent tracers employed must be capable of remaining in neurones for 2-3 months without loss from the cell by either diffusion or leakage from a damaged axon. The cytoplasmic label Fast Blue has these properties (188). In addition the tracers should fluoresce at the same excitation wavelength to allow ease of identification of double-labelled cells. Furthermore, the second tracer used should be slow to diffuse through tissues so that its effect is confined to the skin, and it should ideally label a different cellular feature to facilitate identification. A convenient dye to use for the second tracer is the nuclear label Diamidino Yellow (187). With the combination of these two dyes, double labelled cells have bright blue fluorescent cytoplasm and yellow fluorescent nuclei. It is known that Fast Blue and Diamidino Yellow label the cells of the rat superior cervical ganglion (188), and it has been established that otic ganglion cells are readily labelled by Fast Blue (3.31), but it is not known if Diamidino Yellow can effectively label the rat otic ganglion cells.

Thus a series of experiments was devised to establish these techniques in an animal model of auriculotemporal syndrome. In preliminary experiments the facial sweat glands of the marmoset were studied, and the ability of Diamidino Yellow to label otic ganglion cells in the rat was assessed.

4.2 METHOD

4.21 GENERAL

The experiments outlined have been conducted with the approval of the Animal Ethics Committee of the Queen Elizabeth Hospital (Appendix 4). Rats used in the studies were mature animals (Rattus rattus Strain Sprague-Dawley) of either sex weighing approximately 300 grams, and aged between 10 and 12 weeks. Marmosets (Callithrix jacchus) were adult animals of either sex aged from 4 to 8 years and of approximately 350 grams in weight. Animals were individually housed and allowed free access to water and a pellet diet throughout the duration of the study except when fasted overnight prior to general anaesthetic. Post-operative analgesia appeared unnecessary after the surgical procedures as all animals immediately returned to preoperative feeding and activity levels without constitutional disturbance. At the completion of the experiments the rats' weight had increased to approximately 500 grams. Marmoset weights remained constant throughout the study period.

4.22 ANAESTHETIC PROCEDURES

The anaesthetic technique varied depending on the animal and the procedure being performed.

In the rat, ether was found to be a satisfactory agent for procedures requiring only short periods of anaesthesia, such as for injection of dye. The animal was placed in a glass chamber saturated with ether vapour, until unconsciousness was induced. This state was judged by disappearance of normal righting reflexes. The animal was then removed from the container and the procedure carried out rapidly under a fume hood. The anaesthetic was supplemented as necessary by the use of a nose cone containing saturated ether vapour. The technique allowed a maximum operating time of 10 minutes and the animals made a rapid and complete recovery from anaesthetic 30 seconds to 1 minute after removal of the nose cone. The method had the advantages that it was safe, with consistent results and a relatively large margin for error. No rats died from ether anaesthetic. This was an important consideration, as the loss of an animal at the end of a 2 or 3 month study would have been a major set-back.

Ether had the disadvantages that it gave a relatively short duration of usable anaesthesia and that it is a major explosion risk. It was therefore not an appropriate anaesthetic for prolonged dissections using the operating microscope which had a definite spark risk. For these situations, in the rat, sodium pentobarbitone (60 mg./ml.) was used. The animals were fasted overnight to minimize the risk of regurgitation and aspiration of food; they were also weighed. Using a 27 gauge needle and a 1 ml., syringe each animal was given an intraperitoneal injection of pentobarbitone at the rate of 60 mg. per kg. body weight. Injections were given in the right lower abdominal quadrant in

order to avoid the caecum which tends to lie on the left (176). Anaesthesia developed gradually over the ensuing five minutes and deepened to an extent sufficient to allow surgery in a further five minutes. Anaesthetic depth was judged to be correct when normal responses to painful stimuli had been completely abolished.

By these means a stable anaesthetic was obtained for a period of 60 to 90 minutes. Occasionally, a supplementary intraperitoneal dose of pentobarbitone (6 mg./kg.) was necessary. Recovery from anaesthetic usually took 2 to 4 hours. Initially many animals died either during the anaesthetic or in the early recovery phase. Experimentation with the dose of pentobarbitone demonstrated that the agent has a very narrow therapeutic window for anaesthesia, with slightly higher doses causing death by respiratory depression and lower doses resulting in an inadequate effect. The most efficient pentobarbitone dose was found to be 60 mg./kg.. Deaths in the first 2 postoperative hours were largely a consequence of prolonged respiratory depression followed by cardiac failure. The death rate was ameliorated by allowing the rats to recover in an environment of 70% oxygen in a chamber maintained at 37 degrees Celsius. No post operative deaths were encountered after introduction of these measures.

Animals undergoing auriculotemporal nerve crush operations frequently suffered a profound bradycardia followed by cardiac arrest during or immediately after crushing the nerve. This was believed to be due to a vagally mediated reflex akin to the diving reflex, initiated by stimulation of the auriculotemporal nerve. Premedication of each animal by

intramuscular injection of 60 micrograms of atropine sulphate (600 micrograms /ml aqueous solution) abolished this difficulty.

Marmosets, because of their high cost, required safe reliable anaesthetic agent. The narrow therapeutic window of pentobarbitone made the drug unsuitable for use in these animals. The agent "Saffan" (Glaxo 9 mg. alphaxalone and 3 mg. alphadalone acetate per ml.) is a synthetic steroid with good analgesic and muscle relaxant properties, which has been used by others (213) to provide safe anaesthetic in marmosets. An intramuscular dose of 18 mg./kg. was found to provide 45-60 minutes of operating time after an induction period of 10 minutes.

After an overnight fast each marmoset was caught by the handler using leather gauntlets and weighed using a tared weighing box. The animal was then grasped by the thorax with one hand and with the handler's other hand holding both legs in extension. An intramuscular injection of Saffan was given into the quadriceps muscle using a 27 gauge needle and a one ml. syringe. For full anaesthesia a dose of 24 mg./kg. was given in addition to 60 micrograms of atropine sulphate. This resulted in a stable anaesthetic of 60 to 90 minutes duration after a short induction period. For more prolonged procedures the anaesthetic was supplemented by further intramuscular injections at the rate of 6 mg./kg.. After the procedure the marmoset was placed in a chamber warmed to 37 degrees Celsius and allowed to breathe an atmosphere of 50% oxygen. The animal was usually fully recovered by 45 to 60 minutes and was

returned to the cage whereupon there was an almost immediate return to normal activity and eating patterns.

For procedures which did not demand such a profound depth of anaesthesia, marmosets were given a dose of 12 mg./kg. of Saffan via the same route. This provided sufficient sedation to carry out injections of dye, Starch-iodine testing, removal of sutures and other minor procedures. The recovery time was proportionally shorter and the anaesthetic could be repeated daily if necessary without apparent ill effect.

Using these techniques 6 marmosets were anaesthetised a total of 26 times without death or other complication.

4.23 DIAMIDINO YELLOW LABELLING OF THE RAT OTIC GANGLION.

Diamidino Yellow Hydrochloride was obtained from Dr. Illing (Dr. Illing GmbH and Co KG Makromolekulare und Pharmazeutische Chemie Postfach 1150 D-6144 Gross-Umstadt) and a aqueous suspension of 1 mg. per ml was made and used for parotid injections in 0.5ml. aliquots.

Three rats were treated as described in 3.222. Under ether anaesthetic the parotid glands were exposed and each injected with 0.5 ml of Diamidino Yellow suspension. The animals were allowed to recover and killed 2 days later. The otic and superior cervical ganglia were dissected and removed as previously described. The specimens were handled, processed and examined in an identical manner to that described in 3.222. The Diamidino Yellow labelling rate of the otic ganglion was estimated. Photographic records of the findings were made as before.

Due to the cost of the animals similar preliminary experiments were not carried out on marmosets.

4.24 FACIAL SWEAT GLANDS OF THE MARMOSET

From each of the 6 experimental marmosets biopsies of the facial skin over the parotid were obtained under light Saffan anaesthesia at the time of parotid injection. Biopsies were immersed in phosphate buffered formaldehyde (10% formaldehyde in 130mM phosphate buffer pH 7.0) and sectioned and stained with haematoxylin and eosin according to standard techniques in the Histopathology Department of the Queen Elizabeth Hospital.

The sections were examined by light microscopy using an Olympus microscope with 10X and 40X objectives. An Olympus PM-10-A Photomicrograph System was fitted to the microscope to allow photographic records to be made. Fuji Colour Slide film 100 ISO was used with automatic exposure control.

Three of the marmosets were examined for the ability to produce facial sweat. Under light Saffan anaesthesia both sides of the face were painted with iodine solution and dusted with starch powder in an identical manner to that performed in humans for the starch-iodine test (2.2221). An intramuscular injection of 0.05 ml. of a 2% aqueous solution of pilocarpine, was given. The face was then inspected for evidence of sweating and photographed. The effects of the pilocarpine were reversed with an intramuscular injection of 60 micrograms of aqueous atropine sulphate solution.

4.25 ANIMAL MODEL OF AURICULOTEMPORAL SYNDROME

In the following experiments 30 rats and 6 marmosets were used. The experimental protocols are summarized in Figures 42, 43, and 44.

Initially all animals were injected with 0.5 mg. of Fast Blue in 0.5ml. of water into each parotid (3.222) under the appropriate anaesthetic (4.22).

Animals were next divided at random into two equal groups. One half underwent superficial parotidectomy (4.26) and the other half the auriculotemporal nerve was injured by crushing (4.27). To allow Fast Blue labelling of the otic and superior cervical ganglia two days were allowed to elapse before the selected procedure was carried out. Sham operation was undertaken on the contralateral side in all cases.

All operations were performed using clean techniques. The operating table and dissecting instruments were cleaned with chlorhexidine solution (0.05% Chlorhexidine gluconate 0.5% Cetrimide in 70% ethanol). The appropriate area of the animal was shaved and cleansed with the above antiseptic and the surgeons hands were thoroughly washed with soap and water. An Intervascular "Vascular Graft Cautery" model 629-03 (Neuromedics Inc. Texas U.S.A.) was used when necessary to obtain haemostasis, and a Varistim III Surgical Nerve Locator was used to detect the facial nerve during parotidectomy. All surgical wounds were sutured with 6-0 silk sutures which were removed when necessary at 21 days under light anaesthetic.

Four days prior to sacrifice all animals were observed for signs of abnormal gustatory phenomena. Marmosets were deprived of food for 24 hours and starch-iodine solution applied to both sides of the face after shaving under light general anaesthetic. On recovery the animals were observed whilst eating for signs of gustatory sweating or flushing. Rats were deprived of solid food and faeces for 24 hours. They

were then observed for gustatory piloerection and, after a facial shave, for gustatory flushing. Flushing was difficult to observe in any quantitative or reproducible manner and so attempts were made to measure skin surface temperature with a small thermocouple. These attempts were not successful.

Two days prior to sacrifice each animal received an intracutaneous injection of 0.5 mg. of Diamidino Yellow as an aqueous suspension in 0.2 ml. to each side of the face in the distribution of the auriculotemporal nerve. Injections were made under light anaesthetic using multiple passes of a 27 gauge needle on a 0.5ml. syringe. They were made in a one square centimeter area centred on the line between the tragus of the ear and the corner of the eye, an area which had been shown by dissection to correspond to the centre of the area of skin distribution of the auriculotemporal nerve. The dye was placed in the skin so as to raise an obvious yellow coloured skin wheal. If the injection was too deep no colour could be seen in the wheal. To minimize dye escaping by running out of the needle track dye was only injected with the 1 cm. long needle inserted to the hilt.

Two days after final injection the animals were sacrificed by overdose of anaesthetic and cardiac puncture as described in section 3.221. For rats 3 animals from each group were sacrificed at 10 days as controls, and 6 from each group at 56 and 84 days. For marmosets where numbers were limited, 1 from each group was killed as a control and the remaining 2 animals in each group were sacrificed at 84 days.

After the animals were killed rapid microdissection was performed to remove the otic and superior cervical ganglia

(3.222). The superior cervical ganglia were removed in these studies, as an internal control in order to check that both dyes were present and active, that the fluorescent microscope was functioning correctly and to give an indication of overall consistency of the technique between animals and between opposite sides of the same animal. The ganglia thus obtained were processed by the method described (3.222) for the handling and preparation of material prior to fluorescent microscopy. The specimens were then observed under the fluorescent microscope. For each specimen the number of non-labelled, Fast Blue labelled, Diamidino Yellow labelled and double labelled cells were counted for 10 high powered fields (400X), and photographs taken as previously described (3.222). The mean frequency of occurrence of the variously labelled cells was calculated for each group and compared to the sham operated side, the control group and to the alternate procedure, using student t-tests to test statistical significance. A difference was considered significant if $p<.05$. Statistical analysis was not applied to the data from marmosets.

In addition to the ganglia all animals had both parotids removed and weighed. Those animals in which auriculotemporal nerve crush was performed had the crushed nerve removed in order to inspect it for evidence of damage. The specimens of auriculotemporal nerve and parotid were processed and haematoxylin and eosin staining was performed according to the standard methods employed in the Department of Histopathology at the Queen Elizabeth Hospital. Photomicrographs were obtained as described in 3.221, when necessary.

4.26 SUPERFICIAL PAROTIDECTOMY

Animals were anaesthetised and prepared as already described (4.22) and placed in the lateral position. The operating microscope previously described (3.221) was used throughout. A vertical skin incision was made from just anterior to the tragus of the ear to the angle of the mandible and extended inferiorly as required. It was necessary to divide the inferior auricular muscle of the ear and branches of the facial nerve supplying it, in order to obtain adequate exposure. The skin and fat over the parotid surface was mobilized. The main branches of the auriculotemporal nerve were carefully preserved as was the facial nerve. By meticulous dissection and use of the nerve stimulator (4.25) 70-80% of the superficial lobe of the parotid was removed. Proportionally more of the upper pole of the superficial lobe was removed than the lower pole in order to avoid any damage to the facial nerve deep to the lower pole of the gland in these animals (3.32, 3.33). The upper pole of the gland could not be completely removed either, due to the proximity of the auriculotemporal nerve at the posterio-medial edge of the gland. Having removed as much of the gland as possible careful haemostasis was obtained and the skin closed.

Sham operation included division of the inferior auricular muscle and nerves, exposure of the parotid and limited mobilization including identification of the auriculotemporal and facial nerves. The parotid gland itself was carefully preserved.

The operation was almost identical in marmoset and rat.

4.27 AURICULOTEMPORAL NERVE CRUSH INJURY

The animals were prepared and anaesthetised as described (4.22) and placed in the supine position with the neck extended. A transverse incision was made across the neck between the angles of the mandible. By blunt dissection, with the aid of the operating microscope, the incision was deepened lateral to the posterior facial vein and anterior to the submandibular gland. The auriculotemporal nerve was then exposed by careful dissection as described in section 3.223. The nerve was mobilized and grasped with fine jeweller's forceps and compressed for 30 seconds, so that a visible indentation remained when the forceps were released (Figure 45). The nerve was injured between the point of crossing of the chorda tympani and the branch to the deep lobe of the parotid. At this point there would certainly be secretomotor fibres to the parotid and sudomotor fibres to the skin in coexistence. Occasionally, the two roots of the auriculotemporal nerve were separated by dissection and so it was important to ensure that both branches were crushed by the forceps.

The procedure was performed in an identical manner in marmosets, but due to the narrow mandibular angle and the different facial structure of the marmoset the procedure was much more difficult.

In the corresponding sham operations the auriculotemporal nerve was exposed and mobilized but not crushed.

4.3 RESULTS

4.31 FACIAL SWEATING IN MARMOSETS

Facial skin biopsies showed the presence of sweat glands in the marmoset. An example of a marmoset facial sweat gland is displayed in Figure 46. The glands were most probably apocrine in type as there was evidence of apical decapitation of the cells. The secretory portion of the gland was located in the dermis and consists of a single layer of eosinophilic secretory cells surrounded by myoepithelial cells. Apocrine secretion was visible in the lumen of the duct. The glands were present in moderate numbers in the facial skin of the marmoset. No eccrine type sweat glands were encountered in the sections examined.

The function of the marmoset facial sweat glands was examined using starch iodine testing with pilocarpine stimulation. Figure 47 demonstrates the results of such a test. There was no evidence of function of the facial sweat glands to pilocarpine stimulation in any animal. The dose of pilocarpine did, however, result in profuse salivation and sweating of the palmar and plantar surfaces of the hands and feet. The submental patch of dark discolouration of the skin seen in Figure 47 was created by saliva dribbling from the mouth.

The light Saffan anaesthesia under which the tests were performed allowed the animal to cough and maintain its airway despite the profuse salivation. Intramuscular atropine rapidly and completely reversed the effects of pilocarpine.

4.32 DIAMIDINO YELLOW LABELLING OF THE RAT OTIC GANGLION

Injection of the rat parotid with Diamidino Yellow resulted in labelling of the otic ganglion in all three rats tested. The nuclei of otic ganglion cells were labelled with intense lemon fluorescence (Figure 48). The cytoplasm of the cells was also weakly labelled. The labelling rate was 15 (± 3.2,(3 animals, 60 highpower fields)) cells per high power field of 63 (± 6, (3 animals, 60 highpower fields)) cells, giving a labelling rate of about 24%. This is slightly less than the otic ganglion labelling rate obtained with Fast Blue (31%)(3.3311).

Auriculotemporal nerve ligation experiments were not repeated with Diamidino Yellow. The dye could not be tested in an equivalent fashion in marmosets for economic reasons.

4.33 ANIMAL MODEL OF AURICULOTEMPORAL SYNDROME

4.331 SUPERFICIAL PAROTIDECTOMY IN THE RAT

A total of 15 rats underwent superficial parotidectomy. There were no observed wound infections, facial nerve palsies or other complications of the procedure. No rats died during the course of the experiment. The mean weight of parotid on the non-operated side was 473 milligrams (± 40 mg. N=15) and on the operated side 259 milligrams (± 38 mg., N=15), a statistically significant difference ($p<.001$).

All animals were observed for gustatory piloerection and gustatory flushing prior to sacrifice. Neither phenomenon was observed in any animal. Attempts to measure gustatory changes in skin temperature were abandoned as the rats promptly removed the thermistor.

The labelling rates of the superior cervical and otic ganglia at 10, 56 and 84 days are displayed in Tables 24, 25 and 26 respectively.

Preliminary experiments revealed that there was no labelling of the otic ganglion after simple skin injection in the non-operated animal and so non-operated controls were unnecessary. There were no statistically significant differences in the labelling rates of either the otic or superior cervical ganglia at 10, 56 or 84 days after superficial parotidectomy.

TABLE 24 LABELLING RATES OF RAT OTIC AND SUPERIOR CERVICAL GANGLIA 10 DAYS AFTER SUPERFICIAL PAROTIDECTOMY (MEAN OF 10 HIGHPOWER FIELDS IN EACH OF 3 ANIMALS (SD)). FB = FAST BLUE, DY = DIAMIDINO YELLOW, DL = DOUBLE LABELLED, NL = NON LABELLED.

Procedure	Otic Ganglion				Superior Cervical Ganglion			
	FB	DY	DL	NL	FB	DY	DL	NL
Superficial Parotidectomy	24.6(4)	0	0	34.7(6)	9.3(3)	1.7(.9)	0	40.8(5)
Sham Operation	27.5(7)	0	0	36.1(5)	8.0(2)	1.4(.8)	0	38.4(8)

TABLE 25 LABELLING RATES OF RAT OTIC AND SUPERIOR CERVICAL GANGLIA 56 DAYS AFTER SUPERFICIAL PAROTIDECTOMY. (MEAN OF 10 HIGHPOWER FIELDS IN EACH OF 6 ANIMALS (SD)). FB = FAST BLUE, DY = DIAMIDINO YELLOW, DL = DOUBLE LABELLED, NL = NON LABELLED.

Procedure	Otic Ganglion				Superior Cervical Ganglion			
	FB	DY	DL	NL	FB	DY	DL	NL
Superficial Parotidectomy	26.7(5)	0	0	36.7(5)	9.0(4)	1.2(.5)	0	42.2(4)
Sham Operation	23.5(3)	0	0	37.0(6)	7.6(3)	1.5(.4)	0	37.8(6)

TABLE 26 LABELLING RATES OF RAT OTIC AND SUPERIOR CERVICAL GANGLIA 84 DAYS AFTER SUPERFICIAL PAROTIDECTOMY. (MEAN OF 10 HIGHPOWER FIELDS IN EACH OF 6 ANIMALS (SD)). FB = FAST BLUE, DY = DIAMIDINO YELLOW, DL = DOUBLE LABELLED, NL = NON LABELLED.

Procedure	Otic Ganglion				Superior Cervical Ganglion			
	FB	DY	DL	NL	FB	DY	DL	NL
Superficial Parotidectomy	25.6(3)	0	0	32.7(4)	10.1(4)	1.5(.8)	0	41.6(6)
Sham Operation	20.1(4)	0	0	37.6(6)	8.8(4)	1.7(.7)	0	39.8(7)

The labelling rate of the otic ganglion remained the same after superficial parotidectomy or sham operation for the duration of the experiments. In particular no Diamidino Yellow labelled cells were present in the otic ganglion even 84 days

after superficial parotidectomy. No Diamidino Yellow labelling of the otic ganglion occurred after sham operation. A schematic summary of these results is given in Figure 49.

The histological appearances of the parotid glands of the experimental animals were identical to that seen in Figure 27.

Figure 50 illustrates typical labelling of the superior cervical ganglion of the rat. The appearances of the labelled rat otic ganglia were little different to that seen in Figure 33.

4.332 SUPERFICIAL PAROTIDECTOMY IN THE MARMOSET

A total of 3 marmosets underwent superficial parotidectomy. There were no operative complications or deaths in the postoperative period. The average parotid weight on the non-operated side was 490 milligrams and on the operated side was 290 milligrams. In view of the limited numbers, tests of statistical significance were not applied. Starch-iodine testing was performed on each animal prior to sacrifice. No evidence of gustatory sweating was found in any animal.

Histopathology of the parotid glands were identical to that displayed in Figure 28.

Tables 27 and 28 display the labelling rates and patterns obtained at 10 and 84 days respectively.

TABLE 27 LABELLING RATES OF MARMOSET OTIC AND SUPERIOR CERVICAL GANGLIA 10 DAYS AFTER SUPERFICIAL PAROTIDECTOMY.(MEAN OF 10 HIGHPOWER FIELDS IN ONE ANIMAL (SD)). FB = FAST BLUE, DY = DIAMIDINO YELLOW, DL = DOUBLE LABELLED, NL = NON LABELLED.

Procedure	Otic Ganglion				Superior Cervical Ganglion			
	FB	DY	DL	NL	FB	DY	DL	NL
Superficial Parotidectomy	14.5(5)	0	0	28.6(5)	6.1(2)	1.1(.5)	0	35.7(5)
Sham Operation	12.6(4)	0	0	30.5(6)	5.7(3)	.9(.5)	0	38.6(6)

TABLE 28 LABELLING RATES OF MARMOSET OTIC AND SUPERIOR CERVICAL GANGLIA 84 DAYS AFTER SUPERFICIAL PAROTIDECTOMY.(MEAN OF 10 HIGH-POWERED FIELDS IN EACH OF 2 ANIMALS (SD)). FB = FAST BLUE, DY = DIAMIDINO YELLOW, DL = DOUBLE LABELLED, NL = NON LABELLED.

Procedure	Otic Ganglion				Superior Cervical Ganglion			
	FB	DY	DL	NL	FB	DY	DL	NL
Superficial Parotidectomy	13.2(5)	0	0	29.4(4)	6.7(3)	1.3(.7)	0	34.2(7)
Sham Operation	11.3(4)	0	0	31.1(4)	5.3(2)	1.0(.4)	0	35.3(5)

Due to the small numbers, statistical tests were felt to be inappropriate. However, there appeared to be no major differences between the animals in the labelling rates of otic

or superior cervical ganglia 10 or 84 days after superficial parotidectomy or after sham operation. In particular there were no Diamidino Yellow labelled or double labelled cells found in the otic ganglion after superficial parotidectomy or after sham operation.

The typical appearance of a Fast Blue and Diamidino Yellow labelled marmoset superior cervical ganglion is demonstrated in Figure 51.

4.333 AURICULOTEMPORAL NERVE INJURY IN THE RAT

A total of 15 rats underwent auriculotemporal nerve crush. There were no postoperative complications or deaths from this procedure, although prior to introduction of atropine premedication 50-60% of the of animals died a few minutes after crushing the nerve, apparently due to cardiac arrest. The mean parotid weight on the sham-operated side was 510 milligrams (± 9mg.,N=15). This was not statistically different from the mean weight on the operated side (490 milligrams (± 3 mg. N=5)) at ten days. At 56 and 84 days the mean parotid weights on the operated side of 258 milligrams (± 9mg N=5) and 265 milligrams (± 10 mg. N=5) respectively, were significantly lower than for the control sides (paired t-test $p<.001$). There were no significant differences between the mean parotid weights of the operated sides at 56 and 84 days after auriculotemporal nerve crush.

Haematoxylin and eosin sections of the parotid glands from operated and sham-operated sides were examined by light microscope. Figure 27 demonstrates the appearance of the parotid gland of the sham-operated side whilst the microscopic features of the parotid gland 84 days after auriculotemporal

nerve injury are represented in Figure 52. In this Figure the parotid appears atrophic with patchy fatty infiltration, and irregular nuclei. All glands demonstrated these changes after auriculotemporal nerve injury. The atrophic changes were not obvious 10 days after injury and at 56 days did not differ appreciably from the changes noted at 84 days. These appearances are not noted in normal tissue depicted in Figure 27.

The crushed auriculotemporal nerves were examined for evidence of injury. At 10 days there was evidence of patchy infarction and neutrophil infiltrate at the sight of the crush injury (Figure 53). At 84 days there was evidence of fibrosis and foamy macrophage infiltration consistent with old injury, but there was no neuroma formation (Figure 54).

Prior to sacrifice all animals were observed for the presence of gustatory flushing or piloerection. Neither of these phenomena were observed.

Mean numbers of Fast-Blue-labelled and Diamidino-Yellow-labelled cells per high power field for the otic and superior cervical ganglia at 10, 56 and 84 days are shown in Tables 29, 30, and 31 respectively. Cells labelled with Diamidino Yellow were observed in the otic ganglion 56 and 84 days after operation. At 10 days no Diamidino Yellow labelled cells were observed. The differences were statistically significant ($p<.001$). There was no difference in the rates of double labelling of the otic ganglion seen at 56 or 84 day survival times.

TABLE 29 LABELLING RATES OF RAT OTIC AND SUPERIOR CERVICAL GANGLIA 10 DAYS AFTER AURICULOTEMPORAL NERVE INJURY. (MEAN OF 10 HIGHPOWER FIELDS IN EACH OF 3 ANIMALS, (SD)). FB = FAST BLUE, DY = DIAMIDINO YELLOW DL = DOUBLE LABELLED, NL = NON LABELLED ,ATN = AURICULOTEMPORAL NERVE. *= STATISTICALLY SIGNIFICANT DIFFERENCES (PAIRED T-TEST P<.001).

Procedure	Otic Ganglion				Superior Cervical Ganglion			
	FB	DY	DL	NL	FB	DY	DL	NL
ATN Crush Injury	16.5(3)*	0	0	34.7(5)	8.1(3)	1.4(.9)	0	39.2(5)
Sham Operation	23.2(4)*	0	0	36.9(6)	7.9(2)	1.5(1)	0	37.9(6)

TABLE 30 LABELLING RATES OF RAT OTIC AND SUPERIOR CERVICAL GANGLIA 56 DAYS AFTER AURICULOTEMPORAL NERVE INJURY (MEAN OF 10 HIGHPOWER FIELDS IN EACH OF 6 ANIMALS (SD)). FB = FAST BLUE, DY = DIAMIDINO YELLOW, DL = DOUBLE LABELLED, NL = NON LABELLED. ATN = AURICULOTEMPORAL NERVE *,#,O = STATISTICALLY SIGNIFICANT DIFFERENCES (PAIRED T-TEST P<.001).

Procedure	Otic Ganglion				Superior Cervical Ganglion			
	FB	DY	DL	NL	FB	DY	DL	NL
ATN Crush Injury	14.8(4) *	2.8(1) #	0.9(.6) O	33.4(4)	9.8(3)	1.8(1)	.2(.6)	38.8(5)
Sham Operation	20.5(4) *	0 #	0 O	31.6(3)	8.1(2)	1.5(.7)	.1(.7)	38.8(3)

TABLE 31 LABELLING RATES OF RAT OTIC AND SUPERIOR CERVICAL GANGLIA 84 DAYS AFTER AURICULOTEMPORAL NERVE INJURY (MEAN OF 10 HIGHPOWER FIELDS IN EACH OF 6 ANIMALS (SD)). FB = FAST BLUE, DY = DIAMIDINO YELLOW, DL = DOUBLE LABELLED, NL = NON LABELLED. ATN =AURICULOTEMPORAL NERVE. *,#,0 = STATISTICALLY SIGNIFICANT DIFFERENCES (PAIRED T-TEST P<.001).

Procedure	Otic Ganglion				Superior Cervical Ganglion			
	FB	DY	DL	NL	FB	DY	DL	NL
ATN Crush Injury	14.2(3) *	3.1(2) #	1.0(.8) 0	34.9(4)	8.0(2)	1.7(1)	0	41.7(4)
Sham Operation	19.3(4) *	0 #	0 0	32.5(4)	8.2(2)	1.4(1)	.1(.5)	40.1(3)

However, the Fast Blue labelling rate was significantly reduced in comparison to the sham operated side at 10, 56 and 84 days.

A typical otic ganglion containing cells doubly and singly labelled with Diamidino Yellow and Fast Blue, is depicted in Figure 55.

There were no significant differences in labelling of the superior cervical ganglion between the sham and operated sides at a particular survival time, or between different survival times. Several doubly labelled cells were noted in the superior cervical ganglion, but this was not a statistically significant effect.

Comparison of auriculotemporal nerve injury with parotidectomy, revealed that the only significant differences

in fluorescent labelling was the occurrence of Diamidino Yellow labelled (both double and single labelling) otic ganglion cells at 56 and 84 days. The labelling of the superior cervical ganglion was the same for the two operations at all survival times. Doubly labelled cells were not observed in the superior cervical ganglion after parotidectomy. This difference, however, did not reach statistical significance ($p>.05$).

The results of these experiments are depicted schematically in Figure 56.

4.334 AURICULOTEMPORAL NERVE INJURY IN THE MARMOSET.

Attempts were made to crush the auriculotemporal nerve of three marmosets. The technique was made difficult by the narrow angle of the mandible. No post operative complications were experienced.

The average parotid weight on the operated side was 490 (N=3) milligrams and on the sham operated side 515 (N=3) milligrams.

Haematoxylin and eosin sections of the parotid glands at sacrifice were not noticeably different on the operated or sham sides at either survival time. In particular there was no evidence of parotid atrophy.

Examination of the auriculotemporal nerve sections revealed a significant crush injury only in the animal which survived 10 days.

Tables 32 and 33 show the mean labelling rates of otic and superior cervical ganglia at 10 and 84 days respectively.

Although statistical tests were not applied to these small groups it appears that there was a lower rate of

labelling of the marmoset otic ganglion at 10 days on the side on which the auriculotemporal nerve was crushed compared to the side of the sham operation. There were no apparent differences in labelling rates of the otic ganglion at 84 days between the two sides. More importantly, there was no evidence of Diamidino Yellow labelling of the otic ganglion at 10 or 84 days.

The labelling of the superior cervical ganglia with Fast Blue and Diamidino Yellow seemed consistent for sham and operated sides, at both survival times and after either parotidectomy or auriculotemporal nerve injury.

TABLE 32 LABELLING RATES OF MARMOSET OTIC AND SUPERIOR CERVICAL GANGLIA 10 DAYS AFTER AURICULOTEMPORAL NERVE INJURY (MEAN OF 10 HIGHPOWER FIELDS IN ONE ANIMAL (SD)). FB = FAST BLUE, DY = DIAMIDINO YELLOW, DL = DOUBLE LABELLED, NL = NON LABELLED. ATN = AURICULOTEMPORAL NERVE.

Procedure	Otic Ganglion				Superior Cervical Ganglion			
	FB	DY	DL	NL	FB	DY	DL	NL
ATN Crush Injury	10.8(4)	0	0	30.7(5)	7.5(3)	1.6(.4)	0	37.6(4)
Sham Operation	15.6(4)	0	0	28.4(7)	6.7(4)	1.2(.7)	0	36.5(5)

TABLE 33 LABELLING RATES OF MARMOSET OTIC AND SUPERIOR CERVICAL GANGLIA 84 DAYS AFTER AURICULOTEMPORAL NERVE INJURY (MEAN OF 10 HIGHPOWER FIELDS IN EACH OF 2 ANIMALS (SD)). FB = FAST BLUE, DY = DIAMIDINO YELLOW, DL = DOUBLE LABELLED, NL = NON LABELLED, ATN = AURICULOTEMPORAL NERVE.

Procedure	Otic Ganglion				Superior Cervical Ganglion			
	FB	DY	DL	NL	FB	DY	DL	NL
ATN Crush Injury	13.3(4)	0	0	32.4(3)	5.1(2)	1.6(.4)	0	37.6(6)
Sham Operation	12.9(3)	0	0	30.1(6)	6.8(3)	.7(.6)	0	38.9(5)

4.4 DISCUSSION

In discussing the results of these experiments, it is important to bear in mind several general points.

It is almost impossible to entirely eliminate bias in the process of data collection. Knowledge of the operation performed or of previous results may unconsciously sway the observer's interpretation, especially when appearances are equivocal or subtle. The ideal means of minimizing this effect is to observe all the tissue preparations at the end of the experiment without knowledge of the experimental procedure or tissue. This approach was untenable in the foregoing experiments because it was observed that the Fast Blue fluorescence fades and diffuses from the cell over one or two weeks of dark storage, making interpretation difficult or impossible. Furthermore after a single observation under the

fluorescent microscope both dyes had faded completely after 5 minutes. An alternative method, whilst not ideal, was adopted. The slides were observed in batches of 4 animals without knowledge of the side, the operation, or the ganglion, being evaluated. Although the type of ganglion was usually obvious from its size, the other factors remained unknown. It was felt that by this means interpretational bias would be minimized, although not eliminated.

There were several possible sources of error in the estimation of cell numbers. In the preceding experiments the use of fluorescent dyes which selectively label either cytoplasm or nucleus with distinctive colours helped to minimize counting errors, although occasionally after Fast Blue has been in the cytoplasm for some time dense yellow-orange granules form (186) which could be mistaken for Diamidino Yellow if overlying the nucleus. In addition, on occasions, the Fast Blue labelled cells developed a silvery halo around the nucleus which could be misconstrued as faint nuclear staining with Diamidino Yellow. In order to minimize these types of error, cells with equivocal or subtle nuclear labelling were not counted as Diamidino Yellow positive.

Another area of difficulty in detection of Diamidino Yellow labelled cells is that the dye labels the nucleus only. In the rat and marmoset the nuclei of ganglion cells are 10 microns in diameter while the cell itself is 20 to 40 microns (3.33,186). In using ganglion sections 7 microns thick some 42 microns apart (3.222), although the same cell would be unlikely to be present in adjacent sections, not all cells would be sectioned through their nucleus. The effect would be

minimized if sections were taken at the approximate cell size, that is 40 microns taken 40-50 microns apart to reduce double counting. This is not practicable in a ganglion only 400-500 microns thick, as there would be too few sections for evaluation. The compromise described above was thus used.

Examination of haematoxylin and eosin sections of the ganglia showed that 70-80% of cells in the section were cut through the nucleus. Thus the method was likely to underestimate the rates of cell labelling with Diamidino Yellow by a maximum of 20-30%. In support of this hypothesis is the observation that the labelling rate of the otic ganglion with Diamidino Yellow of 24% after 48 hours was reduced in comparison to that of Fast Blue (31%) (3.3311). Whilst other factors, such as dye solubility and diffusion (188), may alter the rate of labelling, and strictly speaking the above rates are not comparable as they were not obtained in the same animal, the labelling rate appeared to be reduced by about 20%. Apart from this technical difference Diamidino Yellow appeared to label the rat otic ganglion in the same manner as Fast Blue, although glial labelling was a little more pronounced with the former dye (187).

There were also difficulties encountered in estimation of the numbers of Fast Blue labelled neurones. The dye labelled the cytoplasm and the dendrites and neuroglial nuclei after long survival times (185,186,188) and thus in any given section a single cell may be cut so that it appeared to be two cells, and neuroglial nuclei may be counted. In terms of the current discussion glial nuclei were rarely a problem in the sections examined as techniques were used to prevent migration

of dye out of cells (185). When labelled glial cells were present they were easily recognizable as small (5-7 micron) irregular bodies and thus could be excluded from counting. Nevertheless there would almost certainly be an over-estimation of the numbers of Fast Blue labelled neurones for this reason. The magnitude of the effect is impossible to estimate from these studies.

The use of dark field microscopy confounded the estimation of numbers of non-labelled cells. The problem was mitigated to some extent by a faint greyish cytoplasmic fluorescence of these cells. Although the technique provided reproducible results, with consistent non-labelled cell counts between experiments and ganglia, it was probably not an accurate representation of the number of non-labelled cells. To support this contention the total cells per high power field estimated by fluorescent microscopy for otic ganglia was between 60 and 70 whereas at the same magnification of a haematoxylin and eosin section of otic ganglion 90 to 100 cells could be counted. It is therefore likely that there was a consistent underestimation of non labelled cells by dark field fluorescent microscopy. Provided the effect was consistent it should not alter the interpretation of results.

Because of these counting problems labelling rates have been expressed in terms of cells per high power field (400X) rather than ratios of labelled to non-labelled cells, as the latter would serve only to accentuate the inherent counting errors. The labelling rates should be considered as approximations rather than absolute values. Despite the limitations the technique of retrograde neuronal labelling

used in these experiments was highly reproducible. Equivalent injections of dye resulted in consistent labelling rates of the superior cervical and otic ganglia throughout the experiments regardless of survival time, operation, or animal species. Thus valid comparisons could be made between animals of varying survival times and varying operations using the raw number of labelled cells without the need for computation of ratios. Since the data was numerical with up to 60 counted fields per group it was likely to be normally distributed and hence the application of the student t-test of statistical significance was appropriate.

The most significant barrier to interpretation of the results of retrograde neuronal transport is the occurrence of dye diffusion. Diffusion can occur within and between injection sites, between axons in nerves carrying the dye, and from the cell bodies of labelled neurones to surrounding cells. It can occur both in vivo and in vitro. The main implications of this phenomenon is that the specificity of the method is degraded due to the creation of false positive labelled cells. In vitro diffusion can be virtually eliminated by the use of frozen sectioning of samples, controlled contact with formalin solutions, use of high osmotic strength sucrose solutions for dehydration prior to processing, rapid processing, and immediate mounting and air drying of sections (185).

Diffusion in vivo is largely dependent on the nature of the dye used, its lipid solubility, and on the survival time of the experimental animal after injection (185,187). Fast Blue has minimal in vivo diffusion even after long survival

times (186,188). This is supported by the observations that at 56 and 84 days, in the preceding experiments, there was little evidence of neuroglial labelling (an obvious prerequisite for false labelling of adjacent neurones), and that the labelling rate of the ganglia did not increase with increasing survival time. There was a slight increase in labelling from 2 to 10 days but this was more likely to have been due to diffusion of dye within the parotid gland.

Despite these observations it is impossible to state with confidence that no Fast Blue diffusion to adjacent neurones would have taken place with survival times of 56 and 84 days.

With survival times of 3-4 days Diamidino Yellow has some in vivo diffusion to adjacent neuroglial cells (187). In the experiments under discussion the survival time was further restricted to 2 days after Diamidino Yellow injection. This would have the effect of reducing diffusion of this dye to negligible levels.

Diffusion of dye between injection sites is minimized with Fast Blue (186,188) and Diamidino Yellow (188) and in the experiments considered here, the magnitudes of these effects were readily assessed by the use of appropriate controls. Because preliminary experiments indicated that no otic ganglion labelling occurs after skin injections in non-operated animals, non-operated controls were not used. This approach was vindicated by the observation that there was no Diamidino Yellow labelling of otic ganglion neurones after any sham operation. Non-operated controls would thus have been superfluous as they would have duplicated this data without adding any further information.

Before further attention is given to the results obtained with the technique of retrograde neuronal labelling it is important to reflect upon the possible origins of the cellular fluorescence as this facilitates interpretation of the labelling patterns observed.

Any cell containing the cytoplasmic label Fast Blue, derived the dye from the initial parotid injection.

Thus, labelled cells in the superior cervical ganglion represent cell bodies responsible for sympathetic innervation of the parotid. The only other possible explanation is that the dye diffused from the parotid into the skin and thus the labelled cells could represent the sympathetic neurones of the skin.

Otic ganglion cells labelled with Fast Blue must have acquired the dye by retrograde axonal transport along the auriculotemporal nerves as demonstrated in section 3.223, with the possibility of a minor contribution from diffusion between adjacent cells, or, particularly after auriculotemporal crush experiments, death of labelled neurones and local dispersion of the dye. This latter effect is impossible to quantitate but would only effect the validity of conclusions drawn from the presence of double neuronal labelling.

Diamidino Yellow was derived only from injection of the skin just prior to sacrifice of all experimental animals.

Superior cervical ganglion cells labelled with Diamidino Yellow alone must represent the retrograde projection of skin sympathetic nerves. Doubly labelled cells in this ganglion have two possible origins. Firstly, they could occur as a result of diffusion of dyes from the site of injection into

the other depot. Secondly, the cells could represent regrowth of parotid sympathetic fibres into the skin. In experiments under discussion this double labelling was only noted after auriculotemporal nerve injury and sham operation and so the latter explanation is probably the correct one, as, if diffusion were important the occurrence would be expected to be observed in the other experimental situations. The effect is too small to reach statistical significance after auriculotemporal nerve injury in comparison to sham, so probably it in fact simply represents a random event and can be excluded from further consideration. It certainly did not occur in sufficient frequency to allow a clear explanation to be framed.

