The function of the autonomic nervous system in relation to cardiac output is simply to keep the permissive level of cardiac output above that actually required (Guyton 1968). This effect is mediated by the release of the hormone adrenaline into the circulation from the adrenal medulla.

Although estimation of the amount of circulatory adrenaline and noradrenaline is rendered difficult due to their rapid metabolism and difficulties associated with their collection and extraction (Robson 1962), with recent advances in techniques of sampling and analysis, more detailed information may be anticipated (Creutz 1968). It is known, however, that stress markedly increases the plasma level of adrenaline and, provided absorption from the dental injection site is not rapid, the amount of circulatory adrenaline of exogenous origin is small by comparison (Glover 1968).

(b) **Peripheral resistance.** Almost every tissue in the body is capable of regulating its own blood flow, largely through the influence of the oxygen tension of the perfusing blood and the state of oxygenation of the tissues (Guyton 1968). Cardiac output is the sum of the individual rates of flow through all body tissues. Therefore, regulation of cardiac output is dependent
upon factors influencing the volume of venous return. Mean systemic pressure is the main factor involved and, in this regard, venous resistance plays an important part. Mean systemic pressure is the ratio of the circulating blood volume to the momentary circulatory capacity.

The result of sympathetic outflow is a redistribution of blood according to the expected tissue requirements for activity. Accordingly, there is vaso-constriction of the blood vessels of the skin, alimentary canal and associated digestive organs. Blood made available in this way assists in supplying the vessels in skeletal muscle which have been dilated by the effect of circulatory adrenaline. This arrangement permits rapid perfusion of muscle tissue during exercise and, because of the increased mean systemic pressure, maintains an adequate venous return to the harder working heart. Thus autonomic influence on peripheral resistance is the factor which actually regulates cardiac output (Guyton 1968).

(c) The influence on cardiac output of the degree of filling of the circulatory system depends on factors such as loss of circulating blood volume due to haemorrhage, or flaccidity in the peripheral circulation as occurs with neurogenic shock. The result in both cases is a decrease in mean systemic pressure and decreased cardiac output.
A. CARDIOVASCULAR EFFECTS.

The postulated mechanism of action of sympathomimetic amines is dependent on the currently accepted hypothesis that there are at least two types of adrenergic receptor sites; alpha and beta (Ariens et al. 1963, Goldberg 1964, Foster 1966, Rand and Trinker 1966). These differ in their distribution and physico-chemical properties in such a way as to influence their affinity for different sympathomimetic drugs. The receptor component is located in the effector cell and has nothing to do with the autonomic system (Foster 1966).

Because the relative populations of alpha (constrictor) and beta (dilator) receptor sites are not identical for all tissues, adrenaline, at physiological concentrations, has widely differing actions. For example, it constricts the blood vessels of the skin and subcutaneous tissues and dilates those in muscles (Braid and Scott 1966).

When local anaesthetic agents, in combination with adrenaline, are deposited in skeletal muscle, the vasodilatory effect of the former is just offset by the alpha effects of the high tissue concentration of the latter (Dhuner and Lewis 1966, Braid and Scott 1966). Although the adrenaline component influences both alpha
(excitatory) and beta (inhibitory) receptor sites in the smooth muscle of the blood vessels in skeletal muscle, beta receptor sites show greater sensitivity and also are present in larger numbers and therefore local anaesthetic preparations are not entirely localized following intramuscular injection (Tainter and Throntson 1938).

Beta receptors are sensitive to much lower concentrations of adrenaline than alpha receptors, and when conventional doses of local anaesthetic in combination with adrenaline are used extravascularly, the resultant circulatory adrenaline from this source is such that only its beta effect on the vasculature of smooth muscle is evident (Kennedy et al 1966). Since the blood vessels in skeletal muscle constitute a large proportion of the peripheral circulation, the beta (vasodilatory) effect of adrenaline at physiological concentrations, dominates the circulatory pattern and doses, too small to act on alpha receptors, therefore lower peripheral resistance and diastolic blood pressure by beta action (Dobbs and Kader 1950, Goodman and Gilman 1966). Diastolic pressure, that is to say, the constant pressure in the blood vessels, is reduced because peripheral vasodilatation predominates over vasoconstriction, increasing the circulatory capacity (Goodman and Gilman 1966).
The pressor effect of large doses of adrenaline (20 micrograms intravenously per minute), is mainly the result of increased cardiac output and alpha (vasoconstrictor) activity in the peripheral vasculature. As the constrictor effect on alpha receptor sites diminishes with elimination of larger doses, the beta effect persists producing a secondary hypotension or diphasic response. On the other hand, although minute doses of adrenaline also increase cardiac output, beta sensitivity in the peripheral circulation predominates over this effect producing a fall below normal mean arterial pressure without a primary rise (Goodman and Gilman 1966).

Intravenous infusion of adrenaline in normal human subjects (1 μg/Kg/minute) markedly augments the hepatic blood flow and decreases splanchnic vascular resistance (Goodman and Gilman 1966).

The cardiovascular response to adrenaline is further modified in the normal individual by the presence of baroreceptors in the carotid sinus and aortic arch, which are sensitive to changes in blood pressure. Reflexes originating in these receptor sites cause cardiac output and peripheral resistance to antagonise, so as to preserve a satisfactory cerebral supply pressure. Whenever an increase in pulse pressure is recorded, peripheral vasodilation immediately ensues (Sharpey-Schafer 1956).
Many investigators have examined the degree of cardiovascular deflection which follows injection of adrenaline in both normotensive and hypertensive subjects (Jensen 1930, Pickering and Kissin 1936, Tainter, Thronson and Moose 1938, Fatheree and Hines 1938, Salman and Schwartz 1955, Costich 1956, Wallace et al 1956, McCarthy 1957, Cheskin and Prasertsuntarasai 1957, 1958A, 1958B, 1959). To simplify consideration of the problem of cardiovascular response to dentally administered adrenaline, these investigations can be classified as:

(a) Investigations indicating a significant response to dentally administered adrenaline in normotensive individuals (Tainter, Thronson and Moose 1938, Salman and Schwartz 1955, Costich 1956). These investigations demonstrated that when solutions containing adrenaline were deposited submucosally, systolic blood pressure and pulse rate increased whereas diastolic pressure may increase or decline.

Pickering and Kissin (1936) administered .5 ml of 1:100,000 adrenaline intravenously in normotensive and hypertensive subjects. A fleeting rise followed by a drop in blood pressure lasting 25 seconds and then a fairly regular and constant pressor effect lasting 2 or 3 minutes was observed in the normotensive group. The findings in hypertensive persons were much more variable and generally more pronounced.
Fatheree and Hines (1938) investigation on 12 normotensive and 10 hypertensive patients is interesting as they reduced the vasoconstrictor concentration to 1:250,000. At this concentration the magnitude of rise in systolic pressure in both groups was the same. In normotensive patients the diastolic pressure rose whereas with hypertensives it fell. These findings agree with those of Goldberg (1948) who considered that the hypertensive has a greater degree of sensitivity to the beta (vasodilator) action of adrenaline.

(b) Investigations indicating no significant response to dental doses of adrenaline in normotensive subjects (Wallace et al 1956, McCarthy 1957, Cheraskin and Prasertsuntarasai 1958B).

In the experiments of Wallace et al (1956) to detect differences in the systemic effects produced by 2 per cent procaine solution plain, and with 1:50,000 adrenaline, blood pressure was recorded at 2 minute intervals by the auscultatory method. Although the presence of vasoconstrictor did not appear to influence the degree of cardiovascular response, it was acknowledged that transient differences in the cardiovascular effects of the two local anaesthetic solutions may have occurred and been overlooked due to adrenaline's rapid metabolism. These changes are none the less important since it is likely that patients
react more to sudden changes in blood pressure than to those which develop slowly (Tainter, Thondson and Moose 1938).

McCarthy (1957) noted that, at the time of writing, it was impossible to draw accurate conclusions regarding the possibility of pressor effect from adrenaline in dental local anaesthetics. In his investigations, blood pressure and pulse rate were recorded at one minute intervals and he concluded that fear of injection was the cause of marked psychosomatic haemodynamic pressor and heart rate responses. Such sympathetic pressor effects are largely the result of

(i) increased cardiac output due to adrenaline’s stimulatory action on the heart and its vasodilatory effect in skeletal muscle which increase venous return.

(ii) the action of both adrenaline and noradrenaline on the vasculature of the skin and subcutaneous tissues, producing peripheral vasoconstriction.

The work of Cheraskin and Prasertsuntarasai (1957, 1958A, 1958B, 1959) was intended to indicate the changes in haemodynamics which accompany the use of adrenaline in conditions simulating dental office procedure. Unfortunately, post injection blood pressure and pulse rate determinations were made at 5 and 10 minute intervals, during which time patients have been observed to convulse, faint and recover.
(personal observation), and certainly much of the vasoconstrictor is metabolized (Luduena et al 1949, Ship 1960). (c) Investigations indicating no significant difference between the response to dental doses of adrenaline in normotensive and hypertensive subjects (Tainter and Winter 1944, Cheraskin and Prasertsuntarasai 1958B, Vernale 1960). (d) Investigations indicating a significant difference between the response to adrenaline in normotensive and hypertensive subjects (Pickering and Kissin 1936, Fatheree and Hines 1938, Salman and Schwartz 1955, Goldenberg et al 1948). The difference in cardiovascular response in hypertension is manifested as a magnified and variable increase in systolic blood pressure and pulse rate, indicating a general haemodynamic instability. Due to the sensitivity of hypertensives to the beta effects of adrenaline, diastolic pressure is more likely to drop and recovery is slower than in a normotensive subject (Tainter et al 1938).

The effect of adrenaline in dental local anaesthetics on arterial pressure merits further investigation as its property of decreasing diastolic pressure may be more significant than its slight pressor effect (Costich 1956, Foldes and McNall 1961). In this regard, the findings of Martin et al (1966) and Kennedy et al (1966) can be related to the dental use of adrenaline, particularly as
absorption of local anaesthetic solutions from submucosal regions is much faster than from the regions they investigated (Scott 1964, Dhuner et al 1965, Cordh 1963).

