

SYSTEMIC TOXICITY
OF
DENTAL LOCAL ANAESTHETICS.

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CHAPTER I.

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THE NATURE OF THE PROBLEM.

1. INTRODUCTION.

My interest in this aspect of local anaesthesia was stimulated some years ago as a result of occasionally observing mild convulsive reactions following the dental administration of the powerful natural alkaloid cocaine. With the introduction of less toxic local anaesthetic agents in combination with concentrations of vasoconstrictor drugs which, by today's standards, were relatively high, the focus of attention switched to the toxic potential of the latter component. The subsequent discovery of the amide local anaesthetics heralded a new era in local anaesthesia. Generally speaking the amides have a greater affinity for, and stronger depressant effect on, nervous tissue than ester-linked compounds. Systemically, these effects are responsible for the high degree of intravenous toxicity characteristic of the amides while locally, anaesthetic potency is enhanced permitting reduction in vasoconstrictor concentration.

As a result, evidence of intoxication is rarely observed following the dental use of these preparations unless as a direct result of intravenous injection. Even then, the reactions observed are generally mild in nature with spontaneous recovery. Although fatal reactions are

occasionally reported in which the local anaesthetic agent is implicated as the likely cause, reactions of a serious or life endangering nature are uncommon.

The rationale of this review of systemic toxicity is not that the practice of local anaesthesia is fraught with dire consequences, although the possibility of serious complications must be recognised, but simply that it should be a truly local procedure and, as such, evoke no systemic response in the patient.

The need to review the present status of factors influencing the systemic toxicity of dental local anaesthetics arises because of advances in fields related to the practice of local anaesthesia in recent years.

These advances are:

- a) The discovery and use of new local anaesthetic agents which show a trend towards greater local and systemic potency (Tainter et al 1953, Broadbent 1957, Hofmeyr 1959, Truant and Wiedling 1959, Henn 1960, Foldes et al 1960, Dobbs and Ross 1961, Foldes and McNall 1961, Matt 1961, Englesson et al 1962, Luduena et al 1960, Le Chat and Deleau 1961, Wiedling and Tegner 1963, Vallini 1963, Astrom 1965, Foldes et al 1965, Myers 1967, Epstein 1958, Sadove 1962, Ulfendahl 1957).
- b) The development of short duration local anaesthetics, some of which depend for their effectiveness on an increased

concentration of local anaesthetic agent on the one hand and decreased vasoconstrictor content on the other (Adriani 1960, Epstein and Chilton 1959, Weil et al 1961, Glover 1963, Goldman 1964, Goldman and Gray 1963, Epstein 1965, Hiatt 1961). Theoretically these preparations are potentially more toxic.

c) The availability of syringes and local anaesthetic cartridges which allow the aspiration test to be performed easily and efficiently prior to injection (Frye 1963, Black 1967, Kemp and Jolly 1962, Monheim 1965, Shira 1962, Forrest 1959).

d) Changes in the general health of the community. Statistics show that people are living longer (Shepherd 1967). Consequently, the health status of persons seeking dental attention has altered in recent years because an increasing proportion of this group suffer from the chronic disease processes of old age, particularly cardiovascular disease (A.D.A. and A.H.A. 1964). Because of advances in drug therapy, the true state of health may be overlooked unless a relevant medical history is taken for all new patients and followed up on subsequent visits. (Sadove 1952, Toogood 1960, Monheim 1961, Dille 1963, American Dental and American Heart Assoc. 1964, Jolly 1967, Hall 1967, Morris 1967, Hughes 1966, Lavine 1968, Schirger et al 1961).

e) The increased use, in medical practice, of drug regimens which are contraindicated in concurrent therapy with dental local anaesthetic solutions (Heinonen 1966), and particularly with the sympathomimetic vasoconstrictor component of these solutions (Rand 1966, Trinker et al 1967, Jolly 1967, Waterson 1967, Christensen 1967).

The factors which influence the systemic toxicity of dental local anaesthetic solutions are essentially those which influence the toxicity of their principal component drugs; the vasoconstrictor and the local anaesthetic component.

Systemic toxic manifestations due to high blood level of these drugs are referable mainly to the cardiovascular and central nervous systems (Foldes and McNall 1961, Goodman and Gilman 1966), the latter response also influencing respiration via the medullary respiratory centre (Foster 1966).

Manifestations of systemic toxicity due to vasoconstrictor drugs occur mainly in the cardiovascular system whereas those due to the local anaesthetic component are generally the result of central nervous effects (Meora and Bridenbaugh 1961, Steinhaus 1962, Steinhaus 1959).

Local anaesthetic and vasoconstrictor drugs each have characteristic and complex inherent pharmacological actions.

When administered systemically, the local anaesthetic agent has the greater effect on the cerebral cortex and

medulla. This effect is one of stimulation in the respective regions which is followed or accompanied by, depression in those regions of proportionate intensity (Sadove 1952).

Although dental amounts of vasoconstrictor drugs are never sufficient to produce a general stimulation of the cerebral cortex, it is possible that they may affect the brain in localized areas producing a condition of emotional alertness (Goodman and Gilman 1966, Toogood 1960, Robson and Stacey 1962, Sara 1968). In addition, this state may already exist at the time of injection as a result of the effects of circulatory endogenous adrenaline released by sympathetic activity in time of stress. Consequently the cerebral stimulatory effects of dentally administered adrenaline must be taken into consideration despite their minor nature.

In their direct toxic manifestations on the cardiovascular system, local anaesthetics and vasoconstrictors are, to some extent, pharmacological antagonists. If administered simultaneously, the vasoconstrictor's effect predominates (Wiedling 1960, Tainter and Thronson 1938, Wallace et al 1956, Sara 1963, Goldman 1964).

Numerous investigations using animals, have demonstrated that the pressor effects of adrenaline are antagonised by the amide, lignocaine (Wiedling 1964). In contrast, Kimmey and Steinhaus (1958) sometimes observed an elevation of blood

pressure after lignocaine in patients under thiopental-nitrous oxide anaesthesia and premedication with belladonna and an opiate. Also, the results of investigations in man of the intravenous administration of amide local anaesthetic agents, at rates proportional to the concentrations commonly used in regional anaesthesia, indicate that both heart rate and blood pressure are frequently elevated (Foldes et al 1965, Englesson et al 1962, De Jong and Walts 1966).

As opposed to the action of adrenaline which is directly on the heart and blood vessels, the stimulatory cardiovascular effects of local anaesthetic drugs are centrally mediated. Nevertheless reactions have been reported in which the possibility exists that direct depressant toxic action of a concentrated dose of local anaesthetic agent on the myocardium was responsible (Moore 1955). Lignocaine, in common with other local anaesthetics depresses impulse production and conduction in the heart when given intravenously in sufficient doses (Wiedling 1964). Such a situation can occur following rapid intravenous injection in dentistry. As contemporary local anaesthetic practice embraces the use of potent anaesthetic agents in concentrations of 3 percent and 4 percent without the benefit of a sympathomimetic vasoconstrictor, the direct toxic effect of local anaesthetic agents on the heart and peripheral circulation should be recognised (Gordh 1963,

Hiatt 1961, Le Chat and Deleau 1961, Moore and Bridenbaugh 1961).

All drugs have a principal therapeutic action for which they are used and, in addition, subsidiary actions which are often undesirable complications of their intended pharmacological effect (Dille 1963). The classification of a drug's action as principal or subsidiary, depends on the purpose for which it is used. For example, the principal action of adrenaline used in dental local anaesthesia is vasoconstriction; systemic response is an undesirable side effect. If however, the same drug is used intramuscularly in the emergency treatment of anaphylactoid reaction, the principal action intended is systemic and vasoconstriction is the undesirable side effect (Sara 1963).

Vasoconstrictors are as complex in their pharmacology as any drugs in use today (Monheim 1961). On the other hand, the characteristic pharmacological action of local anaesthetic agents is the same for every part of the nervous system, and in all organs in which conduction or transmission of nerve impulses occurs (Astrom 1965, Goodman and Gilman 1966). Local anaesthetic drugs interfere with a process which in the ionic theory of nervous activity (Wood-Smith 1963), is fundamental to the generation of nerve action potential. It has been suggested that they act upon the lipid layer that constitutes

the nerve cell membrane, thereby preventing the large transient increase in its permeability to sodium and potassium ions which precedes the generation of each nerve impulse (Goodman and Gilman 1966, Aström 1965).

Although all local anaesthetics stimulate the central nervous system, with both the synthetic anilide and ester type local anaesthetics the initial stimulatory phase may be slight and overlooked so that there appears to be primary depression (Sadove et al 1952).

It has been suggested that their apparent stimulatory and subsequent cerebral depressant properties are both produced by selective depression of inhibitory neuronal activity (Goodman and Gilman 1966). However, with the exception of the unique cerebral stimulatory action of the natural alkaloid cocaine; anilides have a stronger convulsive effect than esters (Steinhaus 1962, Foldes et al 1960, Foldes et al 1965).

Because of their general depressant effect on nervous tissue, the principal action of local anaesthetics used in dentistry is to block the conduction of afferent nerve impulses. However, at the same time efferent impulses which regulate local vascular tone via the perivascular sympathetic plexus, are also blocked and vasodilatation results (Matthews et al 1959, Bishop et al 1961). This is an undesirable side

effect of all synthetic local anaesthetics which is, nevertheless, caused by the same drug action as the principal effect. Only the site of drug action is different in this instance.

Whether local anaesthetic preparations are administered topically or parenterally, local anaesthesia is not possible without systemic absorption of drugs, since entry into the blood stream is a prerequisite to their detoxification (Steinhaus 1962).

Once in the blood stream the local anaesthetic is circulated and reaches the heart, the cerebral cortex and the vital medullary centres of respiration and circulation. The plasma level of drug attained determines the toxic effect produced except in allergic response. The latter reaction results from the use of minute quantities of drug in previously sensitized individuals (Mitchell 1953, Tillman 1958, Moore 1955, Di Giovanni 1963, Waldman 1967, Holti and Hood 1965, Criepe 1953, Noble and Pierce 1961, Sweets 1963).