Single labelling of otic ganglion neurones with Diamidino Yellow implies that abnormal neuronal connections exist to the skin. False positive labelling of the otic ganglion neurones with Diamidino Yellow could only occur in one of three ways. Firstly, it could diffuse from the skin into the parotid and thus into the otic ganglion via retrograde transport. Secondly, the dye could diffuse from the skin directly into the otic ganglion cells. Thirdly, the Diamidino Yellow could conceivably diffuse directly from the nearby auriculotemporal nerve into the otic ganglion.

These explanations of the occurrence of false positive labelling of the otic ganglion by Diamidino Yellow are untenable for several reasons. Others have noted (187,188) that Diamidino Yellow tends to remain in neurones and axons without diffusion into the surrounding neuroglial cells or other axons, especially after the short survival times of 48

hours used in these experiments. It is therefore highly improbable that false positive labelling occurred as a result of diffusion out of nerve axons or cell bodies containing the dye. These mechanisms could explain the appearance of such labelling after parotidectomy, when the auriculotemporal nerve is still intact. However, after auriculotemporal nerve injury, for these explanations to be the correct, either the auriculotemporal nerve must not have been damaged initially, or parotid innervation had been re-established by nerve regrowth. Auriculotemporal nerve injury in these experiments has been verified by parotid atrophy and by histological examination of the nerve. Since, in neither sham operated nor parotidectomised animals, was there any evidence of Diamidino Yellow in the otic ganglion of either rat or marmoset, diffusion of Diamidino Yellow from the skin into the parotid gland or from the auriculotemporal nerve axons cannot be valid explanations for the presence of this dye in the otic ganglion. Thus, it is unlikely that there is a significant incidence of false positive Diamidino Yellow labelled otic ganglion cells in these experiments.

Double labelled otic ganglion cells could have several possible origins. Theoretically they should represent cells initially innervating the parotid which after the experimental procedure project to the skin. As mentioned earlier diffusional effects may limit the validity of this interpretation. It is unlikely that the diffusion of dye occurs from the skin to the parotid because sham operated animals never developed such double labelling. It is much more difficult to estimate the extent of in vivo diffusion of dye

within the otic ganglion. Because of its nature and short survival time after injection, it is very unlikely that Diamidino Yellow diffused from a labelled otic ganglion cell to a neighbouring Fast Blue labelled cell (188) to create a false positive doubly labelled cell. After long survival times with Fast Blue, there may be some labelling of surrounding neurones. In long term studies Hendry et al (188), however, conclude that very little double labelling would occur by this means. It is possible that death of labelled otic ganglion cells such as may occur after auriculotemporal nerve injury, could result in dye dispersion and false positive double labelling.

Because double labelling of otic ganglion cells is likely to be subject to an unpredictable false positive rate interpretation of results must be cautious.

With the above interpretations and their limitations in mind the effects of parotidectomy and auriculotemporal nerve injury in experimental animals, can be considered.

In rats and marmosets parotidectomy amounted to 30-40% reduction in the mass of the parotid. Approximately 100-200 milligrams of superficial lobe of the parotid usually was left, in order to facilitate preservation of the facial and auriculotemporal nerves, and to provide a relatively large surface area of raw parotid to test for the occurrence of direct regrowth of parotid secretomotor nerves into the skin. In none of the experimental animals could cells either doubly or singly labelled with Diamidino Yellow, be demonstrated up to 84 days after parotidectomy. The only tenable explanation for this is that nerve regeneration by direct regrowth into

the skin does not occur in these animals. Although the technique for detection of abnormal skin innervation is very sensitive, the conclusions based on marmoset experiments may be misleading as only 2 animals were used.

There are several other less likely possibilities which should be explored. Firstly, there is the possibility that the dyes were not working or not injected consistently. The fact that the superior cervical ganglion labelling rates for fast blue and Diamidino Yellow were not significantly different between the sham and operated sides at each survival time and between survival times indicates that the method was consistent and that both dyes were retrogradely transported and visible with the fluorescent microscope system used. The next possibility is that Diamidino Yellow is not transported retrograde in regenerated neurones. This notion is refuted by the work of Hendry et al (188) who have successfully used the technique in nerve regeneration studies, although the nerves involved in his study were sympathetic. In the experiments presented here the dyes were transported in normal parasympathetic nerves and thus, there was no reason that they should not be transported by such nerves after regeneration.

Further, although there would have been ample opportunity for cut secretomotor fibres of the parotid to encounter cut branches of the auriculotemporal nerve (as only the main trunk of the nerve could be preserved), perhaps the time interval of 84 days was insufficient for regeneration to occur. Little is written of regeneration in the parasympathetic nervous system, but in general, mammalian nerve regeneration occurs at the rate of 2 mm. per day after a delay of 7 days (214) and so in

rat or marmoset, if regeneration were to proceed at this rate after parotidectomy, it would be complete in a matter of 2-3 weeks because distance involved is only about 10 mm. In cats and rats regeneration of sympathetic function occurs 6-8 weeks after superior cervical ganglion postganglionic axotomy (139,188). Laage-hellman (72) demonstrated that auriculotemporal syndrome in man occurs after a delay of 2-3 months, and so for the same phenomenon to occur in a much smaller animal 84 days should be adequate time. Furthermore, auriculotemporal nerve injury in the rat was followed by regeneration over much greater distances over the same time interval in experiments to be discussed subsequently.

Finally, perhaps sweat glands or other target tissues in the skin are necessary for development of the reinnervation phenomenon (215). This is an unsatisfactory explanation for the experimental observations as marmosets do possess sweat glands and yet do not develop skin reinnervation with otic ganglion neurones after parotidectomy. Furthermore such skin reinnervation does occur following auriculotemporal nerve injury in rats (vide infra).

In summary neither rats nor marmosets develop significant skin reinnervation by otic ganglion neurones after parotidectomy alone.

Auriculotemporal nerve injury in the rat resulted in reduction of parotid mass on the operated side by 50% and there was evidence of parotid atrophy on section of the gland. The changes consisted of irregular cell nuclei and patchy fatty infiltration. These histological features have been noted in the past after auriculotemporal nerve ligation in the

rabbit (124) and after tympanic plexus destruction (125) with the earliest changes becoming noticeable at 6 weeks. Because of the subjective nature of the histopathological changes and sampling error involved in sectioning, quantitation of the effect was not possible, other than to say that the appearances were not present at 10 days and did not seem to progress between 56 and 84 days. Similarly, the changes observed in the auriculotemporal nerve sections allowed only qualitative confirmation that the nerve had been injured. The patchy fibrosis and foamy macrophage infiltration consistent with old injury were present in sections of all supposedly crushed nerves. The absence of neuroma formation is of uncertain significance, but perhaps this is a feature of response to nerve injury in rats, or alternatively neuroma development may occur later than the 84 day duration of the study.

After auriculotemporal nerve crush injury in the rat, skin projections of otic ganglion neurones as determined by the presence of Diamidino Yellow, developed in approximately 8% of the cells (6% single labelled and 2% double labelled). These appearances were not present on the sham sides or on the operated sides at 10 days. The differences were significant in comparison to controls and the post-parotidectomy state. The labelling did not become more pronounced between 56 and 84 days implying that the phenomenon which produced it was completed between 10 and 56 days after injury. There were again constant labelling rates for Fast Blue and Diamidino Yellow in the superior cervical ganglion of all animals confirming the internal consistency of the method.

The number of Fast Blue labelled cells in the otic ganglion was significantly lower on the operated side for all survival times. This almost certainly resulted from a reduction of the effect of diffusion of the dye within the parotid after auriculotemporal nerve interruption at 2 days. On the sham operated side, and after parotidectomy, Fast Blue labelled more otic neurones by diffusion throughout the remaining parotid tissue and continuing retrograde labelling down the uninterrupted auriculotemporal nerve. The persistence of the effect of the same magnitude to 84 days after auriculotemporal nerve injury helps to confirm the view that few if any cells are labelled with Fast Blue by local diffusion between cells in the otic ganglion.

The number of Fast Blue labelled cells in the otic ganglion may have been expected to increase during the experimental period as a result of parotid reinnervation. However, it is unlikely that sufficient Fast Blue would remain in the parotid for a long enough time in order for the effect to be significant.

In order to investigate the occurrence of such parotid reinnervation which has been found clinically by Glaister et al (74), a third fluorescent label theoretically could be used, by injecting the dye into the parotid gland at the completion of the experiment.

It is unlikely that injection of the parotid with Fast Blue would result in the labelling of all otic ganglion cells responsible for its innervation, especially after auriculotemporal nerve injury, when diffusion of Fast Blue within the gland is limited to the two days between initial

injection of the parotid and crushing the auriculotemporal nerve. Therefore, at least some of the cells labelled with Diamidino Yellow alone, were probably initially neurones responsible for innervation of the parotid or alternatively were neurones originally responsible for the innervation of the minor salivary glands (52). The double labelled cells, as alluded to above, may gain false positive Fast Blue fluorescence by diffusion, nevertheless some of these cells will certainly represent neurones which originally provided secretomotor axons to the parotid. It is not possible to accurately quantitate this effect because the diffusion-induced false positive rate of Fast Blue labelling is not known.

The only other possible means by which Diamidino Yellow labelling of the otic ganglion could occur is by retrograde transport of dye down the auriculotemporal nerve to the damaged area, leakage of the dye out of the damaged axon and into axons which supplied the parotid and thence to the otic ganglion. If this were the case then Diamidino Yellow labelling of the otic ganglion would be expected to be more prominent at 10 days than 56 or 84 days when healing would have progressed. The results clearly refute this possibility.

Thus, it can be concluded that injury to the auriculotemporal nerve in rats results in the development of abnormal otic ganglion connections to the facial skin in a manner analogous to human auriculotemporal syndrome.

The function of these abnormal connections of the otic ganglion to the skin in rats was not apparent. Neither gustatory flushing or piloerection was observed in the

experimental animals, but the techniques used to observe these phenomena were insensitive. It is possible that gustatory flushing could be demonstrated by more sophisticated means such as thermography or studies of skin perfusion. Failure to demonstrate gustatory phenomena in the face of skin reinnervation does not detract from the utility of the animal model of auriculotemporal syndrome as the model would still be valuable for testing techniques for prevention of the condition in humans rather than techniques for the treatment of established gustatory sweating.

The study of marmoset facial skin revealed that these animals, unlike the rat, have facial sweat glands. The glands are of the apocrine type and consequently do not produce normal sweat, but instead a proteinaceous substance is elaborated (206,207). The apocrine glands of these monkeys do not respond to pilocarpine as in man (208). It seems that apocrine sweat glands have the same adrenergic and cholinergic innervation in maraques and man (209,210) and presumably marmosets. Consequently the presence of these glands in the facial skin of marmosets would make this animal a closer analogue to man than the rat, for the purposes of an animal model of auriculotemporal syndrome.

In the two marmosets where an attempt had been made to crush the auriculotemporal nerve, neither had evidence of parotid atrophy, auriculotemporal nerve injury, or gustatory sweating, at 84 days. As would be expected in the absence of nerve injury, there was no evidence of otic projections to the skin. The animal sacrificed at 10 days had histological

evidence of nerve injury but no evidence of abnormal skin innervation.

It must therefore be concluded that in the marmosets which were allowed to survive for 84 days the auriculotemporal nerve had not been crushed effectively at the original operation. The reasons for this failure are two fold. Firstly, the auriculotemporal nerve of the marmoset is deeper than that of the rat and in addition the marmoset has a narrow angle between the mandibular rami which are short. These factors combined to make exposure of the auriculotemporal nerve in these animals very difficult. Thus the nerve was only partially crushed or perhaps a local tendon was crushed by error and the technique failed. The second reason for inability to perform the nerve crush is related to the lack of dissection experience with these animals. Due to the high cost, only one marmoset was dissected prior to attempting the nerve crush operations. Because the animal constitutes a good primate analogue, it would be worthwhile repeating the experiments, perhaps with a modified approach to the auriculotemporal nerve for easier access.

In summary, the use of retrograde neuronal transport of fluorescent dyes provides a useful tool for the detection of abnormal skin innervation from the otic ganglion in the rat and marmoset models of human auriculotemporal syndrome. Such reinnervation of the facial skin has been created successfully in the rat after direct auriculotemporal nerve injury, but not in the marmoset probably due to technical failure. In neither animal does the phenomenon develop after parotidectomy alone.

The marmoset may provide a more useful model than the rat because it possesses facial apocrine type sweat glands, however this animal has disadvantages for technical and financial reasons.

Because of anatomical, neurological and histological similarities between these animals and man (Chapter 3), it is appropriate to extrapolate the model to the human case. Thus on the basis of the foregoing experimental results, evidence is advanced in favour of the theory of aberrant nerve regeneration as the aetiology of auriculotemporal syndrome in humans. In addition, it is probable that the regeneration occurs due to auriculotemporal nerve injury at a point in the nerve where parotid and skin innervation coexist. There is no animal evidence that direct reinnervation of the skin can occur from the cut surface of the parotid gland after parotidectomy. Thus this mechanism is unlikely to occur in humans, a point which has important implications in terms of treatment and prevention of human auriculotemporal syndrome.

CHAPTER 5 GENERAL DISCUSSION AND CONCLUSIONS

5.1 CLINICAL SIGNIFICANCE OF AURICULOTEMPORAL SYNDROME

Auriculotemporal syndrome has remained a subject of controversy since it was described some 230 years ago (1). The debates have persisted partly due to the rarity of the condition and the consequent lack of opportunity to study it. Whilst infection and trauma were the original progenitors of the problem, over the last 50 years parotid surgery has become the main cause of auriculotemporal syndrome. It is notable that the neurologist Lucie Frey, rather than a surgeon gave the first detailed description of the condition which has become largely a complication of surgery. Over the ensuing years surgeons have contributed the bulk of the studies on the subject.

Contrary to the beliefs expressed by some workers (Chapter 1) auriculotemporal syndrome does not occur after every parotidectomy. It follows, therefore, that there must be some variables involved in its genesis which, if they could be identified, could be employed to reduce the occurrence of the condition. Not all patients with the condition are symptomatic; however, those who have symptoms are usually annoyed or embarrassed by them. Because of the unsatisfactory nature of treatment for the problem some surgeons in the past have considered its development as serious as facial nerve palsy.

The scope of the problem extends further than parotid surgery, as gustatory phenomena can occur in a whole variety of clinical situations ranging from post herpetic neuralgia to the autonomic neuropathy of diabetes (Chapter 1). Any research work on the subject may have wider applications than at first envisaged.

Furthermore, because gustatory sweating is most likely to be the result of incorrect neural regeneration, research in this area may find eventual application in the prevention of reinnervation after sympathectomy (157), or regeneration after vagotomy, or enhancement of appropriate regeneration following major peripheral nerve injury. Finally there may be applications in the treatment of chronic pain of malignant disease; for example pancreatic tumours, the pain of which can be temporarily alleviated by sympathectomy only to recur some months later (216,217). The recurrence of pain has been attributed, without much evidence, to involvement of somatic nerves, but could equally be due to inappropriate sympathetic reinnervation. Modification of such regeneration would obviously be of great benefit to the patient.

5.2 A CHEMICAL BASIS FOR NERVE REGENERATION

The study of nerve regeneration is an important physiological topic and in this regard, auriculotemporal syndrome is unique in that it appears to represent the regeneration of the parasympathetic axon into a normally sympathetically innervated structure. This assumption has been made on the basis that division of the preganglionic fibres to the otic ganglion ameliorates the condition, whereas division of the cervical sympathetics has no effect (Chapter 1). An

alternative explanation could be that some of the fibres divided are sympathetic fibres destined for the parotid, with cell bodies in an area other than the superior cervical ganglion. In this case the regeneration necessary to induce auriculotemporal syndrome would be between sympathetic axons which may be a more physiological acceptable explanation. Dale (138), however, saw no physiological conflict in the reinnervation of sympathetic effectors with parasympathetic fibres provided there was compatibility of neurotransmitter. And this belief was confirmed by the work of Anderson (217) on reinnervation of the ciliary ganglion. In the sympathetic nervous system there is a definite lack of specificity of postganglionic reinnervation after injury (219,220) in contrast to preganglionic injury. The same lack of specificity probably exists for reinnervation of the parasympathetic nerves after injury although this hypothesis has not been formally studied.

Much impetus has been given to the biochemical basis for specificity of innervation and reinnervation phenomena by Levi-Montalcini (221,222) who pioneered the discovery of the protein, Nerve Growth Factor, upon which developing sympathetic neurones depend for survival in vivo and in vitro. It is interesting to note that abnormal reinnervation, of the type that causes auriculotemporal syndrome and related gustatory phenomena, occurs in the vicinity of salivary glands from which Nerve Growth Factor was first isolated in the mouse. The precise significance of this observation remains unclear.

Nerve Growth Factor has been purified and extensively characterised physiologically, biochemically and immunologically (223,224,225,234). The protein is also present in the adult sympathetic nervous system of many species (226), and is important in maintenance (224), and regeneration (227) of this system. It has similar effects on both the cholinergic and adrenergic components of the sympathetic system (228). There is on-going controversy about the origin of Nerve Growth Factor in vivo. While most believe that the substance is elaborated by the target tissue (215,226,229,230,231,232,233) and transported in a retrograde fashion in the axon to the cell body, other investigators (235,236,237) have advanced evidence to suggest that it is derived from the neuroglial cells. Denervation of the target tissues results in increases of Nerve Growth Factor activity (233,238,239,240,246) in the sympathetic and parasympathetic nervous system. Exposure of newborn rats to antibodies to Nerve Growth Factor results in an almost complete immunosympathectomy (228,241), and it is likely that there is a similar effect of these antibodies on inhibition of regeneration of the adult sympathetic nervous system (246). Since the discovery of Nerve Growth Factor, many other similar trophic substances have been identified (225,231,242,243,244) but await purification. Some of these substances are specific parasympathetic neuronal growth factors (231,244,245) and are produced by target tissues. They are important in development of parasympathetic nerves and generally have similar physiological activity to Nerve Growth Factor of the sympathetic system (231,233,245). In addition parasympathetic neurones are capable of responding to

Sympathetic Nerve Growth Factor in vivo (246) and in vitro (228,249), but they are not dependent on this protein for survival.

Study of auriculotemporal syndrome could provide a unique opportunity to examine the role of nerve growth factors in crossed regeneration between two types of autonomic nerve. Perhaps the mechanism of this effect is that the cut parasympathetic nerve in the adult rat is incapable of discriminating between the various nerve growth factors and so random regeneration results. Alternatively, it may be that there is higher concentration of neuronal growth factors from skin target cells, than parotid targets, diffusing from the cut end of the nerve, thus resulting in relatively increased inappropriate innervation of the skin effector organs. Finally, perhaps direct nerve injury results in a high concentration of neuronal growth factors from local Schwann cells with a less specific action, and consequent abnormal regeneration. In overall terms, investigation of nerve growth factors in auriculotemporal syndrome may help to provide further understanding of the biology of these proteins.

5.3 GENERAL CONCLUSIONS

In reviewing the literature on auriculotemporal syndrome it was demonstrated that much of the knowledge regarding this condition had been collected in an ad hoc manner. As a consequence, information is patchy and treatment unsatisfactory. Nevertheless, auriculotemporal syndrome is a common clinical phenomenon after parotidectomy. The lack of animal work has impeded the development of effective treatments. The absence of such research is probably because

appropriate techniques have only recently become available and because of the obscurity of the condition, a point which is supported by the fact that most practicing surgeons surveyed in these studies were completely unaware of the disorder, and even those who performed parotidectomy had only patchy knowledge.

The response rate of surgeons canvassed in the survey of parotid surgery was only 51%. Despite this shortcoming, some useful observations have been made from the replies. It seems that in Adelaide, for unclear reasons, the incidence of auriculotemporal syndrome is reduced in comparison to other parts of the world. Possible reasons for this variance have been advanced and include a preference for careful preservation of the auriculotemporal nerve, and apparent increased usage of radiotherapy for malignant and benign disease. Such information complements the observation that the auriculotemporal injury is central to development of the condition. However, the suggestion is tentative as there is no means of knowing whether similar nerve preservation was practiced by surgeons in overseas series.

The study also found that the general surgical knowledge of auriculotemporal syndrome was poor, highlighting the fact that medical knowledge is a dynamic entity, responding to the demands of patients and their common afflictions. Despite the looseness of the study the estimated rates of complication of parotid surgery, other than auriculotemporal syndrome, compare favourably to those derived from other series.

It is interesting to speculate whether 2 or 3 parotidectomies per year is an adequate number to keep

surgical skills optimal. If the complication rates are accurate then this level of operating is probably sufficient.

The case-note review suffered from difficulties of completeness inherent in all retrospective studies. Although the incidences of pathological diagnoses and the cure rates for malignant disease compared well with other series on the subject, the incidences of complications such as auriculotemporal syndrome, facial nerve palsy, salivary fistula, and others, were underestimated when compared the data obtained by direct clinical review of patients. Even this latter group of patients was incomplete as 27% were lost to follow up, so it is possible that the true complication rates are even higher than presently reported. Although strictly, there is no basis to make such a comparison, many of the overall complication rates in this series seem unacceptable, in comparison to the world literature, in particular with regard to permanent facial nerve damage. Most of the studies from which these figures were obtained, however, were retrospective and so are also likely to be in error.

The prospectively determined incidence of auriculotemporal syndrome at the Queen Elizabeth Hospital was 59% which is lower than experienced elsewhere. In the three series (70,105,110) in which all patients were tested by the starch-iodine method, a mean of 98% of patients demonstrated the condition. The possible reasons for this discrepancy have been explored. The development of auriculotemporal syndrome correlated with the removal of a larger tumour and the occurrence of complications, particularly that of ear

numbness. It seems likely that the latter symptom was a marker for auriculotemporal nerve damage.

The technique of prophylactic Lyodura interposition failed to prevent auriculotemporal syndrome in six patients. These observations give indirect support to the idea that auriculotemporal nerve injury itself is the essential prerequisite for development of auriculotemporal syndrome.

Fascial interposition with homografts seems, at least in the short term, to be a successful treatment for established auriculotemporal syndrome, yet when the same principle is applied for prophylaxis, it fails. This is difficult to understand and in addition to the explanations already offered in Chapter 2 the following interpretation may also be important. When fascial interposition is used for treatment of established gustatory sweating, because dissection is guided by starch-iodine testing, the technique results in more complete disconnection of skin sweat glands, than in parotidectomy. At the time of parotidectomy it is not possible to predict the likely area to be involved in gustatory sweating and so it is impossible to place a Lyodura sheet in the appropriate position. Animal evidence has been presented to suggest that no direct reinnervation of the skin takes place from the parotid surface. If this conclusion can be extrapolated to human auriculotemporal syndrome, it is possible that simple disconnection of the sweat glands likely to become involved in gustatory sweating will suffice to both treat and prevent the condition. Patches of skin involved with gustatory sweating have been successfully excised in humans in the past without recurrence. Presumably nerves responsible for

the phenomenon were still present in these cases as were abundant sweat glands, but there was no further abnormal regeneration possible at this level. From the observations of others it is clear that gustatory sweating involves the greater auricular and auriculotemporal nerve distributions, so it is possible that accurate delineation of these nerves preoperatively by the use of local anaesthetic would allow appropriate skin mobilization to be performed at the initial operation. Perhaps the development of gustatory sweating could be prevented by this means without the need for interposition of fascia or other substances.

It is thus possible that the appropriate mobilization of facial skin flaps may be a useful means of prevention and treatment of auriculotemporal syndrome. The hypothesis depends on the validity of extrapolation of animal nerve regeneration studies to man. Other explanations of failure of Lyodura prophylaxis such as instability of the graft, may be equally applicable. The technique of fascial interposition may have a place in treatment of the problem and deserves more critical evaluation.

In regards to detection of auriculotemporal syndrome in humans, the application of the technique of measurement of skin resistance has been shown to be accurate and simple. In addition is not as messy as the starch iodine test and thus is more acceptable to the patient and investigator. It has the disadvantage that it is likely to fail to detect auriculotemporal syndrome when the distribution of the sweating is patchy. To overcome this difficulty the sensitivity of a positive test could be extended with some

loss of specificity, to make the measurement of electrical resistance of the skin a useful, quick and efficient screening test for gustatory sweating. The test would involve a single measurement on the side of the face after maximal gustatory stimulus. A starch iodine test could then be applied to detect false positive results for those with skin resistances between 1.9 and 3.0 megaohms, and to determine the extent of the area affected when desired.

In animals, the technique of retrograde neuronal labelling with fluorescent dyes allowed sensitive and reproducible detection of reinnervation of the skin by otic ganglion neurones in a model of auriculotemporal syndrome. It is probable that the technique is much more sensitive than starch iodine testing in humans, as the former is capable of detecting reinnervation in as few as 1 in 100 neurones.

The neurological, histological and anatomical similarities of the parotid region in experimental animals, to that of man was striking. All mammals rely on their salivary glands for survival (94), and thus their presence and structure have been preserved phylogenetically.

The main difficulty with the model was the inability to demonstrate that functional abnormal neuronal connections had been established. The abnormal neurones function normally in terms of retrograde axonal transport, an active process. Perhaps the means of detection of other neuronal functions were inadequate, or alternatively perhaps the connections have no other functions. However, provided that the mechanism of development of these abnormal neuronal connections is the same

in man and experimental animal, the absence of detectable function does not necessarily degrade the value of the model.

There is a large body of indirect evidence that human auriculotemporal syndrome develops by abnormal neuronal regeneration, both from this study and from elsewhere. It is not certain at what level such regeneration occurs. Two possibilities seem most likely : that regeneration occurs within the auriculotemporal nerve itself or that cut parotid nerve fibres grow directly into the sweat glands of the skin. The observations of auriculotemporal nerve regeneration in rats and marmosets suggest that reinnervation of the skin with otic ganglion neurones occurs only after auriculotemporal nerve injury at a level in the nerve where parotid secretomotor and skin sweat gland innervation exist together. No skin reinnervation appeared to occur directly from the parotid surface to the skin.

The model may be valid for extrapolation to human auriculotemporal syndrome provided that the human facial eccrine sweat glands are no different to marmoset facial apocrine glands in their ability to attract or accept reinnervating nerve fibres. Such a difference would be an unlikely one, given that both types of sweat glands have the same type of innervation in the normal situation.

Extrapolation of the results of these animal nerve regeneration studies to man would lead to the hypothesis that in man, auriculotemporal syndrome only develops due to regeneration within the auriculotemporal nerve after injury during parotidectomy.

Although this hypothesis has not been formally evaluated in these studies, there are several observations which would support it.

1) The observed failure of prophylactic fascial interposition techniques. This technique would not prevent auriculotemporal nerve damage, and would not necessarily result in the mobilization of sufficient skin to disconnect all sweat glands likely to be involved.

2) The observed failure of auriculotemporal nerve avulsion in treatment or prophylaxis. There are multiple superficial branches of the nerve and a relatively fixed point where the nerve pierces the parotid capsule. This limits anatomically the extent of avulsion to the level of the parotid capsule. Avulsion may leave other branches of the auriculotemporal nerve intact and result in their damage by traction.

3) The high incidence of the auriculotemporal syndrome after parotidectomy in man. In humans, there is ample opportunity for damage of the auriculotemporal nerve at an appropriate level, due to the presence of many superficial twigs from sensory branches of the nerve into the parotid.

4) The occurrence of the condition after infection and mandibular fracture. The auriculotemporal nerve is confined to the space between mandible and skull and so is likely to be damaged.

5) The correlation of auriculotemporal syndrome with ear numbness. Damage to the auricular branch of the

auriculotemporal nerve may be a marker for injury to the auriculotemporal nerve at a deeper level.

The alternative hypothesis that direct skin reinnervation does occur in man, could readily account for points 1 and 3 but not the remaining observations. It would also more easily explain the correlation of larger tumour with increased incidence because removal of a larger tumour would provide a greater surface area for direct regeneration to occur. It is of course possible that both explanations occur in man.

In conclusion, therefore, it can be stated that while in animals reinnervation of the skin by otic ganglion neurones occurs only after auriculotemporal nerve injury , the level at which such reinnervation occurs in human auriculotemporal syndrome requires further clinical and experimental evaluation.

5.4 AREAS FOR FURTHER EVALUATION

Obviously, the work embodied in this thesis needs to be further extended in order to allow more complete understanding of the development of gustatory sweating in humans.

There are several pieces of basic information which require clarification.

The fibre composition and function of the auriculotemporal-facial nerve interconnecting branches is not known in man or animals. As suggested in Chapter 3 these structures could be examined using immunofluorescent techniques for detection of protein markers such as Substance P for sensory nerves (246), Vasoactive Intestinal Peptide (228) or choline acetyltransferase (246) for parasympathetic innervation and Tyrosine Hydroxylase for sympathetic nerves

(246). In animals this could be accomplished by careful dissection using photographic records of the location of the interconnections as they are removed for examination.

Fresh human tissue is difficult to obtain, and prolonged dissection in the autopsy room has logistic problems. A possible solution would be to remove the whole parotid gland after the dissection described in 3.1. By cutting the facial nerve trunk and the auriculotemporal nerve trunk the gland could be removed with its nerves for leisurely dissection later. The analysis of these nerve interconnections would not only increase basic knowledge of their function, but also add scientific substance to the suggestion of Hogeman and others (48,49,50) that the communicating branches may play a role in the development of auriculotemporal syndrome.

It would be valuable to examine the skin and parotid glands of patients with auriculotemporal syndrome, with these techniques in order to see if the sweat gland innervation is detectably different from normal. Either operative or autopsy tissue could be used.

The animal model should be extended. Firstly, to lend more scientific credibility to the results with marmosets, both experiments should be repeated with increased numbers of animals. Secondly, so that the human situation may be more closely parallelled, salivary pleomorphic adenomas (247) could be induced and removed. This would simulate the auriculotemporal nerve traction and tension incurred during human parotidectomy. Furthermore attempts should be made to induce the condition in animals by damage to the auriculotemporal nerve at more superficial levels as may occur

in humans. Thirdly, the effects of antibodies to Nerve Growth Factor on the development of abnormal skin innervation could be studied. Not only does this idea have interesting implications for the biology of Nerve Growth Factor, but may also have application in the prevention of human auriculotemporal syndrome. The response to Nerve Growth Factor could be potentially modified by either antibodies, by the use of wheat germ agglutinin (248) or by colchicine, an inhibitor of fast axonal transport (230).

From a more clinical viewpoint, animal and human evidence suggests that prophylactic fascial interposition can be discarded unless more careful attention is paid to mobilization of skin flaps in the entire distributions of the relevant nerves.

A clinical trial could be mounted to formally assess the effects of meticulous preservation of the auriculotemporal nerve on the incidence of auriculotemporal syndrome. However, given that parotid surgery is performed in small numbers by many individuals, the logistics of such a study make the likelihood of success small.

Certainly, the technique of fascial interposition for treatment of auriculotemporal syndrome shows some early promise and its use should be encouraged. This would also provide easy access to skin and parotid tissue in patients with auriculotemporal syndrome for study as proposed in the preceding discussion. Further, it may prove unnecessary to use barriers if appropriate skin mobilization is carried out.

Although complete understanding of auriculotemporal syndrome must await the future, the studies in this thesis

have provoked thought and discussion on the subject, and provided a basis for further investigation of this intriguing surgical complication.

FIGURES

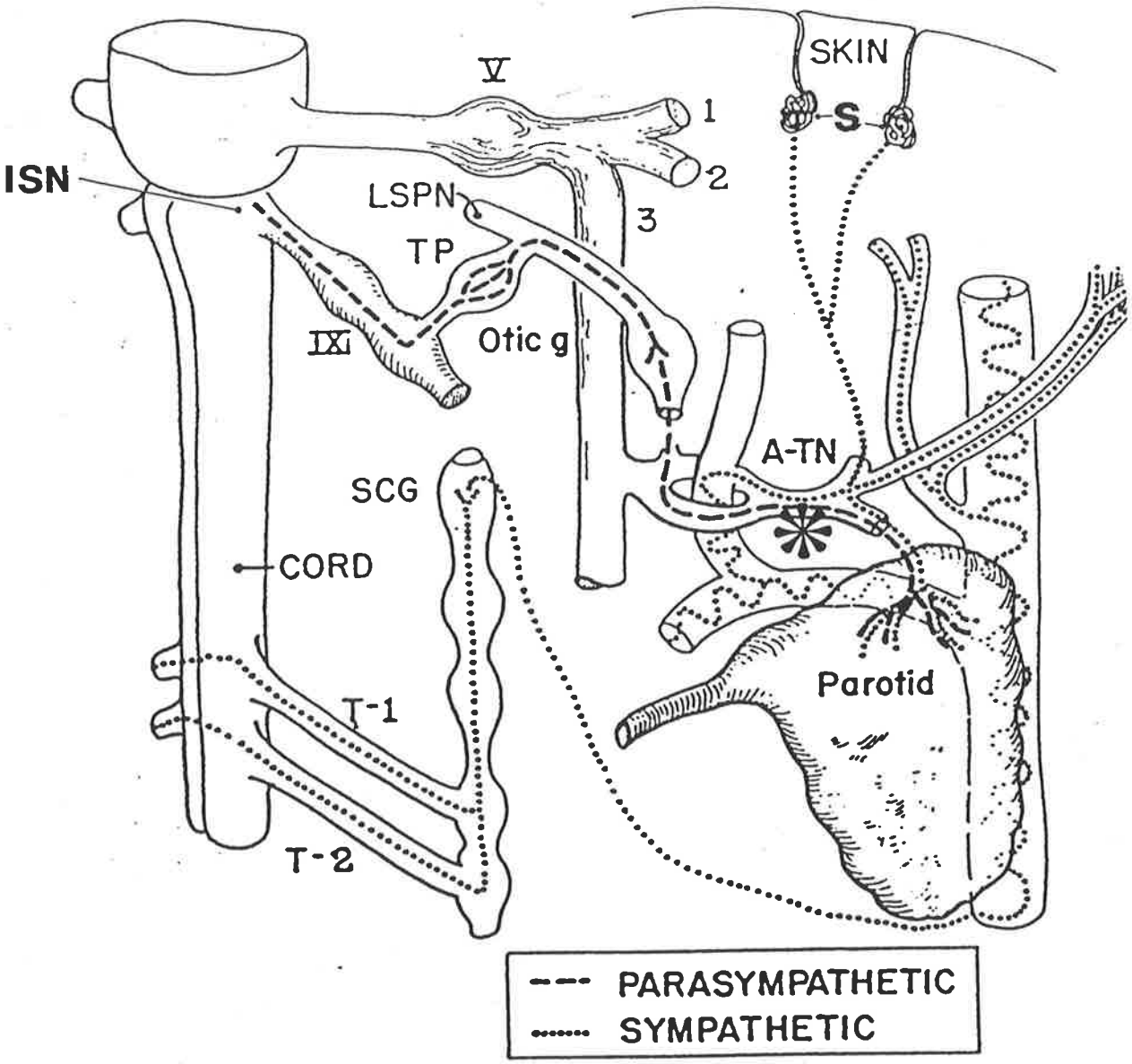


FIGURE 1 Normal Innervation of the Parotid and Facial Sweat Glands
Note that the parotid parasympathetic nerves and sympathetic nerves to the skin coexist in the auriculotemporal nerve (*).
ISN, Inferior Salivatory Nucleus ; S ,Sweat Glands ; V, Trigem inal nerve ; IX ,Glossopharyngeal Nerve ; TP , Tympanic Plexus ; SCG , Superior Cervical Ganglion ; LSPN , Lesser Supreficial Petrosal Nerve ;Otic G , Otic Ganglion ; A-TN ,Auriculotemporal Nerve.
After Chisa et al (83).

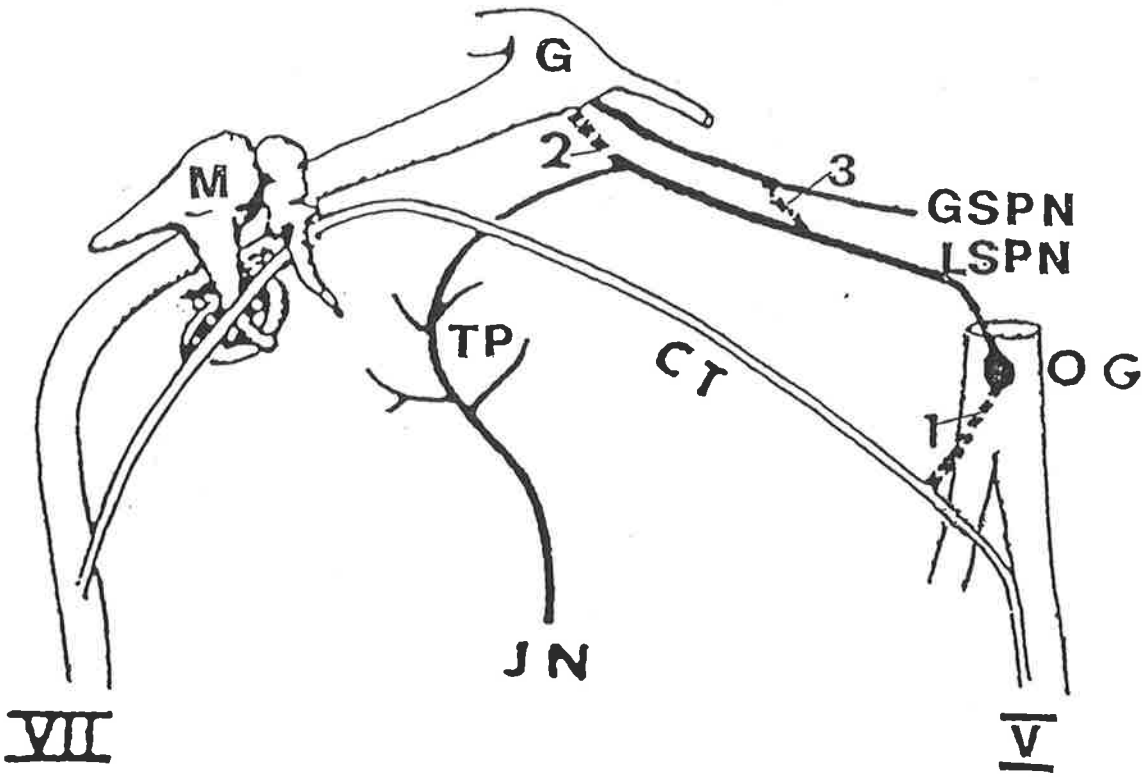


FIGURE 2 Alternative Otic Ganglion Afferent Pathways

Three possible alternate pathways for preganglionic parasympathetic fibers to the otic ganglion (1-3). See text for explanation. M, Middle ear; G, Geniculate ganglion ; VII , Facial nerve ; V , Trigeminal nerve ; CT , Chorda Tympani ; JN , Jacobsons Nerve ; TP ,Tympanic Plexus ; GSPN , Greater superficial petrosal nerve LSPN , Lesser superficial petrosal nerve ; OG Otic Ganglion. After Blumfield et al (88).

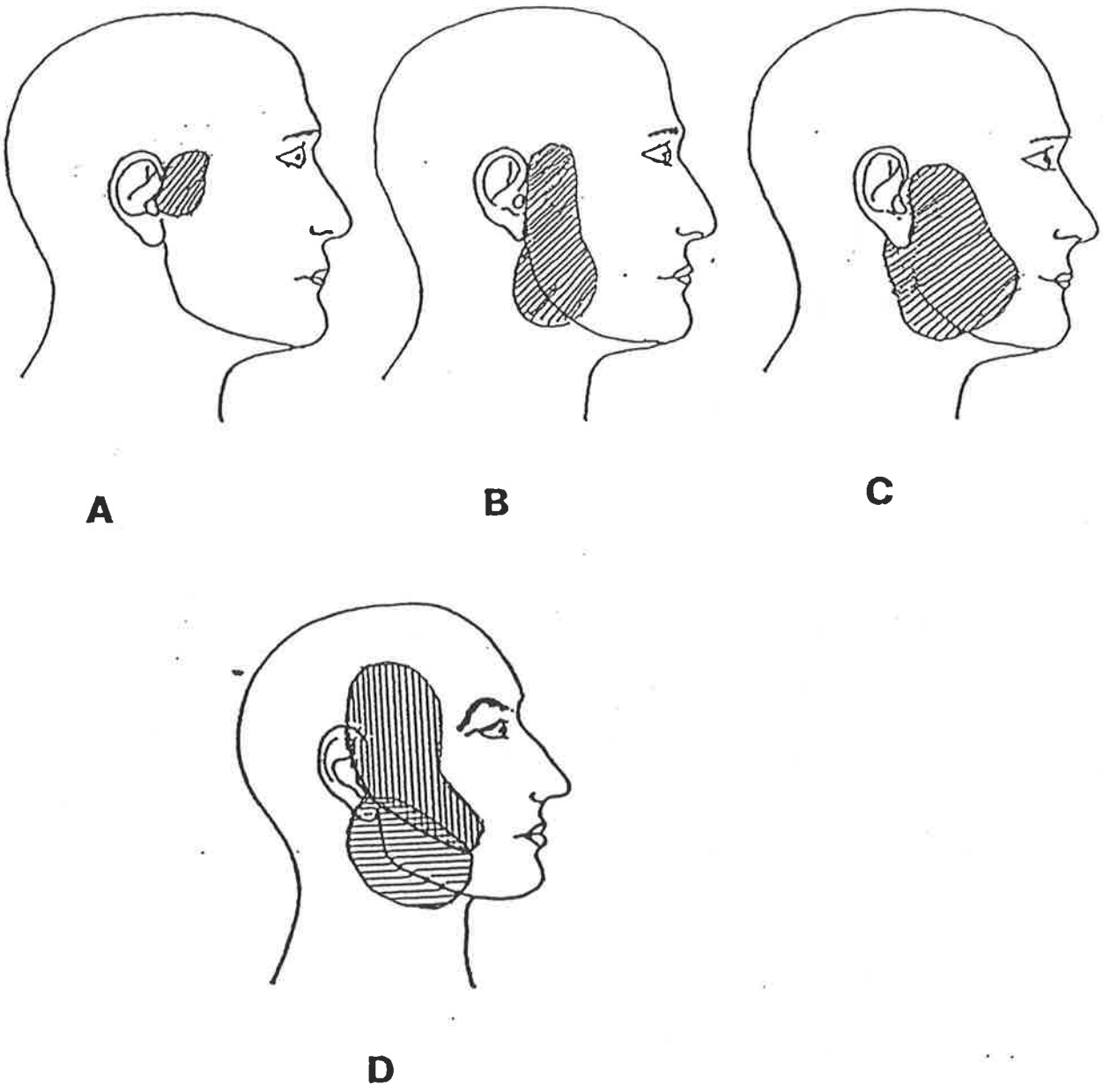


FIGURE 3 Observed areas of Gustatory Sweating compared with the normal distributions of the Auriculotemporal and Greater Auricular nerves.