Martin et al (1966) demonstrated that the absorption of 30 ml of 1.5 per cent lignocaine containing 75 μg adrenaline (corresponding to the amount contained in 7.5 ml of 1:100,000 solution), from brachial plexus blocks caused a significant decrease in peripheral resistance from arteriolar dilatation due to stimulation of beta receptors. Larger amounts of adrenaline further decreased peripheral resistance.

Kennedy et al (1966) investigated medical block techniques using solutions of 2 per cent lignocaine plain, and in combination with 1:200,000 adrenaline. A total dosage of 90 μg of adrenaline (equivalent to 9 ml of 1:100,000 solution), was administered in the latter instance. Absorption of adrenaline from brachial plexus and epidural blocks produced a profound decrease in total peripheral resistance and a drop in mean arterial pressure lasting 90 minutes. The cardiac effects were an increased rate, output, and stroke volume lasting 30 minutes. It is considered that those results represent the beta effects of adrenaline and much larger amounts are required to elicit alpha response.

Goldenberg et al (1948) observed a significant
vasodilator response in muscle vasculature during intravenous infusion of 10 μg of adrenaline per minute. They concluded that the vascular effects of adrenaline under physiological conditions, are predominantly inhibitory; and at dental dosage it acts as a powerful cardiac stimulant and overall vasodilatory drug. The net cardiovascular effect of therapeutic amounts of adrenaline is therefore, increased cardiac output and decreased peripheral resistance with a very small increase in systolic blood pressure.

Adrenaline is a powerful cardiac stimulant and acts directly on the pacemaker and receptors in the myocardium, causing the left ventricle to contract more vigorously giving an increased stroke volume as well as an increased pulse rate; increased venous return also contributes to the increased output. One of the most dramatic sights in all pharmacodynamics is the pressor response elicited by the intravenous injection of minute amounts of adrenaline (Goodman and Gilman 1966).

While using an automatic pulse monitor to record the cardiac response to dental injection, the writer frequently noted the effect of an increase in stroke volume on the pulse in the labial vessels as the lips were held between the fingers, though the heart rate was unchanged.
Adrenaline may alter cardiac rhythm also, as well as produce tachycardia. Williams and co-workers (1963) found a surprisingly high incidence of cardiac arrhythmias in patients undergoing oral surgery. Although it was not intended to imply that all shock like states during oral surgery are of cardiac origin, 26.2 per cent of patients developed cardiac arrhythmias coincident with either the injection of 1 or 2 ml of local anaesthetic containing 1:100,000 adrenaline or during subsequent operative procedures. Nor is it intended to suggest that the arrhythmias were caused solely by exogenous adrenaline, as conventional doses rarely cause premature ventricular extrasystoles (Goodman and Gilman 1966); but rather that an elevation of endogenous catecholamines via an unknown mechanism was responsible (Kaufman 1966, Tolas et al 1967). Ventricular extrasystoles, tachycardia and even fibrillation may be precipitated by the release of endogenous adrenaline when the heart has been sensitized to the action of adrenaline by certain general anaesthetics (e.g. halothane) or in cases of myocardial infarction (Kaufman 1966, Goodman and Gilman 1966, Tolas et al 1967). Hughes et al (1966) found that the incidence of cardiac arrhythmias during oral surgery with local anaesthesia was greater in patients with cardiovascular disease.

Cardiac efficiency, a measure of the relation between
work done and oxygen consumed, is decreased by adrenaline. The discrepancy between the increased oxygen needed and the amount available is further aggravated by mechanical coronary vasoconstriction due to the larger myocardial mass. To overcome the resultant demand hypoxia, adrenaline has a metabolic dilator effect which is primarily responsible for dilation of the coronary vessels (Goodman and Gilman 1966). The physiological response of coronary vasodilatation is mediated by sympathetic stimulation while coronary vasoconstriction is a vagal reflex phenomenon.

The direct result of increased cardiac output is an increase in systolic blood pressure. Receptor sites in the carotid sinus and aortic arch, sensitive to changes in blood pressure, relay this information to the medullary cardio-inhibitory centre, whereupon the pulse rate is generally reduced to slightly above normal by compensatory vagal discharge. The elevated systolic pressure is buffered also by the reactivity of similar reflexes, acting via the medullary vasomotor centre, which produce peripheral vasodilatation. As mentioned previously, even with the larger dosages of adrenaline administered in local anaesthesia for general surgery, usually only its beta effects are evident, viz increased heart rate and force of contraction, and decreased peripheral resistance (Kennedy et al 1966, Martin et al 1966).
At one time it was considered that blood pressure changes reflected the influence of adrenaline on both the cardiovascular and central nervous systems (Tainter, Thronson and Moose 1938). However, in conventional therapeutic doses, adrenaline has little stimulatory effect on the central nervous system (Goodman and Gilman 1966). Interpretation of the central effect of adrenaline is complicated by the predominance of its vascular action. For example as previously mentioned, the medullary vasomotor centre can be depressed or stimulated by blood pressure changes. In addition the central nervous system may be involved indirectly by stimulation of baroreceptors as a result of increased arterial pressure. In this regard, the carotid sinus is sensitized to changes in blood pressure by adrenaline which contracts its smooth muscle fibres (Robson 1962). In certain conditions, for example where patient hypersensitivity exists or when large amounts rapidly enter the blood stream, the alpha (stimulatory) effects of adrenaline on the cardiovascular system produce systemic manifestations which are diagnostic of toxic reaction to adrenaline (Moore 1955). These are:

(a) pallor due to cutaneous vasoconstriction.
(b) a fast, full pulse and elevated blood pressure, both of which are due to adrenaline's stimulatory action on the heart and persist until late in
the reaction when the blood pressure falls acutely.

(c) occasional cardiac irregularities caused by adrenaline's direct effect on the heart.

This type of reaction may precipitate a cerebral vascular accident, coronary occlusion, or may accentuate the pain of an existing angina. In the psychoneurotic individual, existing symptoms may be aggravated.

When confronted with the problem of providing dental treatment for patients assessed as poor local anaesthetic risks, close cooperation with their medical advisor is indicated; so that treatment aimed at minimising the risk of systemic complications can be planned. It is obvious that in people with hypertensive vascular disease or myocarditis, changes in the circulation should be minimised (Tainter and Thordson 1938). There is no doubt that intravascular injection, even of small amounts of adrenaline, produces clinically significant cardiovascular responses and that the presence of certain pathological conditions considerably influences the magnitude and direction of the response.

The potential danger from the dental use of sympathomimetic vasoconstrictor drugs lies in the combination of one or more of the following contributory causes:

(a) rapid intravenous injection,

(b) the presence of certain pathological states, notably thyrotoxicosis, epilepsy and cardiac disorders;
particularly recent coronary occlusion. 
(c) concomitant therapy with drugs which may 
potentiate the systemic effects of adrenaline, e.g. 
monoamine oxidase inhibitors and sympathomimetic 
bronchodilator drugs.

In addition, patients with cardiovascular 
disease and hypertension are likely to be hyper-reactive 
to adrenaline, and prolonged vasoconstriction in such 
individuals is particularly undesirable. Therefore, 
premedication with short acting barbiturates in selected 
cases is considered advisable, in order to minimise the 
stress and anxiety which initiates the release of 
additional amounts of endogenous adrenaline into the 
circulation (Vernale 1960, Steinhaus 1962). The 
 inclusion of adrenaline in local anaesthetic solutions 
 administered slowly, carefully and extravascularly, to 
 these patients ensures more reliable anaesthesia and, 
as a result, less endogenous side effects (Dick 1953, 

B. CENTRAL NERVOUS SYSTEM EFFECTS.

The brain is the most highly developed organ and 
is, therefore, most susceptible to the influence of 
circulatory drugs (Sadove 1952, Moore 1955, Shotwell 1948). 
The cerebral circulation accounts for a relatively large
proportion of the circulating blood volume (Greene 1948) and this in itself, enhances the possibility of circulatory drugs affecting the brain (Scott 1964).

The cerebral cortex comprises areas of sensory and motor control. It is the most highly developed part of the brain and is affected first by circulatory drugs. Sensory stimulation is reflected in signs of restlessness, anxiety and loquacity (Sadove 1952), while motor stimulation produces muscle fasciculations, tremors, and tonic and clonic contractions (Dobbs and Kader 1950). Stimulation increases the oxygen demand of the cerebral cells and, if this requirement is not met, a demand hypoxia may occur (Moore 1955, Sadove 1952). Cerebral stimulation from above downwards affects firstly the cortex, then the vital medullary centres of respiration and circulation (viz: the cardiovascular and vasomotor centres), and is always followed in these regions by depression of proportionate intensity (Epstein 1958). The two processes of stimulation and depression may occur simultaneously with either predominating.

Following inadvertant intravenous injection of dental local anaesthetic solution, the heart is the first organ to experience its direct effect. The central nervous system may be influenced to some degree by the predominantly cardiovascular effects of the adrenaline component (Goodman and Gilman 1966). The abrupt nature of the response which
sometimes follows rapid inadvertant intravenous injection in dentistry, suggests that the direct effect on the heart, of a concentrated depot of drug, may be responsible. On completing the pulmonary circuit and leaving the left ventricle, the intravascular dose of local anaesthetic solution perfuses the aortic and carotid receptor sites which are sensitive to both stretch and to chemical changes in the constituents of the blood (Meilusi 1961). The resultant afferent nerve impulses make connections in the medulla with the nucleus of the vagus nerve, motor fibres of which terminate in the conduction system of the heart. Therefore an intravenous dose of dentally administered local anaesthetic, or vasoconstrictor agent, contacts receptor sites in the heart and blood vessels before reaching the brain (Crawford 1966).

Intravenous infusion of adrenaline in man produces feelings of excitement, expectancy, apprehension and anxiety, particularly in sensitive individuals (Robson and Stacey 1962). In addition there may be coarse tremor of the extremities and an increase in rate and depth of respiration. Sometimes, intravenous administration of adrenaline produces a period of apnoea the mechanism of which is not clear. It has been attributed by some investigators to a transient depression of the carotid body chemoreceptor reflexes and by
others to a transient direct inhibition of the medullary respiratory centre (Goodman and Gilman 1966).