Among the vasoconstrictor agents used in dental local anaesthesia, there is a direct relation between therapeutic efficiency and systemic toxicity (Goodman and Gilman 1966, Dobbs and Kader 1950, Glover 1954, Dille 1963). Fortunately local anaesthetic agents do not exhibit this characteristic to the same degree and the most potent is

not necessarily the most toxic (Foldes et al 1960, Foldes et al 1965, Wiedling 1960, Luduena and Hoppe 1956). However, on rapid intravenous administration there is a close correlation between clinical potency and toxicity (Foldes et al 1965).

The principal therapeutic effect of sympathomimetic agents used in dental local anaesthetic solutions, is their local action of vasoconstriction. When so used, their natural potential to evoke central nervous or cardiovascular response is an undesirable side effect. In order to produce its "chemical tourniquet" effect and thereby regulate systemic absorption of the local anaesthetic solution, the vasoconstrictor component must first overcome the vasodilatory action of the local anaesthetic drug. As metabolism of vasoconstrictors commences in the tissues and is continued in the blood stream and liver following systemic absorption, the latter process should be delayed to minimise toxicity. Rapid absorption of vasoconstrictor into the general circulation not only defeats its therapeutic purpose but also increases the blood level of drug. This should be avoided therefore by injecting slowly and extravascularly.

It can be readily appreciated that, since both local anaesthetic and vasoconstrictor components are eventually absorbed into the blood stream, it is not possible to completely separate their principal therapeutic effects

from their undesirable systemic effects (Dille 1963). Nevertheless, apart from the comparatively rare occurrence of allergy, manifestations of systemic toxicity will only supervene when a toxic blood level of either drug perfuses receptor sites in the central nervous and cardiovascular systems. When small quantities of concentrated local anaesthetic preparations are used, as is most often the case in dental practice, toxic blood level of drug is rarely attained unless as a result of inadvertant rapid intravenous injection.

2. (A) TOXIC BLOOD LEVEL OF DRUG.

Toxic blood level of drug may be either (a) absolute or (b) relative (Moore 1955).

(a) Absolute toxic blood level of drug.

This occurs when each ml. of the circulating blood volume contains an equilibrium concentration of that drug which is sufficient to produce symptoms of intoxication. With lignocaine this corresponds to a blood level of 10 $\mu\text{g/ml}$ (Foldes et al 1960, Matthes and Schabert 1966). Obviously, the mass of drug which eventually enters the general circulation depends upon the mass administered, excluding that proportion of vasoconstrictor drug (Glover 1954) and the small quantities of some hydrolyzable (ester type) local anaesthetic agents detoxified in the tissues (Glover 1963, Smith and Cimasoni 1967).

In addition, the rate at which the drug is absorbed into the blood stream also plays an important part in the attainment of toxic blood level. This is because, once in the blood stream, a number of mechanisms such as redistribution, detoxification and elimination, operate to reduce the plasma concentration of drug. More specifically these factors are:

(i) Binding of free local anaesthetic with plasma proteins or erythrocytes (Eriksson et al 1966, Englesson et al 1962). In this regard anilide type local anaesthetics are bound more strongly by human albumin than esters (Myers 1967).

(ii) Peripheral uptake

(y) by "acceptor" tissues in which no effect is produced (Eriksson et al 1966, Englesson et al 1962, Luduena and Hoppe 1956, Foldes et al 1960).

(z) by "receptor" tissues which, depending on the concentration attained, and individual tolerance, may produce signs of systemic toxicity (Paton 1966, Sara 1967, Foldes et al 1965).

(iii) detoxification

(y) in the blood stream. For example, ester type local anaesthetics (Foldes and McNall 1961) and sympathomimetic agents (Lawrence et al 1966, Goodman and Gilman 1966) are metabolized in the circulation.

(z) in the liver which is responsible for detoxifying all anilide local anaesthetic agents and a large proportion of the vasoconstrictor component. Esters are also metabolized in the liver (Astrom 1965, Lawrence et al 1966, Foster 1966).

Except after rapid intravenous administration, the toxicity of the local anaesthetic component depends primarily on its rate of enzymatic detoxification (Foldes et al 1965, Foldes 1966, Foldes et al 1960).

(iv) renal excretion (Eriksson et al 1966, Beckett et al 1965).

When the rate of entry exceeds the rate at which a drug is removed from the blood stream, the plasma concentration rises. In the dental use of local anaesthetics, not all aspects of their metabolism are equally important. Nevertheless they should be mentioned since the clinical evaluation of new drugs is frequently based on these characteristics. For example, the rapid enzymatic hydrolysis of 2-chloroprocaine (Foldes et al 1960), the rapid metabolism (Astrom 1965) and peripheral uptake of prilocaine (Eriksson 1966), the slower detoxification and cumulative effect associated with repeated administration of lignocaine and mepivacaine (Truant and Wiedling 1959, Foldes et al 1965, Astrom and Persson 1961, Gruber 1962, Knox and North 1961).

However, at dental dosages, rate of entry of local anaesthetic drugs into the bloodstream is the important factor

influencing systemic toxicity. Therefore it will receive special consideration in this paper.

So far, toxic blood level has been presented as a generalized circulatory state resulting from the absorption of relatively large amounts of drug into the circulating blood volume. However, it is also possible for a state of localized toxic blood level of drug to exist temporarily, following rapid intravenous injection. When this occurs, the whole dose of drug is initially contained in that volume of blood which passed the site of venepuncture during infusion. The more rapidly the injection is made, the more concentrated the "slug" of local anaesthetic solution becomes (Crawford 1966, Paton 1960, Sara 1967). The intermittent systemic effect of this "slug" of local anaesthetic, as it circulates past peripheral receptor sites, for example in the aortic arch and the carotid sinus, has been observed to coincide with the circulation time; two or three recirculations being made before dilution reduces its effect (Light 1965, Crawford 1966, Paton 1960).

In this case, it is not the mass of drug administered but its rate of entry into the blood stream which determines the systemic effect produced.

Although the aspiration test prior to injection has not been generally adopted as a safeguard against intravascular injection (Bell 1967, Glover 1967, Schiano and Strambi 1964),

low dosage is frequently cited as the basic safety factor in the dental use of local anaesthetics (Dick 1953, Everett 1949, Haywood 1961). The larger quantities of drug used in some medical analgesic techniques, sometimes in excess of the normal listings of safe dosages (Steinhaus 1962), are also cited as further evidence of the safety of the amounts used in dentistry (Everett 1949, Sachs 1949).

However, there are considerable differences in the amounts of local anaesthetic used by different clinicians for similar dental procedures (Sara 1967, Goldman and Gray 1963), and often more drug is given than is actually required (Broadbent 1957, Mumford and Geddes 1959, Cowan 1959). The latter tendency coupled with the availability of local anaesthetic solutions which are not only more concentrated, but also lack a vasoconstrictor component, reduces this margin of safety based on dosage (Glover 1968, Weil 1961, Lutzki 1964).

Dosage must also take into consideration the site of injection as an influence on rate of absorption, particularly in regions of high capillary vascularity. (Matthes and Schabert 1966, Moore 1955, Anon 1952). Although this aspect of the dental use of local anaesthetics has not been thoroughly investigated, it is known that the rate of absorption is governed by the amount of blood flow through the capillaries at the injection site (Scott 1964,

Abrahamson 1962). Because of the extensive capillary network in the oral submucosa, absorption of drugs from this region is much faster than from subcutaneous tissues for example (Matthes and Schabert 1966, McCarthy 1957). Even topical anaesthetics applied to the intact pharyngeal mucosa, are rapidly absorbed producing blood levels similar to, though less than, those following rapid intravenous injection (Adriani and Campbell 1956, Adriani and Zepernick 1964).

The Scandinavian Pharmacopoeia Council (1957) suggests 200 mg as the maximum dosage for plain lignocaine and 300 mg with adrenaline incorporated. Goodman and Gilman (1966) list 500 mg as the maximum dosage of lignocaine, when used extravascularly, and with a vasoconstrictor to delay absorption. Even higher figures than these are quoted as being within safety limits (British Medical Journal 1952 p. 211). As a 2 percent solution of lignocaine contains 20 mg per ml, at least 25 ml of this solution can be administered before reaching the suggested maximum dosage of 500 mg. However, it is impossible to designate limits of dosage of local anaesthetics, because they vary from individual to individual and even in the same individual at different times (Campbell and Adriani 1958).

The New York Heart Association (1955) recommends .2 mg of adrenaline as a safe total dose, per appointment, even for patients with cardiovascular disease, provided the

drug is deposited extravascularly. A 1:100,000 solution of adrenaline contains .01 mg per ml and so 20 ml of this preparation contain the suggested maximum dosage. Total dosage of either local anaesthetic or vasoconstrictor must of course, take into consideration the factor of time because of rapid detoxification (Wallace et al 1956) and site of injection as an influence on rate of absorption (Dhuner et al 1965, Dhuner and Lewis 1966, Scott 1964).

The maximum volumes and corresponding dosages of some contemporary local anaesthetic solutions for administration to adults, are presented in Table I. (Scandinavian Pharmacopoeia Council 1957, P.P. Guide 1968, Glover 1968). It will be noted that the margin of safety based on dosage is markedly reduced when local anaesthetic agents are used in higher concentrations without a vasoconstrictor to delay absorption. Furthermore, Epstein and Chilton (1959), in testing local anaesthetic preparations of different concentrations, observed that all the solutions were actually stronger than specified.

TABLE I.

Maximum volumes of commonly used local anaesthetic solutions with corresponding dosages of the principal component drugs.

Local anaesthetic solution	Maximum dose by volume	Dosage by weight of local anaesthetic agent	Dosage by weight of adrenaline
Lignocaine HCL 2 per-cent with adrenaline 1:100,000.	20 ml	400 mg	.2 mg (max. dose)
Prilocaine HCL 4 per-cent	9 ml	360 mg (max. dose)	-
Prilocaine HCL 3 per-cent with adrenaline 1:300,000	20 ml	600 mg (max. dose)	.06 mg
Mepivacaine HCL 3 per-cent	7 ml	210 mg (max. dose)	-

The maximum recommended doses of these local anaesthetic agents for administration to children (6-10 years) is approximately one third the recommended adult dosage (Ejorn 1966).

Acute toxic reaction has occurred following the administration of much less than the suggested maximum dosages of either the local anaesthetic or vasoconstrictor component, in patients exhibiting hypersensitivity or allergy to these agents (Wigand 1958, Waldman 1967, Di Giovanni 1963, Tillman 1958, Mercurio 1967).