A , B, and C /// Indicates observed areas of gustatory sweating

D |||| Cutaneous distribution of the auriculotemporal nerve.

≡ Cutaneous distribution of the greater auricular nerve.

Note that the distributions of these nerves overlap significantly and the actual areas may vary between individuals.

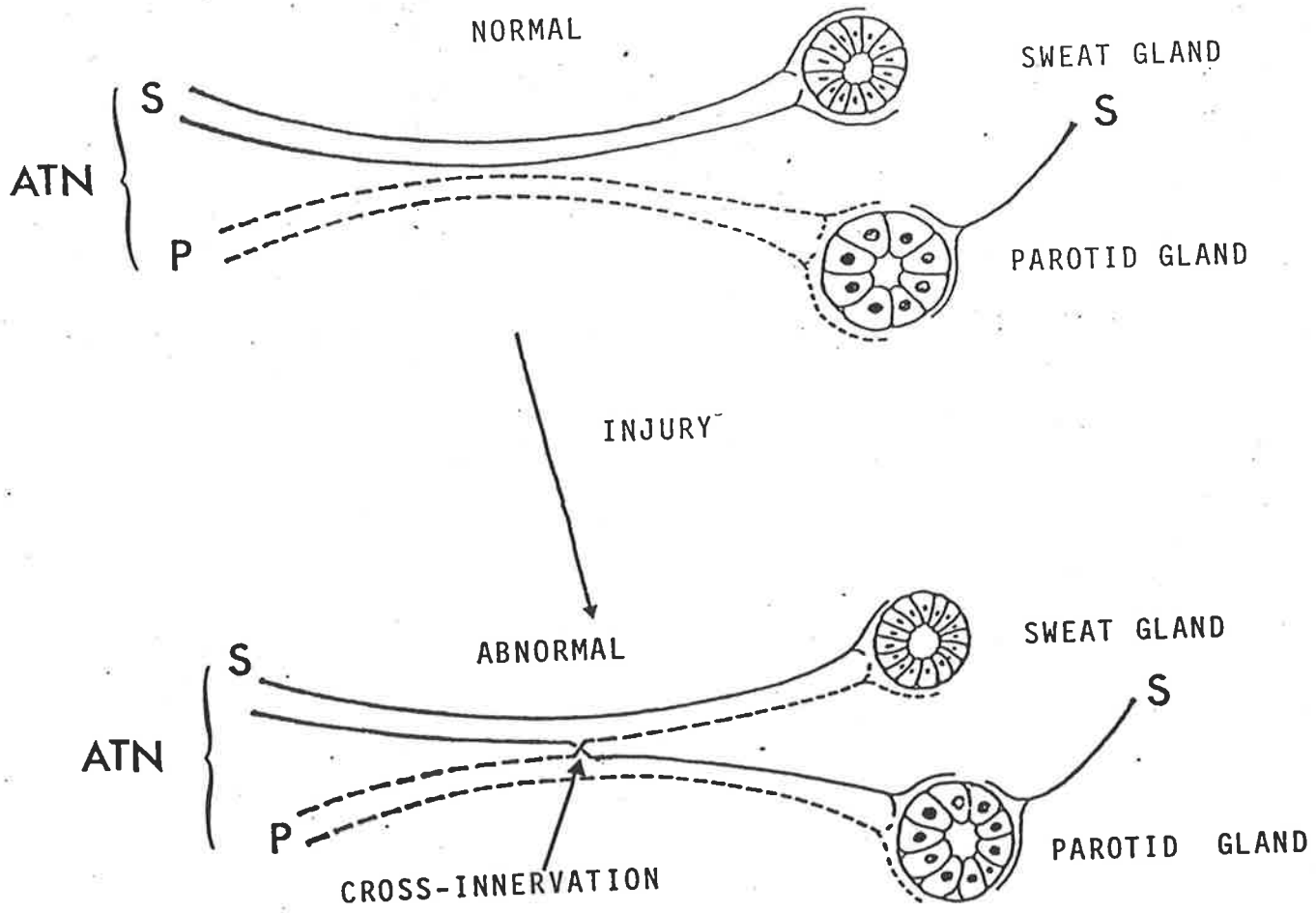


FIGURE 4 The aberrant reinnervation theory of development of Auriculotemporal syndrome.

S , Sympathetic nerves ; P , Parasympathetic nerves ; ATN, Auriculotemporal nerve .

Note that the parasympathetic fibers normally supplying the parotid supply the sweat glands by cross-innervation after nerve injury.

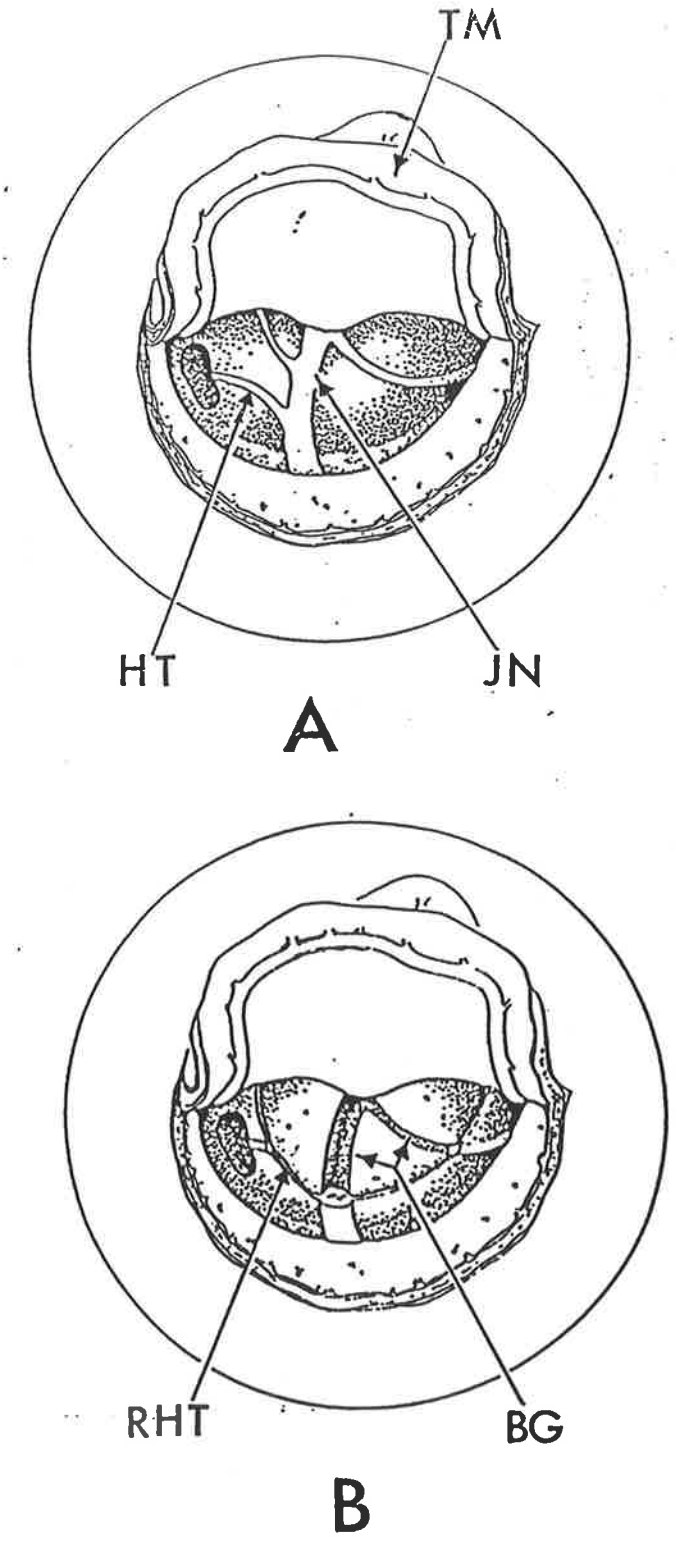


FIGURE 5 Auroscopic views of tympanic neurectomy

TM, Reflected Tympanic Membrane ; HT, Hypotympanic branch of tympanic plexus ; RHT , Resected hypotympanic branch ; BG, bony grooves in cochlear promontory ; JN ,Jacobsons nerve ;

A Exposure of the tympanic plexus by elevation of the tympanic membrane. Arrowed Hypotympanic branch can be missed with inadequate exposure.

B Cochlear promontory stripped of periosteum leaving bony grooves made by the tympanic plexus branches. Hypotympanic branch also resected After Smith et al (96)

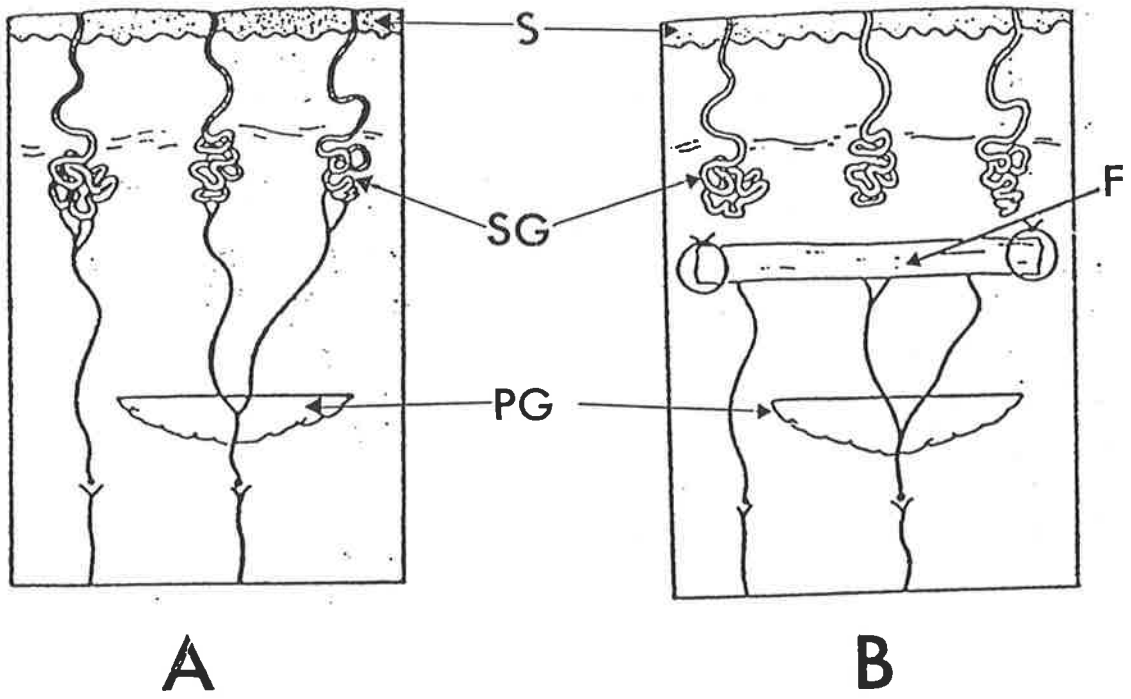
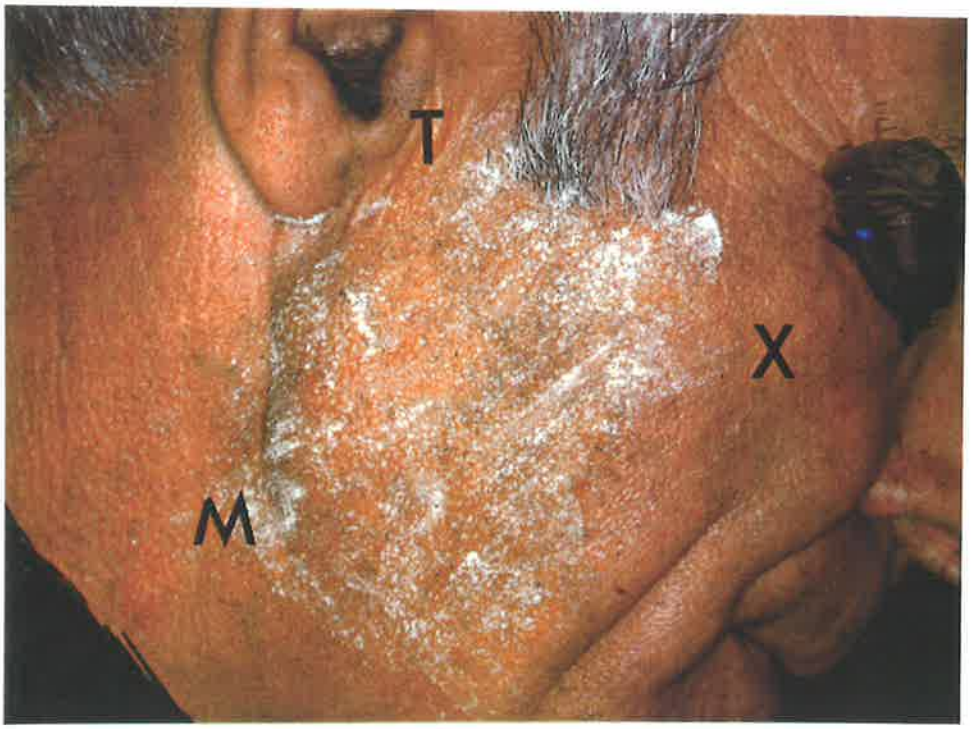


FIGURE 6 Fascial Interposition Technique for prevention of auriculotemporal syndrome.

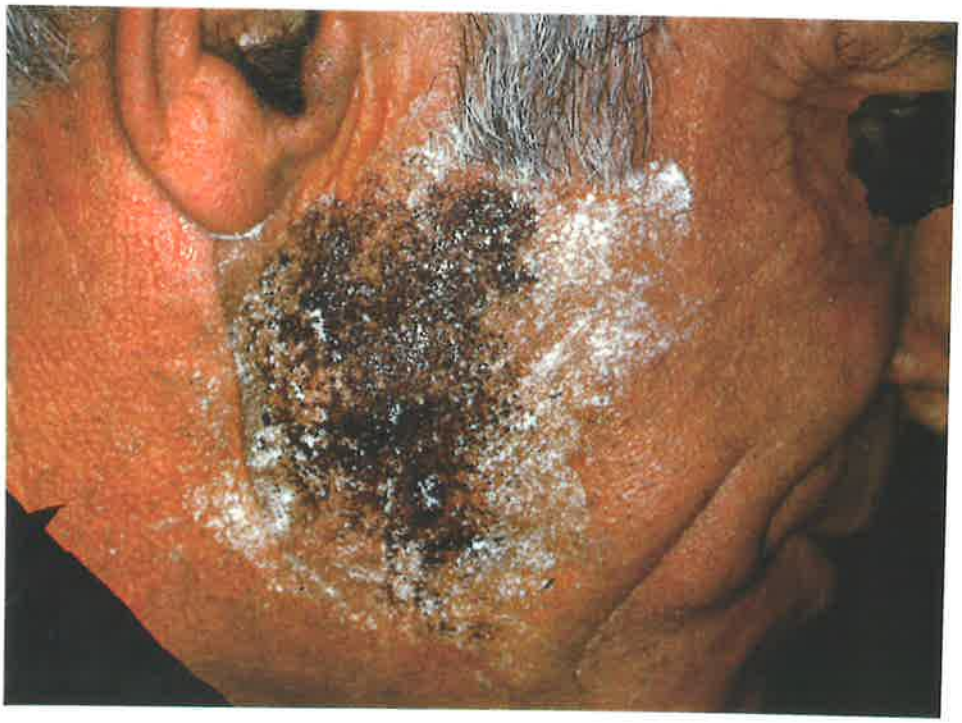
S , Skin; SG, Sweat Glands; PG, Resected Parotid Gland; F, Fascial layer

A Proposed mechanism of development of auriculotemporal syndrome with direct reinnervation of sweat glands by nerve fibers from the parotid parotid surface.

B Fascial layer interposed between parotid surface and sweat glands to prevent such ingrowth. after Sessions et al (107).



A



B

FIGURE 7 The Minor Starch Iodine Test

X, Xygoma; M, Mandibular angle; T tragus of ear.

A Before Minor starch iodine test

B After Maximal gustatory stimulus

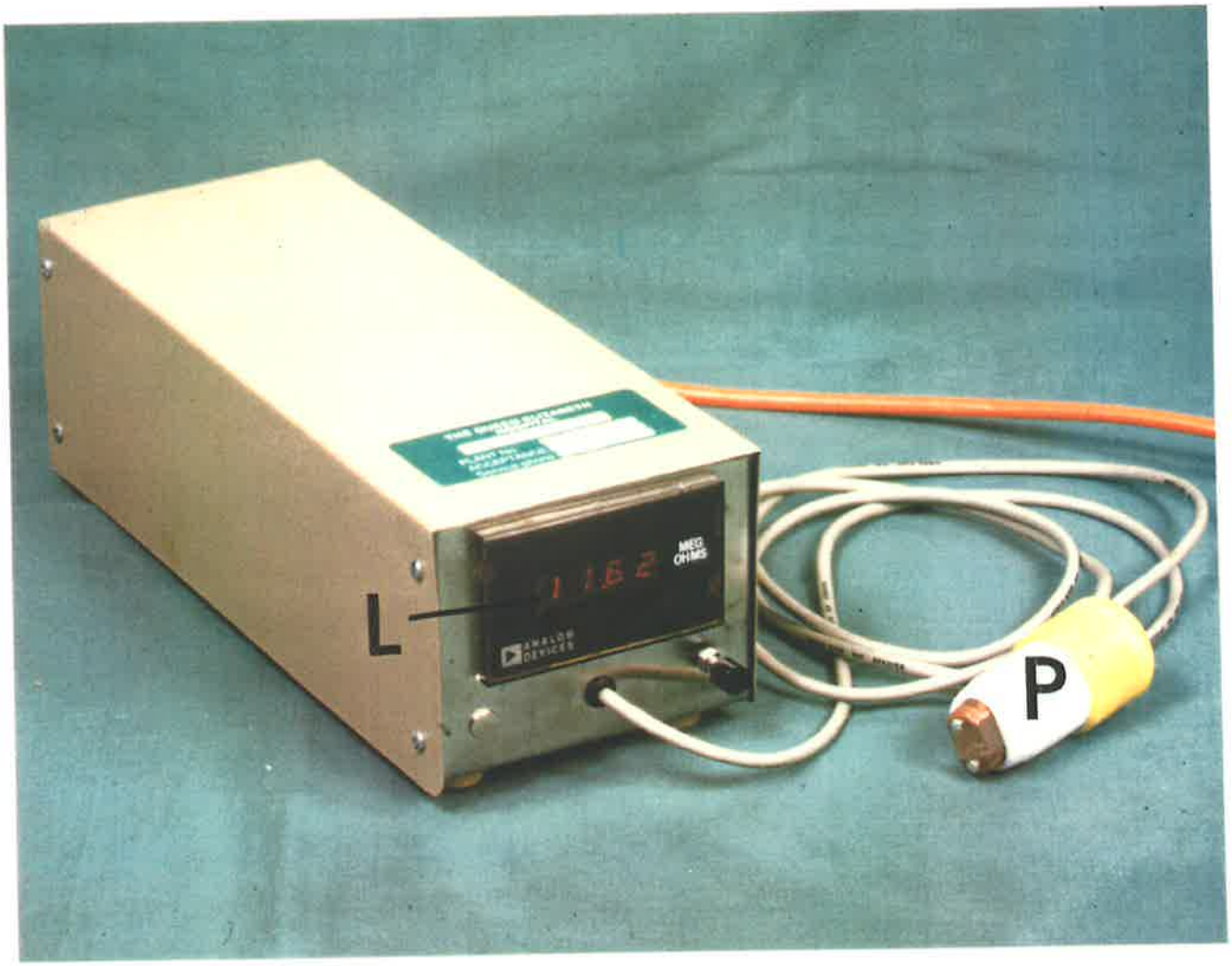


FIGURE 8 Apparatus for measurement of skin resistance

L, LED Display ; P , Probe.

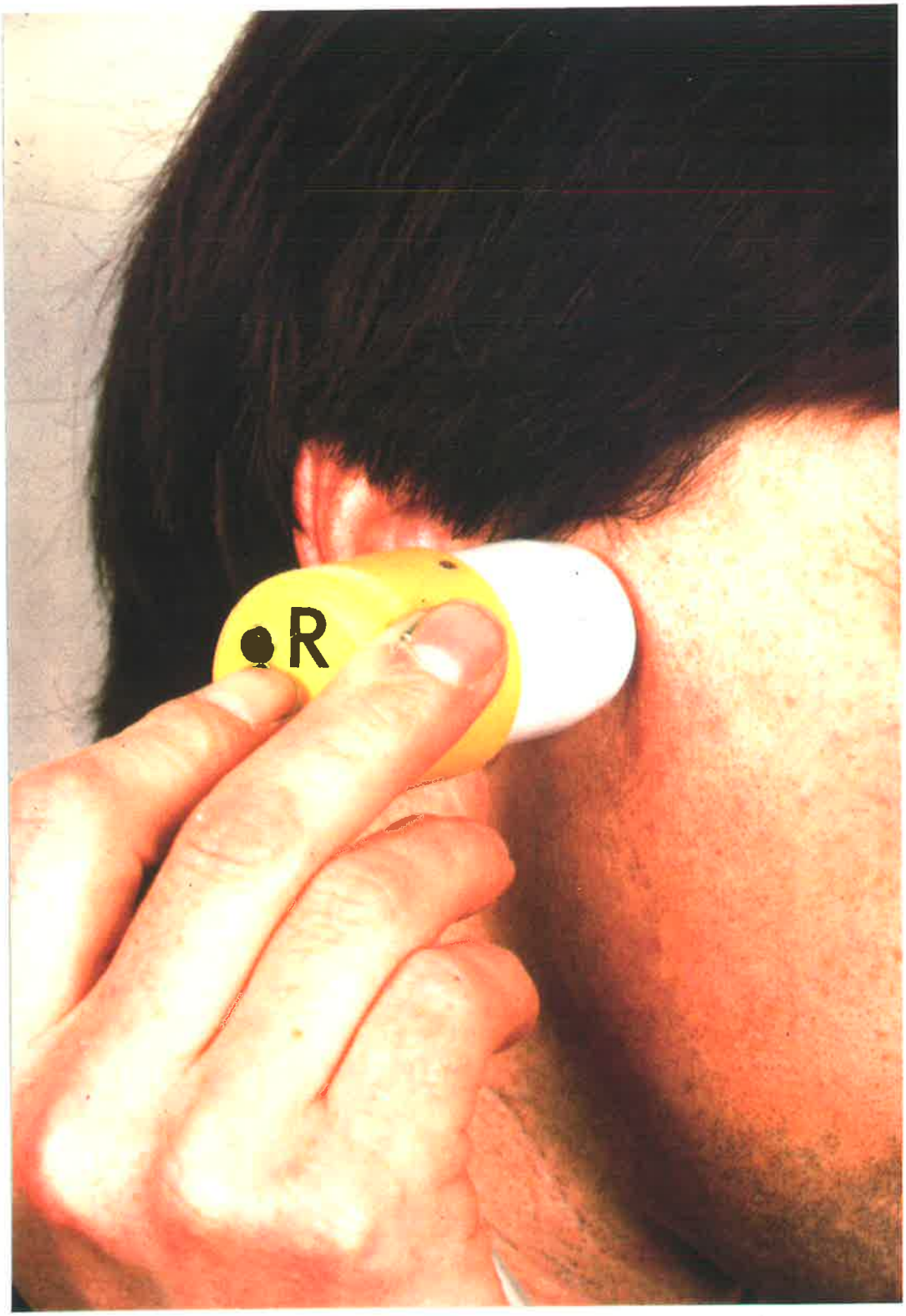


FIGURE 9 Measurement of skin resistance

R, Reset button

Note probe is positioned 1cm. anteriorly to the tragus on the Xygoma.

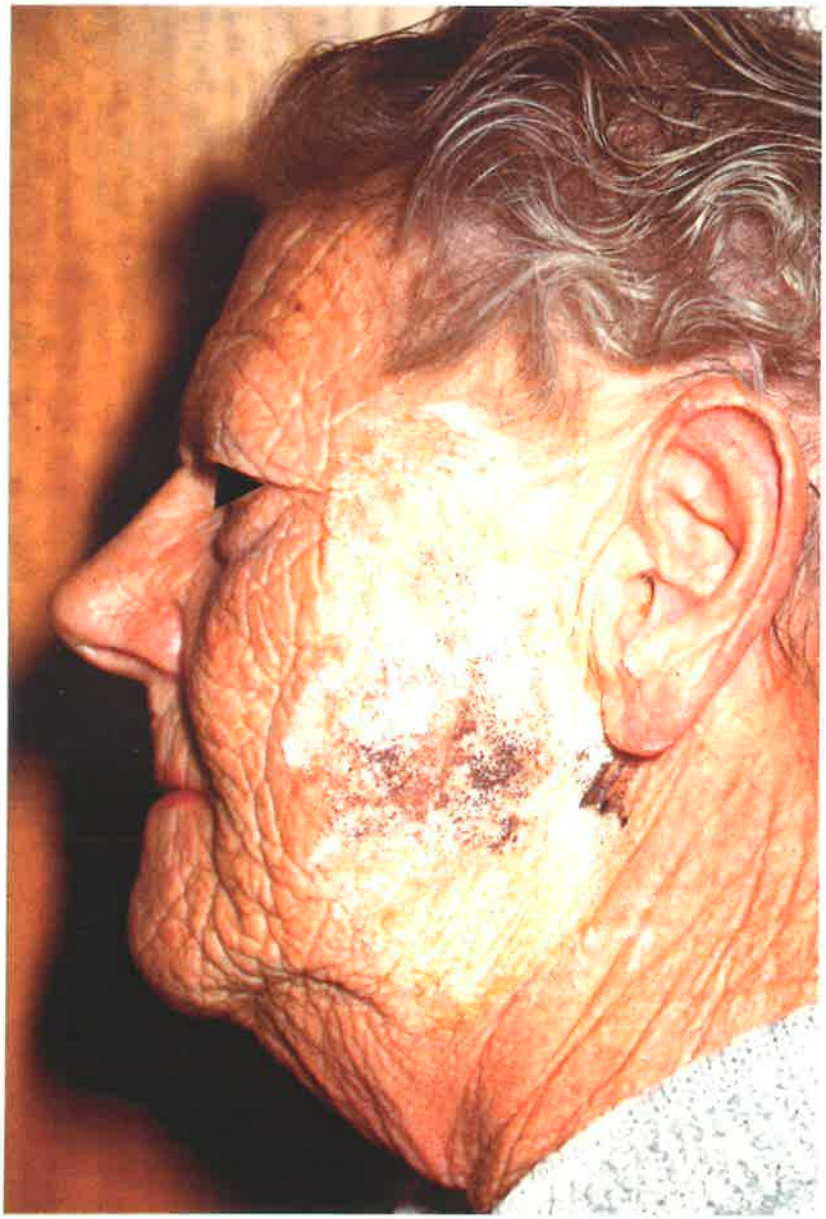
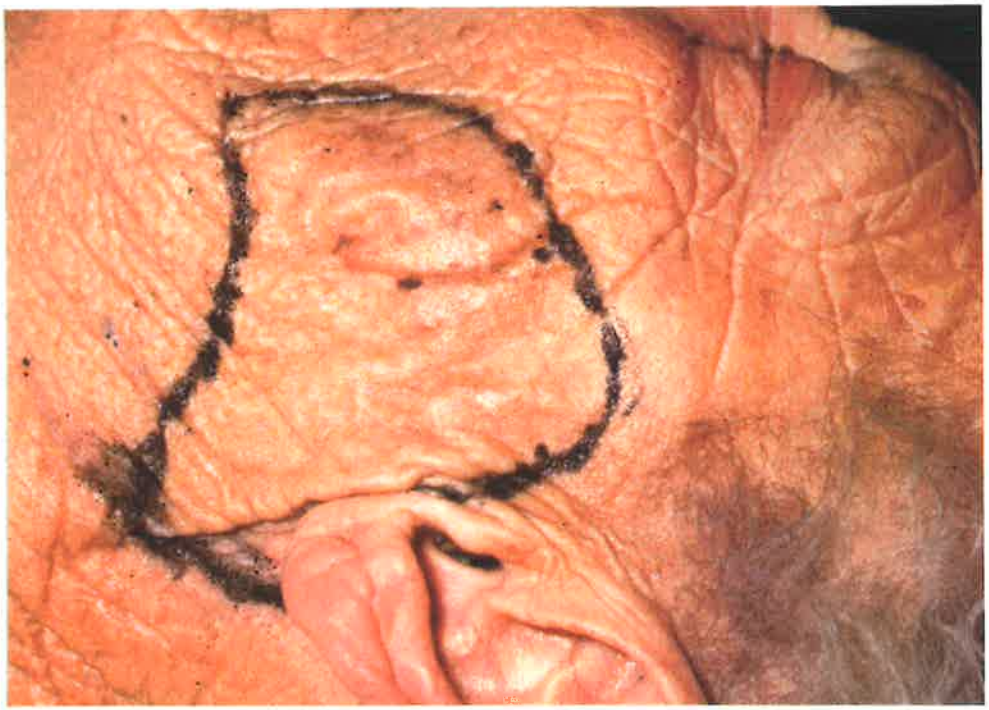
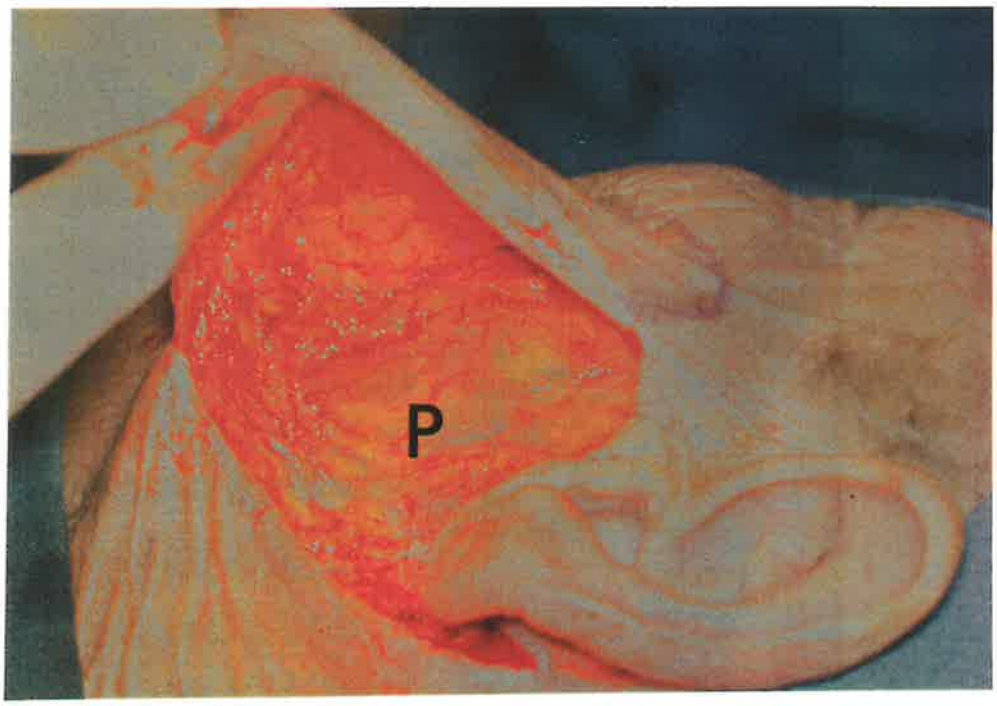


FIGURE 10 Mrs.J.S. Starch Iodine Test
Note that the area of sweating extends behind the ear in addition to the side of the face.



A

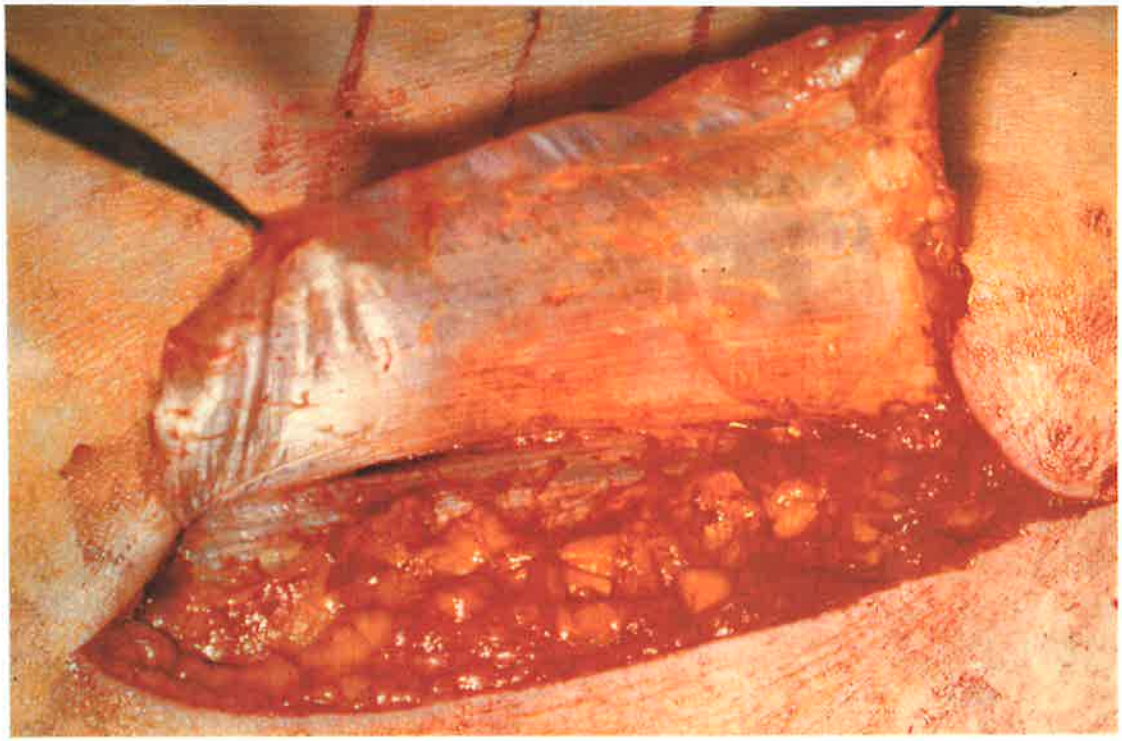


B

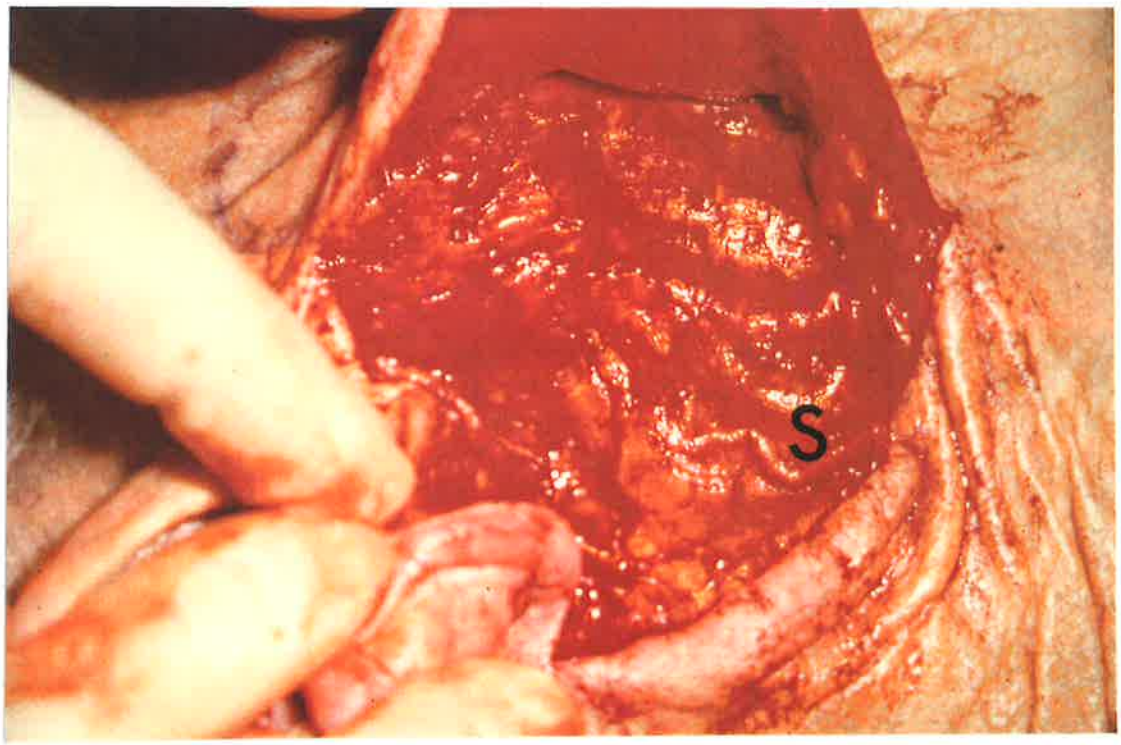
FIGURE 11 Technique of Fascial Interposition for Treatment of Auriculotemporal Syndrome.

A The area of skin involved mapped using the starch-iodine method

B Skin flap is mobilized beyond the involved territory. Parotid gland surface (P) is visible in the base of the wound.



A



B

FIGURE 12 Technique of Fascial Interposition for Treatment of Auriculotemporal Syndrome.

A Fascia Lata is harvested from the thigh via a longitudinal incision .

B The free graft is carefully sutured to the margins of skin mobilization. Note its slightly irregular surface (S).

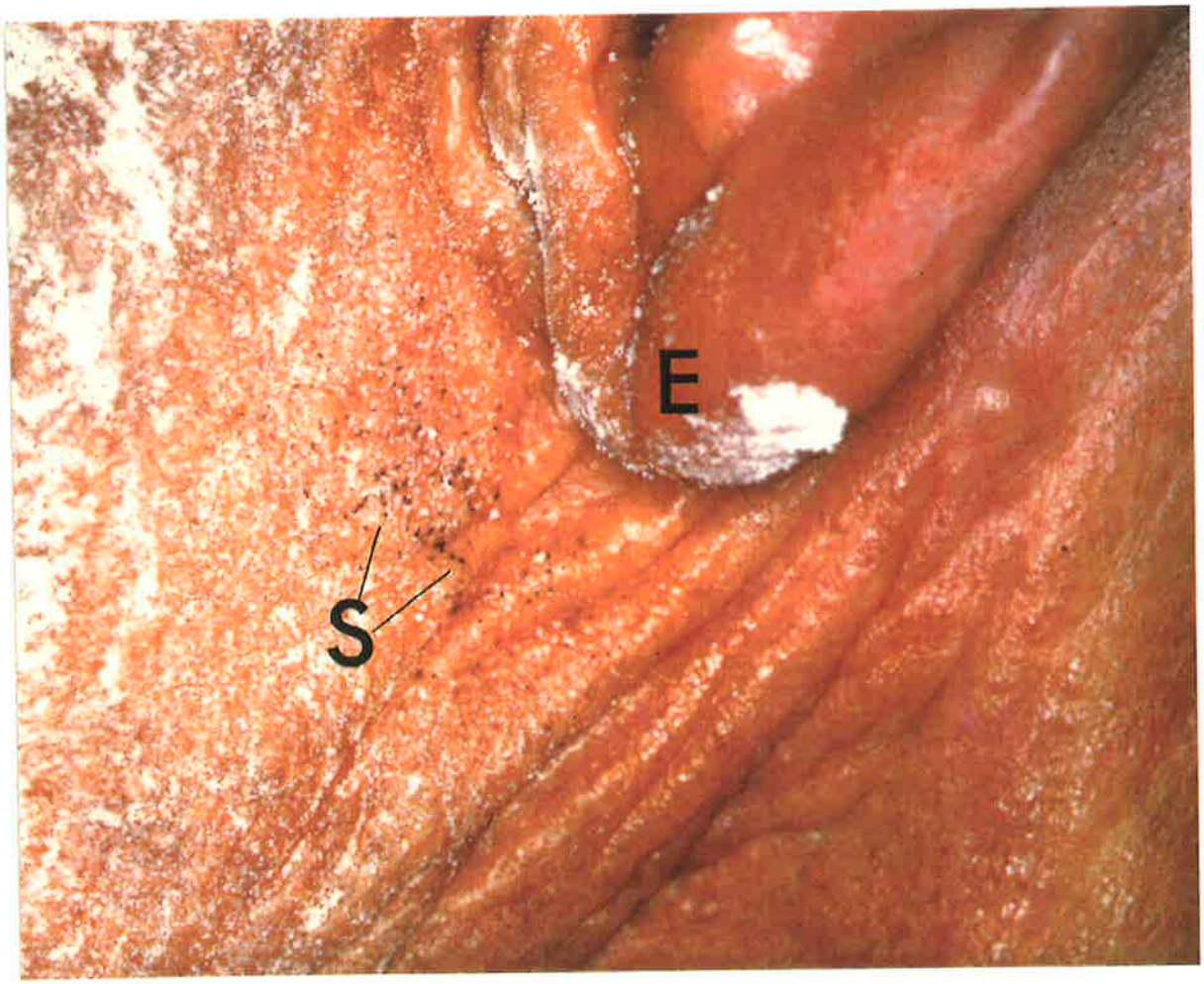


FIGURE 13 Starch Iodine test 10 months after fascial interposition for treatment of auriculotemporal syndrome. Slight recurrence of gustatory sweating is seen as fine dark spots (S) just below the ear lobe (E).