Although the signs of adrenaline intoxication suggest a condition of mild cortical stimulation (Moore 1955), general penetration of appreciable amounts of adrenaline through the blood-brain barrier seems unlikely. However, without passing generally into the brain, adrenaline may act at special sites (e.g. the reticular formation), which are both accessible and sensitive to its effect (Robson and Stacey 1962). The "arousal centre", which is thought to be responsible for consciousness, is located in the reticular formation which extends from the diencephalon downwards throughout the whole central nervous system. The reticular formation has the ability to arouse the entire cerebral cortex (Melzack 1961, Livingston 1953). Stimulation of the reticular formation results in an emotional alertness, but adrenaline, in therapeutic doses, is not a powerful direct central nervous stimulant (Goodman and Gilman 1966). This distinction is noted on comparison with methedrine, which has both the usual sympathomimetic effects of adrenaline plus central nervous stimulatory (analeptic) action (Sara 1963). Adrenaline increases Parkinsonian rigidity and tremor probably due to central action but the extent to which emotional factors influence the response is unsure (Robson and Stacey 1962).
Syncope

Although loss of consciousness may result from depression of the cerebral cortex following its previous stimulation to the point of exhaustion, the more common cause of a temporary suspension of vital cerebral function is a reduction in cerebral blood supply, or a deficiency of essential components in a normal blood supply. Such a condition is known as syncope (Sara 1963, Sharpey-Schafer 1956). Reduction in cerebral blood supply is generally associated with a drop in arterial pressure initiated by either decreased cardiac output, or an acute decrease in peripheral vascular resistance; or a combination of both causes (Barcroft 1944). Although homeostasis is normally maintained by the antagonism of these two processes, mediated through the reactivity of baroreceptor reflexes, the common faint has a strong psychological element and involves mechanisms, which apparently, temporarily overcome reflex buffering of cardiovascular deflections. Acute vasodilatation in skeletal muscle (due to the beta effect of endogenous adrenaline), or in the splanchnic area (due to vagal reflex activity or perhaps the beta effect of adrenaline also), causes decreased cardiac filling pressure and a corresponding decrease in cardiac output which, in turn, is responsible for the drop in arterial pressure associated with the common syncopal episode (Sharpey-Schafer et al 1958).
Cerebral metabolism depends on the oxidation of glucose, and the 7 ml of oxygen normally locally available for this process, are rapidly depleted should the cerebral supply pressure fall below 50 mm Hg. (Bourne 1957). Without oxygen there is a failure of vital function and unconsciousness supervenes. As a high incidence of respiratory difficulty accompanies unconsciousness, prompt treatment, aimed at adequately supporting respiration and maintaining an effective cerebral blood pressure, is essential, as the brain can withstand only several minutes of anoxia before it is irreversibly damaged (Brierly and Miller 1966, Bourne 1957, Sharpey-Schafer 1956).

Conversely, the supply pressure may be adequate but the blood deficient in constituents essential for normal cerebral metabolism. For example, cardio-respiratory difficulty, of whatever cause may produce tidal, alveolar or stagnant hypoxia which is frequently evidenced by cyanosis.

The hysterical patient who hyperventilates washes out carbon dioxide, reducing the \( P_{\text{CO}_2} \) of the blood below the level required for respiratory stimulation and apnoea follows. Both vasodilatation in muscle tissue via central nervous reflex, and the ischaemic anoxia which results from hypocapnic constriction of the cerebral vessels, contribute to a syncope which is characterised by an absence of cyanosis (Hayward 1961, Howard et al 1952).
Although not usually considered a cause of syncope, the signs accompanying the hypoglycaemic reaction occasionally encountered in diabetic patients may resemble those of vasodepressor syncope (Mellusi 1968).

Moore (1955) considers that the vasoconstrictor component is responsible for most reactions of a mild cortical stimulatory type following the injection of local anaesthetic preparations. Although the infusion of dental doses of adrenaline may produce the common subjective symptoms indicative of cerebral cortical stimulation, the drug, when so used, is not a powerful central nervous stimulant. Goodman and Gilman (1966) consider that, as apprehension is clearly initiated in the higher cortical centres, the reaction is psychic rather than from fundamental changes in vital functions resulting from the effect of adrenaline on the central nervous system. However, although adrenaline is not infrequently associated, even in small doses, with tachycardia, palpitations, hypertension and headache which are cardiovascular effects; anxiety, restlessness and tremor also occur which are obviously of central nervous origin (Fisher 1965, Holroyd 1960). Therefore, the differential diagnosis of mild reaction to adrenaline from reaction of a central nervous stimulatory nature due to psychic causes is important, and every effort should be made to identify the nature of each clinical episode. Only by an intelligent
appreciation of the physiological changes involved can
effective preventive and therapeutic measures be given.
(Steinhaus 1962).

Differential diagnosis of mild central nervous
stimulatory type reactions.

Toogood (1960) describes the signs of intoxication
which may be evident soon after injection of .08 mg of
adrenaline in dentistry. The patient is wide awake,
heart pounding, blood pressure increased, extremely pale,
respiration unchanged and exhibiting a coarse tremor of
the hands and an absence of perspiration. These signs
are largely the result of direct stimulation of the
cardiovascular system, although a localized central nervous
stimulatory effect is operative also. Similarly, the signs
which occasionally follow the rapid absorption of smaller
dental doses of adrenaline do not include those of stimulation
and depression of the cerebral cortex and vital medullary
centres. The patient remains conscious and although the
medullary respiratory centre may be briefly mildly stimulated
(Foster 1966), the obvious increase in respiratory effort
which accompanies this type of reaction, is caused by
the direct effect of adrenaline on the heart and lungs.
The functioning of these organ systems is so closely co-
ordinated that action in one soon produces reaction in the
other (Sara 1963).
Despite their stability in the blood stream, vasoconstrictors are metabolized rapidly in the tissues, particularly in the liver (Holroyd et al. 1960), and toxic symptoms from circulatory sympathomimetic drugs have a more rapid onset, persist a shorter time and recede more rapidly than, for example, those caused by local anaesthetic agents (Shotwell 1948). Nevertheless, pulse rate and blood pressure are elevated and remain so throughout the reaction to adrenaline (Moore 1955).

The psychogenic type reaction on the other hand, is characterised by hypotension, the cause of which is acute peripheral vasodilatation (Foldes and McNall 1961). For this reason the reaction is classified as vasodepressor. It is difficult to dissociate the psychological element from any aspect of dental treatment and, while an attempt will be made to define several types of commonly observed psychogenic syncopal reactions, it should be realised that the classification is arbitrary and that clinically, several of these mechanisms may operate concurrently.

When a reduction in peripheral vascular tone occurs from psychic causes, it is mediated by either the sympathetic or parasympathetic nervous systems. The idea that cortical activity and the efferent sympathetic pathway are alone involved in psychological fainting seems untenable (Sharpey-Schafer 1956). The function of the sympathetic...
system is to prepare the body for activity. As mentioned previously, sympathetic outflow increases heart rate and output, and causes vasodilatation in skeletal muscle which are beta-sympathomimetic effects (Barcroft 1944, Ariens 1963). These changes are part of a chain reaction that mobilizes all the body’s resources to meet what may be an emergency situation. Depending to a large degree on the emotional stability of the individual, the sympathetic response to stressful situations may be disproportionate to the degree of activity which actually eventuates. Consequently, blood pools in the dependent limbs of such patients seated upright in the dental chair and as the blood pressure begins to fall, the heart rate is at first increased. However, when the arterial pressure reaches 80 mm Hg., syncope is imminent and an abrupt bradycardia supervenes (Mellusi 1968). At this stage the pulse is weak, slow and thready, being often barely palpable.

Similar signs accompany syncope produced by a purely psychological mechanism, the exact nature of which is unknown except that the patient is able to temporarily avoid confronting a distressing situation by a loss of identity and self control (Mellusi 1968, Sara 1963, Sara 1968). Emotion is often associated with nausea and either or both may cause syncope. Evidence suggests that dilatation of the peripheral venous system precedes hypotension.
in syncope induced by nausea. There are two ways in which emotion tends to empty the heart in normal subjects (a) by increasing the force of contraction thus increasing cardiac output.

(b) by reducing filling pressure due to vasodilatation in the splanchnic area. The latter process occurs first then, as a result of stimulation of receptors in the myocardium, impulses pass to the central nervous system causing reflex vasodilatation in skeletal muscle. The results of this acute decrease in peripheral vascular tone are, decreased cardiac output, cerebral hypoxia and syncope (Sharpey-Schafer et al 1958).

In vasodepressor syncope of parasympathetic origin, the circulatory inadequacy results from vagal reflexes which are cardioinhibitory and vasodilatory in the large splanchnic vascular bed. Although the efferent portion of the reflex arc involved is always vagal, the afferent component may be sensory or vagal. The pulse is slow and readily palpable in this type of reaction (Sara 1963, Sara 1963).

The atria have a relatively rich parasympathetic innervation (Cunningham 1953), and as the right atrium is the first chamber of the heart to experience the effect of an intravenous dose of local anaesthetic agent, it is interesting, in passing, to speculate on the combined
myocardial depressant effects of vagal influence and intravenous local anaesthetic drugs.

If, as a result of decreased cardiac output, the cerebral supply pressure falls below 50 mm Hg. for more than a few seconds, the posterior pituitary gland is stimulated and releases its hormone, producing pallor of the skin which persists for many minutes after a satisfactory supply pressure has been reestablished (Sharpey-Schafer 1956). In psychogenic syncopal reactions, the skin is ashen grey in colour and cold for the reasons just given, and moist as a result of stimulation of sudomotor centres in the cerebral cortex (Dille 1963, Hayward 1961, Mumford and Geddes 1959). The blood pressure is always decreased and, although pulse rate may be briefly stimulated early in the reaction, later it is either slow and thready or slow and palpable. Respiration is slow and shallow. The medullary vomiting centre may be stimulated by the cerebral hypotension and primary oxygen want, producing nausea and vomiting. Cerebral hypoxia may be responsible also for the convulsions sometimes associated with this type of reaction (Moore 1955, Hayward 1961). Toogood (1960) considers that hypoxic convulsions will not occur if the patient is placed in a horizontal position and hence the importance of keeping the patient under constant observation.
Other vasoconstrictor agents.