(b) Relative toxic blood level of drug.

Hypersensitivity to a particular drug can be expected in a small percentage of any given group or population (Ship 1960, Dille 1963). Where hypersensitivity to either of the principal component drugs of local anaesthetic solutions exists, dosages well within the recommended limits of safety amount to a relative overdose and produce similar systemic manifestations to those which follow absolute overdosage in a normal patient (Graubard et al 1947, Knox and North 1961, Anon 1952). Moore (1955) uses the term "hyperegic" to describe this increased susceptibility to normal doses of drug and to distinguish it from "allergy" wherein the pattern of the response is changed and dosage is not a contributing factor.

Toxic blood level of drug for a hypersensitive (or hyperegic) patient is a much lower blood concentration than for a normal individual and therefore is referred to as a relative toxic blood level of drug.

2B. FACTORS INFLUENCING THE ATTAINMENT OF TOXIC
BLOOD LEVEL OF LOCAL ANAESTHETIC AND
VASOCONSTRICTOR DRUGS IN DENTISTRY.

- a. Rapid absorption.
- b. Hypersensitivity.
- c. Allergy.

a. Rapid absorption.

With the added safeguard of vasoconstriction, the quantity of local anaesthetic solution used in dentistry is rarely sufficient to produce toxic blood level of drug unless one of the following factors influences the rate at which it enters the blood stream.

(i) The vascularity of the injection site (Bjorn 1966, Gordh 1963, Lutzki 1964, Mercurio 1967, Luduena 1957). Local anaesthetics are absorbed rapidly from regions of increased blood supply as, for example, may be associated with inflammatory processes. Similarly, absorption from red bone marrow following intraosseous administration is comparable to direct intravenous injection. (Astrom and Persson 1961, Coventry 1957, Gogerty et al 1957).

(ii) An increased absorptive area produced by factors influencing the spread of local anaesthetic solutions. The irrational combination of spreading agents such as the enzyme hyaluronidase with vasoconstrictors

in dental local anaesthetics, facilitates rapid absorption (Dille 1963, Looby and Kirby 1949). A larger absorptive area is created also, when an unnecessarily large number of puncture points are made (Everett 1949).

(iii) Pressure developed within the tissues by the volume of local anaesthetic deposited. The resultant pressure is influenced mainly by the rate at which the solution is deposited and the type of tissue into which the injection is made. Pressure may also be developed by massaging the injection site (Epstein 1958, Shotwell 1948, Holroyd et al 1960, Orinjer 1949).

(iv) Intravascular injection (Adriani 1960).

(b) Hypersensitivity.

(i) Hypersensitivity to local anaesthetic drugs.

The severity of reaction due to a toxic overdose of local anaesthetic agent is a function of the blood level of drug attained relative to the particular individual's tolerance for that drug (Toogood 1960). Although patient hypersensitivity to synthetic local anaesthetic agents is an infrequent condition, a history of previous local anaesthetic experience should always be obtained before injecting. Where there is no previous history of local anaesthesia, extra caution is indicated, particularly in patients who, because of their small body size, have a

smaller circulating blood volume (Scott 1964, Steinhaus 1962, Sadove 1952, Toogood 1960, Ningham and Malherbe 1958).

Physical status plays an important role in hypersensitivity. Patients who are aged, asthmatic, shocked, undernourished or exhausted, tolerate less local anaesthetic drug than those of good physical condition (Walters 1950, Moore and Green 1957, Sadove 1952, Steinhaus 1962). Vitamin C deficiency, presumably because of its associated increased capillary permeability, is cited by Moore (1955) as a cause of increased susceptibility to local anaesthetic agents.

In cardiac disability the sensitivity to local anaesthetics may be increased and, as the heart is the first organ reached following intravascular injection in dentistry, preliminary aspiration is mandatory for patients with cardiovascular disease (Steinhaus 1952).

Moore (1955) doubts the existence of a correlation between temperature changes and patient susceptibility to drugs as reported by James (1955). Although plasma level is the main factor governing the resultant systemic toxicity of local anaesthetic agents, individual variation also is important especially with regard to uptake by the central nervous system (Scott 1964). Christensen (1967) draws attention to the hypersensitivity of epileptics to the

cortical stimulatory effect of local anaesthetic agents and recommends barbiturate premedication of sufficient duration to cover the period required for local anaesthetic detoxification. It has been demonstrated that intravenous barbiturates cause functional decerebration at the level of the pons, thereby obstructing impulses from the cortex and preventing the appearance of convulsions (Gordh 1952). An unusual condition which may cause hypersensitivity to ester type local anaesthetics is cholinesterase anenzymia in which there is an hereditary absence of the necessary detoxifying enzyme systems. Liver disease, toxic goitre and inadequate nutrition are also factors which lower cholinesterase activity (Adriani 1960). Myasthenic patients also often respond abnormally to drugs, although this is not an hereditary disease (Kalow 1963, Wood-Smith and Stewart 1962).

(ii) Hypersensitivity to Vasoconstrictor drugs.

Although the strong stimulatory effect of sympathomimetic vasoconstrictor agents on the cardiovascular system is well known, opinions differ regarding their role in systemic reactions of a cerebral cortical stimulatory type following dental local anaesthesia (Wallace et al 1956, Cheraskin and Prasertsuntarasai 1957, 1958, 1959, Tainter, Thronndson and Moose 1938).

Toogood (1960) notes that submucosal injection of .08 mg of adrenaline may produce noticeable central nervous system response. Gordh (1963) lists 1 mg and .1 mg as the maximum subcutaneous and intravenous dosages of adrenaline respectively and further suggests that the dose for submucosal injection more closely approximates the intravenous figure. Although these figures indicate a reasonable margin of safety in the dental use of vasoconstrictors, when deposited extravascularly, a majority of practitioners favour the clinical impression that increasing the adrenaline concentration increases the incidence of undesirable side reactions (Kutscher and Mercadante 1958, Epstein 1958, Ehrlich 1958).

There are several possible explanations of this apparently exaggerated response to therapeutic doses of vasoconstrictor.

(w) Although, according to Douglas (1965), adrenaline sensitivity is virtually unknown, it seems possible that some patients are truly hypersensitive to this drug (Wallace et al 1956).

(x) In other patients relatively large amounts of endogenous adrenaline are secreted into the general circulation from the adrenal medulla as a result of the psychological and mechanical stimuli associated with most dental procedures (Dick 1953, McCarthy 1957, Cheraskin 1958 A, Glover 1954).

The stress of anticipated oral surgical procedures has been shown to markedly increase adrenal secretion (Shannon et al 1961 A, Shannon et al 1961 B). When signs of toxicity follow the absorption of small amounts of adrenaline, it is likely that the effects of the small increase in circulatory exogenous drug are superimposed on pre-existing endogenous effects.

(y) The administration of adrenaline concurrently with some medical drug regimens may influence not only the degree, but also the direction of the adrenaline response. Certain major tranquillizer drugs (e.g. those classified as phenothiazines), which are sometimes prescribed in anti-hypertensive therapy (American Medical Assoc. 1966), may unexpectedly reverse the action of adrenaline and produce profound hypotension (Jolly 1967). The same drugs also potentiate the action of central nervous system depressants such as general anaesthetics, hypnotics, and local anaesthetics given intravenously.

Sympathomimetic amines in the form of metered aerosol sprays or oral preparations are sometimes used as broncho-dilators in the treatment of asthma. When these preparations have been taken less than four hours before dental treatment, the use of a local anaesthetic with a sympathomimetic component is contraindicated on the basis of summation of effect (Jolly 1967).

The possibility of potentiation of the response to dentally administered adrenaline, noradrenaline or other adrenergic drugs in patients taking monoamine oxidase inhibitor drugs is currently receiving consideration (Rand 1966, Burch 1966, Jolly 1967, Ellis 1967, Trinker 1967, Glover 1967, Waterson 1967, Glover 1968, Christensen 1967). Exogenous noradrenaline is metabolized mainly by catechol-O-methyl transferase and not by monoamine oxidase (Ellis et al 1967). When injected it may act on receptors or be taken up by the adrenergic axon and stored (Rand 1966). When tissue stores of noradrenaline are saturated, e.g. by MAOI drugs, uptake of noradrenaline is inhibited and either injected or released noradrenaline is affected by this alone (Ellis et al 1967). On present indications, caution should be exercised in the concurrent dental usage of sympathomimetic amines and MAOI drugs. The effect of MAOI drugs may persist for several weeks following their withdrawal and the need for adequate patient evaluation through a complete medical history is noted. Adverse reactions following the concurrent administration of sympathomimetic drugs include hypertension, severe headache, and even subarachnoid haemorrhage (Sara 1967).

Local anaesthetic preparations containing adrenaline are sometimes used to supplement light general anaesthesia

and also in surgery, to produce local vasoconstriction (Kennedy 1965). Interaction between adrenaline and cyclopropane or halogenated hydrocarbon general anaesthetic agents, with the production of ventricular fibrillation is a danger associated with this type of concurrent therapy (Holroyd et al 1960, Goodman and Gilman 1966, Waterson 1967, Katz 1965).

(2) The normal cardiovascular response to adrenaline is often magnified and sometimes altered in the presence of certain pathological conditions such as hypertension and hyperthyroidism. The former condition which is frequently encountered, is characterized by a general haemodynamic instability (Jensen 1930, Pickering and Kissin 1936, Goodman and Gilman 1966, Burch 1966, Fatheree and Mines 1938, Salman and Schwartz 1955).

Fisher (1965) considers that the use of adrenaline is marginally cardiovascularly compensated individuals, and in hypertensives is open to question. Certainly in hypertensive vascular disease or myocarditis, changes in the circulation should be minimized and since hypertension sensitizes the myocardium to adrenaline induced arrhythmias (Goodman and Gilman 1966), the use of adrenaline is contraindicated in uncontrolled hypertensive patients (Sara 1963). Goodman and Gilman (1966) emphasize the need for care in administering adrenaline to patients with long standing

bronchial asthma and a significant degree of emphysema who have reached the age where degenerative heart disease is prevalent.