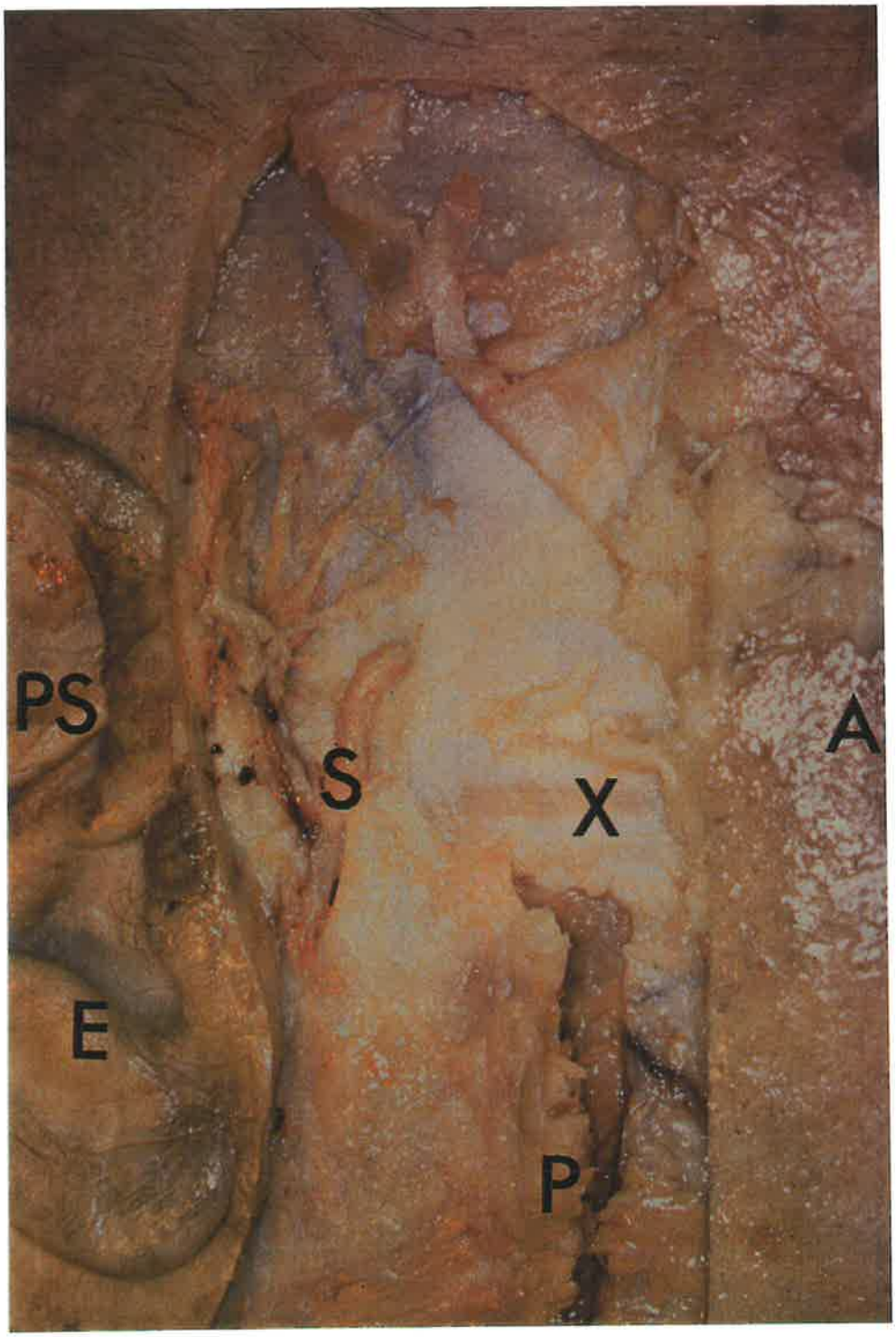


FIGURE 14 Human Auriculotemporal Nerve Dissection I

Note that a skin flap has been removed to expose the parotid gland (P), the superficial temporal nerve and vessels (S) and the Xygoma (X). A, Anterior; E, Ear; PS, Posterior.

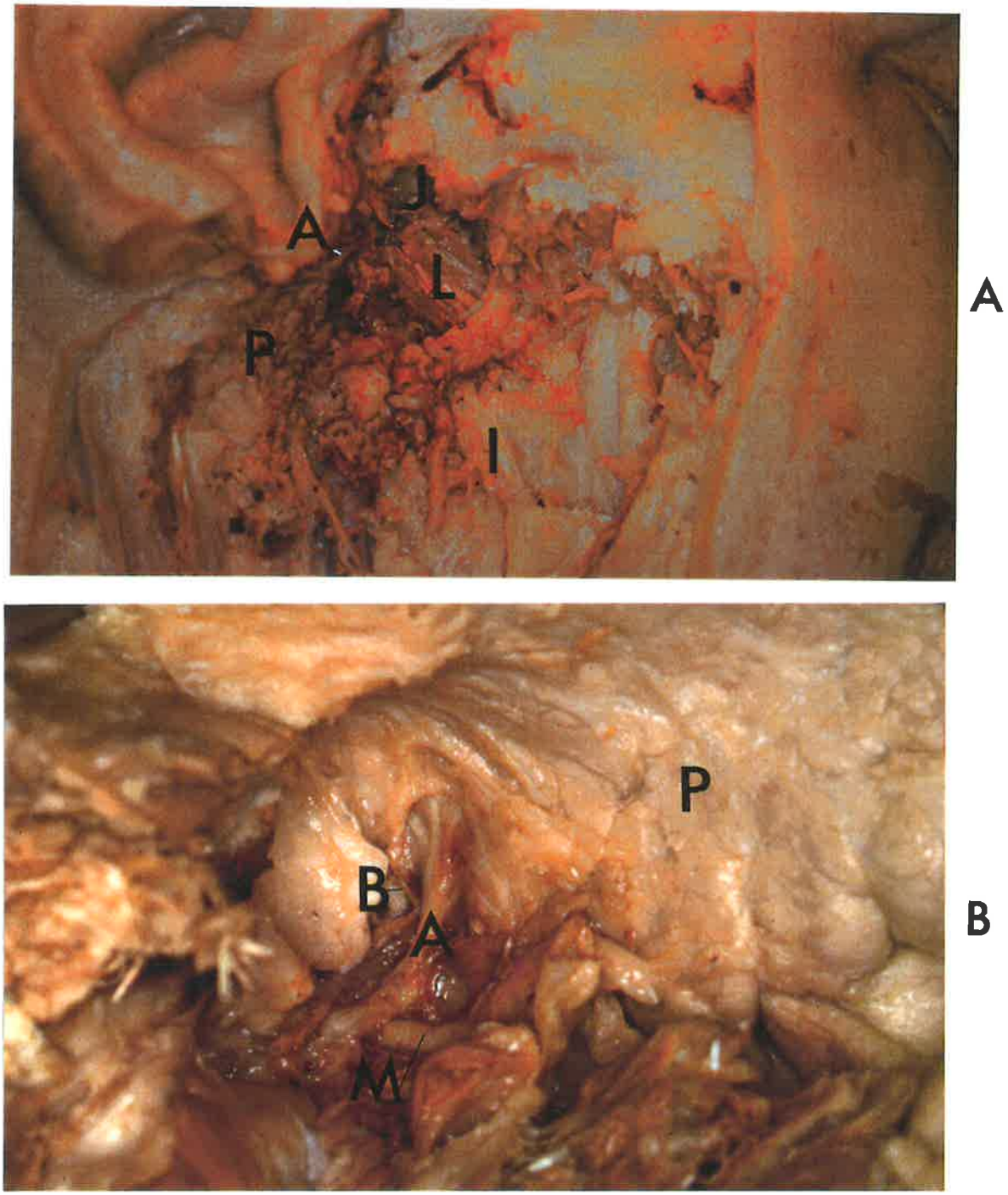


FIGURE 15 Human Auriculotemporal nerve Dissection II

A The ramus of the mandible has been removed and the parotid gland (P) swung posteriorly. The temporomandibular joint (J), lateral pterygoid (L) inferior alveolar nerves and vessels (I) and auriculotemporal nerve trunk (A) are exposed.

B Closeup of the medial surface of the parotid (P) showing the auriculotemporal nerve (A) forming six terminal branches including a branch (B) from the trunk to the deep lobe of the parotid. M, Maxillary artery.

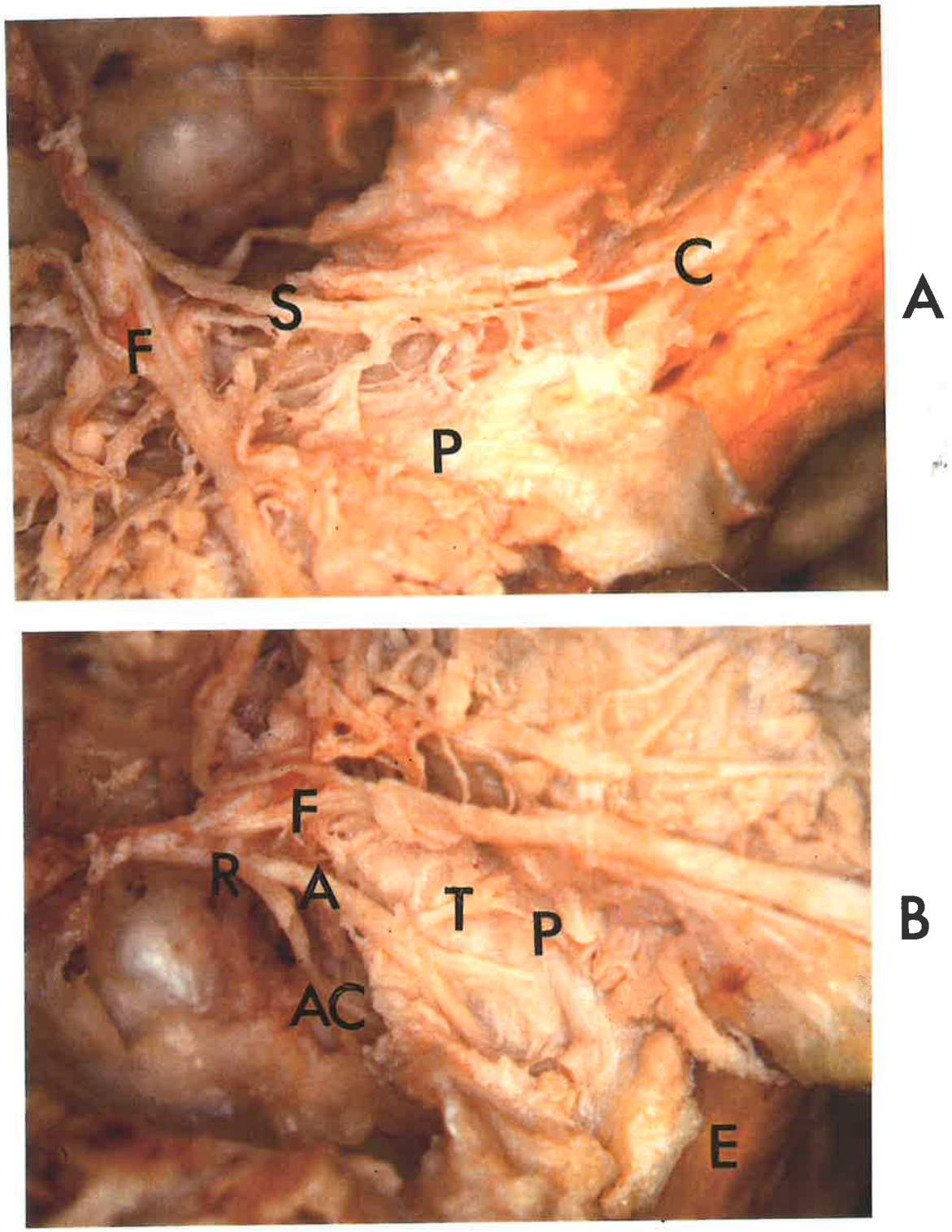


FIGURE 16 Human Auriculotemporal nerve dissection III

AC , Branch to the auditory canal; F , Anastomosis to facial nerve

A Superficial temporal nerve (S) dissected from parotid (P) to display multiple branches (B) entering the parotid gland and the nerve trunk continuing on to supply the skin (C).

B Superficial removed (R) to allow exposure of auricular branch (A) and twigs (T) innervating the parotid (P) and continuing on to supply the ear (E).

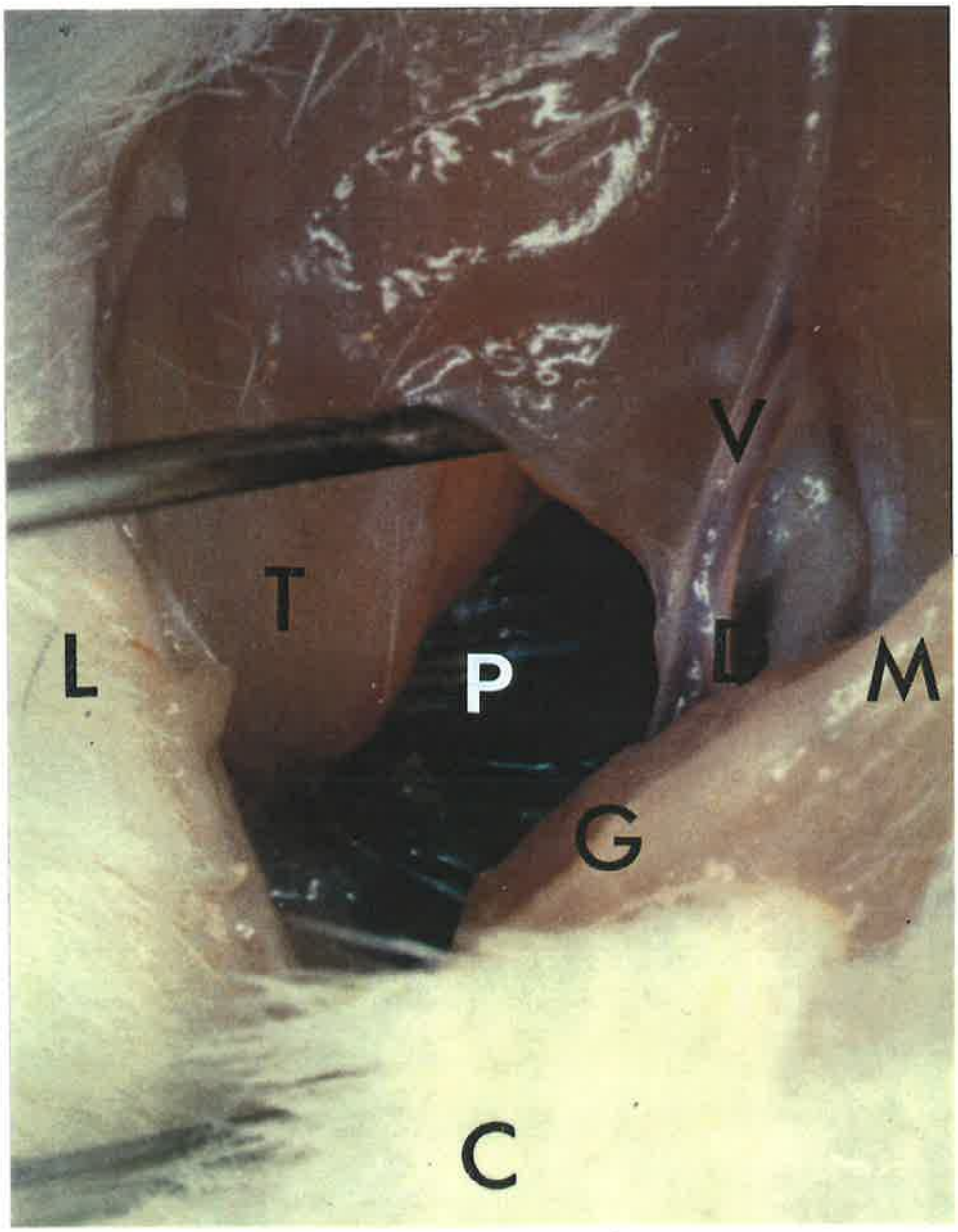


FIGURE 17 Rat Auriculotemporal Nerve Exposure.

A transverse incision has been made in the skin at the level of the angle of the mandible on the right, exposing the Sub-mandibular Gland (G) and Duct (D), the posterior facial vessels (V), masseter (T), and Medial Pterygoid (P). M, Medial; L , Lateral; C, Caudal. Animal supine viewed from above. Magnification X 5

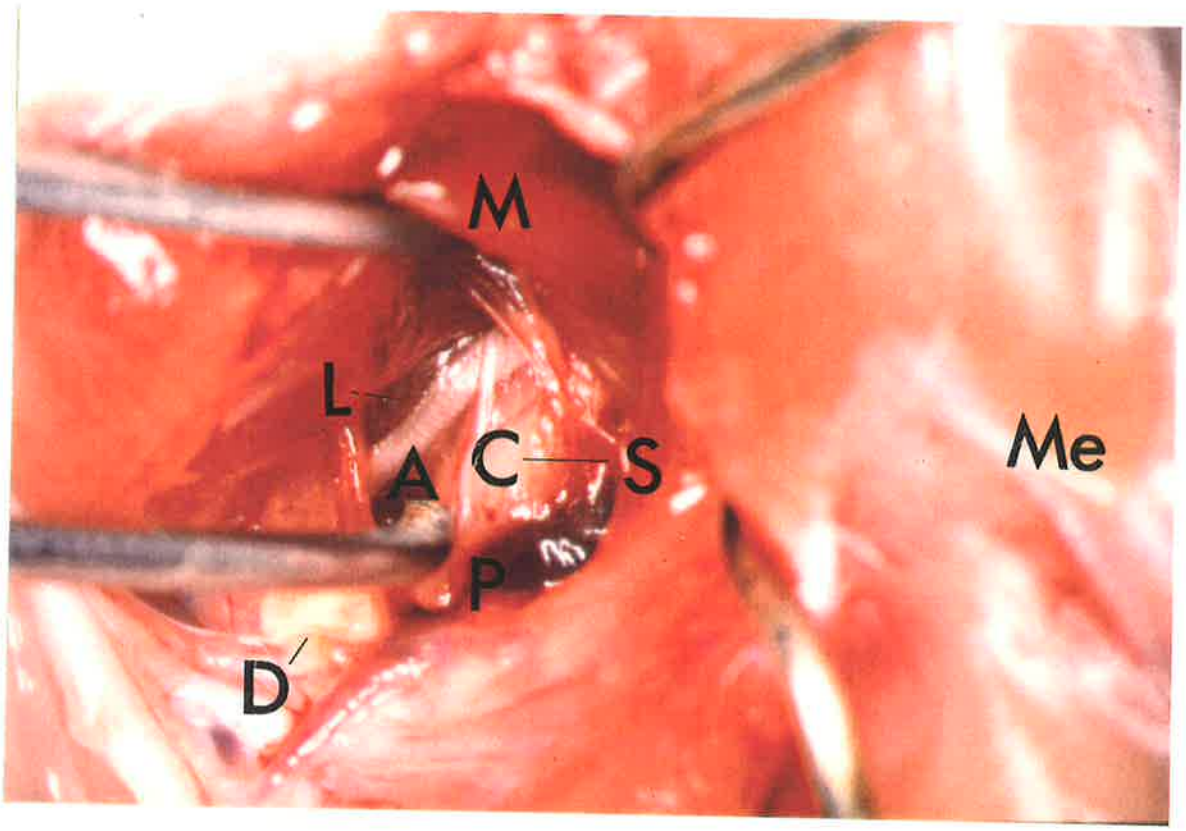


FIGURE 18 Rat Auriculotemporal Nerve Exposure II

The incision has been deepened to expose the right auriculotemporal nerve (A) on the lateral pterygoid muscle (L). The chorda tympani (C) crosses the nerve. The medial pterygoid (M) and pterygoid venous plexus (P) have been retracted. D, Deep lobe of parotid; S, Sphenoid bone; Me, Medial. Animal supine viewed from above. Magnification X 10.

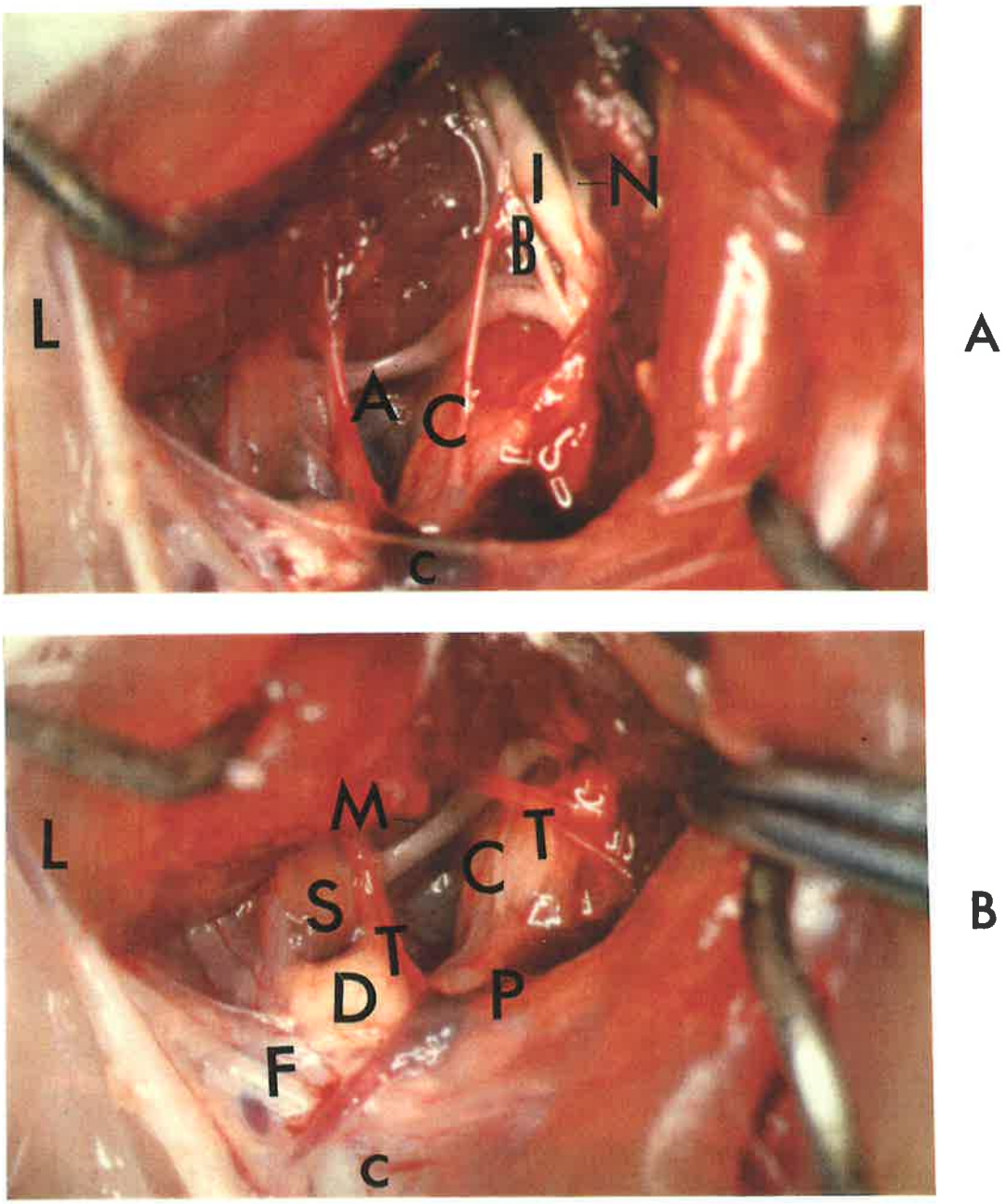


FIGURE 19 Rat Auriculotemporal nerve Anatomy I

A The right mandibular nerve has been exposed by dissection to display the auriculotemporal nerve (A), buccal nerve (B), inferior dental nerve (I), lingual nerve (N) and chorda tympani (C). Note the partial division of the auriculotemporal nerve.

B The auriculotemporal nerve is crossed by the chorda tympani (C) two tributaries (T) of the pterygoid plexus (P) and the stylomandibular muscle (S). The nerve lies on the the lateral pterygoid muscle (M). F, Facial Nerve; D,Deep lobe of parotid. Animal supine extended neck viewed from above, C, Caudal ; L, Lateral. Magnification X 10 .

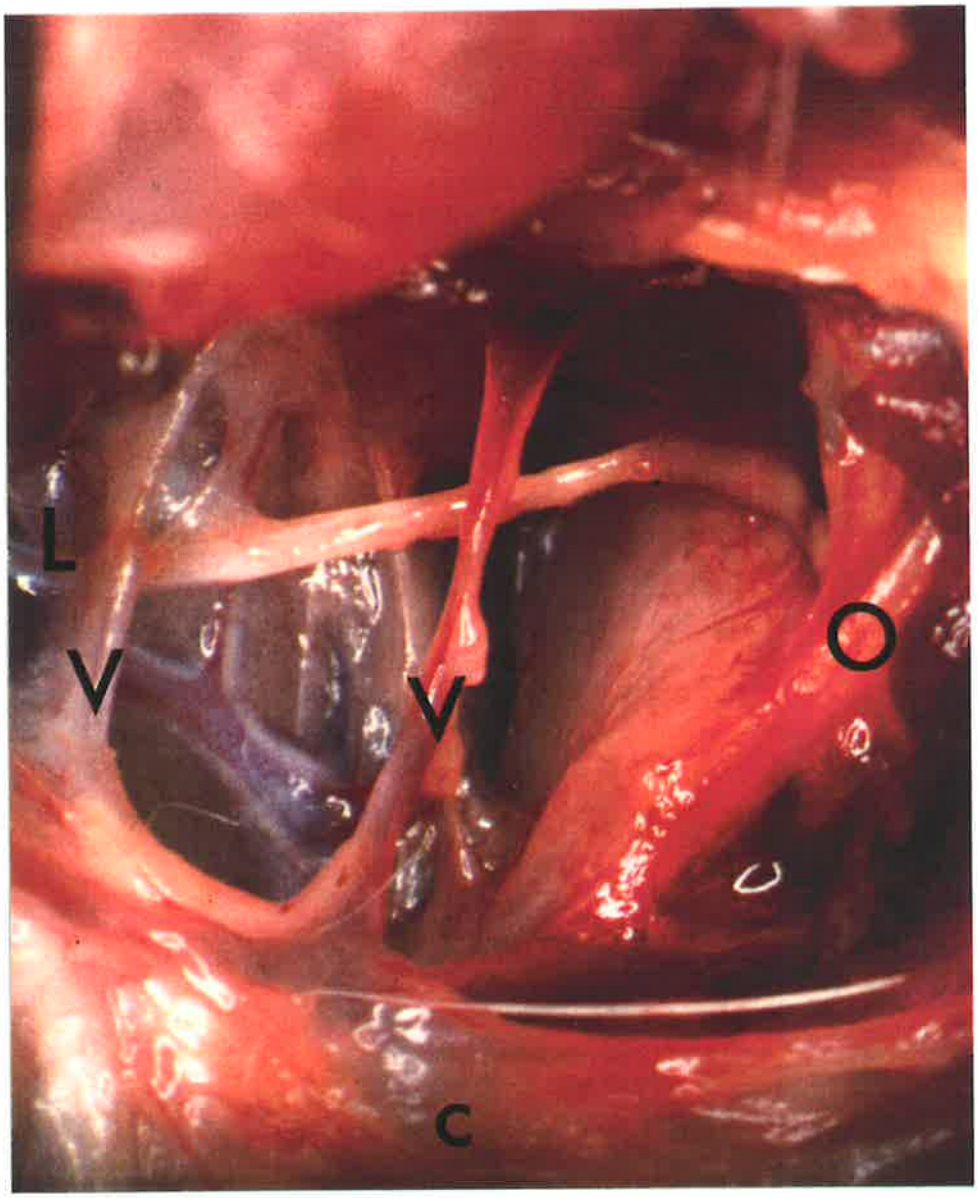


FIGURE 20 Rat Auriculotemporal Nerve Anatomy II
Right auriculotemporal nerve can be seen to emerge from beneath an oblique bar of bone (O) over lying the foramen ovale. Crossing veins (V) are again noted. C, Caudal; L, Lateral; Animal supine viewed from above. Magnification X 10.

FIGURE 21 Rat Auriculotemporal Nerve Anatomy III Left auriculotemporal nerve displaying the branch (B) to the deep lobe of the parotid (D) and two branches (T) to the facial nerve (F). S, Superficial lobe of the parotid; C ,Caudal; L, Lateral. Note facial nerve divides after leaving the anterior border of the parotid (P). Animal supine viewed from above. Magnification X 10.

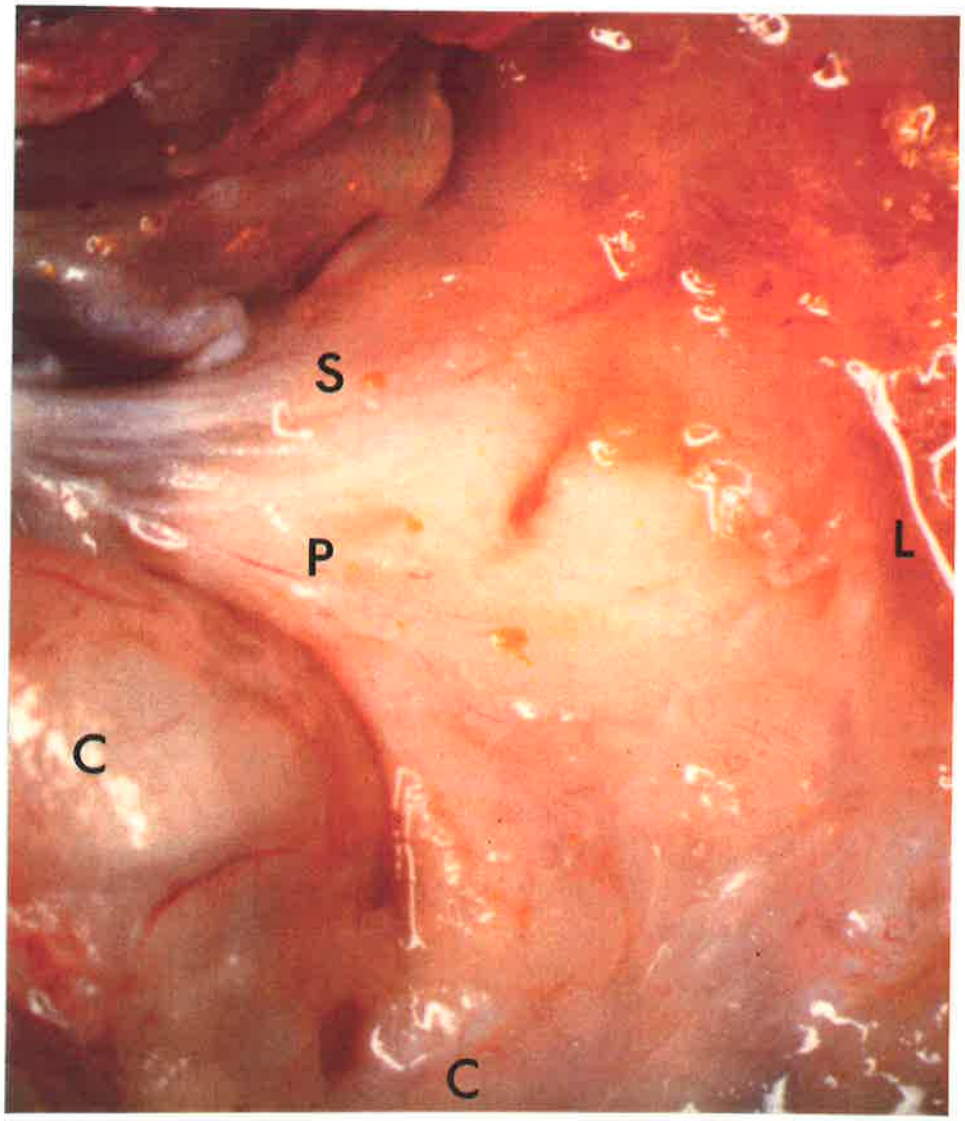


FIGURE 22 Rat Auriculotemporal Nerve Anatomy IV

Superficial temporal branch of the left auriculotemporal nerve. Note branches to the skin (S) (Yellow colour is due to Diamidino Yellow) and superficial lobe of the Parotid (P). C, Cartilagenous portion of external auditory canal ;L, Lateral; C,Caudal. Animal supine viewed from above. Magnification X 15.

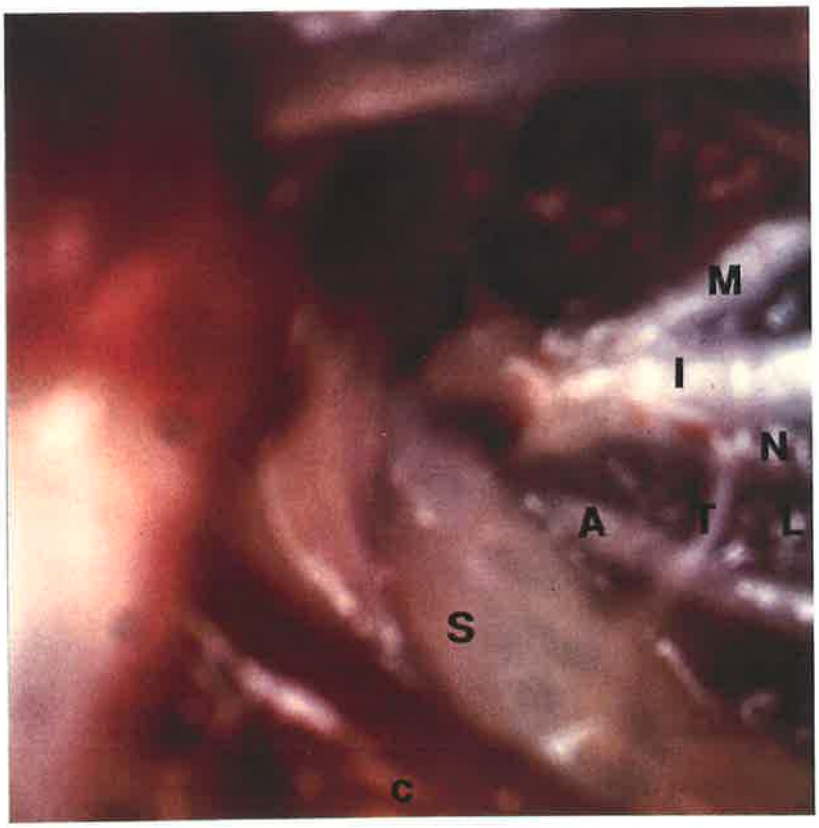


FIGURE 23 Anatomy of the Marmoset Auriculotemporal Nerve I The left mandibular nerve has been exposed to display chorda tympani (T), Auriculotemporal nerve (A), Inferior dental nerve (I), buccal nerve (N), and Lingual nerve (M). S, Sphenoid air cells ; c, Caudal ; L, Lateral. Animal supine ,extended neck viewed from above. Magnification X 15.

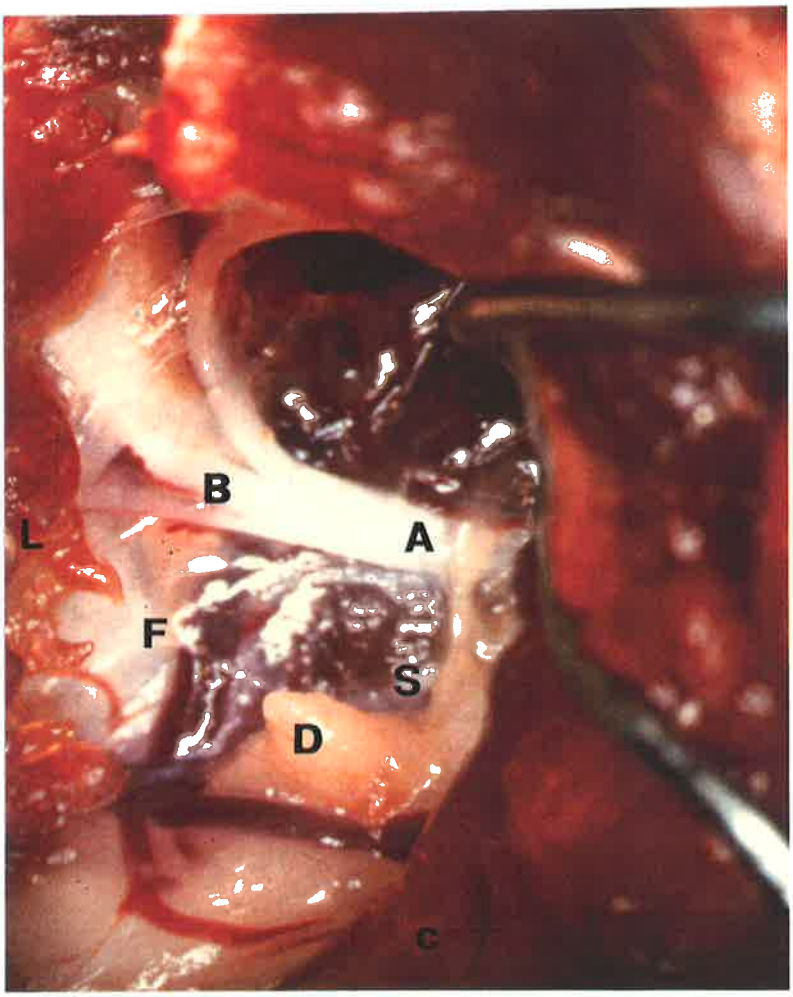


FIGURE 24 Anatomy of the Marmoset Auriculotemporal Nerve II Right Auriculotemporal nerve (A) dividing into at least 3 branches (B) at the level of the superficial lobe (F) of the parotid and a single branch (S) to the deep lobe (D) of the parotid. C, Caudal; L, Lateral . Animal supine viewed from above. Magnification X 15.

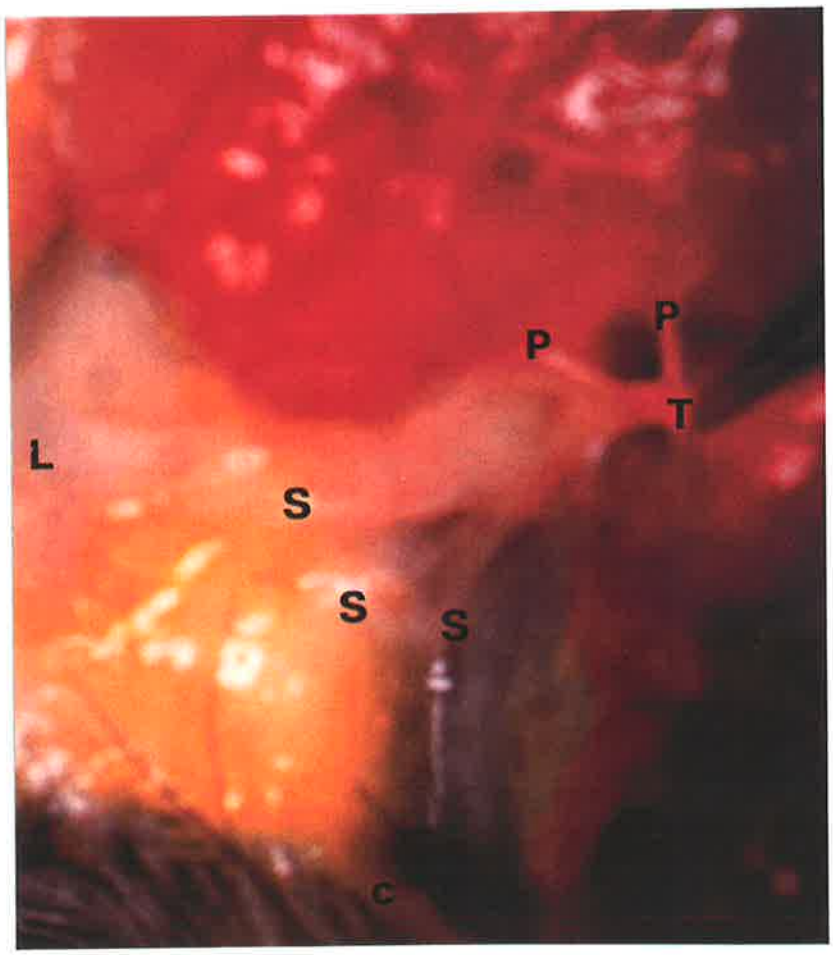


FIGURE 25 Anatomy of the Marmoset Auriculotemporal Nerve III Superficial temporal branch (T) demonstrating branches to the skin (S) and Parotid (P). Yellow colour of the skin is due to Diamidino Yellow. C, Caudal; L, Lateral. Magnification X 10.

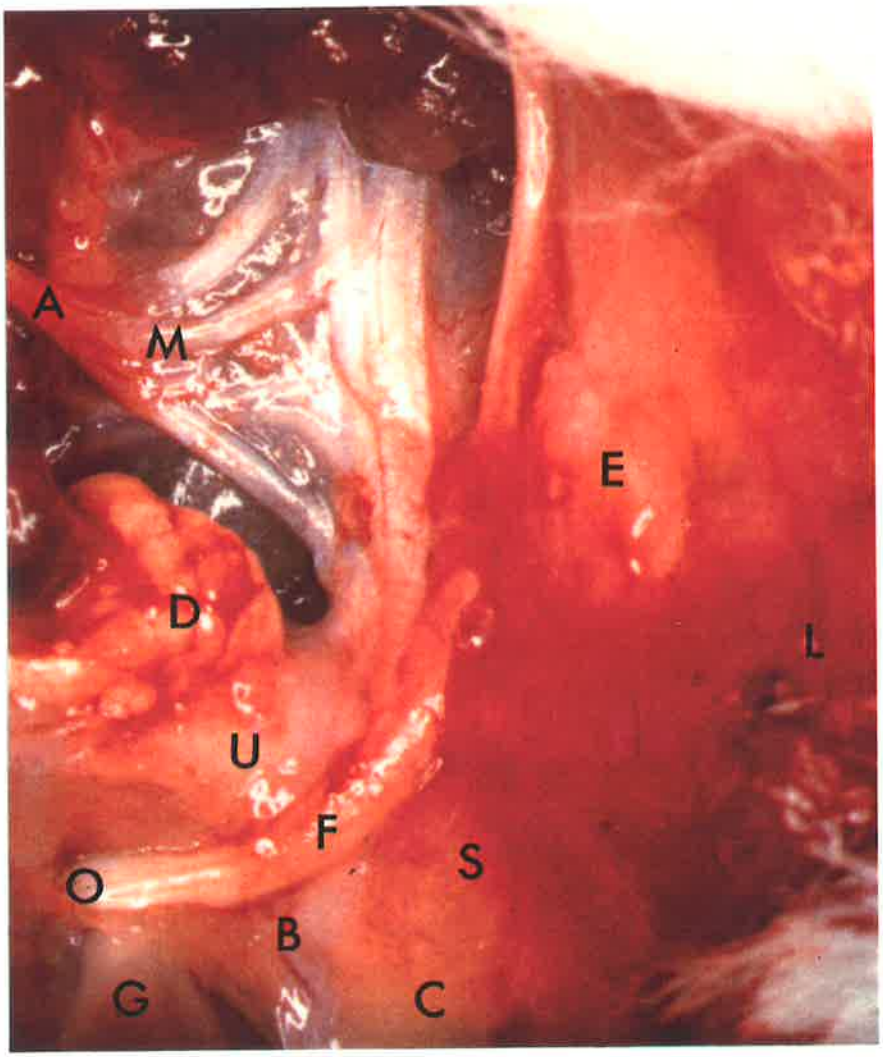


FIGURE 26 Parotid Gland and Facial nerve of the Rat
The facial (F) and auriculotemporal (A) nerves have been exposed. M, Communicating branches; D, Deep lobe of parotid; S, Superficial lobe; E, Extra-orbital lacrimal gland; G, Digastric muscle; B, Branch to auricular muscles; O, Stylomastoid foramen; U, Auditory canal; L ,lateral; C, Caudal. Animal Supine viewed from above. Magnification X 15.