In comparing sympathomimetic vasoconstrictor drugs, adrenaline is regarded by Goodman and Gilman (1966) as the prototype. This is because differences in vasoconstrictors are largely quantitative and, clinically, it is difficult to differentiate between comparable concentrations of the various congeners particularly when extravascular injection is made (Tainter, Thronson and Moose 1938). The main differences are in the degree and duration of the cardiovascular response.

Noradrenaline, though closely related chemically to adrenaline, has notable differences in pharmacological action. Except for coronary vasodilatation, its action on the vascular bed is always one of constriction producing a steady rise in blood pressure and concomitant reflex bradycardia. Toxic manifestations are similar to those of adrenaline but the patient is aware of a slow forceful heart, and may experience photophobia and retrosternal pain (Sara 1968).

Noradrenaline has only one eighth the potential of adrenaline in raising the blood glucose level (McCheesney et al 1949) and is less likely to upset the blood sugar balance of diabetic patients. Its intravenous toxicity is one half that of adrenaline (Tainter et al 1953, Luduena et al 1949). Both drugs are rapidly metabolised in the
tissues and the blood stream. The half time of adrenaline in the blood stream is less than one minute, and that of noradrenaline shorter still (Glover 1954).

Phenylephrine is a much more stable and longer acting non-catecholamine, producing less systemic effect although being locally more irritating. Catefrin, which is isomeric with adrenaline, possesses similar, though weaker, pharmacological properties with the exception that, outside the coronary plexus, its vascular effect is one of constriction.

Posterior pituitary derivatives.
The posterior pituitary anti-diuretic hormone, vasopressin, and its synthetic analogue, desipressin, have found use as vasoconstrictors particularly where adrenaline is contraindicated, e.g. during general anaesthesia using cyclopropane or halogenated hydrocarbon anaesthetics. These polypeptides of larger and more complex molecular structure than sympathomimetic drugs, have three main effects. (a) Pressor, (b) anti-diuretic, (c) oxytocic. At dental concentrations, (less than .05 I.U./ml), vasoconstriction is their only significant effect, much larger quantities being required to elicit anti-diuretic, oxytocic or pressor activity (Berling 1966, Goodman and Gilman 1966).
Although felypressin has only one half the intravenous pressor potency of an equal weight of adrenaline (Glover 1966), it must be remembered that the latter's pressor response is the combined result of stimulatory effects on the heart and blood vessels. Felypressin's vasoconstrictor effect is the result of direct action on the involuntary muscle component of the vascular wall, and this alone is responsible for its more prolonged, if somewhat less pronounced, pressor effect. It is a drug of low toxicity with fewer systemic side effects than adrenaline (Fisher 1965). Toxic manifestations following large doses of vasopressin or felypressin result from direct action on smooth muscle and may be (a) prolonged pressor effect producing a moderately high blood pressure, (b) pallor in the absence of E.C.G. change or faintness, (c) slow forceful heart, (d) intestinal effects (Berling 1966).

The coronary vessels are not exempt from vasoconstriction and this, together with a reflex buffering via the carotid and aortic baroreceptors, produces a transient tachycardia followed by a slight bradycardia. Consequently, there is no metabolic coronary dilator effect as seen with adrenaline and Goodman and Gilman (1966) referring to vasopressin, consider that individuals with coronary disease should never receive this drug. There have been several medical reports of cardiac accidents
following injection of vasopressin (Glover 1954, Slotnick
and Teigland 1957). However, felypressin has less coronary
effect than vasopressin (Fisher 1965), and at dental
concentrations should not be contraindicated (Glover 1966).

As a vasoconstrictor, felypressin is inferior
to adrenaline (Goldman et al 1967) and is less likely
to produce as reliable anaesthesia (Fisher 1965). However,
it compares favourably as an additive in combination with
local anaesthetic agents (e.g. prilocaine), which have
inherent localizing characteristics (Berling 1966, Brown
1968).
CHAPTER V.

LOCAL ANAESTHETIC AGENTS.

1. INTRODUCTION

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LOCAL ANAESTHETIC AGENTS.

1. INTRODUCTION.

The systemic or acute toxicity of local anaesthetic agents depends on (i) inherent toxicity (ii) concentration at sites most susceptible to their effects, viz. the central nervous system and heart (Foldes 1966).

The main cause of toxic reaction to small volumes of concentrated local anaesthetic solution is rapid intravenous injection. On rare occasions small doses have produced allergic response (Hayward 1961). Additional causes of toxic responses associated with larger dosages are, patient hypersensitivity and factors influencing the attainment of toxic blood level of drug. Concentration in susceptible tissues depends primarily on the plasma level of free local anaesthetic agent and also on the tissue's blood flow (Foster 1966).

Except after rapid intravenous injection, plasma level depends on (i) rate of absorption from the site of administration, (ii) inactivation (e.g. by metabolic transformation) at the site of administration or during transit, (iii) binding with serum albumin or other blood constituents, (iv) diffusion from the plasma to the tissues and back, (v) rate of metabolic transformation in the plasma or in various tissues e.g. the liver and kidneys, (vi) excretion (Foldes 1966).
With rapid intravenous injection there is no time for metabolic transformation and consequently toxicity closely parallels clinical potency. Except after rapid intravenous injection, rate of metabolic transformation is the main factor influencing systemic toxicity (Foldes et al 1965).

Accordingly, it is proposed to review firstly those inherent properties of local anaesthetic agents which influence their systemic toxicity, including responses due to hypersensitivity, allergy, and rapid intravenous injection; secondly, their behaviour following absorption into the bloodstream as it affects their uptake by, and concentration in, susceptible tissues in the central nervous and cardiovascular systems; and finally their systemic toxic effects on the central nervous and cardiovascular systems.

2. FACTORS INFLUENCING THE SYSTEMIC TOXICITY OF DENTAL LOCAL ANAESTHETIC SOLUTIONS.

A. RELEVANT PHARMACOLOGICAL PROPERTIES OF LOCAL ANAESTHETIC AGENTS.

It has been demonstrated that, coincident with the propagation of each nerve impulse, changes occur in the nerve cell membrane which result in a sharp reversal of internal polarity (Katz 1961, Eccles 1965). This process, which is self-reinforcing and continues undiminished along the entire length of the axon, is brought about by a large
transient increase in permeability of the axon membrane to the ingress of sodium ions (Astrom 1965, Goodman and Gilman 1966, Adriani 1960).

Although the process by which local anaesthetic agents inhibit the central conduction of nerve impulses is open to debate, it is generally agreed that they exert a stabilizing influence on the nerve cell membrane thereby interfering with its permeability to the passage of ions (Wielding 1964, Astrom 1965). For this purpose, local anaesthetic agents are usually dispensed in the form of the hydrochloride salt of the anaesthetic base. However, for convenience, it is customary to use the name of the base only in describing the various compounds.

It is less than one hundred years ago that Halsted and Hall first demonstrated a technique involving the injection of cocaine as an effective means of establishing infiltration and nerve block anaesthesia (Bjorn 1966). The ensuing years have brought both technical and pharmacological advances in the science of local anaesthesia, and it is notable that the problem of systemic toxicity provided much of the stimulus which resulted in the development of new and improved local anaesthetic agents (Tainter, Luduena and Hoppe 1953). Although chemists have been able to synthesize many new and highly active local anaesthetic agents, their clinical acceptability is dependent upon the avoidance of strong toxic and tissue irritating properties.
All true local anaesthetics come under the common formula (Wiedling 1964).

Lipophilic centre — intermediate chain — hydrophilic centre
(contains hydrocarbon nucleus usually of aromatic type).

There are two basic types of local anaesthetic agents: esters and amides (anilides). The former carries an ester linkage in the intermediate chain between the aromatic ring and the amino group, while the latter includes amides with a variety of different linkages in the intermediate chain (Green 1968). Lignocaine has an amide bond between the intermediate group and aromatic residue (Goodman and Gilman 1966). The natural alkaloid cocaine is an ester of benzoic acid and its early synthetic derivatives were ester-linked compounds of ortho, meta, or para-amino benzoic acid. The clinically suitable injectable local anaesthetics are almost without exception, amines (Adriani 1960).

An almost endless variety of local anaesthetics can be synthesized by substitution within the basic amide or ester type molecular configuration. For example, the presence of a carbonyl group increases local anaesthetic potency due to the greater negativity of its oxygen atom. The addition of electron donating substituents, (e.g. methyl or amino groups), further increases the negativity of the carbonyl oxygen (Myers 1967).
Anaesthetic potency and systemic toxicity of local anaesthetic drugs bear a relation to one another which, fortunately, is not directly proportional provided rapid intravenous injection is avoided (Foldes 1966, Luduena and Hoppe 1956). With other groups of drugs (e.g. the barbiturates), toxic and therapeutic doses are proportional and closely parallel each other throughout the series. This is less true of local anaesthetics (Goodman and Gilman 1966). It is usual today to accept the amide, lignocaine as the standard in evaluating new local anaesthetics for parenteral use (Goldman 1964). It is the prototype of anilide local anaesthetics and the clinical acceptability of new compounds for parenteral use, is usually determined by comparing their pharmacological properties with those of lignocaine.

All local anaesthetic agents are protoplasmic poisons (Nevin 1952) and their solutions are potentially toxic, whether administered parenterally or applied topically, as they are eventually absorbed and enter the circulation. Systemically, they have important effects in all organs in which conduction and transmission of nerve impulses occur, through their general depressant effect on excitable membranes (Goodman and Gilman 1966). Individual susceptibility plays an important part in the degree of response recorded (Toogood 1960).
The brain is the organ affected most by the depressant action of circulatory local anaesthetic drugs. An indication of its sensitivity to local anaesthetics can be gauged from the fact that the perineural concentration necessary to block conduction in a peripheral axon, is many times that which produces central nervous depression (Adriani 1960).

Uptake of drugs by different tissues throughout the body requires penetration of cellular barriers, and this depends in general on the drug’s ability to dissolve in the fatty material of the cell wall. Fat solubility depends partly on the degree of ionization. However, complete ionization decreases fat solubility thereby excluding the drug from cellular entry and to be therapeutically effective, it is necessary that a drug be only partially ionized (Paton 1960).