Both hypertensive and hyperthyroid individuals are particularly susceptible to untoward pressor responses to adrenaline (McCarthy 1957). However, as these patients react more favourably to local, than to general anaesthesia (Shotwell 1948), the vasoconstrictor component may be modified either in type or concentration or even omitted entirely for this purpose. Mepivacaine is the first local anaesthetic agent to produce satisfactory anaesthesia for general dental procedures without the benefit of a vasoconstrictor (Sara 1967, Adriani 1960, Jolly 1967, Dille 1963, Criepp 1953, Foldes and McNall 1961). However, pain initiates the release of much larger amounts of endogenous adrenaline into the blood stream than result from the absorption of small dental doses of adrenaline; provided, of course, it is deposited slowly extravascularly, thereby limiting its own absorption (Bishop et al 1961, Glover 1954). Since the adrenaline component of local anaesthetic preparations enhances their anaesthetic potency, it has been claimed that its presence is rather more desirable than undesirable for use on so called "poor risk" patients (Dick 1953, Wallace et al 1956, Vernale 1960, McCarthy 1957, Harris 1960). Premedication of these patients has been demonstrated to be

of greater significance in reducing cardiovascular deflections, than eliminating the vasoconstrictor component of subsequently administered local anaesthetic solutions (Cheraskin and Prasertsuntarasai 1957, 1958 A, 1958 B, 1959). Where doubt exists as to whether or not a vasoconstrictor should be used, 3 percent mepivacaine, carefully administered, is a satisfactory drug for both infiltration and regional procedures (Sadove and Kolodny 1961).

The dental use of adrenaline in controlled diabetics is uncomplicated provided the patient adheres to his normal dietary routine and the drug is deposited extravascularly (Jolly 1967).

In Parkinson's disease, the characteristic rigidity and tremor are accentuated by adrenaline (Goodman and Gilman 1966, Foster 1966).

Adrenaline is definitely contraindicated in the following pathological conditions in this order of urgency (Sara 1967).

1. Thyrotoxicosis where thyroxin secreted from an overactive thyroid stimulates the adrenal gland. In these patients the metabolic rate is extreme and their prognosis is poor. Adrenaline may produce hypertension and cerebral vascular accident or cardiac failure.
2. Recent coronary occlusion; within the preceding four to six weeks. It is impossible to predict that these patients

are safe from a further occlusion or extension of the existing lesion. The danger in using adrenaline lies in the production of arrhythmia or possibly ventricular fibrillation.

3. Uncontrolled hypertensive subjects.

4. Conditions in treatment of which MAOI drugs are administered (e.g. occasionally has been used in anti-hypertensive therapy).

(c) Allergy to local anaesthetic and vasoconstrictor drugs.

Whereas true allergy to vasoconstrictor drugs must be extremely rare (Moore 1955, Criepe 1953), local anaesthetic agents as a group, together with antibiotics and aspirin, are the principal allergenic drugs used in dental practice (Dille 1963). Although the tendency to produce allergic response is much less with the anilide type drugs than with derivatives of para-amino benzoic acid, occasional reports have appeared in the literature of severe systemic reactions attributed to anilide local anaesthetics, in which the possibility of sensitization appears likely (Criepe 1953, Sweets 1963, Holti and Hood 1965, Noble and Pierce 1961, Di Giovanni 1963, Gordh 1964, Tillman 1958, Waldman 1967, Toogood 1960, Mitchell 1953).

Allergic reactions differ from those due to hypersensitivity in three important respects.

(i) Sensitization from previous exposure to the particular drug or to a drug of similar molecular structure is a prerequisite to allergic response, and not to hypersensitivity (Maywood 1962, Mitchell 1953).

(ii) Whereas in hypersensitivity, smaller doses than expected amount to a relative overdose, only minute amounts of drug are required to produce allergic reaction.

(iii) Hypersensitivity is an exaggerated normal response. In allergy the pattern of reaction is altered. The signs and symptoms of an allergic systemic reaction reflect an attempt by the body to remove a noxious agent. Therefore, even though the allergy results in symptoms of severe illness, it is a purposeful reaction and one of protection (Moore 1955).

Di Giovanni (1963) cites the case reported by Morrisset (1957) of what was believed to be a fatal anaphylactic reaction to .8 ml of 2 percent lignocaine administered for routine dental local anaesthesia. Fortunately anaphylactoid and generalized allergic reactions are infrequent complications of local anaesthesia (Steinhaus 1962, Moore 1955, Sadove 1952). Steinhaus (1962) states that this type of reaction is even less likely in the absence of a history of long standing allergic pattern, while Sadove (1952), considers that an accompanying skin reaction is necessary before a disturbance can be classified "anaphylactic".

3. THE POTENTIAL SYSTEMIC TOXICITY OF LOCAL
ANAESTHETIC AND VASOCONSTRICTOR DRUGS
USED IN DENTISTRY.

Despite the fact that the head and neck comprise regions of extreme vascularity which must be injected with care (Moore 1955, Matthes and Schabert 1966), and higher concentrations of drugs are used than commonly employed in general surgery, dental local anaesthesia has an enviable record in terms of low incidence of serious and fatal complications (Dick 1953, Harris 1957, Hayward 1961, Cripp 1953). Yet, it is a matter of common experience that, where aspiration does not precede the injection of local anaesthetic preparations, intravascular injection is sometimes made and as a result, the patient experiences an abrupt response (Schiano and Strambi 1964, Tainter and Thronsdon 1938). Using accepted contemporary local anaesthetic preparations, dosages and techniques, reactions ranging in severity from pallor through the various intermediate degrees of subjective discomfort to syncope and convulsions, and even to lethal toxic and anaphylactic states, do occur (Shotwell 1948, Sadove 1952, Walters 1950, Harris 1957, Coventry 1957, Monheim 1957, Kutscher and Mercadante 1958, Haywood 1961, Dille 1963, Frye 1963, Black 1967, Douglas 1965, Holroyd et al 1960).

However, as most systemic disturbances associated with dental local anaesthesia are transient in nature, with spontaneous recovery, wide differences of opinion exist as to the importance of limiting the systemic toxicity of local anaesthetics and preserving homeostasis; in other words there is controversy over the importance of keeping local anaesthesia - local. When correctly administered, local anaesthetic preparations should evoke no systemic response whatsoever.

Before proceeding to a consideration of the pharmacological properties of local anaesthetic agents and vasoconstrictors which influence their systemic toxicity (see chapters IV and V), the systemic toxic potential of these agents as used in dentistry should first be established.

(a) The potential systemic toxicity of local anaesthetic drugs as used in dentistry.

Some observers have advocated the absolute safety of the dental use of local anaesthetic agents by citing the much larger dosages administered during intravenous analgesia and anaesthesia (Sachs 1949, Everett 1949, Dubin and Foner 1952). The two therapeutic uses of local anaesthetics hardly seem comparable. Quite apart from the aim that dental local anaesthesia should evoke no systemic response whatsoever, neither the rate at which inadvertant intravascular injection is made, nor the concentration of the drug is comparable with

that used in continuous intravenous infusion (Schiano and Strambi 1964, Harris 1960).

Steinhaus' (1962) opinion appears to have more practical significance. He considers that serious systemic effects would not occur in a healthy, average size patient from the intravenous injection of 100 mg of lignocaine, administered over a period of at least 2 minutes. This agrees with figures obtained by Foldes et al (1960) using human material. Intravenous infusion of lignocaine at a constant rate of .5 mg/Kg/min. resulted in the onset of symptoms of intoxication after 2.8 minutes. That is, after the administration of approximately 100 mg to a healthy, average size patient. Englesson et al (1962) reported that both lignocaine and prilocaine produced subjective symptoms of toxicity, varying in severity, in all 20 volunteers who received intravenous infusion of 200 mg of equipotent solutions of these drugs over a period of 2 minutes 20 seconds.

Although the plasma concentration of lignocaine which produces evidence of systemic toxicity is 10 µg/ml (Matthes and Schabert 1966), rapid intravenous injection produces a concentrated depot of drug which may circulate several times before dilution reduces its systemic effect (Paton 1960, Light 1965). The "slug" of local anaesthetic which results from the rapid intravenous injection of half

of one cartridge of either 2 percent lignocaine (approx. 20 mg) or 3 percent mepivacaine (approx. 30 mg) of similar acute toxicities (Knox and North 1961, Gordon et al 1960, Foldes et al 1965); or even 4 percent prilocaine (approx. 40 mg), despite its lower acute toxicity when deposited extravascularly (Goldman and Gray 1963), is sufficiently concentrated to affect receptor sites in the central nervous and cardiovascular systems.

(b) The potential systemic toxicity of vasoconstrictor drugs as used in dentistry.

The maximum dosage of .2 mg adrenaline per session (20 ml of 1:100,000 solution) suggested by the New York Heart Association (1955) for patients with cardiovascular disease, indicates confidence in its normal dental usage, provided the drug is deposited extravascularly. As previously noted, the clinical impression is that the adrenaline component is often responsible for signs of stimulation of the central nervous system following submucosal injection (Holroyd et al 1960, Kutscher and Mercadante 1958, Tainter, Thronsdon and Moose 1938, Moore 1955, Costich 1956, Fisher 1965). Toogood (1960) considers that .08 mg (8 ml of 1:100,000 solution) may produce noticeable systemic manifestations in the cardiovascular system and, to a lesser extent in the central nervous system soon after submucosal injection.

With intravenous injection however, as little as .005 mg adrenaline (.5 ml of 1:100,000 solution) produces abrupt systemic cardiovascular response lasting only several minutes while metabolism by catechol-O-methyl transferase rapidly eliminates the drug from the blood stream (Pickering and Kissin 1936, Glover 1954).

Tainter and Thronsdon (1938) point out that the distress a patient feels is much more apt to be caused by sudden changes in blood pressure than by those developing gradually. From experiments on cat, they have demonstrated the exaggerated cardiovascular and central nervous disturbances which follow intravenous injection of relatively small doses of adrenergic drugs as compared with the systemic response associated with larger doses administered either intramuscularly or subcutaneously. This effect has special significance in cardio-vascular disease where patients exhibit varying degrees of haemodynamic instability (Jensen 1930, Pickering and Kissin 1936, Cheraskin and Prasertsuntarasai 1959, Goodman and Gilman 1966).