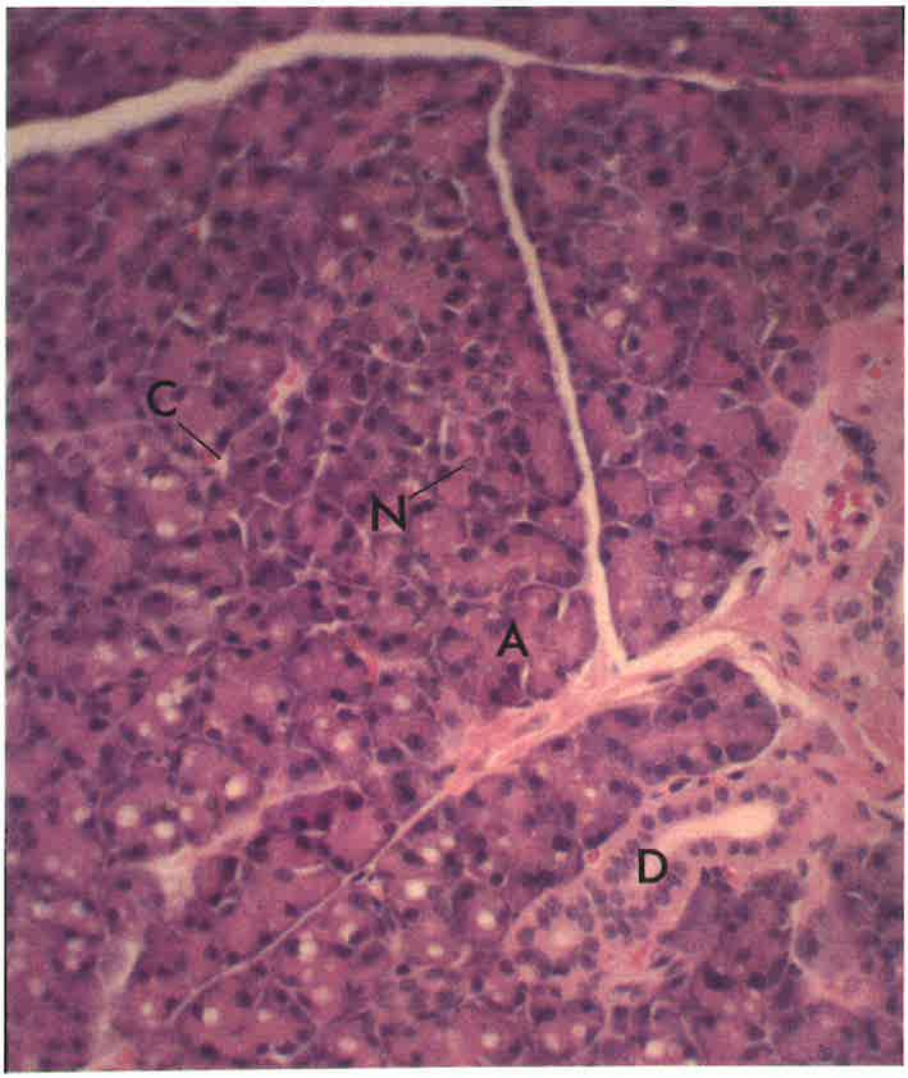


FIGURE 27 Haematoxylin and Eosin Section of Rat Parotid N, Nucleus; A, Acinus; C, Central cannaliculus D, ductule. (X 200) Note absence of fatty infiltration.

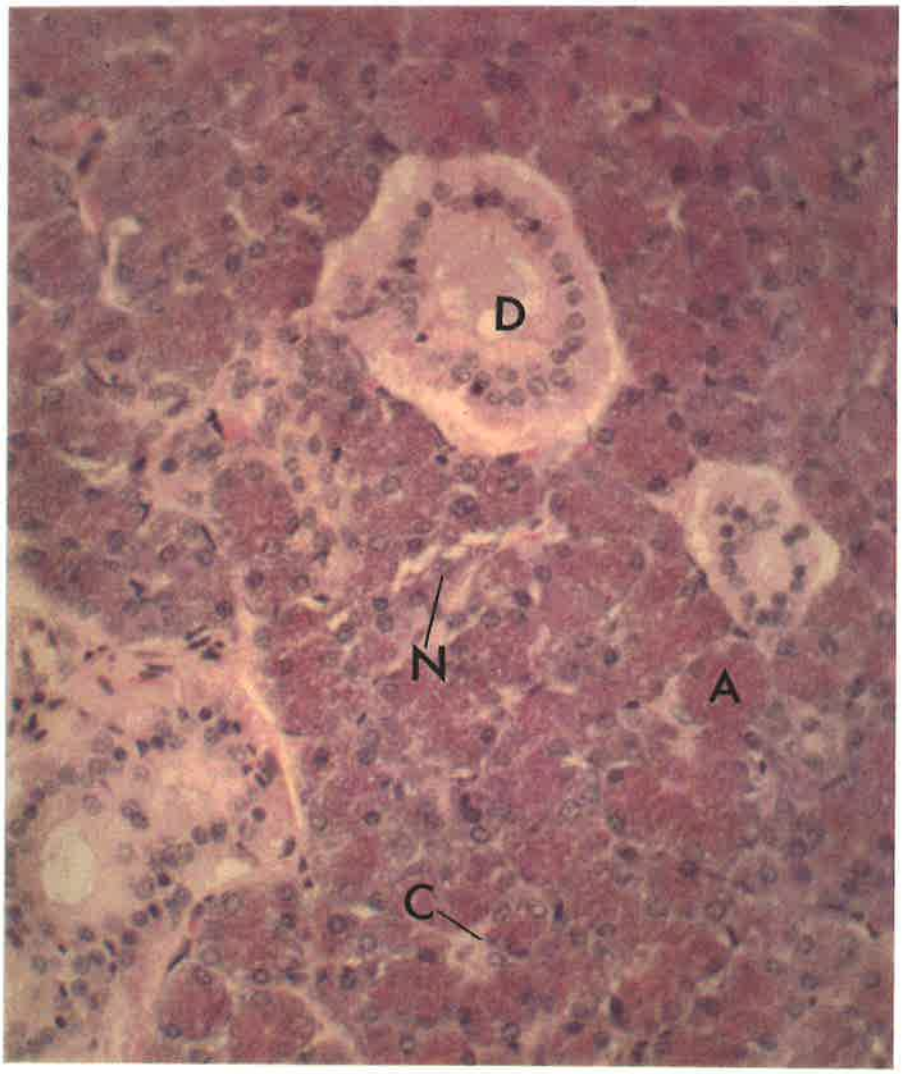


FIGURE 28 Haematoxylin and Eosin Section of Marmoset Parotid N, Nucleus; A, Acinus; C, Central cannaliculus D, ductule. (X 200) Note larger cells and more pronounced zymogen granulation than the rat.

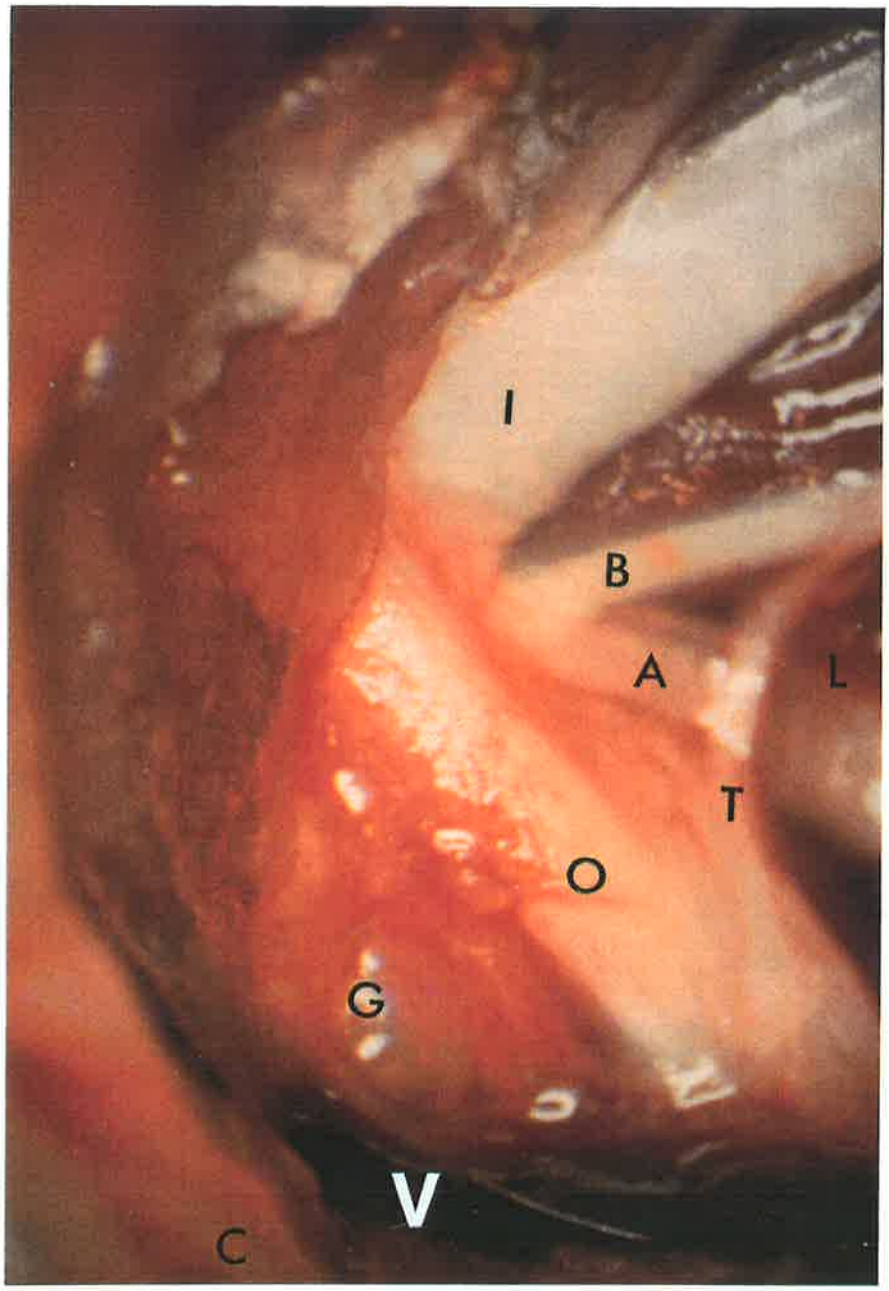


FIGURE 29 Otic Ganglion of the rat I. O, Oblique bar of bone; G, Otic ganglion ; A, Auriculotemporal nerve ; B, Buccal nerve ; T, Chorda tympani ; I, Inferior dental nerve; V, vessel. Animal supine viewed from above. C, Caudal; L, Lateral. Magnification X 20.

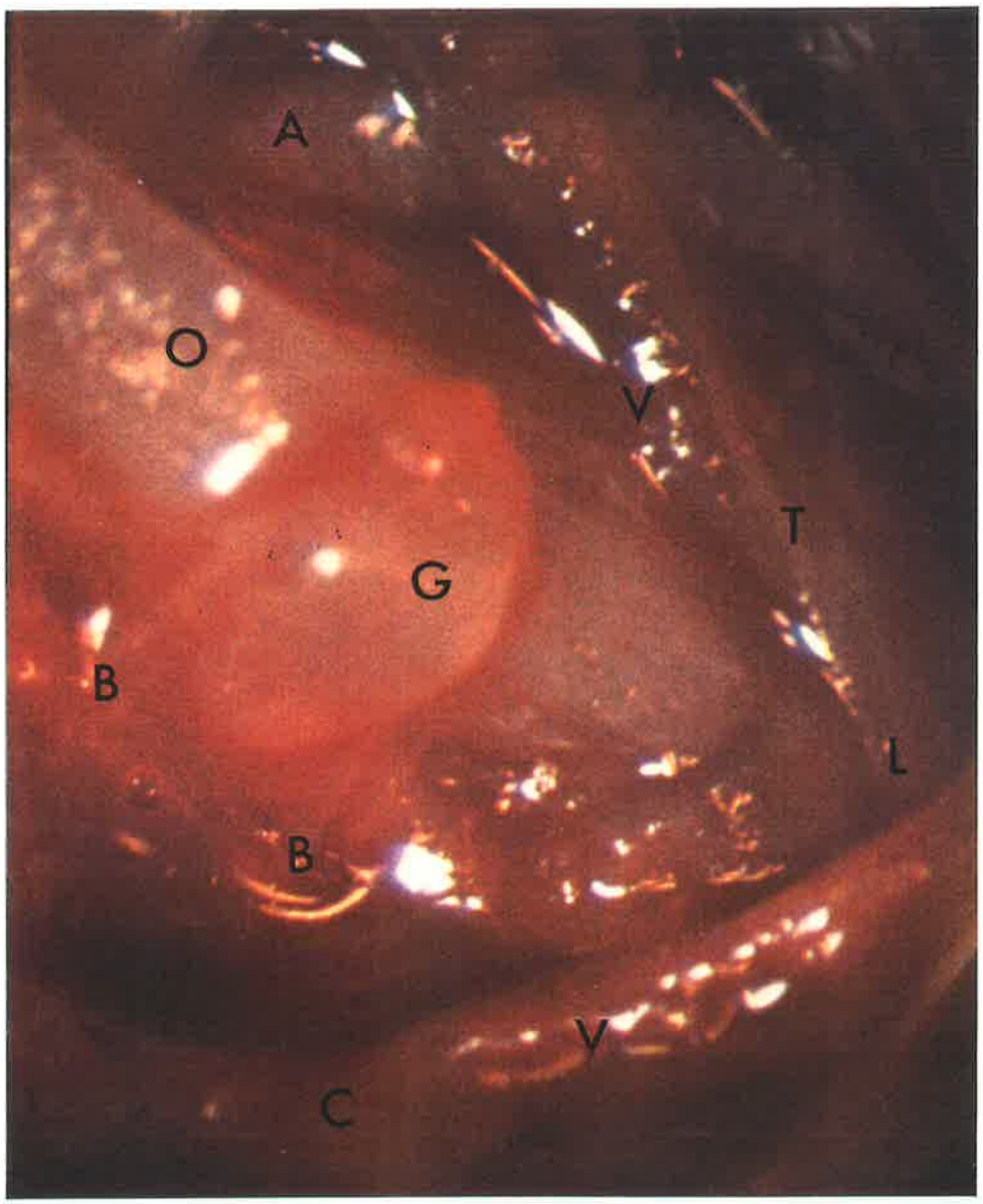


FIGURE 30 Otic Ganglion of the rat II.

O, Oblique bar of bone; G, Otic ganglion ; A, Auriculotemporal nerve ; T, Chorda tympani ; V, vessel ; B, Branches. Animal supine viewed from above. C, Caudal; L, Lateral. Magnification X 40.

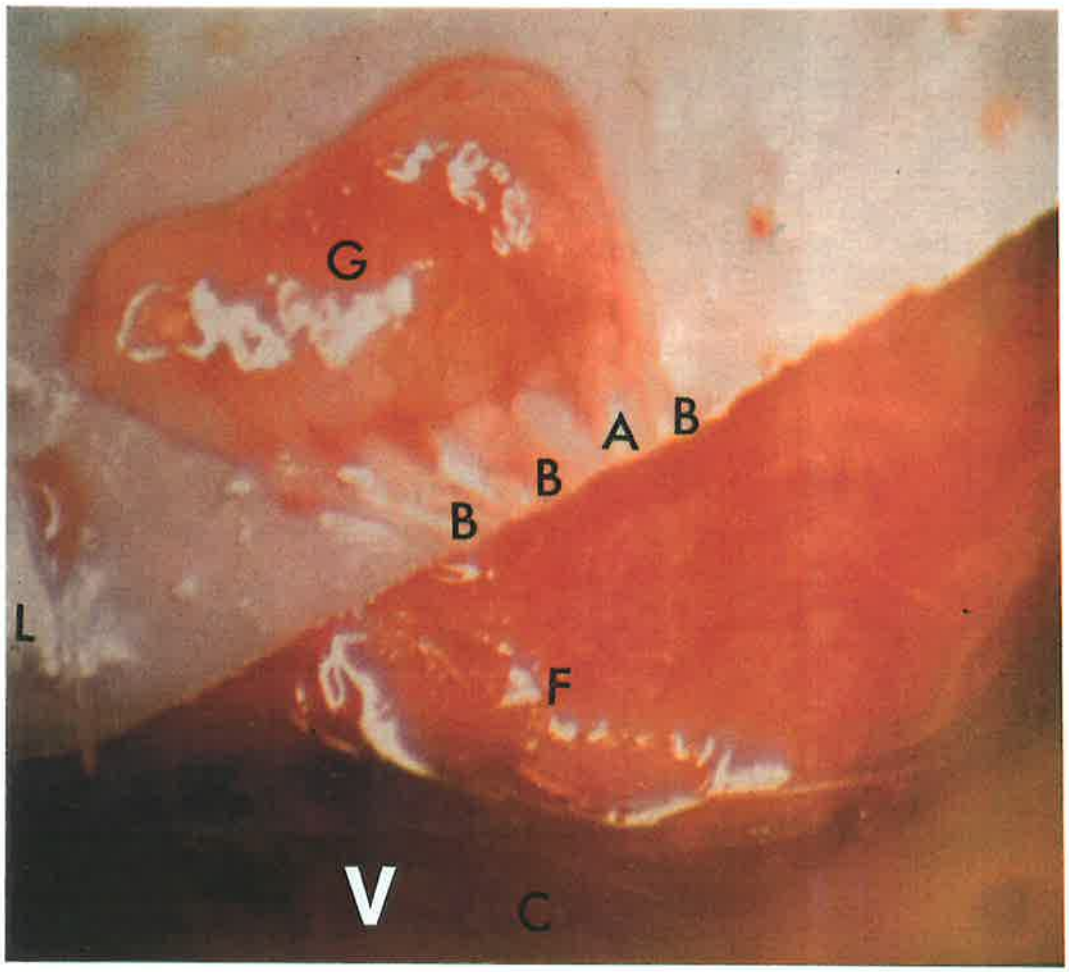


FIGURE 31 Otic Ganglion of the rat III.
The otic ganglion (G) has been dissected free of the otic fossa (F) V, vessel ; B, 6 Branches from otic ganglion ;A, Large constant branch to auriculotemporal nerve. Animal supine viewed from above. C, Caudal; L, Lateral. Magnification X 60.

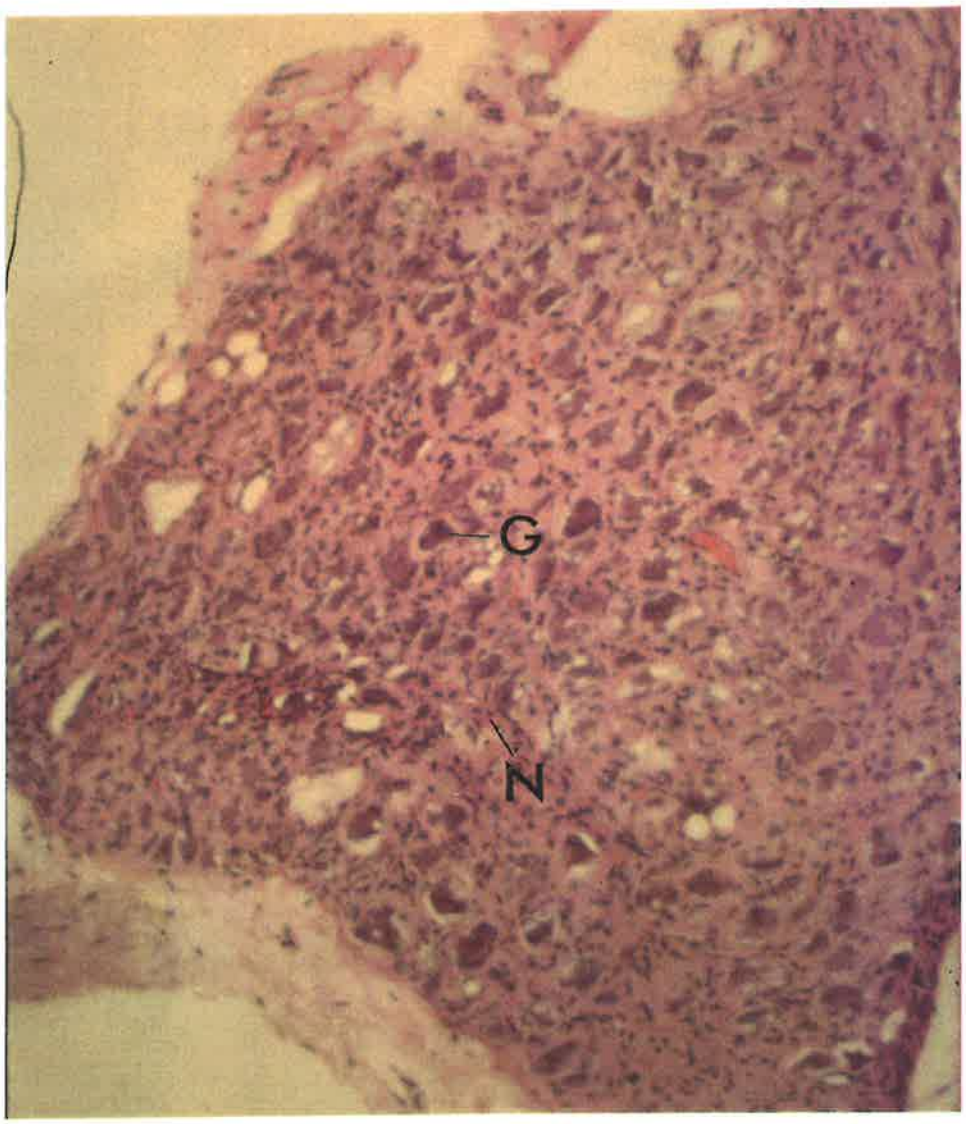


FIGURE 32 Haematoxylin and Eosin Section of the of Rat Otic Ganglion. G, Large neuronal cell bodies; N, Neuroglial nucleus. Magnification X 100.

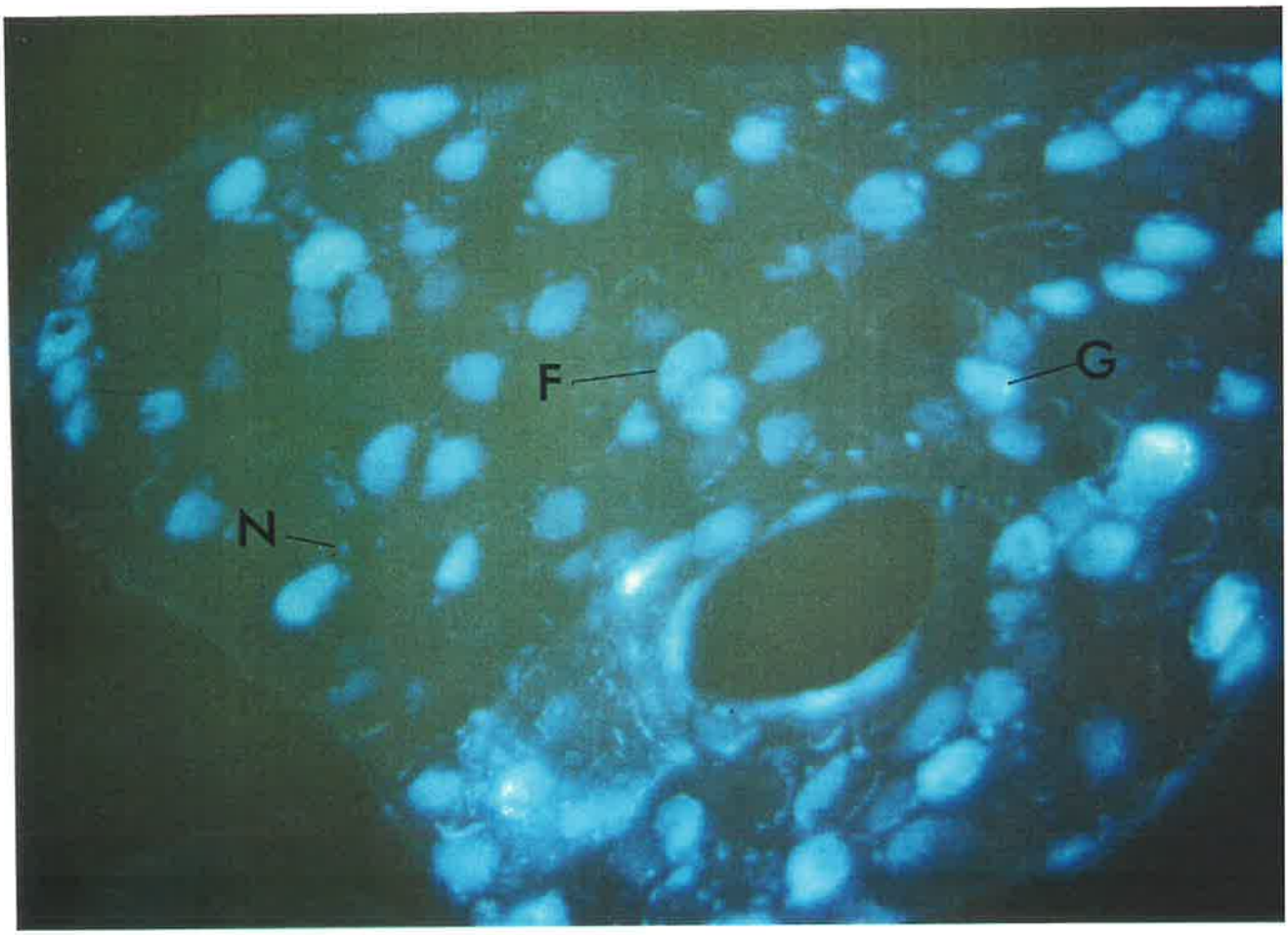


FIGURE 33 Fast Blue Labelled Rat Otic Ganglion

Viewed by dark field fluorescent microscopy. Note cytoplasm is labelled with bright blue fluorescence (F). Some neuroglial nuclei are also labelled (N). Silvery-gold cytoplasmic granules (G) of fast blue are also visible. H, Hole made by 0.1mm. micro-pin used to handle specimen. Magnification X 150.

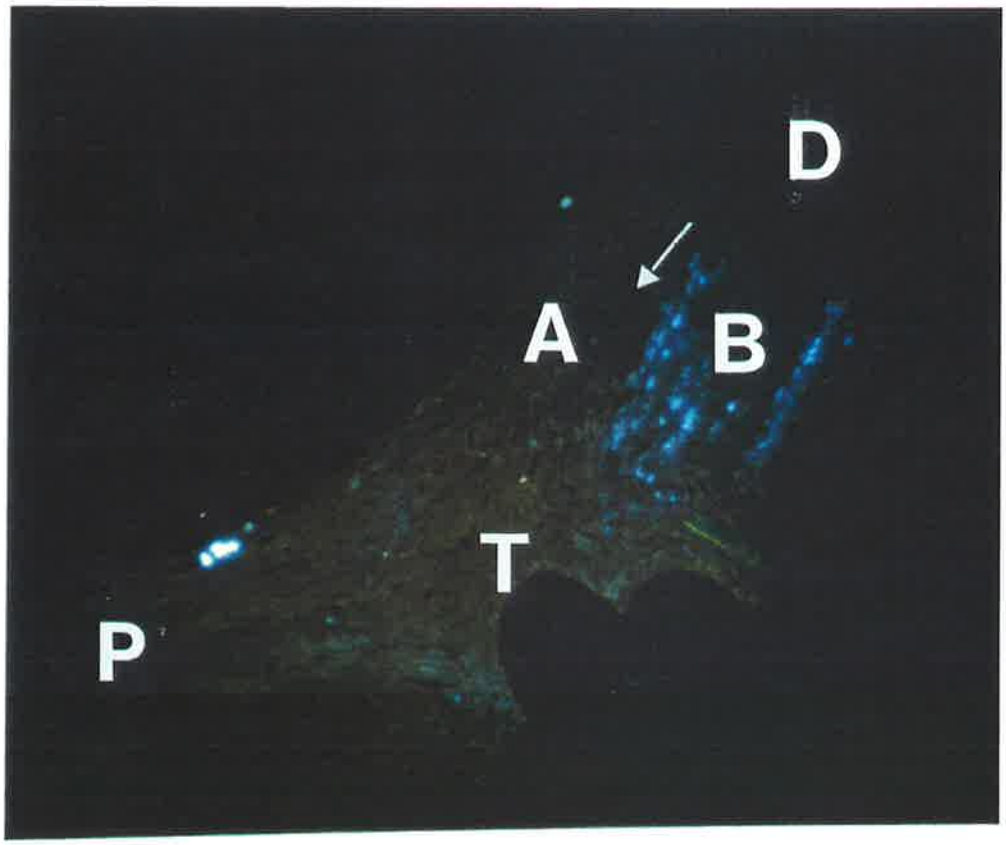


FIGURE 34 Tied Auriculotemporal nerve of the Rat Viewed by dark field fluorescent microscopy. Note build up of dye (B) proximal to tie (T). P, Proximal; D, distal; A, Auriculotemporal nerve. Magnification X 40. Direction of retrograde neuronal flow is arrowed.

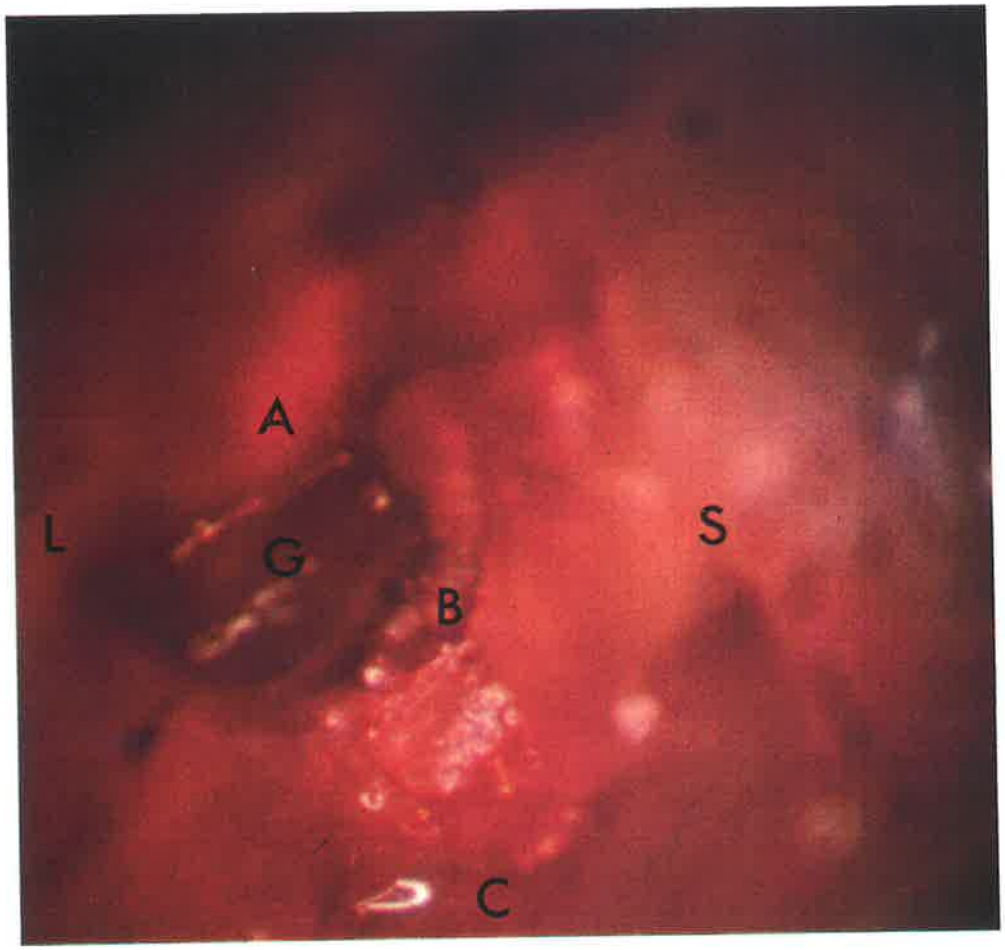


FIGURE 35 Otic Ganglion of the Marmoset.

G, Otic Ganglion; B, Bone removed ; A , Blurred auriculotemporal nerve; S, Sphenoid air sinuses.

C, Caudal ;L, Lateral . Animal supine viewed from above. Magnification X 60.

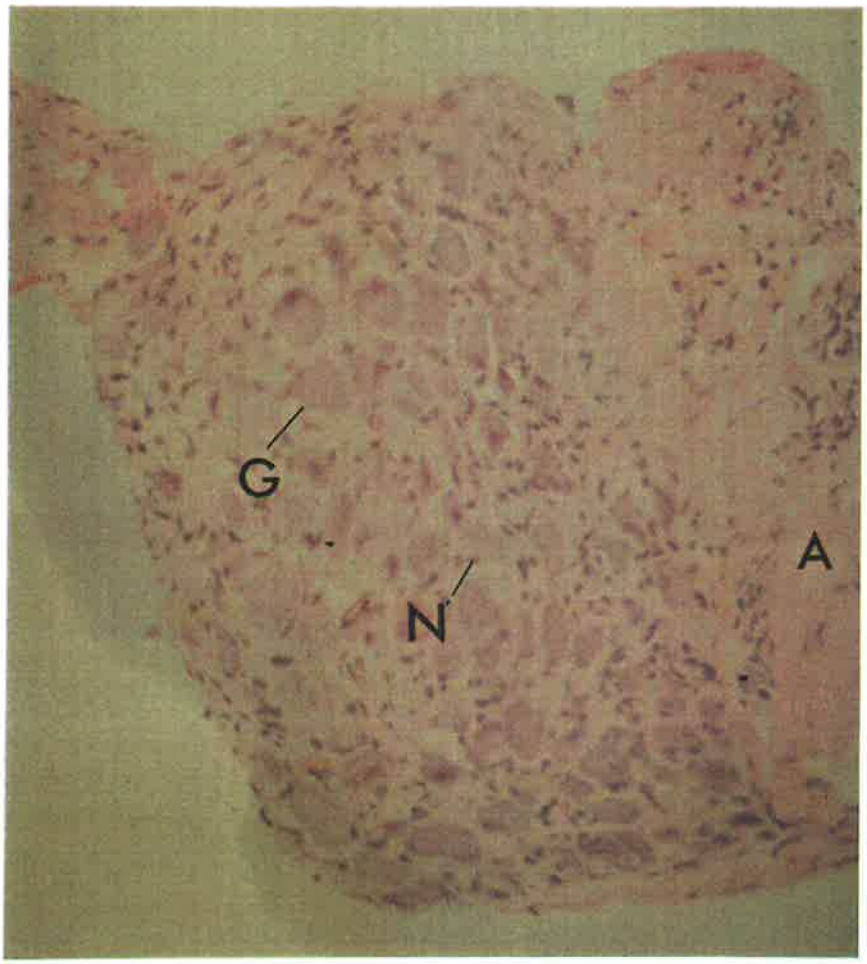


FIGURE 36 Haematoxylin and Eosin Section of the Marmoset Otic Ganglion. G, Large neuronal cell bodies; N, Neuroglial nucleus; A, Auriculotemporal nerve. Note that the ganglion is slightly less densely packed than that of the rat. Magnification X 100

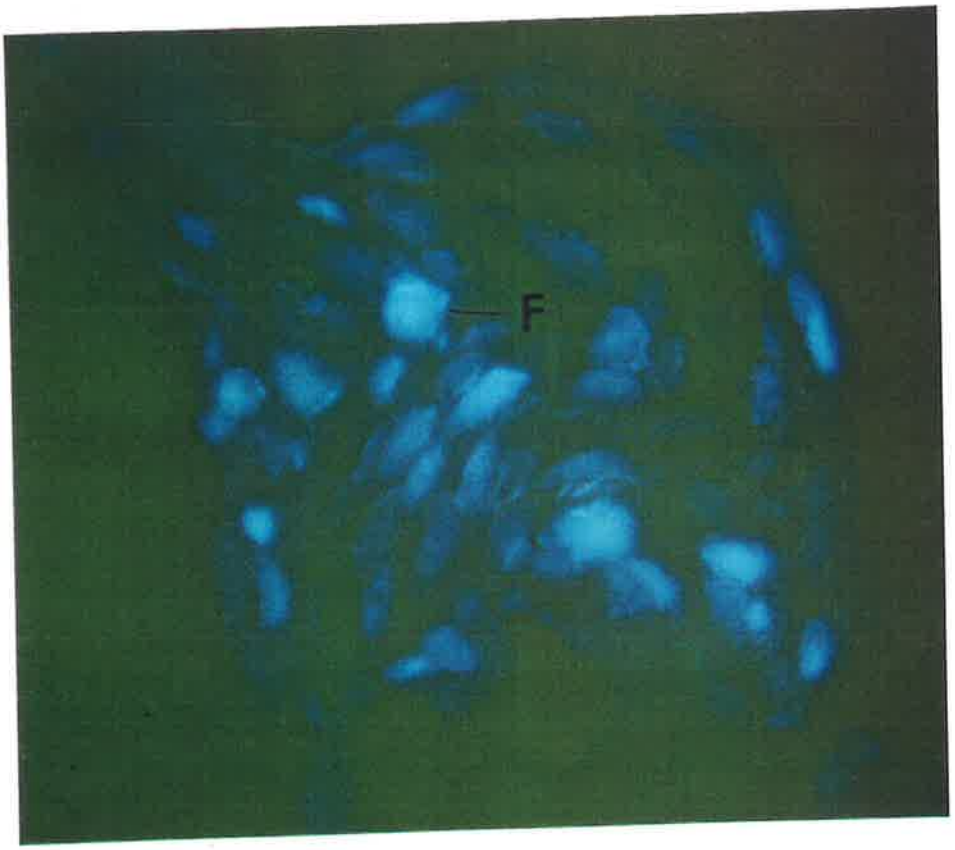


FIGURE 37 Fast Blue Labelled Marmoset Otic Ganglion Viewed by dark field fluorescent microscopy. Note cytoplasm is labelled with bright blue fluorescence (F). No neuroglial nuclei labelling is evident. Magnification X 150

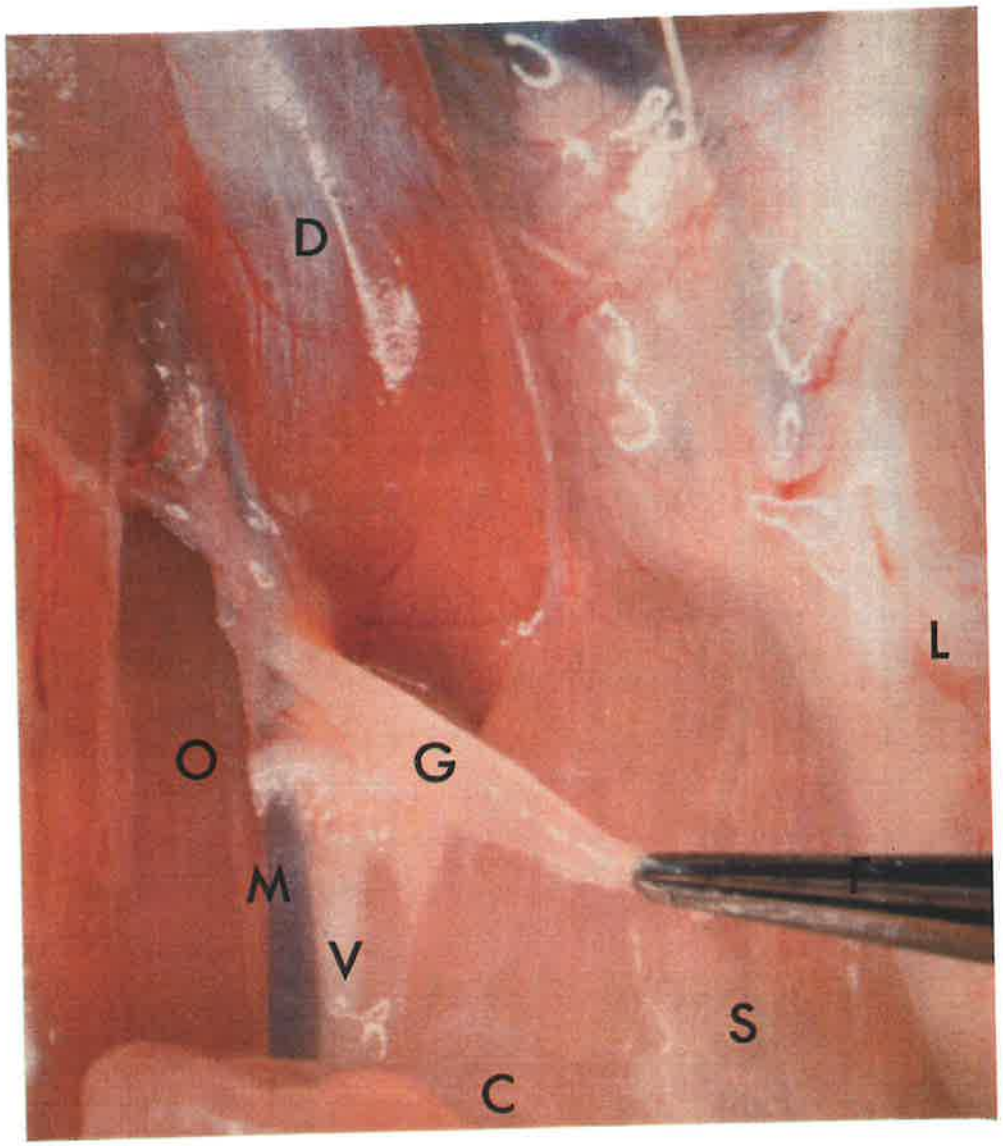


FIGURE 38 The Superior Cervical Ganglion of the Rat The left Superior cervical ganglion (G) has been exposed and grasped with forceps (F). O, Oesophagus; D ,Posterior belly of digastric; S, Sternomastoid; V, Vagus; M, Common Carotid and Internal Jugular; C, Caudal; L, Lateral. Animal supine viewed from above. Magnification X 10.