The more potent local anaesthetic agents show a marked affinity for nervous tissue referred to as a lipophile characteristic (Astrom 1965). Solubility in lipids is responsible for the contact which the local anaesthetic base makes with nerve fibres (Locke 1961, Wiedling 1964). There is a growing concept that if the anaesthetic molecule is too basic it cannot penetrate tissues sufficiently. If, on the other hand, it is less basic (i.e. it exists as free base at physiological pH), it will penetrate freely, but
cannot exist at the nerve membrane as a cation in effective amounts. The active form of the local anaesthetic molecule is thought to be the cation but penetrating efficiency depends on the free base. Therefore, a balance of ionizing potential is essential so that sufficient amounts of both uncharged free base and positively charged cation are available for useful local anaesthetic activity (Myers 1967).

The anilide compounds, lignocaine, mepivacaine, and prilocaine all exist, at plasma pH, as equilibrium mixtures of the charged cationic form and uncharged free base (Eriksson et al 1966, Dobbs and Ross 1961). The more rapid onset of lignocaine's anaesthetic effect indicates a particular facility of membrane penetration, which is probably due to the greater lipophilic properties of its hydrocarbon nucleus. The same property may be responsible also for lignocaine's higher intravenous toxicity as a result of the rapidity with which it penetrates other membranes such as the blood-brain barrier (Foldes et al 1965). Heinonen (1966) considers that both lignocaine and mepivacaine penetrate into the brain at approximately equal rates. However, mepivacaine's slower onset of anaesthesia and lower intravenous potency (Foldes 1965) suggest slower membrane penetration than lignocaine.
In addition to their peripheral effect of interfering with certain processes fundamental to the generation of nerve action potential, local anaesthetics possess characteristic subsidiary pharmacological properties which can collectively be described as respiratory and cardiovascular depressive, and convulsive (Steinhaus 1962, Gorch 1963, Paton 1960).

Both termination of effect and metabolism of local anaesthetic agents depend on their absorption into the blood stream. The behaviour of some hydrolyzable, ester-linked local anaesthetic compounds suggests that their metabolic transformation commences in the tissues at the site of injection (Foldes 1966, Glover 1963). Nevertheless, entry into the blood stream is a prerequisite for the detoxification of all anilide local anaesthetics and is responsible for hydrolysis of the greater proportion of doses of ester-linked compounds (Foldes et al 1965). Therefore the systemic effects of local anaesthetic drugs cannot be completely dissociated from their local effects; however desirable this might be (Dille 1964).

As there is no specific antidote for local anaesthetic drugs once administered, it is essential that their usage be orientated towards the prevention of intoxication, rather than its treatment. Should evidence of systemic toxicity be observed, treatment is limited to controlling
the manifestations of intoxication as they occur, so as to preserve vital function while the toxic dose of drug is being metabolized (Toogood 1960). Therefore mode and rate of detoxification are important elements in the regulation of local anaesthetic toxicity.

Local anaesthetics are used in dentistry exclusively for their peripheral effect of blocking afferent nerve impulses. However, in medicine, use has been made of the normal systemic effects of sub-toxic doses, on nervous tissue throughout the body.

(i) to produce central analgesia. The brain cells involved in pain perception are selectively depressed by intravenously administered local anaesthetic agents so that this sensation falls in intensity before other sensory perceptions are seriously impaired (Livingston 1953). Although this method has been largely discarded as a means of securing analgesia, it is not uncommon for patients receiving moderate systemic dose levels of lignocaine (e.g. 500 mg), to become euphoric, drowsy and appear to enter the first plane of surgical anaesthesia, there being no respiratory or circulatory depression. Their course is usually uneventful with spontaneous recovery (Schiano and Strambi 1964, Steinhaus 1962, Moore 1955, Epstein 1958, Adriani 1960, Wiedling 1964, Goodman and Gilman 1966).

(ii) As anti-arrhythmics. Like vasoconstrictors,
local anaesthetics may have an early stimulatory effect on the heart (Foldes et al 1965, De Jong and Walts 1966, Englesson 1962). However, following sufficiently large doses, the cardiac effect of local anaesthetics is a reduction in irritability and prolongation of the conduction time and refractory period. Both procaine and lignocaine have been used effectively in minimizing cardiac arrhythmias (Steinhaus 1962, Astrom 1965, Wiedling 1964, Goodman and Gilman 1966).

(iii) as anti-convulsants. Although the well known toxic result of the pharmacological action of local anaesthetics is convulsive, a therapeutically important, but less well known normal systemic effect on the central nervous system is their potent anti-convulsant action. It has been suggested that the apparent stimulation and subsequent depression of the central nervous system, characteristic of local anaesthetic agents, are both the result of selective depression of inhibitory neuronal activity (Goodman and Gilman 1966). This single depressant action is the rationale for their use as anti-epileptic agents (De Jong and Walts 1966, Astrom 1965, Adriani 1960, Wiedling 1964).

The plasma level of lignocaine which accompanies its central analgesic effect is approximately 5 μg/ml. By increasing the equilibrium concentration to 10 μg/ml, this effect is exceeded and replaced by signs of systemic toxicity
which have their origin in the cerebral cortex and vital medullary centres (Matthes and Schabert 1966). True toxicity following the administration of local anaesthetics is a poisoning effect due to either overdosage of a normally safe drug, or rapid absorption into the blood stream of smaller doses due to incorrect technique (Sachs 1949).

An important requirement in choosing a local anaesthetic agent for submucosal injection is to select a drug in which the range between satisfactory local anaesthetic dosage and that which produces toxic manifestations is sufficiently wide to indicate clinical safety. Comparable concentrations of most local anaesthetic agents used in dentistry, satisfy this requirement of low systemic toxicity combined with high anaesthetic potency, when used submucosally with a vasoconstrictor to delay absorption. However, when inadvertently administered intravenously, systemic toxicity closely parallels anaesthetic potency. Furthermore as no single preparation is suitable for all patients and for all dental operations, the one local anaesthetic agent may be dispensed in several different forms. These differences are mainly in increased concentration of the local anaesthetic agent and reduced vasoconstrictor content of the total preparation. The main object in varying these components is to limit the duration of submucosal anaesthesia. At the same time however, maximum submucosal
dosage is reduced and intravenous toxicity markedly increased.

B. CONCENTRATION OF LOCAL ANAESTHETIC AGENT.

In addition to the inherent systemic toxicity of local anaesthetic drugs it has been claimed that the ability to produce toxic manifestations increases in geometric progression with increase in drug concentration. Levestadt (1944) found little basis for the geometric progression theory of toxicity and Sadove (1957) believes it merely indicates a trend and needs further corroboration. Increasing the concentration of a drug increases its rate of administration unless the injection rate is correspondingly reduced (Crawford 1966).

Some investigators (Moore 1955, Medalling 1964, Gerdh 1963), consider that the concentration at which a local anaesthetic drug is administered has a marked effect on the plasma level attained. Scott (1964), however, found that although differing vascularization of the site of injection was a significant influence on the subsequent plasma level of lignocaine, concentration had no significant effect until it reached 4 percent. In this regard, two opposing factors determine absorption from the tissues. On the one hand, use of a stronger solution results in a steeper tissue-plasma concentration gradient. Dilution, on the other hand, increases the volume of solution administered thereby presenting a
larger absorptive area to the tissues. Both factors increase the rate of absorption. Whereas Scott (1964) considers that total dosage, not concentration, is important in the avoidance of toxic blood level; Gordh (1965), Bjorn (1966), Wiedling (1964), and Moore (1955) hold the opposite view. Theoretically, increased concentration should increase toxicity, but practically this is not observable (Tainter, et al 1953).

Conditions of shock, including those classified "neurogenic", are characterized by a diminution in the effective volume of circulating blood, and a marked decrease in the mass of tissue perfused. This is brought about by increased shunting of blood which produces the same effect as increasing the concentration of a drug (Crawford 1966).

**Intravenous administration.**

The circumstance in which the concentration of drug affects the resultant manifestations of systemic toxicity most, is rapid intravenous injection (Douglas 1965). Here, the full effect of the concentrated dose of local anaesthetic administered, is immediately felt on those organ systems most sensitive to that effect, viz the cardiovascular and central nervous systems.

Local anaesthetic agents administered rapidly intravenously, do not mix immediately with the whole blood volume, but pass round as a "slug" for at least one and
possibly two circulations (Paton 1960, Light 1965). The blood level of local anaesthetic in this "slug" is much higher than the final equilibrium concentration and depends on factors such as concentration of drug, rate of administration, circulation time and the effective volume of circulating blood (Crawford 1966). The direct action of a "slug" of local anaesthetic on peripheral receptor sites may explain the abrupt cardiovascular effect which follows intravenous administration and may be more important than central nervous system effects (Wiedling 1964, Pickering and Kissin 1938). The receptors which, in part at least, evoke these responses are situated in the aortic body and carotid sinus although stretch receptors are more protected by virtue of their special structure (Crawford 1966, Wiedling 1964).

Endoanaesthetic action is defined as depression and blocking respectively of inner sensory receptors and other afferent structures, produced by local anaesthetic introduced into the blood stream. Lignocaine has an endoanaesthetic action mainly on the cardiac receptors when administered intravenously (Wiedling 1964).

It has been demonstrated that intravenous injection increases the toxicity of local anaesthetic solutions many times that which follows subcutaneous injection (Wiedling 1964, Shotwell 1948). When, in addition, the drug is used at a higher concentration; e.g. mepyricaine 3 percent,
mepivacaine 3 percent, prilocaine 3 and 4 percent; systemic toxicity is further increased. It has become increasingly necessary therefore, to recognise the systemic toxic potential of the local anaesthetic drugs in common use, particularly as most of these drugs possess a high degree of intravenous potency.

Although the systemic toxicity of new local anaesthetic compounds is widely tested in animal experiments, frequently these results are not applicable to man because of species difference in disposal (Goodman and Gilman 1966). Consequently, the most informative data is provided by investigations of the intravenous toxicity of local anaesthetics performed on human volunteers (Foldes et al 1960, Foldes et al 1965, Englesson 1962), and from observations made on patients requiring therapeutic doses of intravenous local anaesthetics (De Jong and Walts 1966).