Therefore, whether reaction follows local anaesthesia or not, the potential to cause systemic disturbance is latent in local anaesthetic preparations as used in dentistry (Monheim 1965). Furthermore, this toxic potential is most likely to be manifested as a result of:

- (a) Hypersusceptibility which may be either
 - (i) true hypersensitivity to local anaesthetic agents.
 - (ii) increased sensitivity to injected adrenaline in psychoneurotic individuals due to a pre-existing autogenous hyperadrenalinaemia (Mumford and Geddes 1959, Goodman and Gilman 1966, Moore 1955, Monheim 1965).
 - (iii) allergy to local anaesthetic agents.
- (b) The presence of pathological conditions such as hypertension, hyperthyroidism or epilepsy which may cause an exaggerated response to normal doses of vasoconstrictor and local anaesthetic drugs (Steinhaus 1962).
- (c) Incompatibility between local anaesthetic vasoconstrictor components and some medical drug regimens when used in concurrent therapy.
- (d) Rapid intravenous injection of local anaesthetic preparations.

4. THE VALUE OF PRELIMINARY ASPIRATION AS A MEANS OF AVOIDING INTRAVASCULAR INJECTION AND LIMITING LOCAL ANAESTHETIC SYSTEMIC TOXICITY.

It is claimed that rapid intravenous injection causes sixteen times the systemic effect of the same amount of drug deposited subcutaneously (Nevin and Puterbaugh 1946, Shotwell

1948), and is the principal cause of systemic toxic reaction to dental local anaesthetics (Monheim 1965).

Although, as a result of the high incidence of vascular injury associated with some dental nerve blocking techniques (Goldman and Gray 1963, Myers 1967, Black 1967, Harris 1957, Nevin and Puterbaugh 1938, Sicher 1965, Schiano and Strambi 1964, Shira 1962, Forrest 1959), preliminary aspiration as a safeguard has been widely advocated (Frye 1963, Harris 1957, Newman 1966, Schiano and Strambi 1964, Wallace et al 1956, Helmore 1964, Douglas 1965, Jolly 1967, The Working Conference of the American Dental Association and the American Heart Association 1964, Dille 1963, The Council of Dental Therapeutics of the American Dental Association), this precautionary measure is observed by only a small percentage of the profession (Black 1967, Glover 1967, Epstein 1958).

A recent survey of dental practices in the State of Texas, U.S.A., provides an example of the profession's failure to appreciate the significance of aspiration prior to injection as a means of limiting local anaesthetic toxicity. Of the dentists, in all types of practice, who replied to the survey, 74.8 percent had oxygen available for the treatment of emergencies yet only 28.7 percent used aspirating syringes (Bell 1967). The following suggestions are offered as possible explanations of the indifferent

attitude which exists towards aspiration.

(a) The small quantities of drugs used.

As already indicated, small dosage of either local anaesthetic or vasoconstrictor drugs offers no safeguard against systemic toxic reaction if administered rapidly intravenously. The manner in which small amounts of either of these principal components of local anaesthetic preparations evoke symptoms of systemic toxicity following intravenous injection will be considered later (see chapters IV and V).

(b) The availability of efficient aspirating cartridge syringes.

The majority of the dental profession use cartridge syringes (Kennedy 1965). Only in recent years has the design of these instruments reached a stage where efficient aspiration is possible, thereby removing a serious obstacle to the general adoption of aspiration as a routine safety measure in local anaesthesia (Kemp and Jolly 1962, Monheim 1965, Black 1967).

(c) Conflicting reports of the incidence of vascular injury associated with various dental nerve blocking procedures.

The results of these surveys indicate only the incidence of vascular injury for the various techniques investigated (Schiano and Strambi 1964, Frye 1963, Harris

1957, Goldman and Gray 1963, Shira 1962, Forrest 1959).

The actual position in which positive aspiration of blood was obtained is not mentioned. Nor is a description included of the technique by which the investigated nerve blocking injections were given. Therefore uncertainty exists as to whether or not the sites of the reported vascular injuries coincided with positions at which local anaesthetic would have been deposited had aspiration not been performed.

Furthermore, since variations in technique probably account for the observed differences in results, the method used for each injection should be clearly established before the investigation commences and adhered to throughout the aspiration survey if it is to provide data of clinical value.

(d) Apparent lack of correlation between cause and effect.

An apparent discrepancy exists between the reported incidence of vascular injury, particularly in block anaesthesia, and the associated incidence of (i) systemic toxic reaction and (ii) anaesthetic failure (Forrest 1959).

For example, the reported incidence of vascular injury with the mandibular block injection ranges from 3.6 percent (Harris 1957) to 12 percent (Shira 1962). There is little correlation between these figures and the observed incidence of the abovementioned complications (Weil 1962).

Nevertheless, Harris (1957) claims that the occurrence of both systemic disturbance and anaesthetic failure is reduced by preinjection aspiration. Goldman and Gray (1963) on the other hand, reported that aspiration prior to injection did not show any influence on the incidence of side reactions.

There are several aspects of this criticism of aspiration which should be mentioned.

(i) The aspiration surveys cited do not specifically indicate the incidence of intravenous injection, but merely the incidence of vascular injury. Therefore, it is wrong to attempt to correlate these figures with sequelae of intravenous injection.

(ii) If differences in local anaesthetic techniques are responsible for the observed differences in the results of aspiration surveys, then differences in technique may also influence the incidence of associated side effects and anaesthetic failures.

(e) Technical difficulties.

The suggestion has been made that the additional manipulation associated with the aspiration test is an "extra trouble" (Dick 1957), and may, itself, create a psychological disturbance in the patient (Mumford and Geddes 1959). These aspects were assessed throughout the aspiration survey which is reported in this paper (see chapter III). No basis has been found to justify these criticisms.

(f) The psychological element operative in dental local anaesthetic procedures.

It has been claimed that 90 percent of all reactions under dental local anaesthesia are of psychogenic origin (Tainter and Thronndson 1938).

However, it should be pointed out that there has been no extensive and careful study of the incidence and relative frequency of the various types of reaction following injection of local anaesthetics in dental practice (Teogood 1960). It is basically difficult to study the clinical problem of toxic reaction to drugs because

- (i) reactions are unexpected.
- (ii) the number of cases which can be observed is comparatively small.
- (iii) an awareness of the problem is probably the best preventive for these reactions and consequently material for observation is reduced (Steinhaus 1952, Tainter, Luduena and Hoppe 1953).

Therefore positive identification of the cause of the various minor systemic disturbances coincident with dental local anaesthesia is difficult. Yet, when aspiration is not attempted and it is possible therefore that intra-venous injection may have occurred, accompanying reactions are often arbitrarily classified "psychogenic", thereby precluding consideration of systemic toxic reaction to

local anaesthetic drugs as a contributory cause.

There is no doubt that the influence of psychological factors in systemic reactions following dental local anaesthesia does overshadow the role played by the local anaesthetic preparations themselves. Yet it would appear inadvisable, through inadvertant intravascular injection, to superimpose further inhibition or stimulation on a cardiovascular or central nervous system, which is already being stimulated or depressed by autonomic activity.

Reflex vagal interference or inhibition of the cardiovascular system is probably the commonest cause of fainting (Sharpey - Schafer 1956, Sara 1963, Mellusi 1967). Plain local anaesthetic agents given intravenously also produce (i) depression of the autonomic system or medullary vasomotor centre and, or (ii) direct depression of cardiac muscle (Goodman and Gilman 1966). A lowered threshold in the vagal reflex arc may produce syncope, even on mild stimulation (Mellusi 1967). Therefore, when concentrated local anaesthetic preparations containing no vasoconstrictor are injected without preliminary aspiration and a cardio-inhibitory type systemic reaction ensues, local anaesthetic systemic toxicity, psychological factors, or a combination of both must be considered as possible causes.

In psychoneurotic individuals and those who are unduly apprehensive of local anaesthetic procedures, large

quantities of endogenous adrenaline are liberated into the bloodstream from the adrenal medulla by sympathetic activity (Goodman and Gilman 1966, Glover 1954). With the patient seated in an upright position, a considerable portion of blood gravitates to the sympathetically dilated blood vessels in the musculature of the dependent limbs and as a result, cerebral anaemia and syncope may supervene (Sara 1963, Bourne 1957, Brierly 1966, Teogood 1960).

Rapid injection of even small amounts of adrenaline should naturally be avoided in such patients as it's vasodilatory effect in skeletal muscle dominates the circulatory pattern causing a drop in diastolic blood pressure (Ludena et al 1949).

Consequently, the association of a strong psychological element with many dental procedures emphasizes the need to avoid intravenous injection of local anaesthetic solutions and is an argument for, rather than against the adoption of aspiration as a routine preinjection procedure. As Helmore (1963) points out, most emergencies in dental practice arise from some type of local anaesthetic or associated surgical procedure. Consequently, routine evaluation of the patient's physical and emotional state should be made whenever procedures requiring penetration of tissues are contemplated.

- (g) The minor nature and infrequency of reactions associated with dental local anaesthesia.

Writing of the advisability of preliminary aspiration as a safeguard against intravascular injection, Harris (1957) warns that one of the most insidious dangers in therapeutics is the complacency which develops when undesirable reactions are infrequent. Although the incidence of fatality with dental local anaesthesia is extremely low (Harris 1957, Hayward 1961, Griep 1953, Seldin 1958), reports have appeared in the literature of reactions of varying severity to small amounts of local anaesthetic solution which, on rare occasions, have terminated fatally (Gordon 1963, Graubard 1947, Knox 1961, Mercurio 1967, Di Giovanni 1963, Wigand 1958, Anon 1962, James 1955, Noble and Pierce 1961, Sweets 1963, Holti and Hood 1965). To say the least, a patient's confidence can be easily destroyed by careless local anaesthetic technique which produces even minor systemic disturbances. The converse is equally true and therefore every effort should be made to confine the effects of local anaesthetic preparations to the site of injection.

Syncope may be defined as a loss consciousness due to an acute decrease in cerebral blood flow (Sharpey-Schafer 1956). Although, when recovery is rapid, syncope is often regarded as a minor systemic disturbance, Sara (1963) emphasizes several important aspects associated with any reaction of this type.