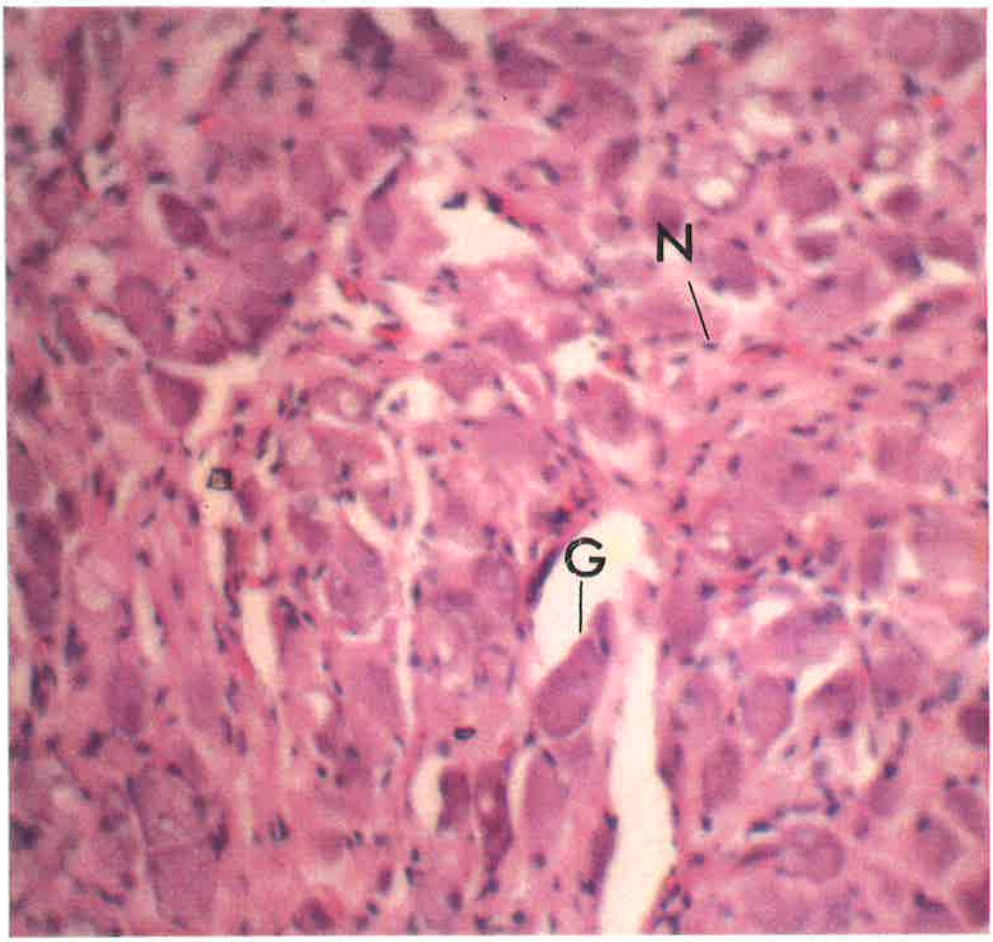


FIGURE 39 Haematoxylin and Eosin Section of Rat Superior Cervical Ganglion.

Note densely packed large ganglion cells (G) and numerous neuroglial nuclei (N). Magnification X 100.

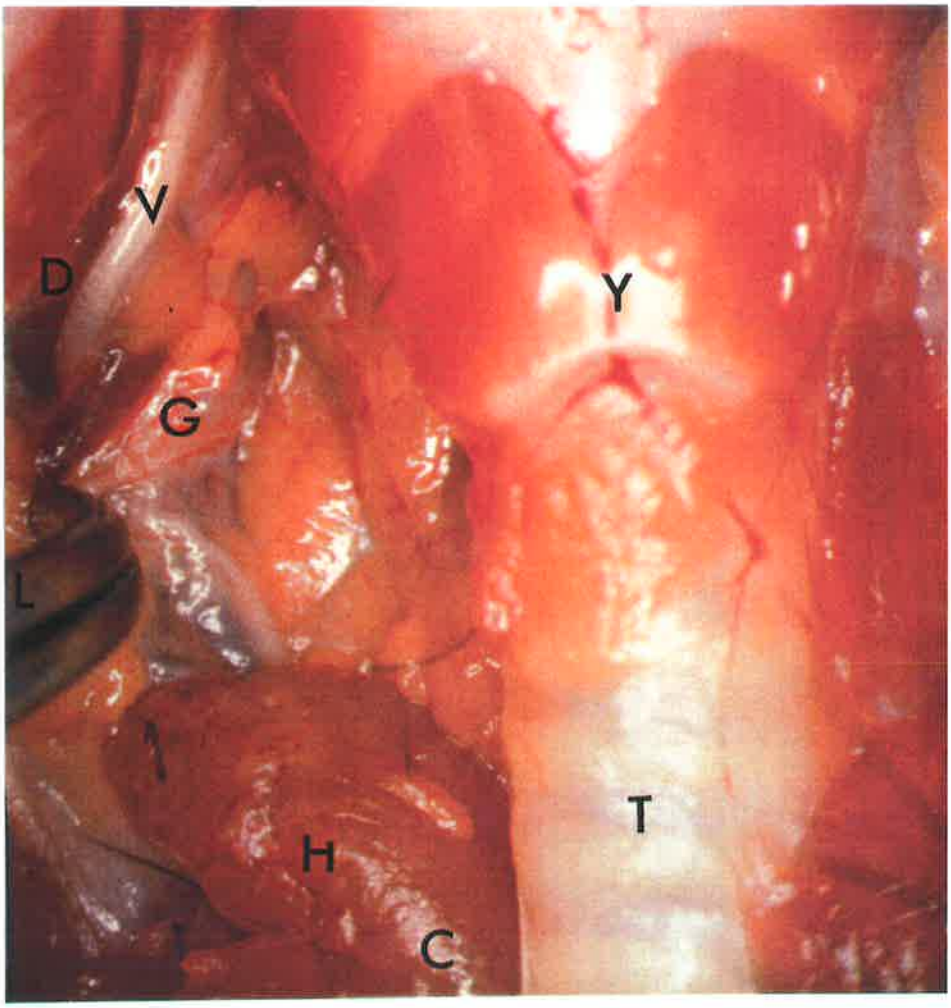


FIGURE 40 The Right Superior Cervical Ganglion of the Marmoset.

The superior cervical ganglion (G) has been exposed and the Vagus (V), and Carotid (D) retracted laterally. Note the fat surrounding the ganglion. T, Trachea; Y, Larynx; H ,Thyroid. L, Lateral; C, Caudal. Animal supine viewed from above. Magnification X 5.

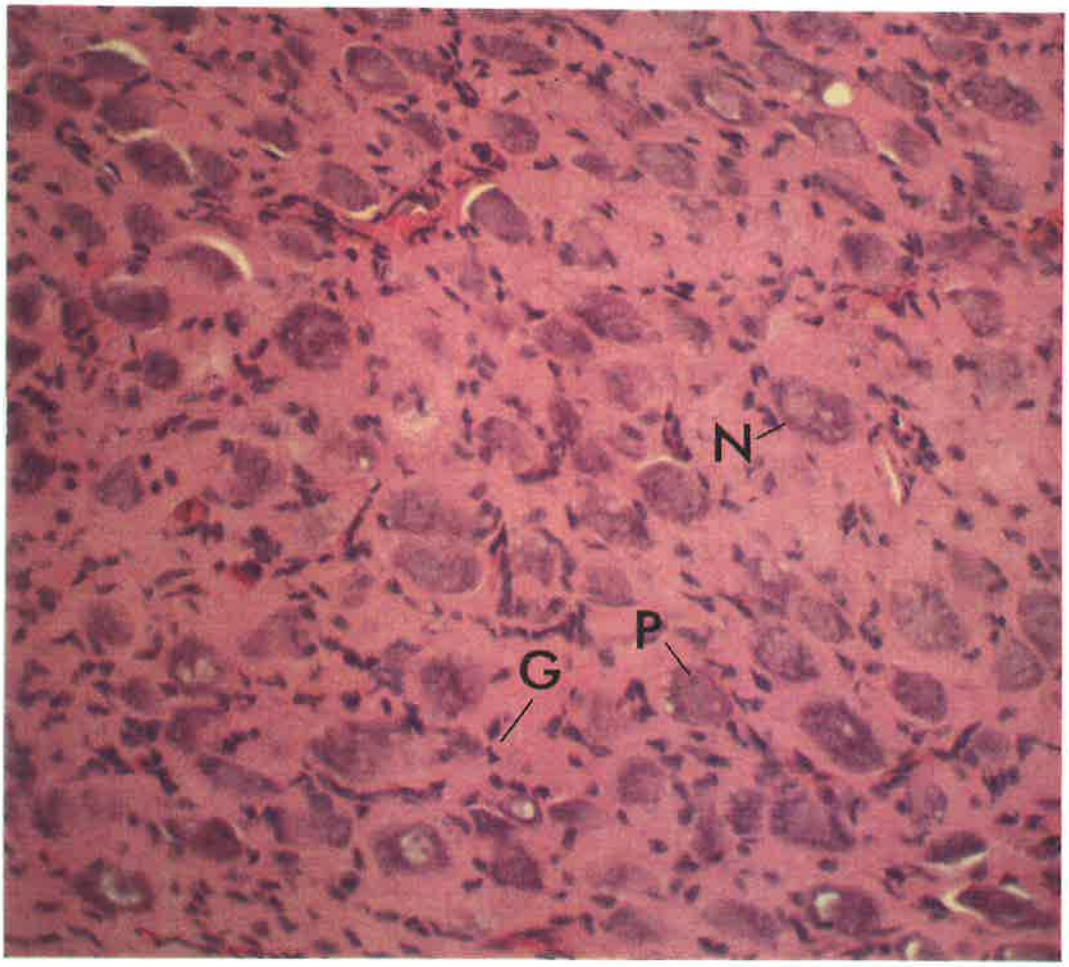


FIGURE 41 Haematoxylin and Eosin Section of the Superior Cervical Ganglion of the Marmoset.
Note the large neuronal cell bodies (N) and prominent nucleoli (P). The cells are not as densely packed as the rat. There are numerous glial nuclei (G). Magnification X 100.

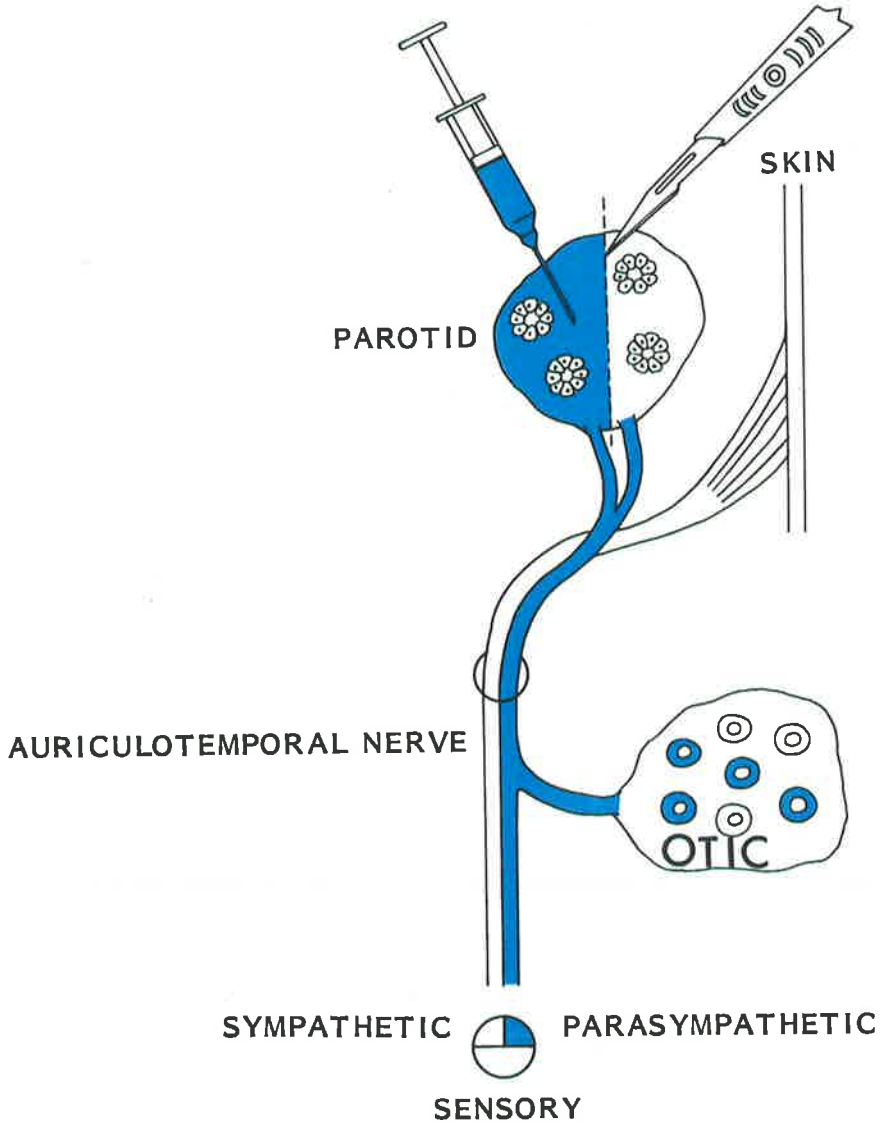


FIGURE 42 Schematic representation of superficial parotidectomy. Note that Fast Blue (blue colour) labels the otic ganglion cells prior to operation.

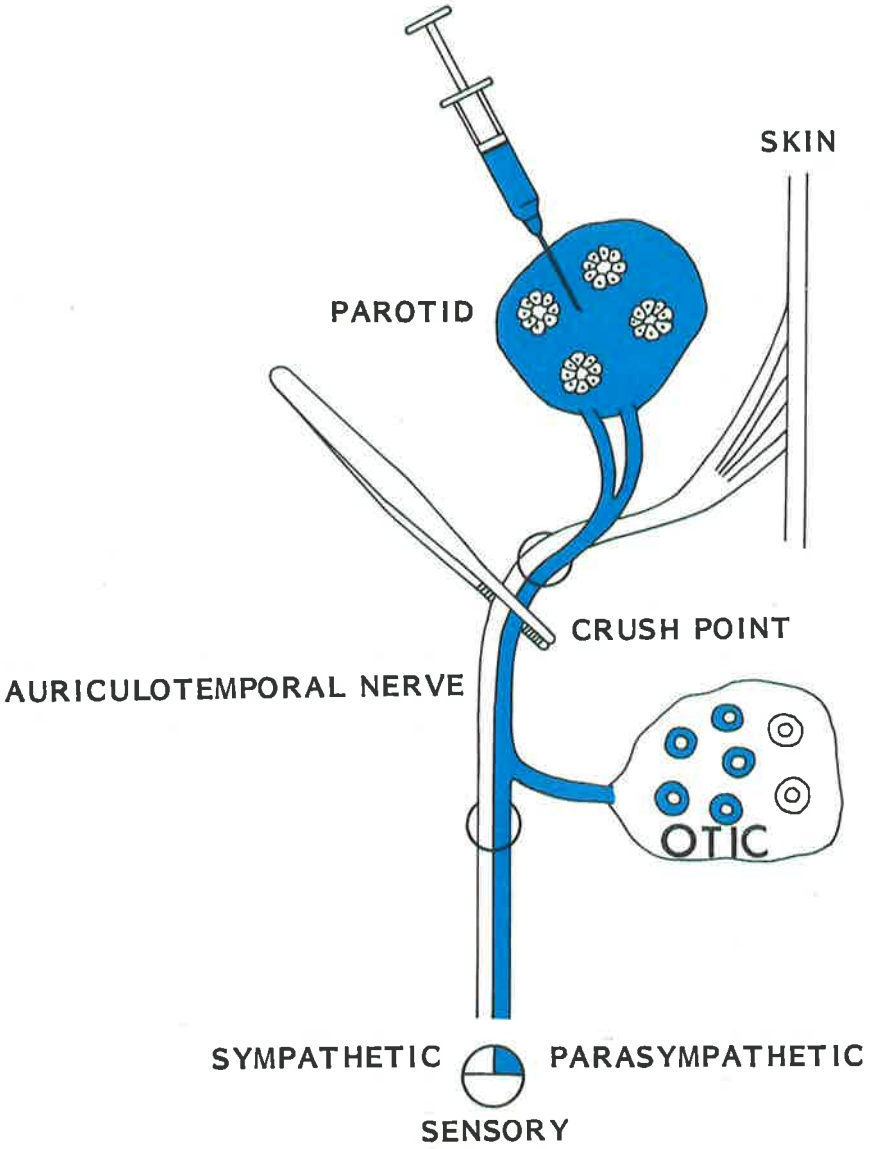
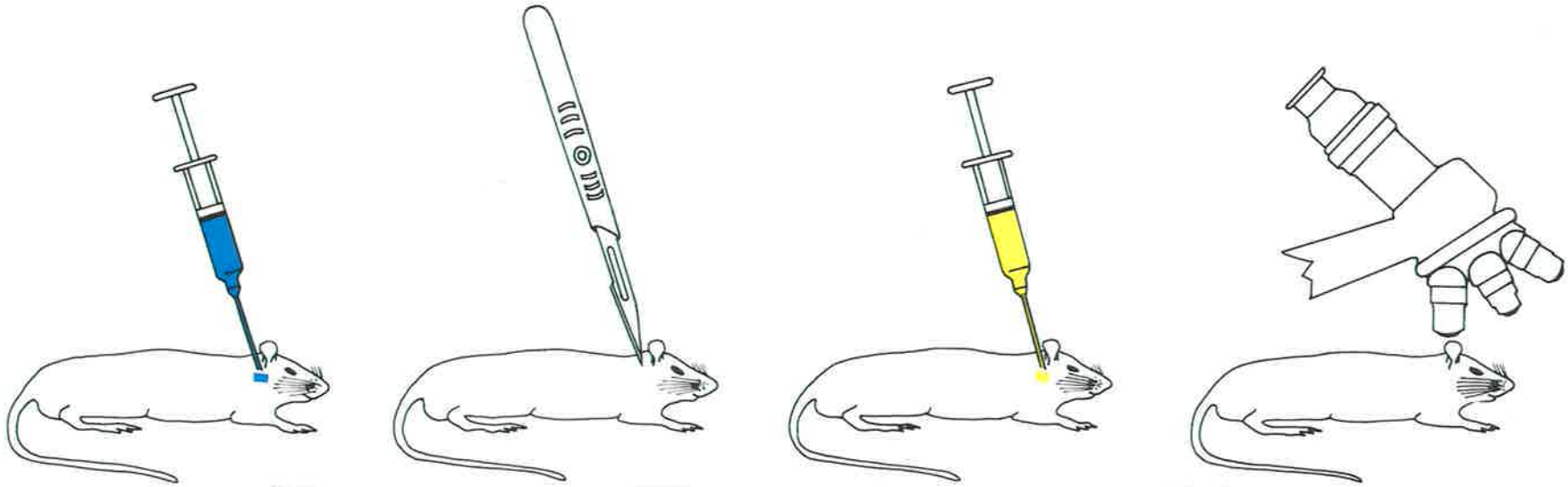


FIGURE 43 Schematic representation of auriculotemporal nerve injury. Note that the otic ganglion cells are labelled prior to operation by Fast Blue (blue colour).



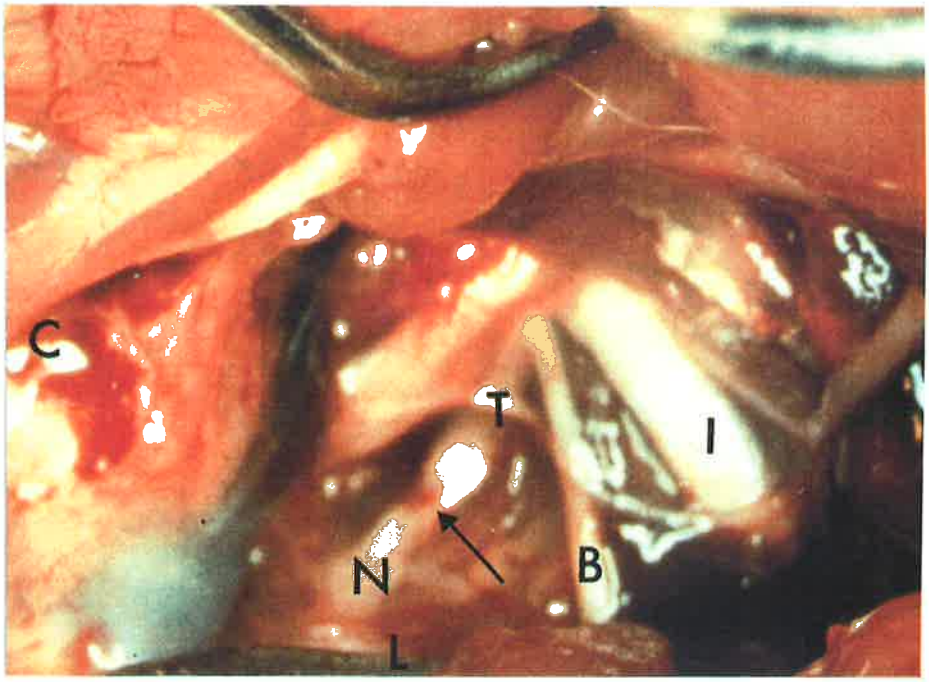
PAROTID INJECTION
FAST BLUE
ALL ANIMALS
DAY 1

OPERATION A OR B
ALL ANIMALS
DAY 2 - 3

SKIN INJECTION
DIAMIDINO YELLOW
CONTROLS DAY 8
EXPERIMENTAL DAY 54 AND 82

MICRODISSECTION/FLUORESCENT MICROSCOPY.
CONTROLS DAY 10
EXPERIMENTAL DAY 56 AND 84

FIGURE 44 Schematic representation of the timing of dye injection, operation and dissection in rats. Operation A = superficial parotidectomy; Operation B = auriculotemporal nerve crush. The identical protocol was used for marmoset experiments with the exception that no animals were sacrificed at 56 days.



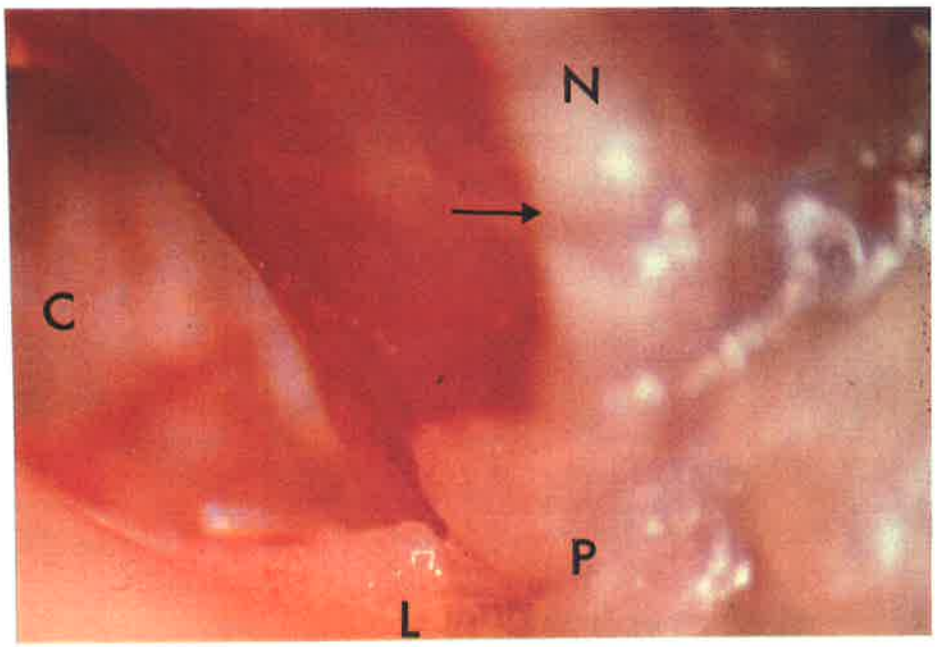


FIGURE 45 Auriculotemporal Nerve Crush Operation.

A Mandibular nerve and branches exposed 10 X magnification.

B Close up of auriculotemporal nerve (X 60).

N, Auriculotemporal nerve; P ,Lateral pterygoid; R, Parotid; T, Chorda tympani; B, Buccal nerve; I inferior dental nerve. Crush point arrowed. C, Caudal; L, lateral. Animal supine viewed from above.

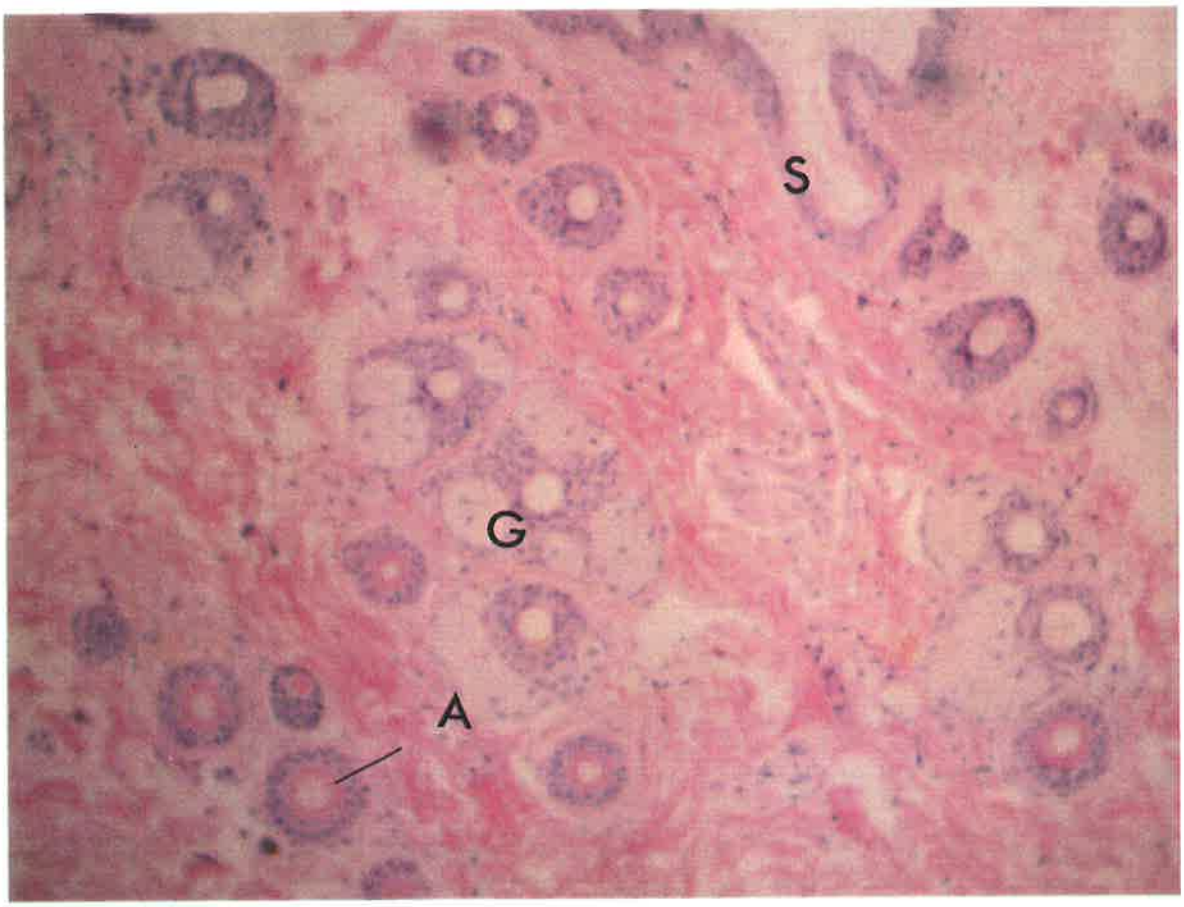
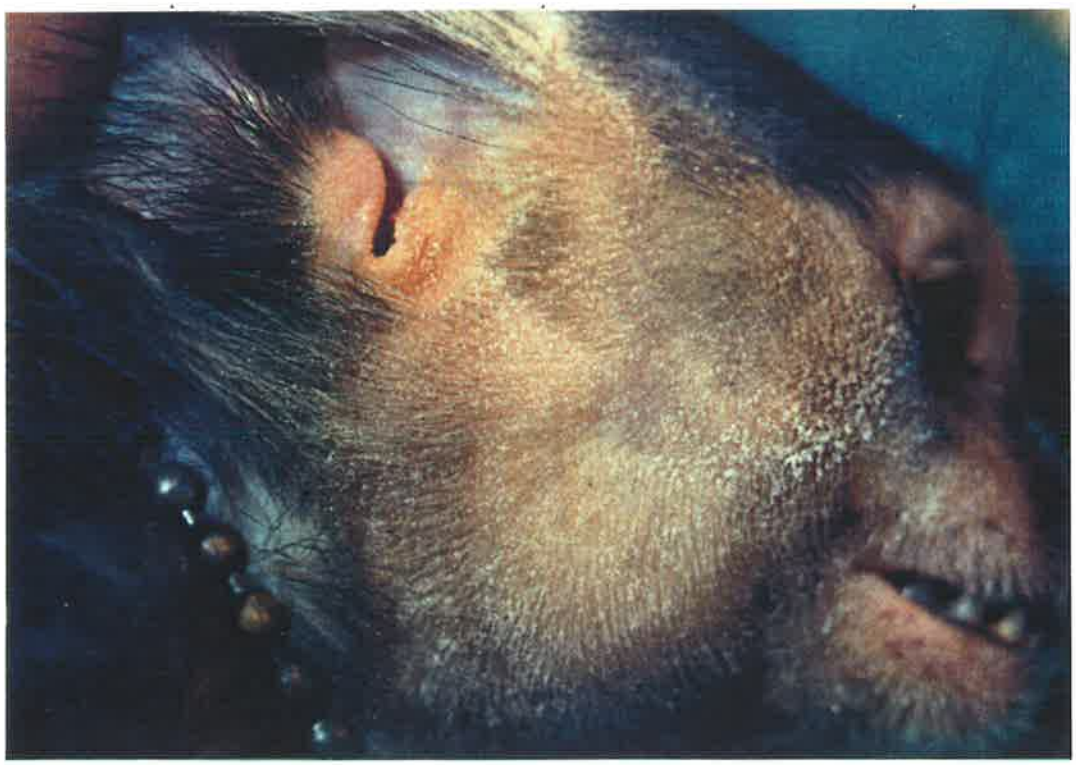


FIGURE 46 Haematoxylin and Eosin Section of Marmoset Facial Skin. Note multiple coiled sweat glands (G) in the dermis. Acidophilic material (A) can be seen in the lumen of the gland. S, Skin. Magnification X 100.



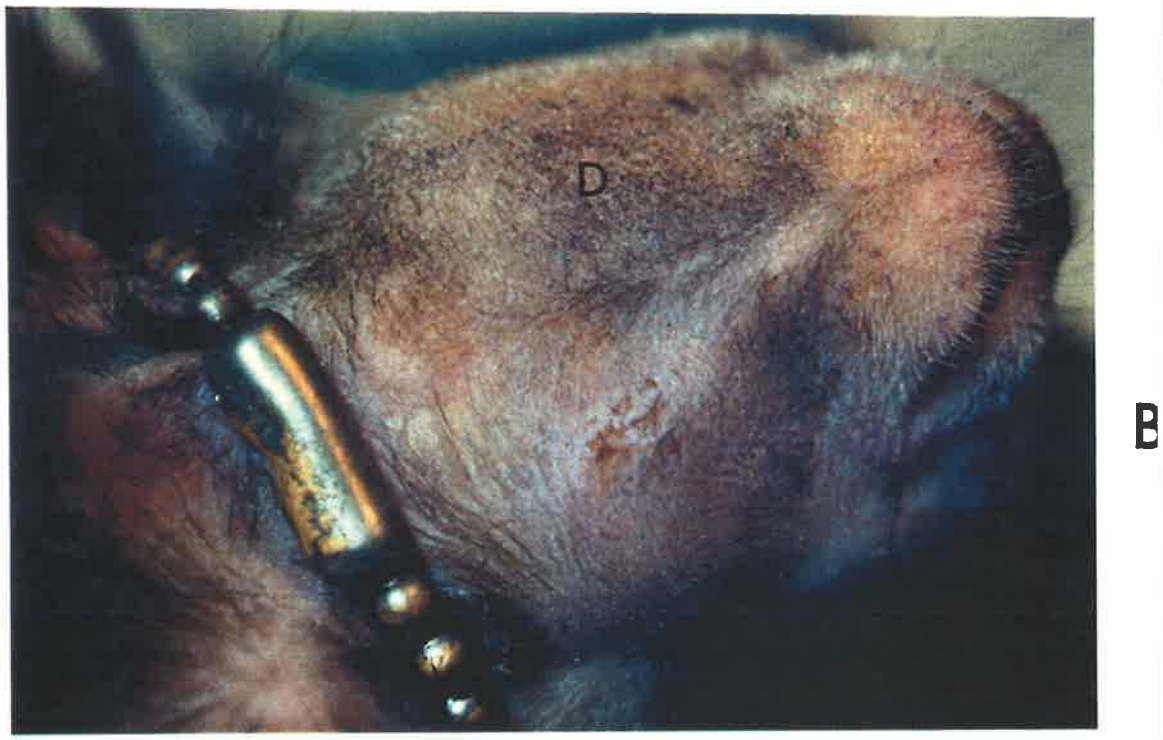


FIGURE 47 Pilocarpine Induced Sweating in Marmosets.

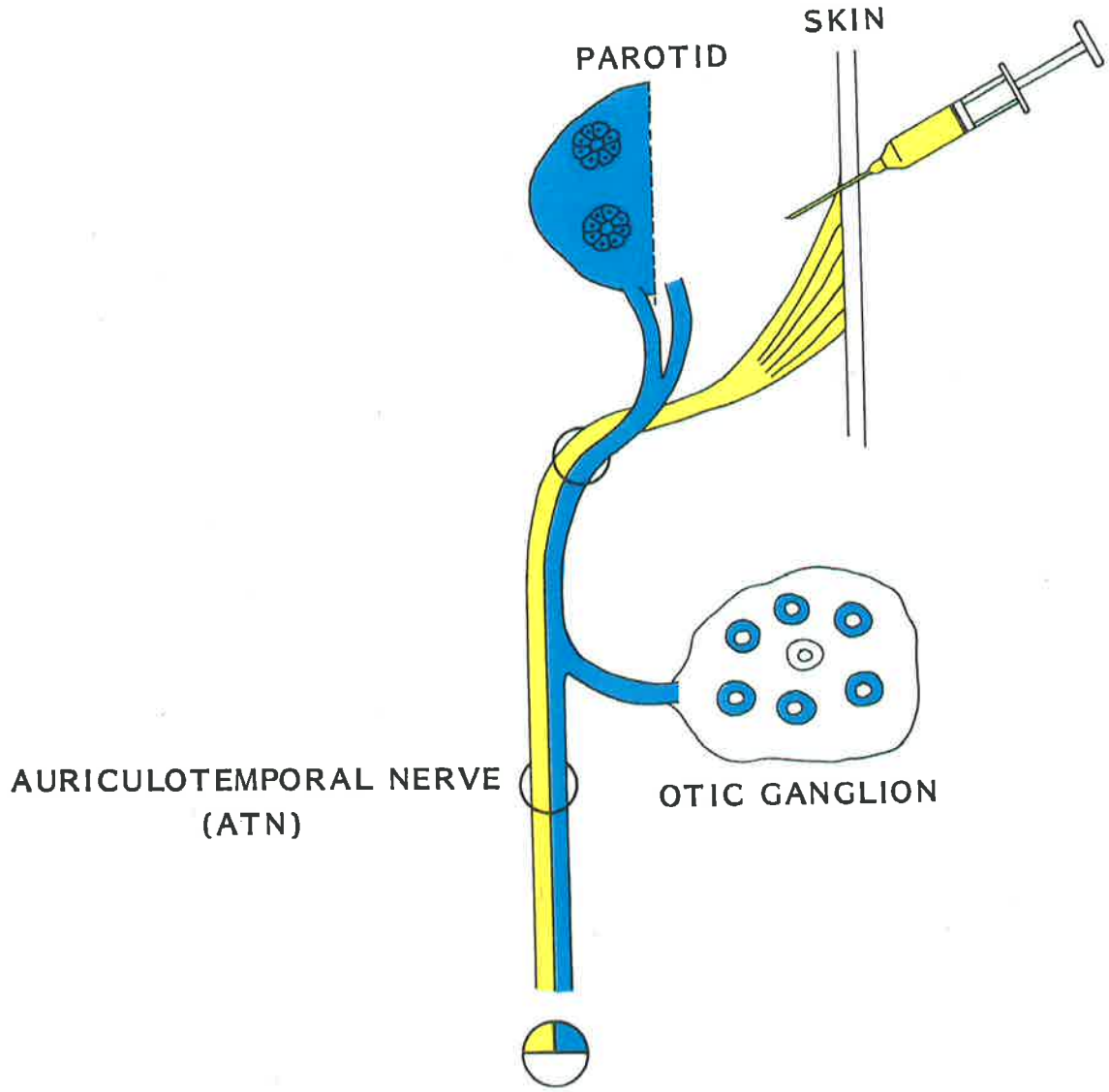
A Starch Iodine test has been performed after pilocarpine injection.

A Lateral view of face.

B View of the submental region.

Note Absence of sweating on the side of the face. The discoloured area (D) was caused by saliva dribbling from the mouth, not sweat.

FIGURE 48 Diamidino Yellow Labelling of Rat Otic Ganglion. Note that the nuclei of the neuronal cells are labelled yellow (Y). There is also a faint pale yellow labelling of the cytoplasm. There is some neuroglial labelling (N). The cytoplasm of the non-labelled cell (C) has a grey appearance. Magnification X 400.



	LABEL		
DAY	FB	DY	FB + DY
10	41 %	-	-
56	43 %	-	-
84	44 %	-	-

FIGURE 49 Schematic representation of results of parotidectomy in rats. FB, Fast Blue; DY, Diamidino Yellow. There are no otic ganglion neurones projecting to the skin after this procedure.

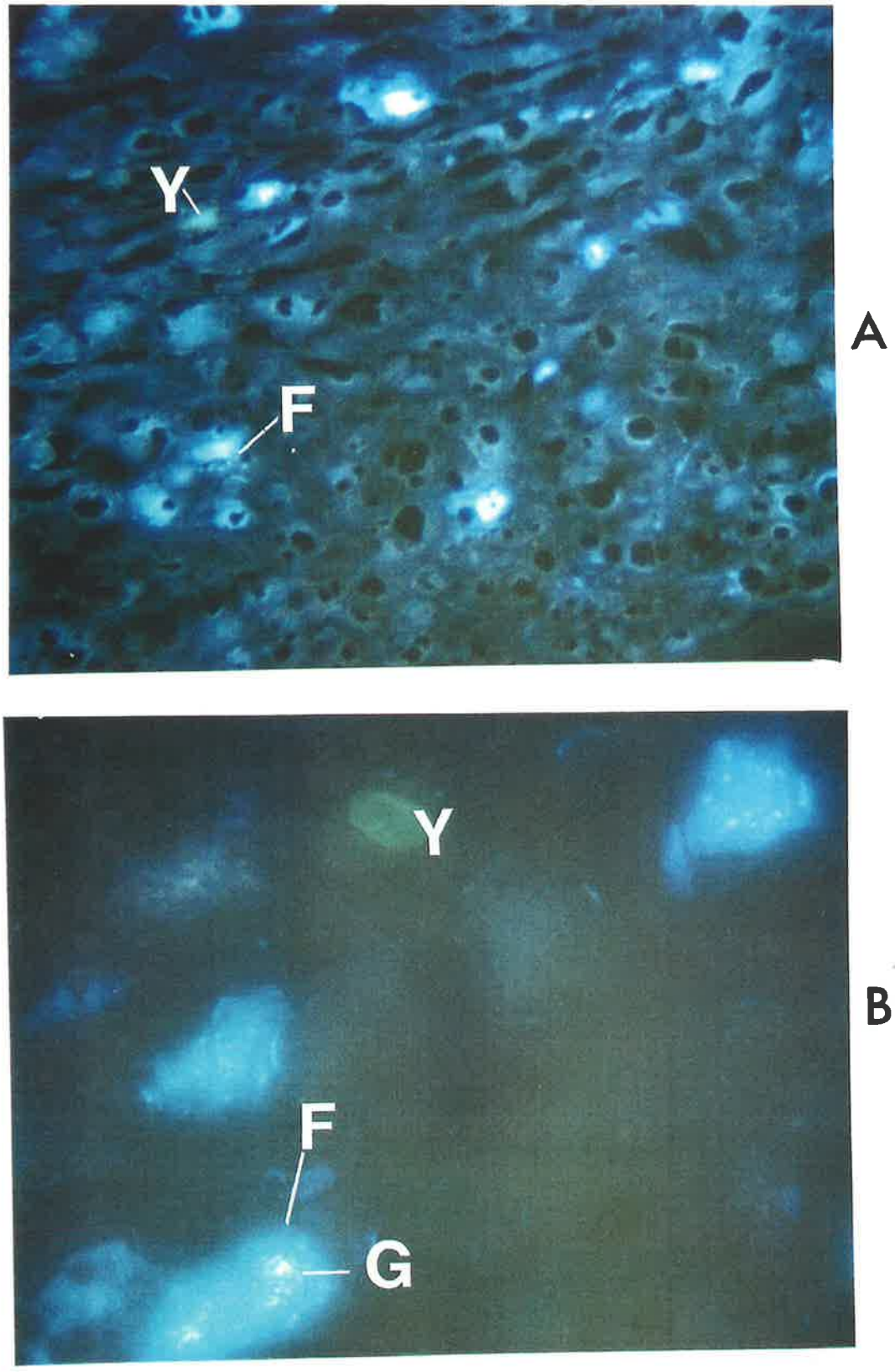


FIGURE 50 Appearance of Rat Superior Cervical Ganglion Labelled with Fast Blue and Diamidino Yellow.