Foldes and co-workers (1960, 1965) investigated the intravenous toxicities of the hydrolyzable ester-linked compounds meprylcaine, isobucaaine, procaine, 2-chloroprocaine, and tetracaine, as well as the structurally related amides, lignocaine and mepivacaine. Englesson (1961) also compared the intravenous tolerances of lignocaine and prilocaine. The results of these investigations indicate that the more rapidly hydrolyzable esters generally have a lower degree of intravenous toxicity than the more stable amides. A notable exception to this generalization is the readily hydrolyzable
isobucaine, which shows an unexpectedly high degree of intravenous toxicity, presumably due to rapid uptake by the central nervous system (Foldes et al 1966). Of the drugs investigated, the one used most frequently in dentistry, lignocaine, possessed the highest degree of intravenous toxicity as judged by the tolerated length of infusion. Lignocaine's higher toxicity following continuous intravenous infusion and its greater propensity to elicit side effects has been demonstrated also in animal experiments (Vallini and Gaiatto 1963, Ulfendahl 1957). However, when rapid intravenous injection is made; lignocaine, prilocaine, and mepivacaine are equipotent, and consequently extravascular injection is necessary to benefit from the use of these more potent compounds (Foldes 1966, Wiedling 1963). Amido type local anaesthetics are bound more strongly by human albumin than are esters, a property which may play a significant part in their inactivation and in the differences seen in different amidos (Meyers 1967).

It is claimed (Astrom and Persson 1961, Knox et al 1961), that lignocaine, as well as mepivacaine, shows a prolongation of toxic effects following repeated administration, indicative of a cumulative property. However, Luduena et al (1960) could not demonstrate a cumulative toxic effect with lignocaine nor is it evident with prilocaine (Bjorn 1966). Mepivacaine has a high degree of anaesthetic
potency attributable to the reactivity of its side chains whereby it is bound more closely to nervous tissue than lignocaine (Truant and Wiedling 1959, Gruber 1962). As a result, it is eliminated more slowly and successive doses tend to be cumulative (Hofmeyr 1959). The duration of both anaesthesia and toxic symptoms is longer with mepivacaine although it has a higher intravenous tolerance than lignocaine (Lechat and Deleau 1961, Luduena et al 1960).

When using drugs of high systemic potency, concentration as it affects overall dosage, is an important influence on systemic toxicity.

G. Vasoconstrictor content of the total preparation.

All synthetic local anaesthetic drugs are vasodilators (Bishop et al 1961, Dhuner and Lewis 1966). This vasodilatory effect, although not fully understood, is thought to be the result of two pharmacological actions.

1) because of their general depressant effect on nervous tissue, local anaesthetics also block the conduction of vasomotor impulses in the perivascular sympathetic plexus producing vasodilatation at the injection site. However, if this were the only cause of vasodilatation, the strength of response would be independent of the agent used, which in fact is not so.

2) it is likely therefore that vasodilatation is the combined result of sympathetic blockade and the direct
effect of the local anaesthetic agent on the smooth muscle component of the vascular wall. The latter property is an inherent characteristic, peculiar to each drug and probably accounts for the observed differences in vascular effect (Dhunor and Lewis 1966, Braid and Scott 1966).

Although most local anaesthetic agents require a vasoconstrictor to limit their rate of absorption, mepivacaine and, to a lesser extent, prilocaine, are less vasodilatory and have a marked affinity for human albumin which is responsible for their "built in" localizing characteristics (Ericksson et al 1966, Astrom 1965). Mepivacaine is the first synthetic drug to produce satisfactory local anaesthesia for general dental purposes without the benefit of a vasoconstrictor (Weil et al 1961, Adriani 1960). Consequently when plain solutions of these amides are deposited extravascularly, the absence of a normal vasoconstrictor component does not greatly affect their systemic toxicity from the point of view of rapid absorption. However, if deposited intravascularly, the systemic effects of the total preparation are at once apparent. With plain solutions, only the pharmacological effects of the local anaesthetic drug are observed. When a vasoconstrictor component is included, the combined effects of the adrenaline and local anaesthetic agent, particularly on the cardiovascular system are evident.
In this regard, it has been claimed that amide local anaesthetics and adrenaline are antagonistic; the net cardiovascular response being the result of subtraction of the former's depressor effect from the latter's pressor effect (Goldman 1965, Wlodling 1964). Wlodling (1969), demonstrated that the inhibitory effect of 2 percent lignocaine on the blood pressure of rats was balanced by 5 µg/ml of adrenaline. When a 2 percent solution of lignocaine, containing 10 µg/ml (1:100,000) adrenaline, is deposited intravenously in man, the cardiovascular effect of the adrenaline predominates (Sara 1963), though somewhat reduced in comparison with the effect of a plain 1:100,000 adrenaline solution (Goldman 1966).

The effect of plain local anaesthetic agents on the heart seems to depend mainly on the dose administered and the rate at which it enters the circulation. The condition of the heart may also influence the response, as it may be sensitized to the action of local anaesthetics by tissue hypoxia and following myocardial infarction (Steinhaus 1952). Large doses of local anaesthetic prolong the conduction time and depress the contractility of the myocardium (Foldes 1960). When a large dose of dentally administered local anaesthetic is inadvertently, rapidly deposited intravenously, the first organ to experience the impact of the drug's systemic effect is the heart and bradycardia or even cardiac arrest may occur.
Reactions of the latter type are sudden in onset and collapse is rapid and complete. Moore (1955) has emphasized the need for further research to ascertain the part played by direct cardiac depression in systemic toxic reactions to local anaesthetic agents; and particularly in those fatalities occasionally reported (Gordh 1965, Di Giovanni 1963), which occur immediately following injection and in which, the usual toxic manifestations of central nervous origin are absent.

It is generally agreed that, whereas the vasoconstrictor is mainly responsible for minor systemic disturbances, the local anaesthetic agent is associated with the more serious, life endangering reactions (Epstein 1958, Wallace et al 1956, Sadove et al 1952). In view of the fact that lignocaine, mepivacaine and prilocaine are equipotent when administered rapidly intravenously, and are sometimes used at concentrations of 2, 3 and 4 percent respectively, without the benefit of a vasoconstrictor, theoretically their solutions possess a high toxic potential. This potential toxicity must be attenuated by depositing these solutions slowly and extravascularly (Hiatt 1961).

In the previously mentioned investigation of human tolerance to continuous intravenous infusion of ester type local anaesthetics and the amide lignocaine (Foldes et al 1960), electrocardiographic tracings indicative of
deteriorating cardiac activity were frequently encountered despite the relatively minor nature of the accompanying functional disturbances. However, in a similar investigation involving the esters meprylcaine and isobucaine, and the amide mepivacaine, no evidence of myocardial depression was observed (Foldes et al 1965). In both these experiments the local anaesthetic agents were infused at milligrams per kilogram per minute rates proportional to the concentrations in which they are employed for production of regional anaesthesia. Mepivacaine and lignocaine were administered at a rate of .5 mg/kg/min. Therefore the amount of local anaesthetic infused in one minute, to an average sized patient, was approximately the amount contained in 2 ml of a 2 per cent lignocaine solution or 1 ml of a 3 percent mepivacaine solution. At this rate of infusion, the effect on the cardiovascular system of all the local anaesthetics investigated was often stimulatory being evidenced by an increase in pulse rate and blood pressure.

Englesson et al (1962) compared human tolerances to intravenous lignocaine and prilocaine and reported a slight but insignificant rise in blood pressure. Pulse rate was mostly unchanged, though several patients exhibited tachycardia which was more pronounced with lignocaine. The rate of administration in these experiments was 200 mg in 2 minutes 20 seconds.
De Jong and Walts (1966) administered 100 mg doses of lignocaine intravenously over a period of 60 seconds, a somewhat similar rate of administration to that used by Englesson et al. (1962), and noted the following cardiovascular signs. Pulse rate rose during injection, the electrocardiograph tracing showing only signs of sinus tachycardia. Instead of the hypotension they expected to develop, there was marked systolic hypertension, the diastolic pressure being less affected.

Therefore, continuous intravenous infusion of both ester and amide type local anaesthetics at rates approximately proportional to the concentrations in which they would be used for regional anaesthesia, often has a stimulatory effect on the cardiovascular system, which is the result of central nervous system excitation. It is possible for the medullary cardiovascular centre to be simultaneously stimulated and depressed with either effect predominating. The infusion of local anaesthetic in the investigations cited was discontinued before central and peripheral depression of the cardiovascular system occurred.

The cardiovascular effects of large intravenous doses of local anaesthetic drugs are, bradycardia and hypotension. The former is the result of either direct depressant action on the conduction system and myocardium or, depression of the medullary cardiovascular centre. The
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latter is the result of peripheral vasodilatation due to either, depression of the autonomic system and medullary vasomotor centre or, direct effect on the blood vessels (Sara 1963).

Using contemporary dental local anaesthetic agents, at concentrations from 2 to 4 percent, it is possible to inadvertently administer 40 to 80 mg intravenously in several seconds if preliminary aspiration is not observed. Compared with the rates of infusion observed in the investigations previously cited, this represents a large single dose of local anaesthetic agent.

The stimulatory action of adrenaline on the heart tends to increase cardiac irritability and produce arrhythmia. Adrenaline produces tachycardia and increases systolic blood pressure, while at the same time, decreasing peripheral resistance and diastolic pressure. From the results of intravenous injection of local anaesthetic agents in man, it is apparent that, although the cardiovascular effects of adrenaline and local anaesthetics may be antagonistic, it is not a simple matter of subtraction of the depressor effect of the latter from the pressor effect of the former. The direction and magnitude of the cardiovascular response to local anaesthetic agents is influenced by the rate of administration as well as the dose administered.
Like adrenaline, local anaesthetic agents frequently have an initial stimulatory effect on the heart, producing tachycardia, hypertension, and possibly cardiac arrhythmia (Foldes et al 1965). However, with increasing dosage the depressant effect of all synthetic local anaesthetics on the cardiovascular system is evident (Wiedling 1964, Goodman and Gilman 1966). With a single large intravenous dose this depressant effect may be primary (Moore 1955).

The net cardiovascular response following intravenous injection of a solution containing both local anaesthetic agent and adrenaline, is usually an increase in systolic blood pressure and pulse rate, and possibly a decrease in diastolic blood pressure with a corresponding increase in pulse pressure. However lignocaine, as well as other synthetic local anaesthetic agents, may increase the brief drop in blood pressure which follows the initial rise resulting from the intravenous injection of adrenaline (Wiedling 1964, Pickering and Kissin 1936).