- (i) To the patient, the reaction is not "minor".
- (ii) At the onset, minor collapse and collapse of a more serious nature may not be accurately distinguished (Sara 1963, Spiro 1966, Lundy 1939)
- (iii) Even syncope that commences as a minor event, may be the prelude to further difficulties. For example, in patients with advanced cardiovascular disease, the blood vessels of the heart and central nervous system may not reopen after the period of hypotension invariably associated with the faint (Sara 1963, Lundy 1939).
- (iv) In any unconscious patient, notwithstanding the cause of the unconsciousness, the incidence of respiratory difficulties is high, and if these are allowed to persist, then serious cerebral and cardiac sequelae can be expected (Sara 1963, Bourne 1957).

An appreciation of (a) the systemic toxic manifestations of the anaesthetic and vasoconstrictor components of dental local anaesthetic solutions and (b) the vital signs which accompany other systemic disturbances incidental to local anaesthetic procedures, is essential to satisfactory emergency treatment. These will be discussed in the chapters dealing with the pharmacology of local anaesthetic and vasoconstrictor drugs.

Though emergency treatment is essentially treatment of the vital signs presenting (Moore and Bridgenbaugh 1961), every effort should be made subsequently, to establish the cause of each systemic reaction following dental local anaesthesia. Satisfactory preventive and therapeutic measures can then be adopted for future local anaesthetic procedures (Steinhaus 1962).

From the foregoing review of factors associated with the production of systemic toxic reaction to dental local anaesthesia, it appears that prevention depends mainly upon

- (i) adequate pre-operative assessment of the patient's local anaesthetic status. This requires the taking of a relevant medical history for each patient and using this information, supplemented if necessary by medical opinion, to establish details of the correct local anaesthetic procedure for each operation (Schirger et al 1967, Morris 1967, Jolly 1967).
- (ii) The most significant preventive measure - the adoption of preliminary aspiration as a means of avoiding intravascular injection (Monheim 1965, Adriani 1960, Council of Dental Therapeutics 1961).

Because the present state of knowledge on the subject of aspiration prior to injection of dental local anaesthetics provides scope for further study, it was decided to pursue an investigation of some aspects of this problem.

5. A SUMMARY OF THE INVESTIGATIONS CARRIED OUT.

(a) Purpose of the investigations.

Of the local anaesthetic techniques routinely used in general dental practice (Kutscher and Mercadante 1958), viz mandibular block, greater palatine nerve injection, naso-palatine nerve injection and labial, buccal, palatal and lingual infiltration injections; the regions considered to be most productive of vascular injury are the pterygomandibular space and the hard palate (personal observation). Other less frequently used regional techniques such as the spheno-palatine, infra-orbital, mental and posterior superior alveolar nerve block injections also yield a relatively high incidence of vascular injury (Fryc 1963, Forrest 1959, Schiano and Strambi 1964). These latter techniques have in common the occasional complication of development of a large deep-seated haematoma (Sicher 1965, Monheim 1965, Nevin 1952). For this reason, when simpler alternative infiltration techniques will suffice, there is a tendency to avoid their use in general dental practice (Lindsay 1948).

In addition to the clinical impression that the pterygomandibular space and the hard palate are the most frequent sites of vascular injury associated with local anaesthesia in general dental practice, I am also of the opinion that such injury most often results from puncture of a vessel which has been caught between the needle point and the underlying bone.

(b) Method of investigation.

So as to test the feasibility of the latter suggestion and also to examine factors which may influence the results of aspiration surveys, dissections and histological examinations of the pterygomandibular space and hard palate were first carried out. As the results of these investigations were encouraging, it was decided to initiate an aspiration survey on patients receiving local anaesthetic injections in private dental practice to establish the validity of these clinical impressions.

At the same time, the opportunity would be taken to ascertain the incidence of vascular injury at certain positions in the hard palate and within the pterygomandibular space, particularly at the lingual and inferior alveolar nerve injection sites. Previous investigations of this type have provided no details of the actual location of vascular injury and as previously mentioned, even the reported overall incidence of this complication in mandibular anaesthesia has varied considerably (Schiano

and Strambi 1964, Frye 1963, Harris 1957, Forrest 1959, Goldman and Gray 1963, Shira 1962). Consequently they leave the most pertinent question unanswered; if aspiration had not been attempted, would the figures given represent the incidence of intravascular injection? In other words, did the positive responses to aspiration occur at positions where local anaesthetic is deposited? The clinical value of these investigations has been limited by their failure to indicate

- (i) the significance of the aspiration test prior to injection as a means of limiting local anaesthetic toxicity.
- (ii) methods whereby the incidence of vascular injury may be reduced, and local anaesthetic technique improved.

It is intended that this investigation should accentuate the value of both (i) an injection technique based on anatomical principles, and (ii) applying the aspiration test prior to injection, as safeguards against intravenous injection in regions containing large blood vessels.

On establishing the technique to be used for each type of injection, and after consideration of factors influencing the results of aspiration surveys, a method of investigation involving a detailed aspiration survey was

devised and carried out on a large number of patients over a period of several years. The results of this survey are recorded in table form, and descriptions and illustrations of the dissections and histological examinations are included in the text.

(c) Outline of the main conclusions derived.

- (i) Of the commonly used dental local anaesthetic techniques, the sites found to be most productive of vascular injury were the pterygomandibular space and the hard palate.
- (ii) The likelihood of intravenous injection occurring at the lingual and inferior alveolar nerve injection sites, if aspiration is not performed, is recorded for a particular mandibular block technique.
- (iii) The manner in which most vascular injuries occur during mandibular block injection is established and evidence suggesting the likely cause of similar injury with the greater palatine nerve injection is presented.
- (iv) Attention is drawn to the significance in the inferior alveolar nerve injection, of withdrawing the needle 3 mm from contact with bone, as a means of disengaging blood vessels punctured against bone.

- (v) With the greater palatine nerve injection, recommendations are made which eliminate the incidence of serious vascular injury associated with this injection.

CHAPTER II.

DISSECTIONS AND HISTOLOGICAL EXAMINATIONS OF THE
PTERYGOMANDIBULAR SPACE AND HARD PALATE.

1. INTRODUCTION.
2. MATERIALS AND METHODS.
- 3A. DISSECTION OF THE PTERYGOMANDIBULAR SPACE.
B. DISCUSSION OF ANATOMICAL AND HISTOLOGICAL OBSERVATIONS.
- 4A. DISSECTION OF THE HARD PALATE.
B. DISCUSSION OF ANATOMICAL AND HISTOLOGICAL OBSERVATIONS.

DISSECTIONS AND HISTOLOGICAL EXAMINATIONS OF THE
PTERYGOMANDIBULAR SPACE AND HARD PALATE

1. INTRODUCTION.

The dissections described in this chapter were done with the purpose of observing the vasculature of both the pterygomandibular space and the hard palate. The relation of blood vessels to bone and to needle pathways used in regional anaesthesia was of particular interest.

For this reason it was decided to approach the pterygomandibular space from the pharyngeal aspect rather than follow the more usual lateral approach in which the relation of blood vessels to bone is lost with the removal of portion of the ascending ramus (Jamieson 1962).

It is interesting to note that the region known as the "pterygomandibular space" is not described as such in text books dealing with general anatomy, although descriptions of the intra-temporal fossa include details of this region (Cunningham 1953, Gray 1962, Jamieson 1962). It is primarily a region of dental interest and therefore well defined in text books describing oral anatomy (Sicher 1965, Nevin and Puterbaugh 1938). The pharyngeal approach, in dissecting this region, could also be described as a "dental" approach, as this is the direction from which access to the pterygomandibular space is obtained in mandibular block injection.

Since no details could be found in the literature of dissection of the pterygomandibular space from the pharyngeal aspect, notes were kept during the course of this dissection from which the following description was written.

2. MATERIALS AND METHODS.

Preparation of the material for dissection and histological examination.

The head was removed from a cadaver at the level of the sixth cervical vertebra and frozen overnight to facilitate cutting with a band saw through the mid-sagittal plane. The left half was then prepared for dissection of the pterygomandibular space and hard palate. In view of the forward projection of the vertebral bodies, access to the side wall of the pharynx and infratemporal region, in the divided head, is rendered difficult. It was therefore necessary to remove the anterior arch of atlas, odontoid process and body of axis, and the body of the third cervical vertebra by sawing through their respective transverse processes.

The superior and middle constrictor muscles could then be retracted and pinned with stilettes to permit better access to the side wall of the pharynx.

The tongue was also pinned in a fully protruded

position, thereby allowing a better view of both the lateral wall of the pharynx and the vestibule of the buccal cavity.

The specimen was then ready for dissection to proceed of the left pterygomandibular space and hard palate from a medial approach.

A palatal specimen for microscopic examination was obtained from the right half of the divided head by coronal section, 2-3 mm anterior to the greater palatine foramen, through the palatine and alveolar processes of the maxilla together with the overlying muco-periosteum.

In this way the anatomy of the dissected left palatal region was supplemented by histological examination of the corresponding region of the opposite side (Fig. 6).

A block of tissue containing the pterygomandibular space was removed from the infratemporal region of another cadaver by making the following saw cuts and incisions. Two saw cuts were made through the ramus in horizontal planes at levels immediately below (a) the mandibular notch and (b) the mandibular foramen. Another saw cut was made in a coronal plane passing through the temporal crest on the anteromedial aspect of the ramus. An incision in the coronal plane immediately behind the posterior border of the ramus completed the outline of the block of tissue.

The depth to which these cuts were made was such that a sagittal incision in that plane allowed removal of

a block of tissue which included, on its medial aspect, fibres of the medial pterygoid muscle. The soft tissues overlying the ramus were then resected and the remaining material processed so that horizontal sections could be made of the pterygomandibular space at approximately 120 micron intervals from the level of the maxillary vessels to the mandibular foramen. Both these and the palatal specimen were then processed for histological examination by staining with haematoxylin and eosin.

Figures 7 to 14 are photomicrographs of the serial sections of the pterygomandibular space at eight magnifications and Figure 6 shows the palatal specimen at fourteen magnifications. The post-mortem appearance of the blood vessels in their collapsed state is shown.

3A. DISSECTION OF THE PTERYGOMANDIBULAR SPACE.

The description which follows applies to one dissection only and is presented in a supplementary capacity to the literature on the subject which has been cited. Furthermore, the relations observed within the pterygomandibular space in this investigation were those existing when the mouth was almost closed and not fully opened as required for the inferior alveolar nerve block injection.