A Magnification X 150

B Magnification X 400

F, Fast Blue Labelled cell; Y , Diamidino Yellow labelled cell; G, Cytoplasmic granules of Fast Blue.

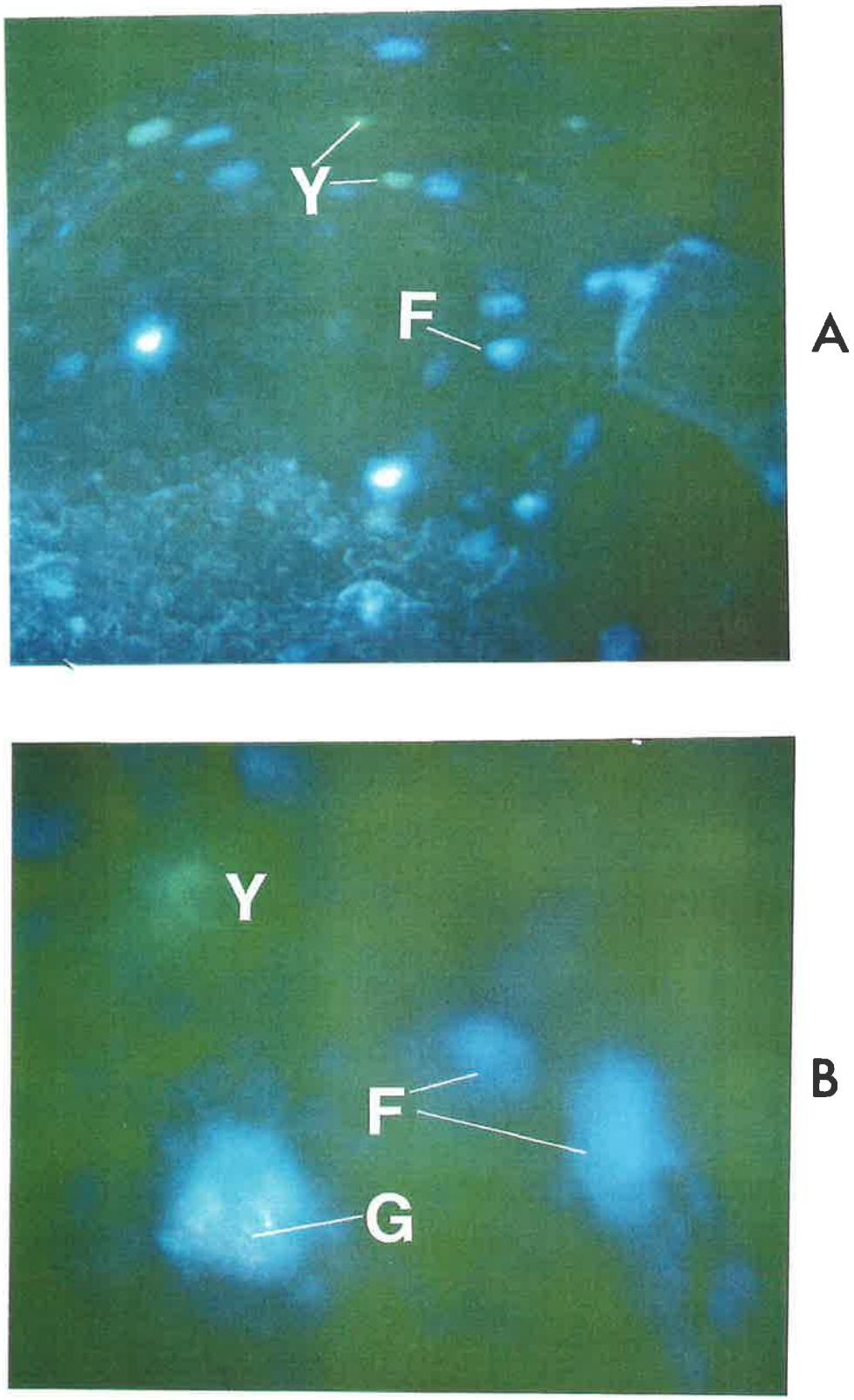


FIGURE 51 Appearance of Marmoset Superior Cervical Ganglion Labelled with Fast Blue and Diamidino Yellow.

A Magnification X 150

B Magnification X 400

F, Fast Blue Labelled cell; Y , Diamidino Yellow labelled cell; G, Cytoplasmic granules of Fast Blue.

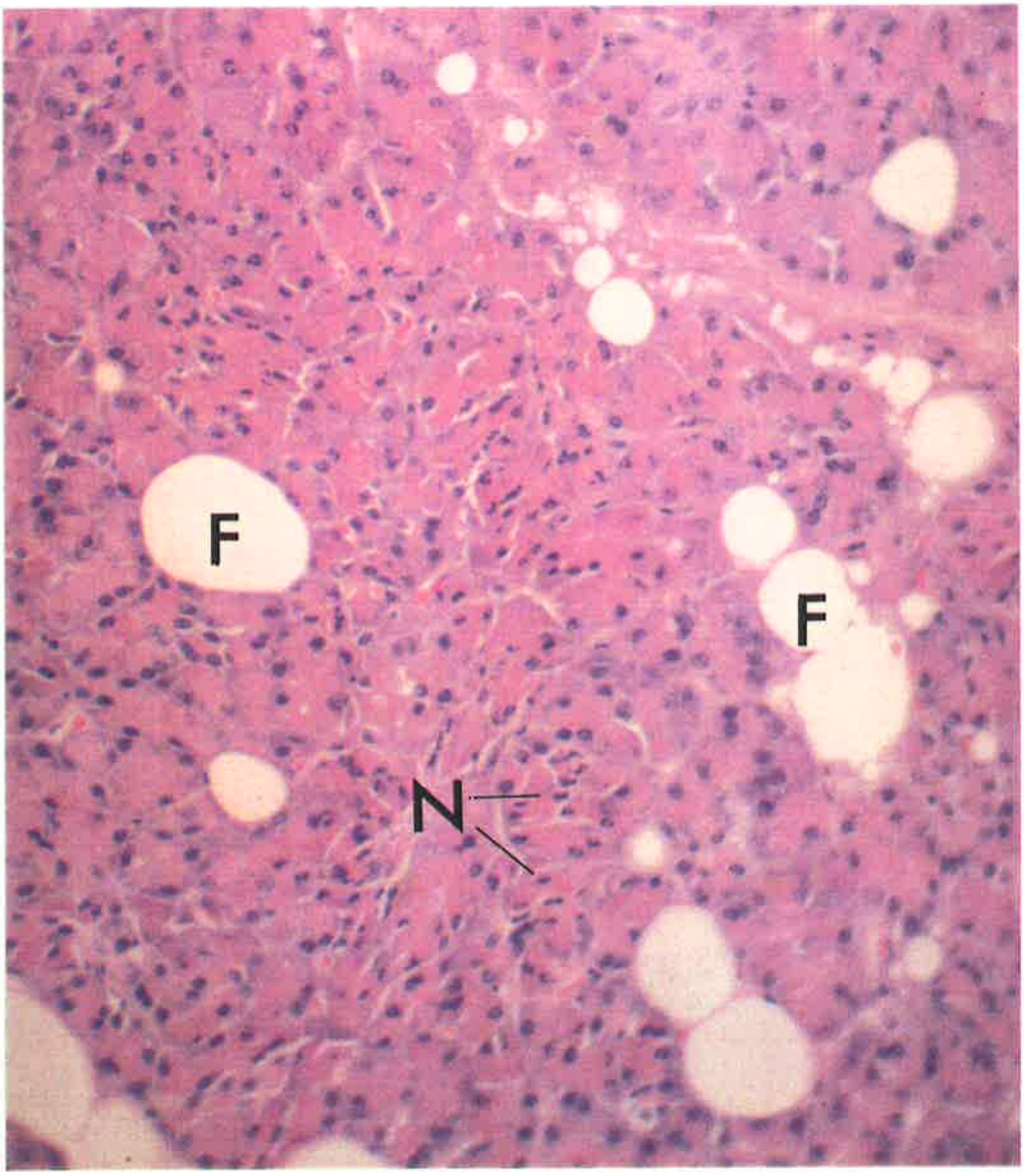


FIGURE 52 Haematoxylin and Eosin Section of Rat Parotid 84 days after Auriculotemporal Nerve Crush. Note the presence of pyknotic nuclei (N) and fatty infiltration (F) consistent with parotid atrophy.

Magnification X 100.

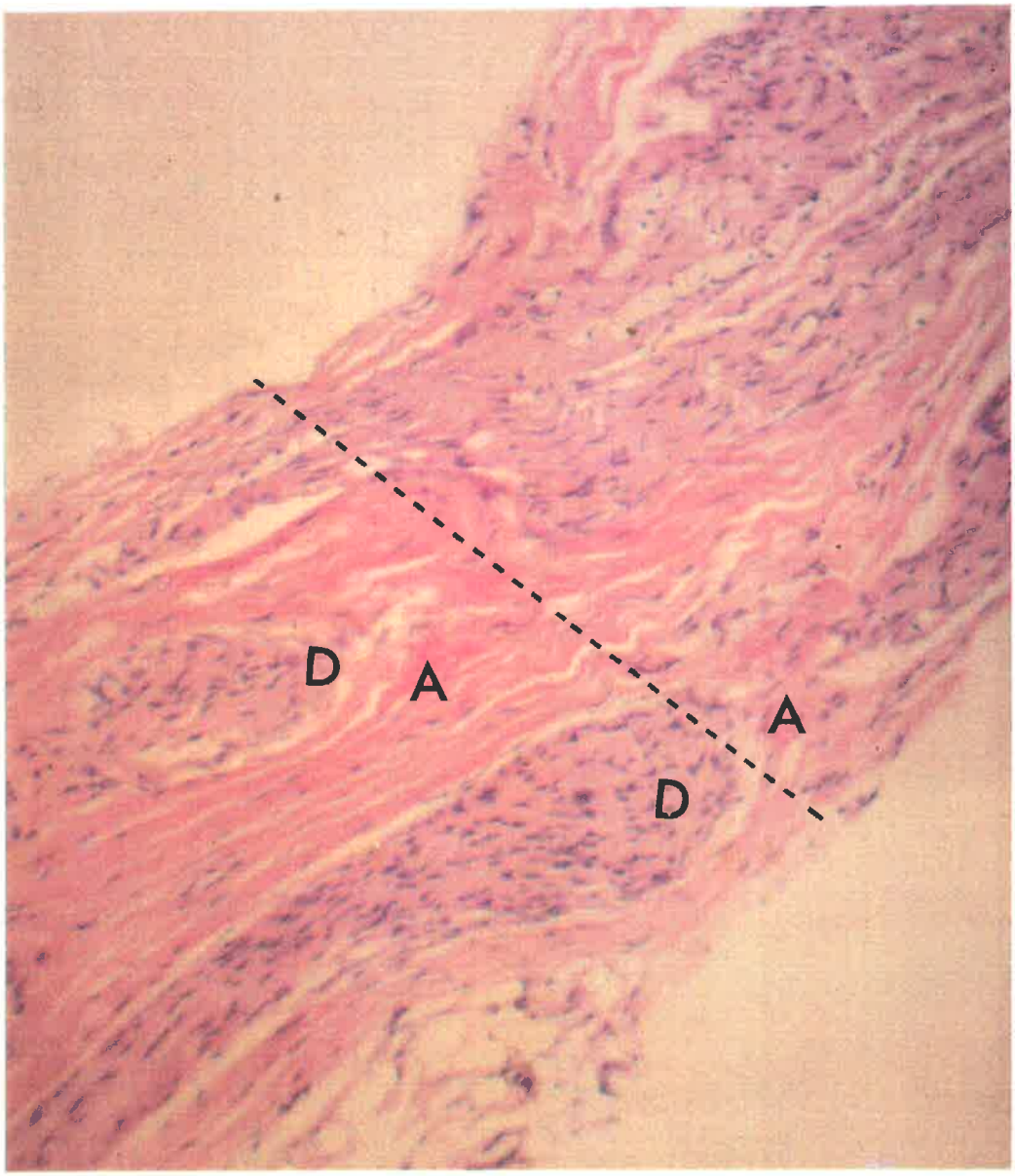


FIGURE 53 Haematoxylin and Eosin Section of Auriculotemporal nerve 10 Days After Crush Injury. Dotted line indicates the area of the injury. Note acidophilic areas (A) and disrupted axon bundles (D) consistent with recent injury. Magnification X 100.

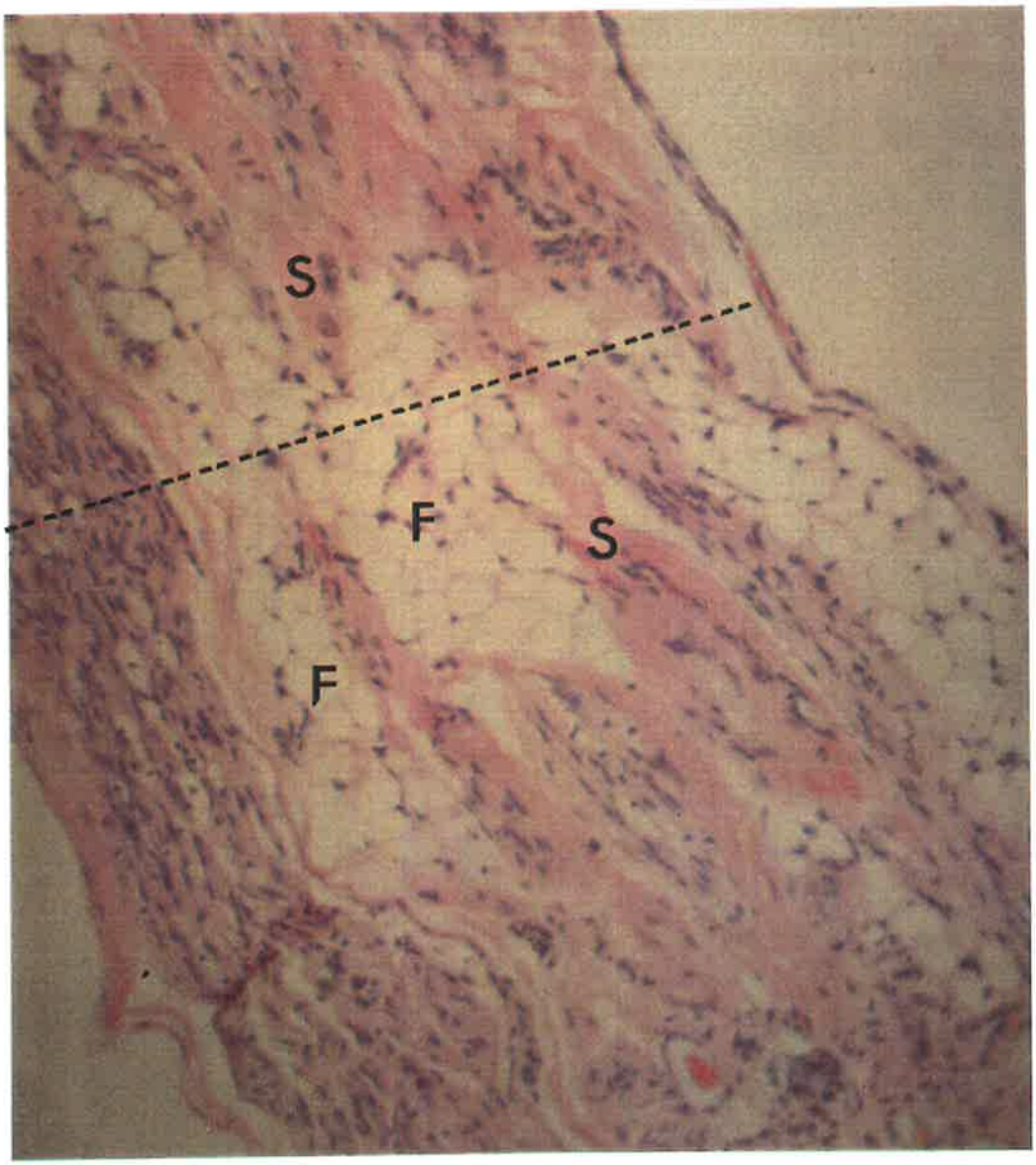


FIGURE 54 Haematoxylin and Eosin Section of Auriculotemporal nerve 84 Days After Crush Injury. Dotted line indicates the area of the injury. Note Fatty replacement (F) and areas of scar (S) consistent with old injury. Magnification X 100.

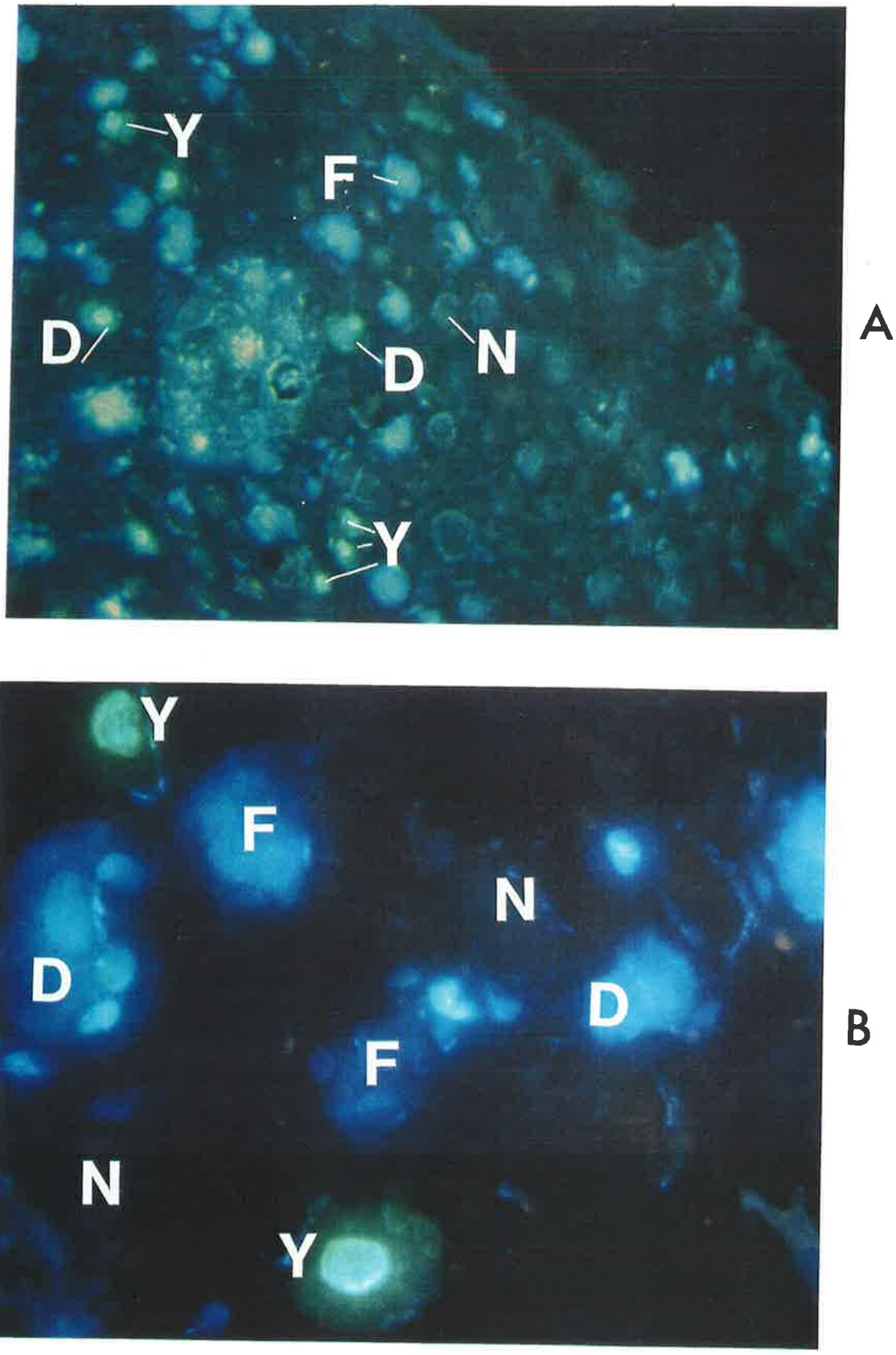
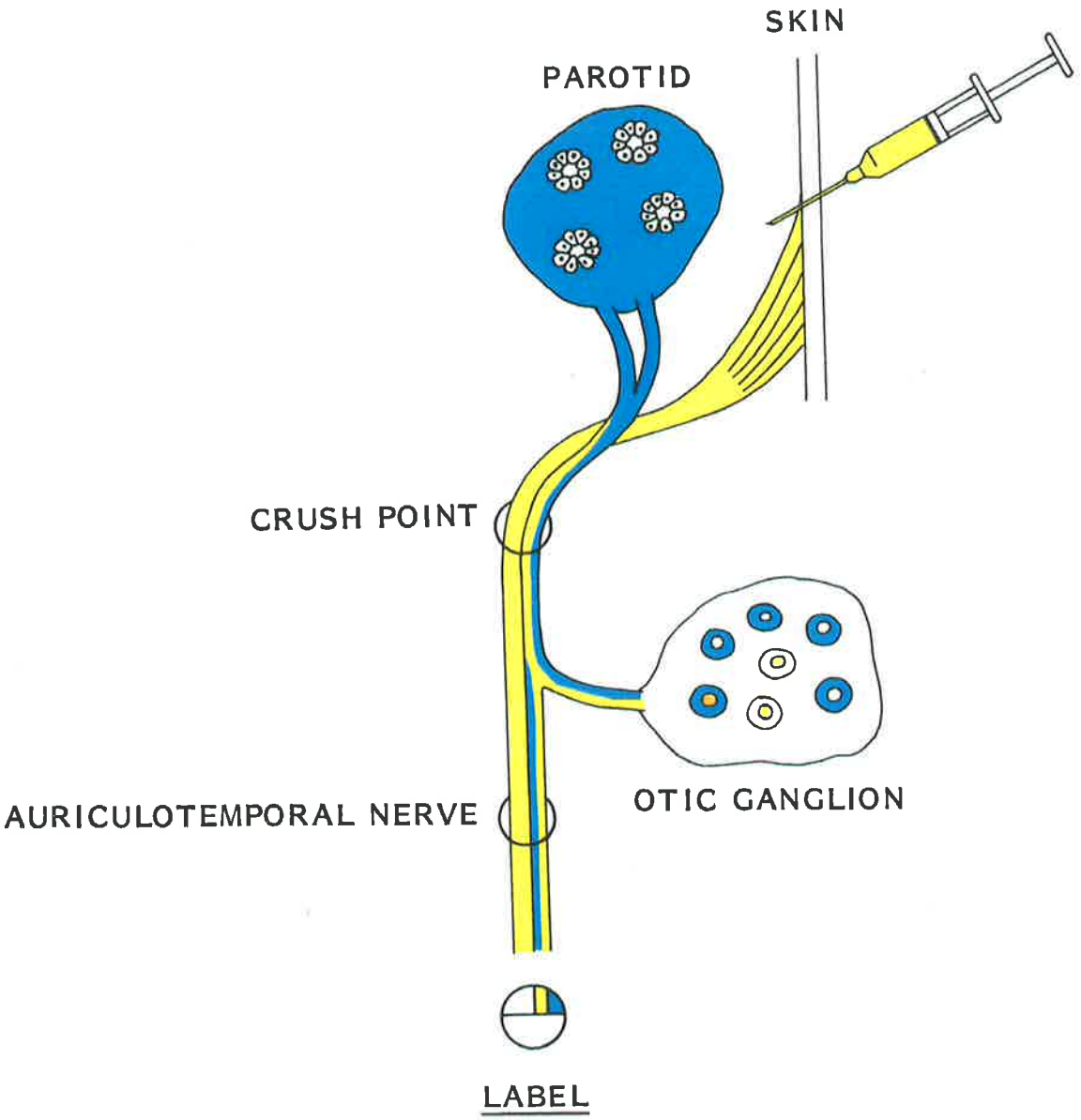


FIGURE 55 Double Labelling of the Otic Ganglion 84 days after Auriculotemporal nerve Crush Injury.

A Magnification X 150

B Magnification X 400

F , Fast Blue Labelled cells; Y, Diamidino Yellow Labelled Cells ; D , Double Labelled cells; N, Non labelled Cells.



DAY	FB	DY	FB + DY
10	32 %	-	-
56	28 %	5.4 %	1.7 %
84	27 %	5.7 %	1.9 %

FIGURE 56 Schematic Representation of the Results of Auriculotemporal Nerve injury in the Rat. Note double labelling of the otic ganglion due to nerve regeneration at the crush point. FB, Fast Blue; DY, Diamidino Yellow.

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APPENDICES

APPENDIX 1 FRENCH-ENGLISH TRANSLATION OF PAPER BY DUPHENIX (1)

OBSERVATIONS ON FISTULAS OF STENON'S DUCT

ON A COMPLICATED WOUND OF THE JAW IN WHICH STENON'S DUCT WAS DIVIDED

By the late M. Duphenix

In November 1726, the head gamekeeper of the Duke of Chantilly was hunting 3 leagues from Chantilly when he was unseated from his horse by a stag he was chasing. He was thrown a distance of 6 feet to the ground and lay unconscious. He recounted this to me several hours later. At that time I found that he had two wounds made by the stag's antlers. The first wound was in the upper half of the left arm, and the second was in the face on the same side. It is the latter wound which will be the subject of this memoir, started at the angle of the mandible, penetrated the masseter and continued under the cheek bone. Having placed my finger in the base of this wound I was able to easily detect that a portion of the bone which forms the floor of the orbit was fractured in several pieces. In addition the coronal joint at the angle of the zygoma was split with a separation of 3 cm.. The swelling was considerable, with all the areas near and inside the eye full of extravasated blood. Firstly I adjusted as best as I could the pieces of mobile bone and in order to keep them in position I placed pieces of fine linen in the base of the

wound and under the cheek bone. This was supported with suitable compresses and bandages. Continuing coma and unconsciousness left no doubt that there had been considerable concussion as a result of either the antler blow, or due to the violent fall that the patient had sustained as a result of being unseated from his horse or perhaps both.

In order to prevent complications it was important to perform many large bleedings of the arm and foot. The frequency of these bleedings was dictated by the state of the pulse. After the eighth bleeding the coma resolved, and consciousness returned a little. Urine flow which had been suppressed began again and the swollen wound dehisced.

Then I started to give the patient chicken broth and couch tea by bottle passed between the teeth because the mandible was tightly closed. Despite the repeated large bleedings the face became considerably swollen.

From the 39th to the 41st days several spicules of bone discharged from the wound and a few days later it became smaller in size. Once the patient began to move his jaw a large quantity of saliva discharged from the small opening that remained of the wound. This fact convinced me that Stenon's duct had been torn and divided by the antler as I had suspected initially.

If the canal had been divided in the position where it passed through the buccinator I would not have hesitated in immediately making a communication into the mouth in order to, by this means, conserve an artificial channel for passage of saliva. Because the opening was near the posterior border of the masseter I did not believe that in this position a

successful communication with the mouth could be created. The primary reason for this was that the scar was large and depressed due to the several episodes of suppuration. Secondly, because such a tract cannot be created without staying anterior to the masseter and finally because the coronoid process of the mandible when lowered would pass in front of the place where it would have been necessary to create the channel.

These problems caused me to attempt to use external compression in order to slow the fistula output.

To this end I applied increasing compression to the end of the canal. The compression was supported by a firm bandage. Whilst the jaw was still, no saliva passed, but with the smallest movement saliva sprang from the point of support and soaked the compresses and bandages. This forced me to put another form of compression into use.

I took a piece of cork about half an inch thick almost as much wide and 1.5 inches long. I wrapped this in fine linen and applied it close to the ear from the zygomatic arch to the angle of the mandible. Over the top I placed compresses and bandages. This compression allowed the patient to eat and even to chew a little without loosing even a drop of saliva from the fistula. However the next day the parotid gland became considerably swollen and painful. This made me doubt the success of the compression, but before removing the bandage I wished to be present when the patient ate. I noticed that in proportion to the amount of chewing an large number of small droplets of thin transparent liquid formed on the skin over the parotid. These grew and joined with one another to form

several trails of liquid which ran down the neck in such a quantity that it was necessary to place a cloth underneath to collect it. This discharge reduced the pain in the gland a little. Twelve hours after application of the cork the swelling of the gland had not diminished, and fearing that inflammation or suppuration were becoming established I could not see any advantage in compression, and so discontinued this treatment. Once the duct was freed saliva began immediately to flow from the fistula.

I made the patient chew a crust of bread which vastly increased the discharge of saliva and but a moment later the swelling of the gland was nearly completely dissipated as was the pain. It was evident that the liquid which had earlier appeared on the skin had been nothing but saliva the natural course of which having been interrupted by compression.

Meanwhile saliva was running continually from underneath the patch of plaster applied to the small opening of the fistula. When the patient ate it would run so abundantly that it would fall in multiple drops such that while he ate he was obliged to place on his shoulder a napkin doubled several times to receive this fluid. Curious to know how much saliva he produced during a meal, I collected it in a goblet.

The first time that I carried out this test I found that 2 ounces one gros of saliva collected in 15 minutes. On the second occasion 2 ounces 6 gros were produced in 18 minutes. On another day I collected 3 ounces 2 gros in 23 minutes and on the fourth occasion 4 ounces 1 gros was produced in 28 minutes.

It was easy to see by these experiments that the parotid gland only produced large quantities of saliva during mastication. If one were able to measure accurately the amount of saliva coming from the other salivary glands one would be amazed at the total quantity produced during a meal particularly when firm solids are eaten.

At the end of January 1727 this overseer resumed normal duties except for the use of the horn, with which he was unable to make any sound. This was because it was impossible for him to bring the top lip to meet the bottom lip on the side of his wound. The top lip remained numb and paralysed with occasional twitching movements, thus allowing air to escape involuntarily on the affected side. In a similar manner, saliva moistens the side of the mouth and face as it does in all those who are afflicted with paralysis in this area.

The patient continued to hunt till 15 March of the same year, always hopeful that the lip would improve sufficiently to allow him to blow the horn. I, however, was not as optimistic as he, as there was no doubt that most of the nerves distributed to the lip and its muscles were destroyed by the considerable damage that the antler had caused. The discharge of saliva which continued from under the plaster became so unpleasant for the overseer and those who saw him daily that I was pressed by the Duke and the patient himself to work toward a cure. Therefore I became determined, despite the difficulties of which I have already spoken, to form a communication into the mouth. I achieved this in the following

manner after having first prepared the patient by general remedies.

I arranged first of all, equipment which consisted of belts for compression polished wire, needles and a lead cannula of the size of the pipe of a writing pen and the length of 30 cms. This cannula was bevelled at one end and at the other end there were two parallel openings through which I could pass two silk threads.

All the necessary things being prepared I placed the patient in a convenient position. I examined closely the contracted irregularly shaped scar. This inevitable deformity depends so they say on the considerable loss of tissue and resulting scar contracture. The scar was 26 mm long and 14 mm wide at its mid point.

As my plan was to suture the skin after having made the communication into the mouth it was necessary to remove all the scar whilst at the same time preserving as much skin as possible. To this end I measured the distances between the irregular points of the scar and having taken the true dimensions I marked points in appropriate places in order that the angles of the wound that I was going to make could fit together sufficiently well to allow prompt healing. I then made a mark with pen and ink passing through the points I had marked. Next I took out this scar with a sharp scalpel by following the pen line I had made. I used my instrument in such a manner as to lift this piece off. This left a large external wound with a small depth only penetrating a little more than half the thickness of the masseter muscle.

I placed the index finger of my left hand into the mouth. I examined the point where it would be necessary to make the communication and without moving my finger I took a sharp and straight knife and placed its point into the depths of the wound opposite Stenon's duct. I pushed the knife from outside to inside toward the masseter muscle. I moved the knife back and forwards and in and out until in the mouth. Then I turned the blade of the instrument to the side and cut in all directions in order to allow me to position my cannula. I removed the knife and in its place inserted a stillet in the shape of a needle with two silk threads attached to the cannula. I manoeuvred the stillet into the mouth and having taken the ends of the threads with my left hand I pulled them within, and with my other hand placed the cannula in the communication hole and conducted it into the mouth. It was positioned such that the bevelled end pointed outward and rested in the base of the wound. The tip of the bevel rested under and opposite the canal. After wiping the wound and passing a sound through the cannula to remove coagulated blood I approximated the wound edges and passed three needles at convenient distances with sutures tied in the usual manner. I arranged the threads of the cannula in the mouth so as they were between the jaw and the gums such that it would be easy to retrieve them when the time came to remove the cannula. I applied to the suture line a simple gauze soaked in hot wine, the necessary compresses and a bandage to hold the mandible firmly in position and immobile against the maxilla in order that no saliva would flow to endanger the healing of the external wound. I then confined this patient to bed with

strict instructions to sleep on the side opposite the wound in order to ensure that saliva which came through the canal would pass by the cannula into the mouth.

In order to prevent inflammation I bled the patient three times in quick succession, and did not allow him to take food for the first eight days except for thin broth and tea by bottle in a similar manner I had been forced to employ at the time of his initial injury.

The day after the operation the patient noticed that saliva was flowing through the cannula and into the mouth. As he was able to push the saliva out of his mouth by blowing, I was able to observe that it was mixed with a little blood. The forth post operative day large amounts of clear saliva passed from the cannula and I even noticed several specs of purulent material in it.

On this day I removed my dressing for the first time. The wound seemed healed and there was no fluid which augured well the success of my operation. For dressing I again used only hot wine in which the gauze and compresses were soaked.

On the seventh day I dressed my patient for the second time. I found that the wound had healed perfectly except for some oozing and suppuration from the suture line. I removed the needles which were no longer useful and syringed the three suture points with hot wine and three days later they were completely healed.

On the sixteenth postoperative day I pulled the cannula from the mouth by means of the threads which I had placed between the jaw and the gum. The artificial channel was patent and saliva ran from it continually and freely and the scar

remained sound. The tissue wasting, and closure of the wound by suture had resulted in considerable reduction of the skin over the jaw causing the angle of the mouth on that side to be drawn toward the ear. I suggested that the patient bathe in the waters of Bourbon. This had a noticeable effect in that his mouth became practically straight. However both the momentary twitching of the mouth and the difficulty in approximating the lips persisted, such that he could not blow the horn at all. After I had had the honour on several occasions of conferring with the Duke on this problem, and the means of remedying it easily, the Duke, who had a taste for the mechanical, devised an instrument which he designed at once and had made. It was a mouthpiece for the trumpet which was armed with a cup or plaque with a spring to hold it on to the deformed lips. The result satisfied the Prince's notion. He had complete success with this device, which I named the obturator of the lips. The spring, responding to the action of the air held the instrument in the mouth. The overseer was so well served by this instrument that he could play with nearly the same ease and force as before the accident. The use of this device is not limited only to the case for which it was designed. The same principle could be applied in all cases of mutilation of the lips in order to prevent the escape of air. This instrument would allow air to be conveyed easily into the mouthpieces of wind instruments such as oboe, bassoon, flute, hunting horn and others.

APPENDIX 2 FRENCH-ENGLISH TRANSLATION OF PAPER BY LUCIE FREY (10)

NEUROLOGICAL REVIEWS

ORIGINAL ARTICLES

NEUROLOGY

THE AURICULOTEMPORAL NERVE SYNDROME

by Miss Lucie Frey
(working at the Neurology Clinic at the University of Warsaw)
Professor C. Orzechowski

The auriculotemporal nerve, the pathological study of which has been largely ignored by contemporary neurologists, contains as well as sensory fibres, vasomotor and sudomotor fibres from the autonomic system and secretory fibres to the parotid. The skin of the face, rich in sweat glands, constitutes an area where vasomotor action is more intense and visible than elsewhere in the body. It is astonishing therefore that disorders of the nerves of the face producing sudomotor and vasomotor disturbances have not drawn more attention. This especially concerns lesions of the

auriculotemporal nerve. The functional disturbances of this nerve allow special observations to be made on the reflex pathways arising from gustatory stimuli acting on the glossopharyngeal nerve. Autonomic disturbances of the auriculotemporal nerve combined with sensory changes, are characterized not only by its unique location but also by autonomic symptoms which are foremost. The condition which we have now recognized demonstrates a multitude of clinical signs which can be grouped into an irritation syndrome. To this syndrome will be added later as a further complication, symptoms which have interesting repercussions for the local autonomic apparatus, and which give rise to the irritation phenomena situated in these regions. The following case will well illustrate the syndrome in question:

Ch. B. aged 25 years was wounded in the mandible by a rifle bullet toward the end of 1920. Although this wound was only superficial the patient fainted and because of this was unable to recall anything that followed.

He was taken to hospital. Having regained consciousness he noticed that the whole of the left side of his face was greatly swollen. A week later he had developed typhoid fever and after a further 4 weeks he had developed exanthematic typhus. During the time that these two illnesses lasted the swelling of the jaw persisted and about 4 weeks after the wound, the patient noted that pus discharged from his left ear. A diagnostic specialist detected the presence of a fistula in the external auditory canal without tympanic perforation. Having made an incision at the level of the original wound the swelling soon diminished and the face

little by little returned to normal. About a month later the patient noticed that whilst eating the left half of his face became the site of abundant sweat accompanied at the same time by a strong sensation of warmth. These symptoms gradually increased and several months later they were pronounced enough to be noticed by others. The patient then consulted a physician, not so much because of these symptoms, as the moral uneasiness he was feeling. In effect, he had convinced himself that the abnormal sweating was due to his large appetite and he was ashamed of it. On the advice of this physician the patient attended our clinic in early January. There was nothing important to note in this man's past history and his blood Wassermann reaction was negative.

Examination of the patient:

The muscles were well developed and in the dorsal spine a mild scoliosis was evident. The right tenth rib was mobile. There was vasomotor hyperexcitability, the patient blushing at the least provocation. The hands were a little cyanosed and constantly damp. In general the patient sweated very easily and after exertion his whole body and face were covered with sweat. A slight facial asymmetry could be could be discerned, seen as a turning back of the left jaw and as a deviation to the left of the nasal septum. This asymmetry was visible on a photograph taken before the wounding. It is likely that the asymmetry gave rise to the mild anomalies of innervation which could be observed on the left side of the face and these thus are only of minor importance. The left naso-labial fold was slightly more obvious, and in addition the innervation of the brow by way of compensation was a little less marked.

Electrical examination of the facial nerve was normal as was. the external auditory meatus.

Behind the left angle of the mandible a firm bean-sized swelling could be felt. This tumour was lightly adherent to the skin and was quite mobile. It was a little tender to the touch. The parotid on the side of the injury was not palpable but it was easily detected on the other side. The general state of the nervous system remained normal; however on examination of the face the following conditions were observed:

On the left the pupil and the palpebral fissure were a little larger than the right. In the area which corresponded exactly to the distribution of the auriculotemporal nerve there was hyperaesthesia. When the patient ate or sucked a sweet after 1-2 minutes the face became red and warm in this area and abundant sweating occurred. The sweat appeared first of all as many droplets flowing after joining in true gutters. These symptoms did not appear when the patient took liquids. The area of the face affected by this phenomenon is in the form of a triangle the base of which corresponds to the opening of the ear and the peak of which extends almost to the corner of the mouth. The superior angle of the triangle is truncated as it penetrates the hairline.

Neither masticatory movements alone nor digital excitation of the lingual mucosa could provoke these changes. However, they appeared each time a gustatory stimulus was given to the posterior part of the lingual mucosa without masticatory movements or suction. Allowing that, in healthy individuals, the least emotion likewise caused profuse

sweating, not only in the usual regions of the nose and brow, but also in our pathological triangle, even without the act of mastication.

Examining the mouth of our patient we ascertained that the mucous membrane in the region of the middle of the left side of the jaw was less moist than that of the right, and that its surface was much more dull. These appearances were more pronounced after an injection of pilocarpine.

Finally, there was almost constant pilomotor erection of the neck. The region affected was limited medially by the midline and inferiorly by the sternomastoid muscle.

Pharmacological tests gave the following results:

After a subcutaneous injection of 1 milligram of atropine dryness of the buccal mucosa lasted about three hours. During this time eating failed to provoke flushing or sweating in the inferior part of the pathological triangle while the upper half was covered very lightly with sweat. The border of these two regions was a horizontal line passing through the zygomatic arch. An injection of 1 milligram of adrenalin was without effect from the point of view of sweating induced by eating but on the other hand the temporal and mental regions on the same side were cooler in comparison with the other side. These changes were detectable by hand and by a noticeable pallor. The general reaction to the adrenalin was rather mild. After injection of 10 milligrams of pilocarpine there was abundant salivation without flushing. Whereas the right Stenon's duct issued fluid saliva that from the left duct was much thicker and more foamy. Similarly the orifice of Stenon's duct on the left was noted to be more wide open than

on the right. In other respects the injection produced only a mild sweating on the rest of the body. Notably on the face sweat appeared in the usual areas and was accentuated in the area of our pathological triangle. Emphasising this fact was the observation that sweat was totally absent from the analogous area on the healthy side. Allowing the patient to eat whilst the pilocarpine action was starting to fade the sweating in the pathological region became more intense than usual. Under the influence of pilocarpine pilomotor phenomenon of normal intensity appeared on the body only after several stimuli, and the persistent pilomotor activity of the neck was unchanged. A hypodermic injection of Physostigmine provoked pallor and lowering of temperature of the left side of the face, and a general state of mild nausea. When amyl nitrate was given its action was identical on both sides of the face.