When local anaesthetics are used extravascularly at dosage levels approximating the recommended maxima, it is important that their rates of absorption be controlled so that toxic blood level of drug does not occur.

Absorption of local anaesthetics is a complex problem involving the circulation of the injected region at
capillary level. The vascular response produced by both vasoconstrictors and local anaesthetics varies from tissue to tissue (Dhuner and Lewis 1966). For example, to produce vasoconstriction when deposited intramuscularly, the alpha sympathomimetic effect of the vasoconstrictor component of a local anaesthetic solution has to overcome the strong vasodilatory response of the local anaesthetic component. Consequently local anaesthetic solutions are not entirely localized in muscle tissue (Tainter and Thondson 1938, Braid and Scott 1966, Martin et al 1966, Dhuner and Lewis 1966). Local anaesthetic agents have less vasodilatory effect on the submucosal vessels (Dhuner and Lewis 1966).

Although adrenaline has subsidiary analgesic properties of its own which may, in combination with local anaesthetic agents, augment their effect (Harris 1947), its property of prolonging anaesthesia is generally accepted to be the result of its ability to delay absorption of the total preparation. Conversely, termination of anaesthesia by facilitating absorption of the local anaesthetic - vasoconstrictor preparation, is best accomplished by the administration of sympatholytic drugs, although vasodilators and drugs which increase diffusion are effective also (Luduena 1957).

The vasoconstrictor's role in delaying absorption of local anaesthetic solution is clear. However, the
inherent localizing characteristics of some amide local anaesthetics also influence their rate of absorption and the resultant plasma concentration. Investigations by Dhuner et al (1965), and Scott (1964), on blood levels of local anaesthetic following regional anaesthesia, suggest that the influence of adrenaline on the absorption of local anaesthetics from regions of poor capillary vascularity, may be less than believed. Clinical experience of the behaviour of local anaesthetic preparations, with and without adrenaline, in the pterygomandibular space, a region of relatively poor capillary vascularity, supports this view.

D. HYPERSENSITIVITY.

Manifestations of the systemic toxic effects of local anaesthetic agents occur when toxic blood level perfuses receptor sites in the central nervous system and cardiovascular system. However, individual susceptibility plays an important part in determining the magnitude and type of response. Englesson et al (1962) noted that the systemic toxic manifestations due to high blood level of local anaesthetic drug, were always of the same type for each subject, but varied from individual to individual. De Jong and Waits (1966) also found that many patients exhibited individually characteristic symptoms due to toxic blood level of local anaesthetic agent.
A small proportion of any given group or population will show either hypersusceptibility or resistance to local anaesthetic drugs (Dille 1963). The blood level of drug which produces signs of systemic toxicity in the hypersensitive subject is lower than for a normal subject and is therefore a relative toxic blood level of drug. In hypersensitivity, there is an exaggerated normal response and Moore (1955) uses the term "hypereegy" to distinguish this type of reaction from allergy, in which the pattern of the response is altered.

Although true patient hypersensitivity is an inherent characteristic (Waldman 1967, Wigand 1958), the systemic response to local anaesthetic agents is also influenced by,

(a) physical condition
(b) pathological conditions and concurrent drug therapy.
(c) climatic conditions.

Physical condition

(a) The importance of patient size and physical condition in determining local anaesthetic dosage is emphasized by Steinhaus (1962) and Moore and Green (1957). Particular care is required in administering local anaesthetics to patients in the extremes of age who, because of their smaller body size, have a smaller circulating blood volume and can, therefore, tolerate less drug (Ningham and Malherbe 1958, Bjorn 1966, Toogood 1960). The same applies to the
condition of neurogenic shock which is characterized by a marked decrease in the circulatory blood volume and mass of tissue perfused. The shocked patient has greater vulnerability to the propensity of intravenously administered local anaesthetics to induce hypotension and bradycardia (Crawford 1966).

Starvation and vitamin C deficiency have been shown to increase the susceptibility of animals to the toxic effects of local anaesthetics; the latter presumably by increasing capillary permeability and rate of local anaesthetic absorption (Moore 1956).

Debility, particularly with regard to liver and renal dysfunction, increases local anaesthetic toxicity by retarding detoxification and elimination respectively (Moore 1955).

(b) Pathological conditions and concurrent drug therapy

Although in the normal patient the cardiovascular system is not as sensitive to local anaesthetics as the central nervous system, disease may predispose the heart to their depressant effects (Steinhaus 1957). In addition, both local anaesthetics and vasoconstrictors can produce cardiac arrhythmia particularly in patients with cardiovascular disease (Hughes 1966).

Epiloptics are invariably on anti-convulsant therapy and require careful treatment because local anaesthetics
tend to produce small focal centres of stimulation in the cerebral cortex which may lead to the firing of an epileptic fit (Locke 1961, Christensen 1967). Individuals with a family history of epilepsy may also have a lower seizure threshold than normal (Toogood 1960). The central nervous system effects of local anaesthetics depend on the concentration in the blood; hence the importance of avoiding rapid intravenous injection. Low concentrations of lignocaine have a salutary effect on the incidence of epileptic seizures of the petit mal type (Bjorn 1960). With increasing concentration however, a spectrum of central nervous system manifestations is seen which starts with anticonvulsant action and progresses to grand mal seizures and loss of consciousness (De Jong and Walts 1966).

The systemic response to local anaesthetic drugs may be modified by hereditary conditions affecting the systems responsible for their metabolism. Variants of the enzyme cholinesterase, which are responsible for the hydrolysis of ester-type local anaesthetics, are controlled by at least four different genes. Cholinesterase anemia is an hereditary disease in which cholinesterase is lacking (Kalow 1964). In patients with genetically or pathologically induced low plasma cholinesterase levels, toxic plasma concentration may accumulate even after the use of rapidly hydrolyzable local anaesthetic agents.
(Foldes et al 1965). Myasthenic patients also often respond abnormally to drugs (Wood-Smith and Stewart 1963, Kalow 1964). The absence of an ester linkage from the anilide molecular configuration indicates that it is not hydrolyzed by plasma esterases. Metabolism of anilides is by an entirely different mechanism involving enzymes in the liver microsomes (Lawrence 1966, Myers 1967). It has been demonstrated that drugs, such as potent monoamine oxidase inhibitors and chloramphenicol, which inhibit protein synthesis and depress enzymatic metabolism in the liver, prolong local anaesthetic narcosis (Heinonen 1966). The converse is equally true and agents such as phenobarbital which activate the hepatic enzymes, shorten the toxic effects of anilide local anaesthetics.

c. Climatic conditions.

James (1955) considered that changes in climatic conditions have a bearing on the incidence of systemic disturbances accompanying dental local anaesthesia. It is doubtful that a similar correlation exists with extremes of temperature (Moore 1955, James 1955).

B. ALLERGY

Allergic response to local anaesthetic agents may take the form of either skin reactions of the delayed type
of contact dermatitis, or generalized systemic responses usually centred in the cardiovascular system (Dille 1963). The signs and symptoms of an allergic systemic reaction reflect an attempt by the body to remove a noxious agent. Therefore, even though allergy results in symptoms of severe illness, it is a purposeful response and one of protection (Moore 1955).

Although the tendency to develop allergy may be inherited, the specific reaction itself is acquired and is dependent upon previous exposure to a particular drug (Tillman 1958). Sensitization is acquired following administration of the drug, by the production of antibodies as a result of which the reactivity of the tissues is changed. Subsequent doses of antigen then cause an antigen-antibody reaction with liberation of anaphylatoxin (thought to be histamine), which is very damaging to cells, particularly reticulo-endothelial cells (Dille 1963). If, as with local anaesthetic agents, the antigen is non-protein, it may conjugate with protein constituents of body tissues (amino acids) and in this form, cause the production of antibodies (Dille 1963, Dobbs and Kader 1980). Criep (1953) described a serum sickness type reaction with fever, hives, joint symptoms and malaise occurring 1 to 12 days after a single initial dose of procaine.
Following sensitization, the actual dosage of subsequently administered antigen is relatively unimportant in the production of allergic response (Moore 1955). Furthermore, since no premonitory signs accompany sensitization, prevention of allergic reaction is difficult and rests solely on pre-anaesthetic evaluation. Reports of previous allergic reactions must be regarded seriously. However, complications arising out of local anaesthesia are sometimes conveniently dismissed as "allergic" (Morris 1967), and it is most important that indiscriminate use of the term be avoided as one is bound to accept the report of a patient that he is "allergic" to a particular drug.

Although the scratch test and intradermal injection are useful diagnostic tools of the allergist, for determining drug sensitivity (Dille 1963, Morris 1967, Tillman 1958), they are of no value in predicting generalized allergic responses of the anaphylactic type (Toogood 1960). Furthermore, since anaphylaxis can follow the use of infinitesimal amounts of local anaesthetic, even small trial doses can be dangerous (Moore 1955). Holti and Hood (1965) reported a peculiar skin test reaction to lignocaine in which there was little local wheal but widespread urticaria indicative of a high degree of allergic sensitivity.

The allergic potential of local anaesthetics depends on their chemical structure (Tillman 1958). Sensitivity to
local anaesthetic derivatives of amino benzoic acid is more common than to amides and is due to the position of the amino group (Epstein 1958). Derivatives of para-amino benzoic acid are the most allergenic; ortho substituted compounds are least and meta-amino benzoic acid derivatives occupy an intermediate position (Tillman 1958). Cross sensitization is possible with other compounds containing a para-amino benzoic acid base, e.g. sulphonamides, vitamin B (Mitchell 1953, Broadbent 1957).

Allergy to lignocaine, which is an ortho derivative of acetanilid, is rare. Nevertheless there have been reports of allergy to lignocaine, prilocaine and mepivacaine (Holtt and Hood 1965, Di Giovanni 1963, Noble and Pierce 1967, Tillman 1958, Waldman 1967).

The irritation of a skin reaction, sometimes provides an early indication of impending generalized allergic response. A systemic disturbance characterized by redness of the face instead of the usual pallor also suggests allergy (Toogood 1960). It is doubtful if any reaction can be classified as anaphylactic or allergic unless it is accompanied by a skin reaction (Sadove 1952), or a history of long standing allergic pattern (Steinhaus 1962).