However, the inferior alveolar nerve and vessels are in closer relation to bone when the mouth is fully

opened than when closed (Sicher 1946). This should be borne in mind when viewing the illustrations of the dissection and the photomicrographs of the serial horizontal sections of the pterygomandibular space.

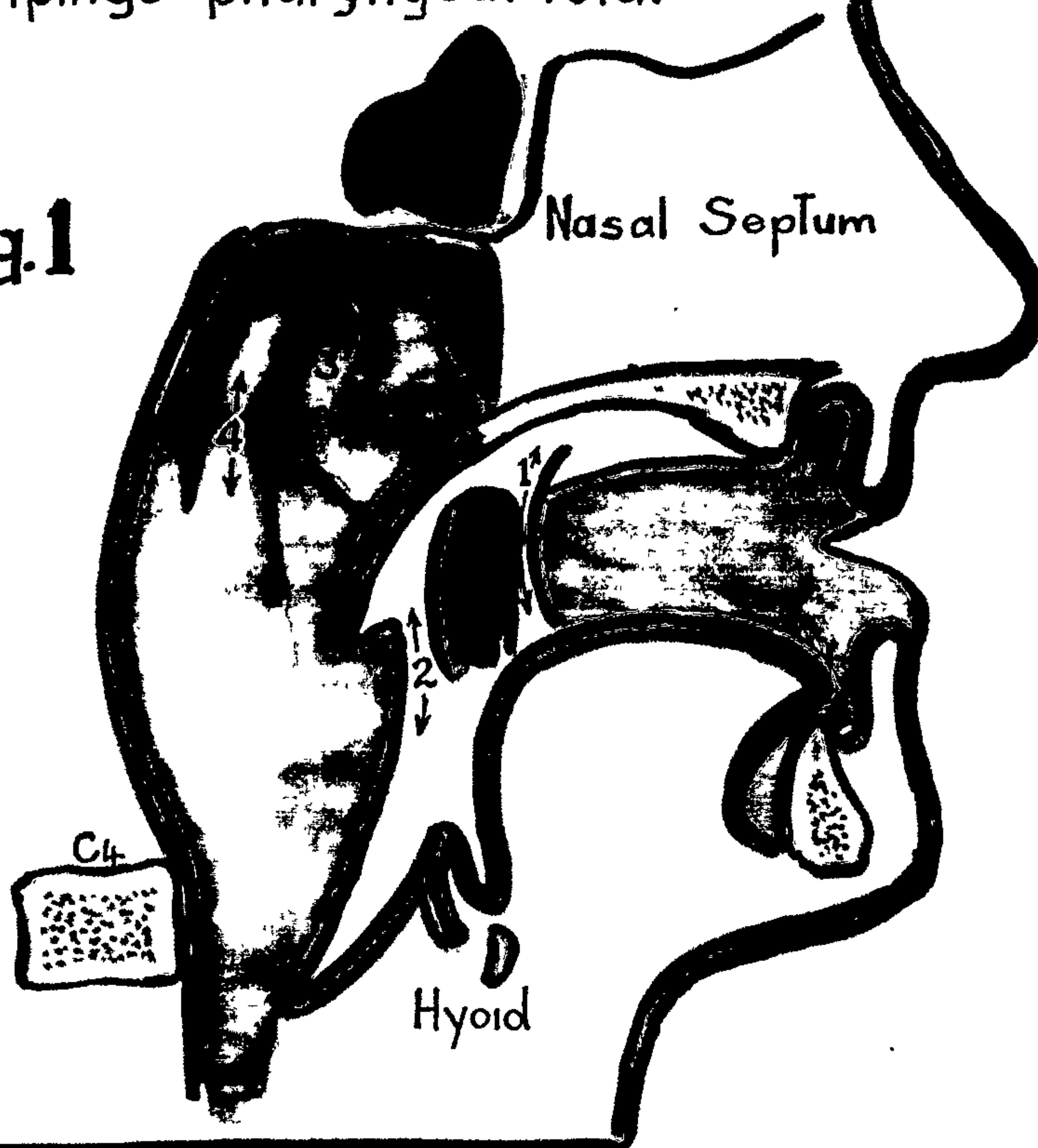
The landmarks noted are the nasal septum and hard palate which posteriorly form the medial and inferior borders respectively of the posterior nasal aperture with the sphenoidal sinus in close relation superiorly. The soft palate separates the naso-pharynx from the oro-pharynx.

The most noticeable feature of the naso-pharynx is the pharyngeal opening of the pharyngo-tympanic tube, bounded superiorly and posteriorly by the C-shaped cartilaginous, tubal elevation and inferiorly by the prominence of the levator palati muscle as it passes to its insertion into the soft palate. The salpingo-pharyngeal fold can also be traced downwards from the tubal elevation to where it blends with the palato-pharyngeus and stylo-pharyngeus muscles to form a thin but broad layer of vertical fibres inside the middle constrictor muscle of the pharynx.

In the oro-pharynx the soft palate gives origin to the arches of the palato-glossus and palato-pharyngeus muscles between which lies the palatine tonsil. The pharyngeal surface of the tongue forms the anterior boundary of the lower half of the oro-pharynx. The symphysis menti and the

- 1 Palato-glossal arch.
- 2 Palato-pharyngeal arch.
- 3 Pharyngo-Tympanic Tube opening.
- 4 Salpingo-pharyngeal fold.

Fig.1



bodies of the hyoid bone and the fourth cervical vertebra are noted in approximately the same horizontal plane at the level of the upper half of the laryngo-pharynx. The epiglottis marks the anterior boundary between the laryngo-pharynx and the oro-pharynx (Fig. 1).

In the course of this dissection the origins and insertions of all the muscles which form the soft palate were encountered. In order to gain access to the full extent of the superior constrictor muscle, it was necessary, at this stage, to remove the posterior edge of the horizontal plate of the palatine bone and the soft palate. The origins of the palato-pharyngeus and palato-glossus muscles, the insertions of the levator palati and tensor palati muscles and the entire musculus uvulae were included in the excision.

The superior and middle constrictors of the pharynx were uncovered by removing the mucosa, the palato-glossal arch, and palatine tonsil, and further posteriorly, the palato-pharyngeus and salpingo-pharyngeus muscles.

From this medial approach, the inferior border of the superior constrictor overlapped the superior border of middle constrictor creating a triangular gap anteriorly through which passed the stylo-pharyngeus muscle. This muscle gains partial insertion in the pharyngeal wall, together with the palato-pharyngeus and salpingo-pharyngeus muscles, as mentioned previously.

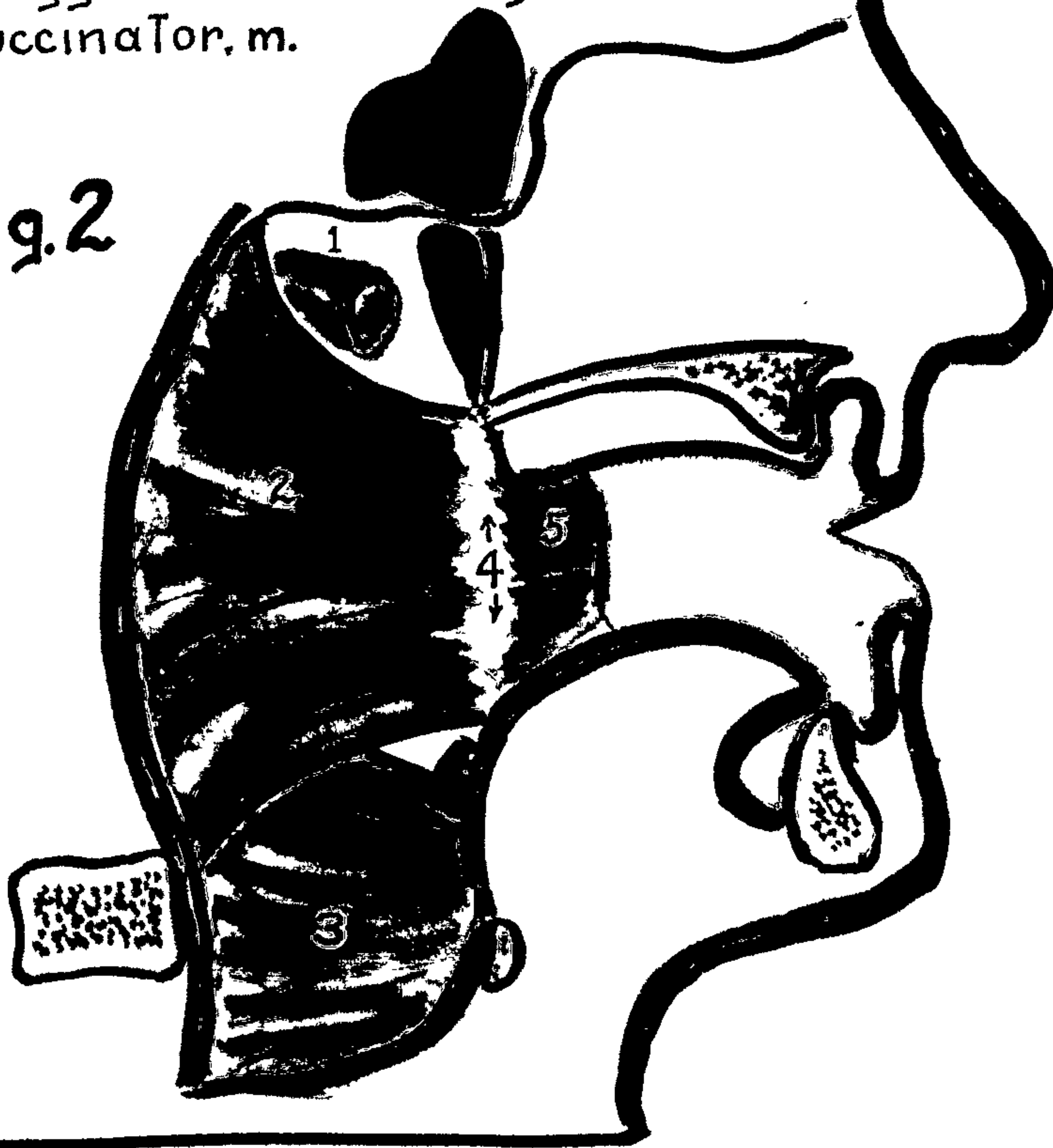
Removal of soft palate and palatine crest disclosed the lower half of the posterior border of the medial pterygoid plate terminating inferiorly in the pterygoid hamulus. The pterygomandibular ligament is an extremely fine fibrous band formed by fusion of the fascial coverings of the adjacent horizontal fibres of the superior constrictor and buccinator muscles and forms the common boundary between these two muscles. The proximity of the anterior edge of the medial pterygoid muscle to this ligament, as it extends from the hamulus to the posterior end of the mylo-hyoid ridge of the mandible, helps to accentuate its outline making it a valuable landmark in inferior alveolar nerve block injection (Lindsay 1948).