To add to this a surgeon independently from us injected with alcohol the region of the facial nerve in the neighborhood of the scar. After this injection there was no facial paresis but for several days the pathological region of the face no longer reddened in the course of a meal the temperature of this area became notably lower, and the sweating was considerably diminished. Moreover, during these days the scar remained indolent and insensitive to touch. One could deduce that the injection had penetrated the auriculotemporal nerve fused in the scar rather than the facial nerve. It was on this date that we had made our injections of adrenalin and physostigmine.

In the case cited above the diagnosis lies in a disorder of the auriculotemporal nerve of which, in the first instance

irritation is the most likely explanation. To wit firstly a hyperaesthesia of the skin to all modes of sensation in the area innervated by the nerve; secondly a profuse continuous sweat following emotion, physical effort or under the influence of pilocarpine. These phenomena are so much the more remarkable in that this region usually only contributes little to the sweating of the face. The territory supplied by the auriculotemporal nerve coincides with the area of sweating when this patient eats which is due as we have demonstrated to a reflex provoked by gustatory stimuli. We will return to this point later.

Finally, the redness and elevation of temperature of the region in question betrays likewise a state of nerve irritation. It is generally accepted that nearly all the sudomotor and vasomotor fibres of a given region run in the sensory nerves of the region. In our case, these would course in the auriculotemporal nerve. Aside from these irritative phenomena damage to the auriculotemporal nerve declares itself by qualitative and quantitative disturbances in the secretions of the parotid which is innervated by fibres coursing in this nerve. According to the physiologists the action of the parotid gland is controlled by the glossopharyngeal nerve, the parasympathetic nervous system (thin saliva), and the sympathetic system (thick saliva). In the case which interests us the presence of thick saliva forces us to admit that in our patient secretion is effected largely under the influence of the sympathetic system and that the parasympathetic fibres have partially lost their function.

We have therefore verified, aside from irritation of diverse fibres, a partial paralysis of the secretory parasympathetic fibres destined for the parotid. It is naturally necessary to take account equally of the pathological changes present in the parotid which, of themselves, are only able to influence salivary secretion in a quantitative fashion.

When our patient eats the reflex sweating which occurs on the surface of the face innervated by the auriculotemporal nerve is initiated, as we have already said, by gustatory stimuli on the posterior portion of the tongue. The reflex arc which is set in play is probably the same which regulates the physiological secretion of the parotid. Here is the pathway :

Gustatory fibres gain by way of the glossopharyngeal nerve the inferior salivatory nucleus. This nucleus for its part gives rise to new fibres which hitch-hike with the glossopharyngeal nerve to the petrous ganglion. They run next in Jacobson's nerve and finally follow the course of the lesser superficial petrosal nerve. With this nerve the fibres attain the otic ganglion in which they synapse. The postganglionic fibres travel in turn along the auriculotemporal nerve (branch of the third division of the trigeminal nerve) and arrive finally at the parotid gland. We know from elsewhere, (Muller) that the sympathetic fibres also penetrate the otic ganglion. These fibres having arisen from the superior cervical ganglion follow the vessels of the neck and their branches. They thus arrive via the temporal artery and thence to the otic ganglion. Leaving this ganglion they penetrate the auriculotemporal nerve. It is thus highly

probable that it is exactly these sudomotor and vasomotor fibres which cause the reflex sweating and flushing present in our patient. Still, we must acknowledge that this reflex sweating, made up of an assemblage of vegetative phenomena, could exist equally, albeit to a lesser degree, in healthy individuals during eating. Following certain gustatory stimuli these phenomena sometimes occur, always in persons of bearing an exceptional importance. These phenomena are present in considerable intensity in the course of convalescence from grave illnesses (Redness of the face, sweating and a general feeling of warmth.). (This question has been studied for example by Brown-Sequard who studied his own distressing reflex. His face covered itself with profuse sweat each time he ate sweet or spicy foods. This author noticed that mastication itself played no role in the production of this reflex, and that it was not produced by other gustatory stimuli.)

In our patient, the state of irritation of the auriculotemporal nerve affected primarily the vegetative fibres of the nerve.

Two special characteristics are present: firstly there are none of the usual symptoms of irritation, sensitivity, paraesthesia and pain, and secondly, the nerve irritation only occurs in certain conditions, for example, when the patient eats, or following the injection of pilocarpine etc. Consequently this state of irritation can be considered to exist in a somewhat latent manner. The fact that the irritation of the vegetative fibres of the auriculotemporal nerve is observed uniquely on the pathological side only when

the patient eats, is because physiological sweating for example reflex sweating, insufficient to in itself to cause the symptoms under consideration, is superimposed on a pathological state of latent irritation. It is the association of these two factors that gives rise to the symptoms described previously, giving plain indication of true irritation of vegetative fibres of the auriculotemporal nerve.

It remains for us to explain two other symptoms:

Pilomotor erection of the neck and dilation of the pupil. They can be connected by a single property of the vegetative system which Thomas has named "reverberation". This author has cited a large number of cases in which hypertonia or exaggerated pilomotor reflexes is not limited to the region of the injured nerve, but invades the neighboring nerve territories. Thus one may observe an exaggeration of pilomotor tone in the whole upper limb in a case where only the median nerve is injured. In our patient the irritation is thus able to extend to neighboring areas, manifested as piloerection of the neck. Dilation of the pupil can similarly be explained in terms of reverberation. Reverberation is thus a common symptom which occurs also in diverse non-nervous diseases and in locations more or less distant from the nerve affected.

Several words will now be spent in order to try to clarify the aetiology of the auriculotemporal nerve irritation displayed by our patient. The auriculotemporal nerve transverses the parotid parenchyma and leaves between the styloid process and the angle of the mandible. This space corresponds well both to the position of the original wound and to the surgical intervention.

The nerve irritation syndrome was thus possibly caused by compression by scar resulting from the long term suppuration, or alternatively became irritable as the result of neuritis caused by proximity to a purulent focus. The first of these explanations seems the most plausible, as the symptoms in our patient appeared slowly coinciding with the period of scar development.

Regarding the most annoying symptom for our patient, that is the excessive sweating in the parotid region of the face, we were able to choose between several treatments. We intended to entrust our patient to a surgeon skilled in scar ablation thus allowing liberation of the entrapped nerve. This is indeed a delicate operation in the midst of an anatomically complex region. The operation requires a perfect understanding of the topology of the area in order to avoid cutting the facial nerve. We also gave equal consideration to the possibility of an alcoholic neurolysis or even a partial extirpation of the auriculotemporal nerve. The sequel of this radical intervention, anaesthesia of the skin and cessation of parotid secretion on the treated side are of little consequence. Likewise there is no need to fear facial asymmetry produced by total atrophy of the parotid gland because this would be compensated for by the presence of scar tissue. Unfortunately our patient left our clinic and was lost to follow-up. We are thus unable to verify indisputably by an operation the correctness of our opinion. Aside from the case described by Lipszat in Polish, I have been unable to find any other reports in the modern medical literature. On the other hand I have found in older publications several references to

parotid sweating during eating which evidently correspond to the phenomenon we have observed. Thus we have read publications by Baillarger, Bergounhioux, Botkin, Bouveret, Royer and others. In Botkin's case as with the majority of the others reported by the authors above, the pathological sweating was a consequence of parotid infection; when the subjects ate one could observe an exaggerated sweat on nearly all of that half of the face and also the same side of the body in some cases (reverberation of Thomas.)

From the historical point of view these old cases caused a heated arguments between Baillarger and Bergounhioux. The first of these authors believed that the exaggerated secretion was composed of saliva which following obliteration of Stenon's duct was forced through the skin. Bergounhioux on the other hand used the acid reaction of the liquid secreted to demonstrate that it was sweat. Baillarger's hypothesis was even supported by the physiologist Bernard. Finally we must mention that the German anatomist Henle was of the same persuasion when this condition occurred following parotitis complicating the course of typhoid fever.

The authors cited above, just as Lipszat, failed to attribute the sweating to an easily determined and specific lesion of the auriculotemporal nerve.

The literature cited proves that the condition which we have concerned ourselves with is relatively common. Identical cases must have arisen in the course of the last great war, following the wounds of varying complexity in the parotid gland and surrounding regions. The complete lack of publications on this subject serves to prove how little

interest syndrome has aroused in the eyes of observers. It must not indeed be forgotten that Neurology until recent times interested itself little with peripheral vegetative function. Our publication constitutes a modest contribution to the study of pathological processes of vegetative fibres.

Disorders of the auriculotemporal nerve can give rise to a syndrome made up of primarily vegetative features: secretory (parotid gland) sudomotor, vasomotor, and perhaps also in certain circumstances trophic symptoms. Concerning the principal symptoms of our syndrome (vasomotor and sudomotor) it seems that as a special characteristic they are generated by a reflex pathway, following gustatory stimuli conveyed in the glossopharyngeal nerve.

Because of this special feature and the fact that the region of pathological effects followed the sensory distribution of the auriculotemporal nerve, the symptoms cited above were considered pathognomic for a disorder of the auriculotemporal nerve.

One last piece of evidence in favour of this localization is suggested by the fact that there is impairment of superficial sensation in the distribution of the nerve in question.

Thanks to the property of the sympathetic nervous system to show reverberation the affliction is able to spread proportionally and invade little by little neighbouring nerve territories causing sudomotor phenomena in the case of Botkin, vasomotor and pilomotor phenomena in our case. We have only invoked a syndrome of sympathetic irritation in this explanation. It may however be possible to observe in certain,

conditions mixed vegetative syndromes with symptoms of paresis and irritation. Our case is probably in this mixed category, because we have seen, in addition to sympathetic irritation there was, as mentioned before, an interruption parasympathetic secretory fibres to the parotid.

Based on the cases cited above and on our own observations we conclude that suppuration in the parotid region is an important factor in the aetiology of the auriculotemporal nerve syndrome we have described.

APPENDIX 3 CLINICAL STUDIES OF AURICULOTEMPORAL SYNDROME

23/03/87

The University of Adelaide
Department of Surgery
The QEH
Woodville S.A.

Mr R.B.Davey
220 Melbourne St.
North Adelaide

Dear Mr Davey,

I am spending 1987 doing research into Freys Syndrome in the Department of Surgery at the QEH. I would be most grateful if you would spend the time to fill in the enclosed questionnaire and return it to me in the envelope provided. The purpose of this questionnaire is to define the approximate incidence of parotid surgery and certain complications especially Freys Syndrome. In addition , data on surgical technique ,pathology,local recurrence rate , treatment techniques will be collected. The questionnaire is completely voluntary and anonymous. The information gained will be treated as confidential but will form part of a scientific presentation at a later date. I hope you are able to help me . If you would like a copy of the results of the questionnaire please enclose your card with your response.

If you have any queries, I can be contacted at the QEH on 450222 extension 7355.

Thanking you in anticipation ,
yours faithfully,

Greg Otto
Temporary Lecturer in Surgery QEH

QUESTIONNAIRE -PAROTID SURGERY

Most of the answers are yes/no responses or require a few words only. When numerals are required approximate answers only are necessary.

If you do not do any parotid surgery please complete the first two questions only.

This questionnaire is completely confidential.

1)GENERAL

What is your Registered Surgical Specialty ? .....

What is your age ? .....

Approximately how many operations under general anaesthetic do you perform per year ? .....

About how many of the following operations do you personally perform per year on average?

Total parotidectomy .....

Superficial parotidectomy.....

As a rule how long do you follow patients after parotidectomy ?

Benign disease ..... Months

Malignant disease .....Months

2) FREY'S SYNDROME

What phenomena other than gustatory sweating make up Frey's Syndrome ?

.....

What is the generally accepted incidence of Frey's Syndrome ?

.....%

In a few words how would you treat symptomatic facial gustatory sweating following parotid surgery?

Medically.....

Surgically.....

3) TECHNIQUE

When you dissect the facial nerve do you commence anteriorly or posteriorly'

.....

Do you use any technique in an attempt to prevent the development of facial gustatory sweating ?

.....

If yes, what technique ? .....

QUESTIONNAIRE -PAROTID SURGERY

	YES	NO	SOMETIMES
Do you use a nerve stimulator routinely ?	....	....	.....
Do you attempt to preserve the auriculotemporal nerve ?	....	....	.....
Do you attempt to preserve the greater auricular nerve ?	....	....	.....
Do you use diathermy on the parotid gland ?	....	....	.....

4) PATHOLOGY

What is the commonest benign tumor you resect from the parotid?

.....

What is the commonest malignant tumor you resect from the parotid?

.....

In your experience, what is the local recurrence rate for parotid tumors ?

Benign .....%

Malignant .....%

5) POST OPERATIVE TREATMENT

Do you use radiotherapy for :	YES	NO	SOMETIMES
Completely resected malignant tumors	....	....	.....
Incompletely resected malignant tumors	....	....	.....
Incompletely resected benign tumors	....	....	.....
Recurrent benign tumors ?	....	....	.....

6) COMPLICATIONS

In your experience:

What is the approximate incidence of salivary fisltula ?..... %

What is the approximate incidence of wound breakdown ?..... %

What is the approximate incidence of permanent facial nerve damage

Benign tumors.....%

Malignant tumors?.....%

QUESTIONNAIRE -PAROTID SURGERY

In your experience:

What is the approximate incidence of temporary facial nerve dysfunction

Benign tumors.....%

Malignant tumors?.....%

Approximately how frequently do patients complain of local facial hypersensitivity or burning pain (dysthesia) several months after parotid surgery ?

.....%

What is the approximate incidence of ear numbness as a post-operative complaint of parotidectomy patients ?

.....%

What is the approximate incidence of facial numbness as a post-operative complaint of parotidectomy patients ?

.....%

Approximately how many post-parotidectomy patients with facial gustatory sweating have you encountered ?

.....

Have any of your post-parotidectomy patients experienced gustatory sweating severely enough to warrant treatment ?

.....

If yes :

What form of treatment did you recommend?.....

Was the treatment successful ?.....

Thanks for taking the time to complete this questionnaire.
If you desire a copy of the composite outcome when it becomes available please enclose your card .

yours sincerely,

Greg Otto

THE QUEEN ELIZABETH HOSPITAL
WOODVILLE, SOUTH AUSTRALIA 5011
Telephone: 45 0222 Telex: 'QEHOSP' AA 89365

16 January, 1986

The Chairman,
Research Review Committee,
The Queen Elizabeth Hospital

Dear Sir,

Please find enclosed 2 copies of a proposed research project on Frey's Syndrome and Parotid Surgery.

I submit the proposal for your perusal and approval.

Yours sincerely,

Gregg Otto

C.C. Mr. W. Proudman

TO: ETHICS COMMITTEE THE QUEEN ELIZABETH HOSPITAL

FROM: DEPT. OF SURGERY THE QUEEN ELIZABETH HOSPITAL

TITLE: FREY'S SYNDROME POST PAROTIDECTOMY - THE QEH EXPERIENCE 1975-1985

INVESTIGATORS: DR. G. OTTO
MR. W. PROUDMAN

PURPOSE OF STUDY

Study has a threefold purpose: 1. to define the true incidence of Frey's syndrome after parotidectomy at this hospital, 2. to elucidate the facts involved in the production of Frey's syndrome, 3. to compare two methods of detection of Frey's syndrome. The first method is the minor starch iodine test (1,13), which is to be compared to the use of skin galvinometry. (16)

BACKGROUND

Frey's syndrome is a relatively infrequent but important complication of parotid surgery. Its incidence after parotidectomy varies from 1% to 100% (2,3).

It was first described in 1757 (4) but bears the name of Lucie Frey who in 1923 described the syndrome of gustatory sweating (5) as a consequence of parotid injury by gunshot wound.

Frey's syndrome consists of gustatory sweating usually in the distribution of the auriculo-temporal or greater auricular nerves. It is postulated that this results from innovation of sweat glands by post ganglionic parasympathetic fibres responsible for salivation and cut at the time of surgery. (7)

There has been a vogue for the use of barriers of various sorts in order to prevent the development of Frey's syndrome for example fascia lata or sternomastoid muscle. (7,9,10)

Others believe that skin flap thickness is important in the development of the syndrome but thicker skin flaps seem only to delay the onset of the complication. (8)

Frey's syndrome usually develops between 10 and 18 months after surgery. it is often progressive, occasionally painful and can be quite disabling to the patient. (11,12).

Treatment varies from the use of topical scopolamine, systemic atropine (4), division of glossopharyngeal nerve, local radiotherapy, alcohol injection of otic ganglion (2,15), tympanic plexus neurectomy (7), to insertion of fasciolata or other materials as barriers (9). Success is limited. (11)

It is an important aim to attempt to define the development of Frey's syndrome in order to facilitate preventative treatment.

PRELIMINARY STUDIES

A retrospective case note study of parotidectomy at the QEH from 1975-1985 has been undertaken.

There were 82 cases in the series. 10 patients have subsequently died.

35 of the patients were private and so no followup information is available. The average followup time was 4 months. The incidence of Frey's syndrome was 2 patients in 1982. The incidence is expectedly low because of the short followup period and the high number of private patients with no followup.

It is important to define the true incidence of Frey's syndrome in this group in a prospective fashion.

SUBJECTS AND SELECTION CRITERIA

In this study attempts will be made to interview and test all patients in the retrospective study group who are still alive. Permission would be sought from all consultants concerned. Attendance by the patient would be on a purely voluntary basis and patients too infirm to come to outpatients would be excluded from the study.

METHOD

Each patient would be invited by mail to attend an outpatient appointment on two occassions. (see attached letter).

The patients would be questioned about gustatory sweating and its development according to a standard questionaire (see attached sheet 2).

On the second attendance they would be tested using the minor starch iodine test (13) and simple skin galvinometry.

The minor starch iodine test involves painting the skin of the face and neck of the affected side with a solution of 3gm of iodine 20g castor oil and 200ml of absolute alcohol. When this solution is dry the face is dusted with starch. The patient is then asked to chew a segment of lemon. The area involved with Frey's syndrome turns blue as the starch and iodine react. The area affected can be documented by measurement and photograph.

The iodine is removed by a 5% sodium thiosulphate solution.

The galvinometry test would involve application of two electrodes in the area affected by Frey's syndrome. The skin current will be measured before and after stimulation of salivation using a segment of lemon. The affected side would be compared to the normal side and the skin conductivities measured and expressed as a ratio.

This method has not been described in the past and it is hoped that it will allow sensitive quantitation of Frey's syndrome, thus allowing accurate observation of the development of the syndrome and its extent. It is anticipated that this test will correlate more readily with clinical symptoms than the minor starch iodine test.

Comparison will then be made between the clinical assessment of Frey's syndrome, and assessment by the above two tests in each patient. It is anticipated that the 30 to 40 patients will be tested using these techniques.

The incidence and extent of Frey's syndrome in those patients who have had a lyodura barrier inserted will be compared to those patients who have had no barrier inserted.

It is anticipated that once calibrated the technique of skin galvinometry will be used in a small number of patients in order to follow the development in a longetudenal sense.

EFFICACY

The efficacy of the minor starch iodine test is documented in the literature (1,3,13), and it is a standard test used in this field. A skin galvinometry test is as yet untried, for Frey's Syndrome, but has been used for detection of peripheral nerve injuries. (16)

SAFETY

No safety hazards are inherent in either test.

ETHICAL CONSIDERATIONS

Patients will only be interviewed and tested with the permission of the consultant concerned. No management changes will be made on the basis of the test results. If some change in patient management is required the patient will be referred back to the consultant concerned.

FINANCIAL CONSIDERATIONS

The Pharmacy will be asked to prepare the solutions for the minor starch iodine test.

The hospital will be asked to bear the cost of this and the cost of contacting patients by mail.

ANALYSIS AND REPORTING OF RESULTS

Results will be analysed by appropriate statistical methods and reported in a reputable journal.

CIRCULAR TO ALL PATIENTS

Dear

My name is Dr. Greg Otto and I am a surgical registrar at the Queen Elizabeth Hospital.

I am interested in studying the after effects of surgery on the parotid gland.

A survey of the hospital records has revealed that you had some surgery on your parotid gland in .

I wonder if you would be interested in participating in my survey. It would involve two visits to outpatients during which time you would be interviewed and some simple skin tests carried out. There are no blood tests involved.

Participation in this survey is completely voluntary. Should you wish to take part please telephone Dr. Greg Otto on 45 0222 and I will arrange an outpatient appointment for you.

Yours faithfully

Greg Otto

APPENDIX 3

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THE QUEEN ELIZABETH HOSPITAL
WOODVILLE ROAD, WOODVILLE, SOUTH AUSTRALIA 5011
Telephone: (08) 450222 Telex: "QEHOSP" AA 89365

BHJ:CF

24th February, 1986

Dr. G. Otto,
Surgical Registrar,
The Queen Elizabeth Hospital

Dear Dr. Otto,

At its meeting on Monday, 17th February, 1986 the Ethics of Research Committee considered your protocol entitled "Frey's Syndrome Post-Parotidectomy - The Queen Elizabeth Hospital Experience 1975-85" (2/86).

Would you please forward:-

i. a letter of support from Pharmacy

ii. a modified "Circular to all patients" which would enable a patient to consent in writing to participate in survey and which states that the participant may freely withdraw from the survey at any time without prejudice to further treatment.

Yours sincerely,

B. H. JEANES
Chairman
Ethics of Research Committee

THE QUEEN ELIZABETH HOSPITAL
WOODVILLE ROAD, WOODVILLE, SOUTH AUSTRALIA 5011
Telephone: (08) 45 0222 Telex: "QEHOSP" AA 89365

BHJ:KT

1st April, 1986

Dr. G. Otto,
Surgical Registrar,
The Queen Elizabeth Hospital

Dear Dr. Otto,

Thank you for the Consent Form applying to your protocol entitled "Frey's Syndrome Post-Parotidectomy - The Queen Elizabeth Hospital Experience 1975-85" (2/86). The Consent Form requires:-

i) Description of tests

ii) Statement that there will be no untoward side effects.

A copy of the modified consent form is required for the committee's records.

Pharmacy has indicated support for your protocol.

Approval is now granted.

Please inform the Committee should any variation of protocal occur, and if there are any adverse reactions.

Yours sincerely,

B. H. JEANES
Chairman
Ethics of Research Committee

THE QUEEN ELIZABETH HOSPITAL
WOODVILLE ROAD, WOODVILLE, SOUTH AUSTRALIA 5011
Telephone: (08) 45 0222 Telex: "QEHOSP" AA 89365

TO:
QEH RECORD NUMBER

DATE :04/03/87

DEAR

MY NAME IS DR. GREG OTTO AND I AM A SURGICAL REGISTRAR AT THE QEH.

I AM INTERESTED IN STUDYING THE AFTER EFFECTS OF PAROTID GLAND SURGERY.

A SURVEY OF THE HOSPITAL RECORDS HAS REVEALED THAT YOU HAVE HAD PAROTID GLAND SURGERY IN THE PAST.

I WONDER IF YOU WOULD BE KIND ENOUGH TO AGREE TO PARTICIPATE IN MY STUDY ? IT WOULD REQUIRE ONE OUTPATIENT VISIT DURING WHICH YOU WOULD BE INTERVIEWED AND SOME SIMPLE SKIN TESTS WOULD BE PERFORMED. THE TESTS ARE NOT PAINFUL OR DANGEROUS AND THERE NO BLOOD TESTS REQUIRED. IT WOULD ONLY TAKE UP 20 MINUTES OF YOUR TIME.

PARTICIPATION IN THE SURVEY IS COMPLETELY VOLUNTARY. SHOULD YOU AGREE TO TAKE PART PLEASE TELEPHONE ME ON 45 0222 EXT 7355 AND I WILL ARRANGE AN OUTPATIENTS APPOINTMENT FOR YOU .

YOURS FAITHFULLY

DR.G.M.OTTO

THE QUEEN ELIZABETH HOSPITAL
WOODVILLE. SOUTH AUSTRALIA 5011
Telephone: 45 0222 Telex: 'QEHOSP' AA 89365

DATE :04/03/87

TO:
QEH RECORD NUMBER

DEAR

MY NAME IS DR. GREG OTTO AND I AM A SURGICAL REGISTRAR AT THE QEH.

I AM INTERESTED IN STUDYING THE AFTER EFFECTS OF PAROTID GLAND SURGERY.

A SURVEY OF THE HOSPITAL RECORDS HAS REVEALED THAT YOU HAVE HAD PAROTID GLAND SURGERY IN THE PAST.

I WONDER IF YOU WOULD BE KIND ENOUGH TO AGREE TO PARTICIPATE IN MY STUDY ? IT WOULD REQUIRE ONE OUTPATIENT VISIT DURING WHICH YOU WOULD BE INTERVIEWED AND SOME SIMPLE SKIN TESTS WOULD BE PERFORMED. THE TESTS ARE NOT PAINFUL OR DANGEROUS AND THERE NO BLOOD TESTS REQUIRED. IT WOULD ONLY TAKE UP 20 MINUTES OF YOUR TIME. I WROTE TO YOU ABOUT THIS LAST YEAR BUT THE LETTER MUST HAVE GONE ASTRAY AS I RECIEVED NO REPLY.

PARTICIPATION IN THE SURVEY IS COMPLETELY VOLUNTARY. SHOULD YOU AGREE TO TAKE PART PLEASE TELEPHONE ME ON 45 0222 EXT 7355 AND I WILL ARRANGE AN OUTPATIENTS APPOINTMENT FOR YOU .

YOURS FAITHFULLY

DR.G.M.OTTO

CONSENT FORM

I, , DO HEREBY AGREE TO PARTICIPATE IN THE SURVEY OF THE AFTER EFFECTS OF PAROTID SURGERY , AS EXPLAINED TO ME BY DR. G.M.OTTO . I UNDERSTAND THAT TWO SIMPLE SKIN TESTS WILL BE PERFORMED AND THAT THESE ARE NOT PAINFUL AND HAVE NO UNTOWARD SIDE EFFECTS. I ALSO UNDERSTAND THAT I MAY FREELY WITHDRAW FROM THE SURVEY AT ANY TIME WITHOUT PREJUDICE TO FURTHER TREATMENT.

SIGNED .....

WITNESSED.....

DR.G.M.OTTO

DATE.....

PATIENT DATA FORM

NAME :

HOSPITAL UR :

OUT PATIENT APPOINTEMENT DATE :

REPLY TO LETTER ? IF SO WHEN? :

IF NOT, SECOND LETTER SENT? DATE:

	Y	N
ARE YOU ALLERGIC TO IODINE ?		
HAVE YOU HAD ANY PROBLEMS WITH THE OPERATION ?		
IF SO WHAT WERE THEY ?		
HAVE YOU NOTICED ANY SWEATING OF THE FACE OVER THE SITE OF THE OPERATION ?		
WHEN DOES THIS OCCUR?		
HAVE YOU EVER NOTICED THIS SWEATING DURING MEALS?		
MINOR STARCH IODINE TEST POSITIVE? DATE:.....		
SKIN CONDUCTION TEST POSITIVE? DATE :.....		

APPENDIX 4 ANIMAL STUDIES OF AURICULOTEMPORAL SYNDROME

THE QUEEN ELIZABETH HOSPITAL AND THE UNIVERSITY OF ADELAIDE

ANIMAL ETHICS COMMITTEE

APPLICATION FORM FOR ANIMAL HOUSE FACILITIES
INVOLVING THE USE OF ANIMALS

N-17-87

If answers are not typed, clear legible script must be used.

1. Name(s), position(s) and location(s) of worker(s) to be actively involved with the research.

DR. G. M . OTTO LECTURER DEPT OF SURGERY Q.E.H.

2. Name(s), position(s) and location(s) of senior research worker(s) responsible (if different from the above).

MR.W.E.ROEDIGER SENIOR LECTURER DEPT OF SURGERY Q.E.H.

3. Name(s), position(s) and location(s) of secondary research worker(s) involved with the project and utilising Animal House facilities.

MR.K.PORTER OFFICER IN CHARGE ANIMAL HOUSE Q.E.H.

4. Title of project.

RETRO GRADE AXONAL LABELING OF CRANIAL PARASYMPATHETIC NERVES OF THE RAT WITH FAST BLUE AND DIAMIDINO YELLOW.

5. Objectives, methods involved, and potential significance of the project.

AIM : THIS PROJECT IS INTENDED TO ALLOW THE DEVELOPMENT OF THE TECHNIQUE OF RETROGRADE FLUORESCENT DOUBLE LABELLING OF PARASYMPATHETIC AND SYMPATHETIC NERVES IN THE HEAD AND NECK OF THE RAT.

METHOD : UNDER ETHER ANAESTHETIC THE RAT PAROTID GLAND WOULD BE EXPOSED AND A 10 MICROLITER ALIQUOT OF 0.05% FAST BLUE SOLUTION INJECTED. A 1MICRO-LITRE INJECTION WOULD BE MADE SUBCUTANEOUSLY 1WEEK LATER. FOUR DAYS AFTER THE SECOND INJECTION THE ANIMAL WOULD BE SACRIFICED AND THE OTIC AND SUPERIOR CERVICAL GANGLIA WOULD BE REMOVED AND INSPECTED WITH A FLOURESCENT MICROSCOPE.

SIGNIFICANCE : THIS PROJECT WILL ALLOW THE DEVELOP MENT OF EXPERTISE IN THE TECHNIQUES OF RETROGRADE AXONAL LABELLINGREQUIRED IN THE STUDY OF FREY'S SYNDROME IN MARMOSET MONKEYS.

6. Is this a new or continuing project?

NEW

7. What is the proposed starting date and what is the estimated duration of the project?

1/3/87 1MONTH

8. What animals are required - specify species/strains if relevant.

SPRAGUE DAWLEY RATS

9. Optimal number of animals to be housed at any one time. Minimum and maximum number of animals to be housed at any one time.

2

10. Minimum and maximum number of animals anticipated to be used for the project.

2- 10

11. Details of financial support to cover costs.

DEPARTMENT OF SURGERY

12. Please detail any special conditions, facilities, care, requirements and preparation necessary for the animals.

NIL

13. If the project involves surgery, who will perform the surgery?

DR. G. M. OTTO

14. What anaesthetic will be used and who will be responsible for the anaesthesia?

ETHER DR. G.M. OTTO

15. Does the project use either neuro-muscular blockade or neuro-leptanalgesia?

NO

16. What post-operative measures are to be taken?

NIL IN PARTICULAR THE RATS ARE TO SURVIVE FOR APPROXIMATELY 2 WEEKS

17. Will this project involve a serious disturbance to the function of the animal following recovery from the experimental procedure? If so, detail.

NO

18. Does the experiment require the death of the animal?

YES

19. Does the experiment involve implanted devices?

NO

20. What is the method of disposal of the animal following termination of the experimental procedure?

INCINERATION

21. Does the project involve the use of potential environmental hazard, e.g. radioactivity, mutagen, pathogenic organism, etc.? If so, please state.

THE DYES TO BE USED HAVE SOME MUTAGENIC POTENTIAL.

21. (a) Please note that this project will NOT be approved until you have submitted a photocopy of this Application together with a completed "Application to Use Radionuclides in an Animal Experiment" form to the Chairman of the Radiation Safety Committee, and received approval.

22. Are you aware that animals may harbour special diseases injurious to man?

YES

23. Are you aware that pregnant women should not work with rodents, cats or dogs as they may carry toxoplasmosis? In addition, certain anaesthetic gases may be hazardous to pregnant women.

YES

I have read "The Code of Practice for the Care and Use of Animals for Use in Australia 1979" and I am in agreement with the principles inherent in this publication, I accept full responsibility for compliance with the conditions imposed by the Animal Ethics Committee both for myself and for my research workers. I recognise that if approval is granted for this project, the maximum time interval granted will be the end of the current calendar year. I am aware of the financial costs necessary to maintain the animals, and agree to make a contribution to the costs of maintaining allocated animals unless exempted by the Animal Ethics Committee. I agree to provide the Animal Ethics Committee with a report of the activities of this project at the end of the calendar year.

Signature of Senior Research Worker

27/7/87

Date

Signature of Departmental Head

2/3/87.

Date

Project Approved

Chairman

10/3/87

Date

SPECIAL CONDITIONS:

THE QUEEN ELIZABETH HOSPITAL AND THE UNIVERSITY OF ADELAIDE
ANIMAL ETHICS COMMITTEE

APPLICATION FORM FOR ANIMAL HOUSE FACILITIES
INVOLVING THE USE OF ANIMALS

If answers are not typed, clear legible script must be used.

1. Name(s), position(s) and location(s) of worker(s) to be actively involved with the research.

DR. G. M . OTTO LECTURER DEPT OF SURGERY Q.E.H.

2. Name(s), position(s) and location(s) of senior research worker(s) responsible (if different from the above).

MR.W.E.ROEDIGER SENIOR LECTURER DEPT OF SURGERY Q.E.H.

3. Name(s), position(s) and location(s) of secondary research worker(s) involved with the project and utilising Animal House facilities.

MR.K.PORTER OFFICER IN CHARGE Q.E.H. ANIMAL HOUSE

4. Title of project.

AN EXPERIMENTAL MODEL OF FREY'S SYNDROME IN MARMOSET MONKEYS

5. Objectives, methods involved, and potential significance of the project.

PURPOSE : THE AIM OF THIS PROJECT IS TO DEVELOP AN EXPERIMENTAL MODEL OF FREY'S SYNDROME(POST PAROTIDECTOMY GUSTATORY SWEATING IN HUMANS)., AND TO USE THIS MODEL TO ELUCIDATE THE NEUROANATOMY OF THIS PHENOMENON AND ITS AETIOLOGY.MONKEYS, BEING PRIMATES ,REPRESENT THE IDEAL ANIMAL MODEL.PRELIMINARY EXPERIMENTS INDICATE THAT MARMOSETS HAVE FACIAL SWEAT GLANDS SIMILAR TO HUMANS.

METHOD UNDER GENERAL ANAESTHETIC IT IS PROPOSED THAT THE ANIMALS HAVE A UNILATERAL PAROTIDECTOMY AND BILATERAL IMPLANTATION OF FAST BLUE.WEEKLY MINOR STARCH IODINE TESTS WOULD BE PERFORMED.WHEN FREY'S SYNDROME DEVELOPED A BILATERAL SUBCUTANEOUS INJECTION OF DIAMIDINO YELLOWWOULD BE GIVEN AND THE ANIMALS SACRIFICED 4 DAYS LATER.THE OTIC AND SUPERIOR CERVICAL GANGLIA WOULD BE EXAMINED FOR FLUORESCENCE, AND THE FACIAL SKIN AND PAROTID GLAND EXAMINED HISTOCHEMICALLY.

SIGNIFICANCE : THIS PROJECT HAS POTENTIAL SIGNIFICANCE REGARDING THE NEUROANATOM AETIOLOGY AND PREVENTIONOF HUMAN FREY'S SYNDROME. THIS IS A COMPLICATION OF PAROTID SURGERY IN 60% OF CASES, AND SO AMOUNTS TO A COMMON CLINICAL PROBLEM FOR WHICH THERE IS NO CURE AT THIS TIME.AN ANIMAL MODEL OF THIS UNUSUAL CONDITION ALSO HAS RELEVENC TO THE STUDY OF NERVE REGENERATION IN THE AUTONOMIC NERVOUS SYSTEM. AT THIS TIME THERE IS NO EXPLANATION FOR THE GROWTH OF PARASYMPATHETIC NERVES INTO A NORNALLY SYMPATHETICALLY INNERVATED STRUCTURE.

../2

6. Is this a new or continuing project?

NEW

7. What is the proposed starting date and what is the estimated duration of the project?

1/3/87 FOR 1YEAR INITIALLY

8. What animals are required - specify species/strains if relevant.

MARMOSET MONKEYS

9. Optimal number of animals to be housed at any one time. Minimum and maximum number of animals to be housed at any one time.

1-3

10. Minimum and maximum number of animals anticipated to be used for the project.

1 INITIALLY TO TEST THE VALIDITY OF THE METHOD ; TO A MAX OF

11. Details of financial support to cover costs.

DEPARTEMENT OF SURGERY

12. Please detail any special conditions, facilities, care, requirements and preparation necessary for the animals.

NIL

13. If the project involves surgery, who will perform the surgery?

DR. G. M. OTTO

14. What anaesthetic will be used and who will be responsible for the anaesthesia?

INTERMITTENT SAFFAN INTRAVENOUSLY DR.G. M. OTTO

15. Does the project use either neuro-muscular blockade or neuro-leptanalgesia?

NO

16. What post-operative measures are to be taken?

THE ANIMALS WILL BE ALLOWED TO RECOVER FROM ANAESTHETIC
NO SPECIAL MEASURES NEED TO BE TAKEN.

17. Will this project involve a serious disturbance to the function of the animal following recovery from the experimental procedure? If so, detail.

NO

18. Does the experiment require the death of the animal?

YES

19. Does the experiment involve implanted devices?

NO

20. What is the method of disposal of the animal following termination of the experimental procedure?

INCINERATION AFTER THOROUGH AUTOPSY .

21. Does the project involve the use of potential environmental hazard, e.g. radioactivity, mutagen, pathogenic organism, etc.? If so, please state.

THE DYES USED MAY HAVE MUTAGENIC POTENTIAL.

21. (a) Please note that this project will NOT be approved until you have submitted a photocopy of this Application together with a completed "Application to Use Radionuclides in an Animal Experiment" form to the Chairman of the Radiation Safety Committee, and received approval.

22. Are you aware that animals may harbour special diseases injurious to man?

YES

23. Are you aware that pregnant women should not work with rodents, cats or dogs as they may carry toxoplasmosis? In addition, certain anaesthetic gases may be hazardous to pregnant women.

YES

I have read "The Code of Practice for the Care and Use of Animals for Use in Australia 1979" and I am in agreement with the principles inherent in this publication, I accept full responsibility for compliance with the conditions imposed by the Animal Ethics Committee both for myself and for my research workers. I recognise that if approval is granted for this project, the maximum time interval granted will be the end of the current calendar year. I am aware of the financial costs necessary to maintain the animals, and agree to make a contribution to the costs of maintaining allocated animals unless exempted by the Animal Ethics Committee. I agree to provide the Animal Ethics Committee with a report of the activities of this project at the end of the calendar year.

Signature of Senior Research Worker

27/7/87

Date

Signature of Departmental Head

2/3/87.

Date

Project Approved

Chairman

16/3/87

Date

SPECIAL CONDITIONS:

THE QUEEN ELIZABETH HOSPITAL
WOODVILLE ROAD, WOODVILLE, SOUTH AUSTRALIA 5011
Telephone: (08) 45 0222 Telex: "QEHOSP" AA 89365

THE QUEEN ELIZABETH HOSPITAL AND THE UNIVERSITY

OF ADELAIDE SPECIAL RESEARCH LABORATORIES -

ANIMAL ETHICS COMMITTEE

N-17-87

TO: DR. G. OTTO
DEPT. OF SURGERY

DATE: 13-3-87

Dear Dr./~~Mr~~ OTTO

The Animal Ethics Committee has considered your project entitled RETROGRADE AXONAL LABELLING OF CRANIAL PARASYMPATHETIC NERVES OF THE RAT.

The committee has approved your request for animals and animal house facilities for the period 13-3-87 to 31/12/87.

Could you please contact Mr. Ken Porter on Ext. 6681 at the animal house to arrange commencement of your project?

Yours sincerely,

Chairman
M. Alp

c.c. Mr. K. Porter
Minutes Secretary

SPECIAL CONDITIONS .....

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THE QUEEN ELIZABETH HOSPITAL
WOODVILLE ROAD, WOODVILLE, SOUTH AUSTRALIA 5011
Telephone: (08) 450222 Telex: "QEHOSP" AA 89365

N-16-87

THE QUEEN ELIZABETH HOSPITAL AND THE UNIVERSITY

OF ADELAIDE SPECIAL RESEARCH LABORATORIES -

ANIMAL ETHICS COMMITTEE

TO: DR G. OTTO

DEPT. SURGERY

DATE: 13-3-87

Dear Dr./Mr. OTTO

The Animal Ethics Committee has considered your project entitled EXPERIMENTAL MODEL OF FREYS SYNDROME IN MARMOSET MONKEYS

The committee has approved your request for animals and animal house facilities for the period 13-3-87 to 31/12/87.

Could you please contact Mr. Ken Porter on Ext. 6681 at the animal house to arrange commencement of your project?

Yours sincerely,

Chairman

M. Alp

c.c. Mr. K. Porter
Minutes Secretary

SPECIAL CONDITIONS (1) USE OF ANIMAL FROM RENAL DEPT. ONLY (2) WRITTEN REPORT REQUIRED PRIOR TO APPLICATION FOR FURTHER ANIMALS.

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APPENDIX 5 PRESENTATION

Abstract of paper presented at the Annual Scientific Meeting of the South Australian Branch of the Royal Australian College of Surgeons July 1987.

Title & Author/s GUSTATORY SWEATING AFTER SUPERFICIAL PAROTIDECTOMY (1975-1985)
Dr. G.M. Otto, Mr. W. Proudman, Department of Surgery, Q.E.H.

Abstract: This study was undertaken in order to determine the incidence of Post Parotidectomy Gustatory Sweating (Frey's Syndrome (FS)), to test the usefulness of skin galvanometry in the detection of FS, and also, to evaluate the effectiveness of the prophylactic use of 'Lyodura' in the prevention of FS.

Method: A retrospective casenote study was carried out on 88 patients who had undergone superficial parotidectomy at The Queen Elizabeth Hospital between 1975 and 1985. Of the 80 patients who were contacted by mail 54 consented to participate in the study. Each patient was subjected to skin galvanometry on both sides of the face before and after maximal salivary stimulus. The Minor Starch Iodine test was performed on the operated side. An attempt was made to correlate the presence of FS with: positive skin galvanometry, surgeon status, time elapsed since operation, the amount of parotid resected, the age and sex of the patients, and the presence of prophylactic 'Lyodura'.

Results: 32 patients had demonstrable FS (61%) and of these 17were symptomatic. The incidence of FS after prophylactic 'Lyodura' was 6 out of 6 patients(100%). The correlation between skin galvanometry and the Minor test for the detection of gustatory sweating was 100%.

Conclusions: Although skin galvanometry is a useful technique for the detection of FS , the prophylactic use of a 'Lyodura' barrier seems to have no effect on the development of the syndrome. The incidence of FS in this study is similar to that reported elsewhere.

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