The terms "shock tissues" or "shock organs" indicate the site of the allergic manifestation (Moore 1955). Di Giovanni (1963) draws attention to the brain as a possible
"shock organ", although it is not usually classified as such, and suggests that convulsive disorders following repeated careful administrations of small doses of local anaesthetic agent may be due to sensitization of the central nervous system. Sadove (1952) felt there was no conclusive evidence to support the theory of sensitization following repeated injection.

Signs and symptoms of allergy to local anaesthetic agents arise in a variety of "shock tissues", (a) angioedema may be localized or generalized. When it occurs in the upper respiratory tract it may cause severe respiratory obstruction (Moore 1955), with difficulty and prolongation of expiration and audible wheezing, or complete respiratory arrest (Dille 1963). (b) the skin is the site of urticaria and pruritus, (c) cardiovascular manifestations are sudden hypotension, tachycardia, cardiac pain and possibly nausea, vomiting, perspiration, dizziness and syncope (Dille 1963). (d) with the rare occurrence of clinical anaphylactic shock, the shock tissues are located in the cardiovascular and respiratory systems. The reaction is characterized by sudden onset of respiratory and cardiovascular collapse following the administration of a minute amount of drug (Moore 1955, Sweets 1963).
Some individuals show a marked tendency to develop allergy. Eczematoid or atopic dermatitis is an intrinsic form of allergic dermatitis, dependent on the same hereditary factors that predispose to asthma, allergic rhinitis and urticaria, and is often associated with these in such a patient (Tillman 1958). Pre-anaesthetic evaluation therefore should include a history of previous allergic disorders of whatever kind (e.g. hayfever, asthma), as well as hereditary connections which may predispose the patient to allergy (Mitchell 1953).

Where allergy to one of the basic molecular configurations is known, a local anaesthetic belonging to another group must be employed (Waldman 1967). In patients with allergic manifestations to conventional local anaesthetics, antihistamines have been used as alternative drugs (Goodman and Gilman 1966).

3. THE FATE OF LOCAL ANAESTHETIC AGENTS FOLLOWING ABSORPTION.

The fate of local anaesthetic agents following their absorption into the bloodstream determines the plasma concentration attained. As previously mentioned, except after rapid intravenous injection, plasma concentration of drug is the main factor determining local anaesthetic toxicity. The plasma level attained depends on
(a) absorption
(b) distribution - concentration in or exclusion from certain tissues.
(c) metabolism in the plasma or body tissues, e.g. liver, kidneys.
(d) excretion,
plus the time relation of these factors (Paton 1960).
(a) absorption

Local anaesthetic drugs should produce profound anaesthesia of sufficient duration with minimal latency, and be absorbed at a rate consistent with the body's capacity to metabolize and thus prevent toxic accumulation in the blood stream (Steinhaus 1962).

Dental local anaesthetics gain access to the blood stream either directly as a result of accidental intravascular injection, or indirectly by absorption from the injection site. Signs and symptoms of systemic toxic reaction to high plasma concentration of local anaesthetic agent usually follow a typical pattern of gradual progression although slight differences may characterize the individual response (Foldes et al 1965, Englesson 1965, De Jong and Walts 1966). When the typical pattern is condensed so that the manifestations of toxicity apparently occur simultaneously, rapid intravenous injection is
responsible (Moore 1955, Sara 1963).

With the exception of degradation and excretion, all the major factors governing plasma level of local anaesthetic drug following extravascular administration, are in the control of the anaesthetist and dependent upon his choice of solution and method of its administration. Choice of solution should take into consideration the influence of site of administration on the rate of absorption and plasma level of drug attained (Scott 1964). Matthes and Schabert (1966), consider that for injection of the face, oral, and pharyngeal regions, allowance should be made for rapid absorption and increase in blood level of local anaesthetic agent, with a corresponding need to reduce dosage and concentration. However, little is known of the influence on rate of absorption of the different injection sites encountered in dental regional and submucosal procedures.

With the exception of the role played by the anaesthetic agent, the other factors influencing absorption have been discussed in the preceding chapters.

The rate of absorption of plain solutions of local anaesthetic agent is influenced by the inherent localizing characteristics of the drug itself (Astrom and Persson 1961). In this regard amides are less vasodilatory than ester-type local anaesthetics. In addition they have an affinity
for human albumin which contributes to their retention at the injection site. Yet despite these characteristics, amides show a remarkable spread of local anaesthetic effect (Sadove 1965).

Plain solutions of the amides prilocaine and mepivacaine at suitable concentrations are sufficiently retained at the injection site to establish submucosal anaesthesia of limited duration. Satisfactory mandibular anaesthesia may be accomplished by depositing plain solutions of the amides prilocaine, mepivacaine and lignocaine in the pterygomandibular space. Luduena and Hoppe (1956) considered that greater localization of prilocaine at the injection site contributed to its lower acute toxicity when compared with lignocaine. Mepivacaine's stronger binding with nervous tissue is thought to be responsible for its more prolonged anaesthetic effect when compared with lignocaine (Gruber 1962).

(b) distribution = concentration in, and exclusion from, certain tissues.

Having entered the blood stream local anaesthetics may be taken up by constituents of the blood or adsorbed by peripheral tissues. The extent of binding of prilocaine and lignocaine, in vitro, with serum proteins was studied by Eriksson et al (1966). Prilocaine showed a lower protein binding by a higher percentage in the filtrate. In addition,
to the proportion bound to plasma protein, a considerable amount of local anaesthetic was taken up by the red blood cells; prilocaine more so than lignocaine (Astrom and Persson 1961).

Concentration in the tissues is primarily determined by the plasma level of free drug (Foldes 1966). Comparison of the differences in arterial and venous blood levels of lignocaine and prilocaine following constant speed infusion indicates either peripheral uptake or metabolism of considerable amounts of the injected drug (Eriksson et al 1966). Fifty percent of prilocaine in arterial blood is taken up by peripheral acceptor tissues and is thus temporarily withdrawn from the circulation. The figure for lignocaine is 25 percent. The lower blood concentration of prilocaine than lignocaine following administration of identical doses may be the result of, (i) greater localization at the injection site, (ii) peripheral uptake, (iii) more rapid metabolism (Luduena and Hoppe 1956). Adsorption of lignocaine and prilocaine by the tissues is similar. Rapid metabolism alone does not explain the lower plasma level of prilocaine. A possible explanation lies in differences in distribution between intra and extracellular fluid (Englesson et al 1962).

Adsorption of local anaesthetic by peripheral tissues requires passage through cellular barriers. In general, it
is agreed that this is dependent upon the drug's ability to dissolve in the fatty material of the cell wall (Paton 1960). Although, in vitro, lignocaine and prilocaine pass into a lipid phase with identical speed, lignocaine has the higher lipid solubility (Eriksson et al 1966).

The differing rates of onset of anaesthesia characteristic of local anaesthetic agents suggest differences in penetrating efficiency. It has been suggested that ability to rapidly penetrate cellular barriers influences not only onset of anaesthesia but also the rate of uptake by other tissues throughout the body (Foldes et al 1965). In some tissues the drug is merely adsorbed and produces no response. Those which are susceptible to the effects of adsorbed local anaesthetic agent are known as receptor tissues (Foldes et al 1960). Local anaesthetics (e.g. lignocaine, isobucaaine), which pass rapidly from the blood to vital receptor tissues (e.g. by penetrating the blood-brain barrier), temporarily escape detoxification and may attain toxic proportions in such tissues (Foldes et al 1965).

(c) metabolism in the plasma or body tissues.

The two basic types of local anaesthetic agent are metabolized by entirely different processes; the esters by enzymatic hydrolysis in the plasma, the amides by detoxifying enzymes mainly in the liver (Lawrence et al 1966). Once a local anaesthetic has been absorbed into the blood stream,
the plasma level attained depends mainly on its rate and method of detoxification (Foldes et al. 1965).

Esters are generally less toxic than amides because of their different metabolism. They are hydrolyzed mainly in the plasma by the enzyme cholinesterase to their pharmacologically inactive acids and alcohol components (Foldes and McNall 1961). Although esterases in the liver also contribute to their metabolism (Goodman and Gilman 1966), enzymatic hydrolysis rates and quantitative or qualitative changes in plasma cholinesterase activity are the main influences on systemic toxicity of ester linked compounds (Kalow 1964, Foldes et al. 1965).

The absence of an ester linkage in the amide molecular structure indicates that they are not metabolized by plasma esterases (Myers 1967). Amides undergo a series of oxidative changes in the liver microsomes (Lawrence et al. 1966, Aström 1965). Lignocaine is initially de-ethylated to acetaldehyde and subsequent degradation leads to splitting of the amide linkage and presumed hydroxylation of the aromatic ring (Myers 1967).

Prilocaine, which evolved from attempts to improve the safety margin of lignocaine, contains no ethyl group. Consequently it is metabolized faster than lignocaine as it can be attacked directly by the enzyme amidase (Foldes 1966).
Prilocaine's rapid metabolism has the occasional side effect of producing methaemoglobinæmia (Sadove 1965). Although normally only associated with the administration of large doses of prilocaine; exceeding 10 mg/Kg body weight (Onzi and Tyuma 1965); methaemoglobinæmia can follow the use of conventional doses in susceptible individuals (Wigand 1958).

Conditions affecting the detoxifying enzyme systems in the liver have a particular bearing on the rate of destruction of amide type local anaesthetics such as lignocaine, prilocaine and mepivacaine (Heinonen 1966). Cumulative toxicity studies on rats showed that depression of hepatic enzyme systems markedly increased the toxicity of lignocaine but not of the ester-type local anaesthetic agents (Lawrence et al 1966). The influence on toxicity of drugs which inhibit or stimulate the liver enzymes responsible for amide metabolism has been mentioned earlier in this chapter (Heinonen 1966, Myers 1967).

(d) excretion.

The kidneys complete the elimination of those local anaesthetics which are slowly detoxified by the liver, viz amides. Less than 1 percent of an intravenous dose of 50 mg of lignocaine was subsequently recovered from the urine, and renal excretion has little effect on toxicity even when larger doses are administered (Beckett et al 1965).