The superior constrictor of the pharynx arises from the exposed portion of the medial pterygoid plate, the pterygomandibular ligament, the mylo-hyoid line and from the musculature of the side of the tongue and is quite slender at its origin though increasing in bulk posteriorly. The crescentic interval between the upper border of the superior constrictor and the base of the skull is occupied by pharyngo-basilar fascia and transmits both the cartilaginous portion of the pharyngo-tympanic tube and the levator palati muscle. The latter muscle passed from its double origin in the quadrate area of petrous temporal and the medial side of the pharyngo-tympanic tube, along the

Figure 2.

- 1 Cartilaginous Pharyngo-Tympanic Tube.
2 Superior Constrictor of Pharynx.
3 Middle Constrictor of Pharynx.
4 Pterygomandibular Ligament.
5 Buccinator, m.

Fig. 2



inferior border of the tube's pharyngeal opening, to its insertion in the soft palate which had already been resected (Fig. 2).

At this stage it was an aid to orientation to remove the brain and by retracing the branches of the middle meningeal artery, identify the foramen spinosum.

Both the superior and middle constrictor muscles were then separated from the prevertebral muscles and carefully removed to uncover the important structures on their lateral surfaces (Fig. 3).

Blunt dissection in the fatty and areolar tissue immediately anterior to the prevertebral muscles progressively revealed (a) - the sympathetic trunk and superior cervical ganglion. (b) - the internal carotid artery passing to the base of the skull which it entered through the carotid canal. (c) - the internal jugular vein with the vagus nerve situated deeply between it and the internal carotid artery.

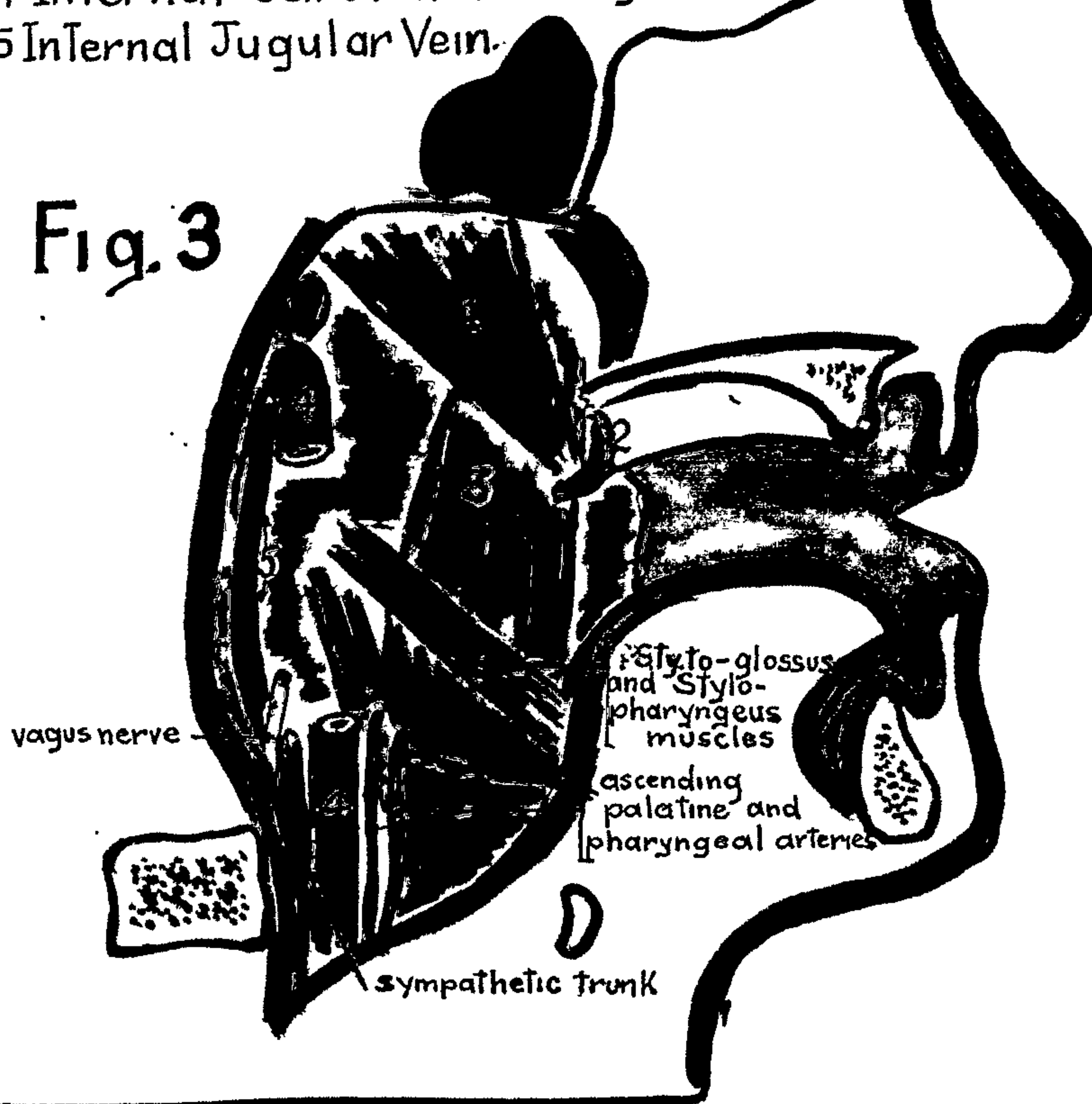
The pharyngeal and superior laryngeal branches of the vagus nerve, the glossopharyngeal and hypoglossal nerves are also encountered at this stage of the dissection.

Other blood vessels noted were:

(d) The pharyngeal venous plexus on the lateral surface of the pharyngeal wall, drained by the pharyngeal veins which are tributaries of the internal jugular vein.

- 1 Tensor Palati Muscle.
- 2 Pterygoid hamulus.
- 3 Medial Pterygoid Muscle.
- 4 Internal Carotid Artery.
- 5 Internal Jugular Vein.

Fig. 3



(e) The ascending pharyngeal artery in close relation and medial to, the large internal carotid artery inferiorly, and remaining upper portion of the stylo-pharyngeus muscle superiorly.

(f) Further anteriorly the ascending palatine branch of the facial artery passing upwards between the stylo-pharyngeus and the stylo-glossus muscles as the latter swept forward beneath the superior constrictor and the mylo-hyoid muscles to be inserted into the side of the tongue.

The bony origin of the levator palati muscle was then dissected and the cartilaginous portion of the pharyngo-tympanic tube removed to its osseous continuation, whereupon the entire origin of the tensor palati muscle from the scaphoid fossa to the spine of sphenoid was exposed. From this origin the fibres of the tensor palati muscle converged inferiorly into the slender tendon which passed around the pterygoid hamulus.

Exposure of the medial pterygoid muscle was completed by removing the tensor palati muscle and pharyngo-basilar fascia superiorly and the stylo-glossus muscle inferiorly. The fascia at the base of the skull is very dense and enclosed the otic ganglion at the posterior border of the medial pterygoid muscle. The spine of sphenoid was then identified and its relation to the foramen spinosum gauged from the middle cranial fossa.

Following resection of the remaining fibres of the stylo-pharyngeus muscle, and the adjacent fascia, the exposed lobe of the parotid gland was removed piecemeal to reveal firstly, the external carotid artery and immediately adjacent laterally, the posterior facial (retromandibular) vein.

The medial pterygoid muscle forms the medial boundary of the pterygomandibular space. The posterior boundaries of the space are, medially, the posterior facial vein in the substance of the parotid gland and laterally, the convex posterior edge of the medial surface of the ascending ramus which is continuous superiorly with the ridge of the mandibular neck. This landmark, which is known also as the crista colli, forms the posterior boundary of the mandibular sulcus. Based on the examination of several hundred mandibles, Nevin (1938) stated that "the mandibular sulcus is a depression that is always present, surrounding the mandibular foramen but extending more superiorly and posteriorly". Sicher (1946) draws attention to the importance of the groove of the mandibular neck (Sulcus colli) and its adjacent ridge (crista colli), because of the proximity of the inferior alveolar nerve to the groove when the mouth is fully opened.

The insertion of the medial pterygoid muscle into the angle of the mandible below the mylo-hyoid groove was

cut and the muscle reflected to disclose the pterygo-mandibular space (Fig. 4).

The Pterygomandibular Space.

The first structure encountered within the space was the spheno-mandibular ligament which is a thin layer of connective tissue with indistinct anterior and posterior borders (Sicher, 1965), and was reflected along with the medial pterygoid muscle.

The reflected lateral surface of the medial pterygoid muscle showed a ramification of small veins which formed part of the pterygoid venous plexus. These veins appeared to be tributaries of two small vessels, closely applied to bone immediately behind the mandibular foramen which, in turn, became part of the inferior alveolar vascular bundle (Figs. 4 and 5). This term is used, because, although the inferior alveolar artery was a discrete entity, its venous counterpart comprised several smaller vessels which were closely related to the artery during part of its course in the mandibular sulcus.

Removal of the medial pterygoid muscle was accomplished by resecting its double origin from (a) the medial surface of the lateral pterygoid plate and the posterior surface of the tubercle of the palatine bone and, (b) the area of the maxillary tuberosity which gives origin to the small superficial head.

- 1 Mandibular Ramus and Lingula.
- 2 Mandibular, Inf. alveolar and Lingual nerves.
- 3 External Carotid Artery.
- 4 Maxillary and Middle meningeal arts.
- 5 Inf. Alveolar art. & veins.
- 6 Posterior Facial and Maxillary veins.

Fig. 4

