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CHEMICAL STRUCTURE OF LOCAL ANAESTHETICS

BY

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Local anaesthetic properties have been demonstrated in compounds possessing many different chemical groups (fig. 1). Literally hundreds of compounds have been synthesized in an effort to find the ideal local anaesthetic. Few, however, have been subjected to clinical trial and even fewer have achieved lasting success in clinical practice. Some of the reasons for this state of affairs are that compounds possessing a high systemic toxicity, or causing a local irritation at the site of injection, or which following continued use can be associated with the development of allergy, are immediately rejected. Other factors which determine the success or failure of what would otherwise be a successful agent, are chemical instability, which is associated with a short shelf life, and costly methods of synthesis.

Group	Structure
Ester	—COO—
Thio-ester	—COS—
Amide	—CONH— —NHCO—
Amino alkyl ethers	—O—$(CH_2)_n$—N<
Amidines	—C(=NH)—NH—
Guanidines	—NH—C(=NH)—NH—
Urethans	—NH—C(=O)—O—
Amino ketones	—CO—$(CH_2)_n$—N<

FIG. 1
Chemical groups.

Physical properties of local anaesthetic solutions.

The majority of local anaesthetics are basic compounds, which are usually made available as the more stable water soluble hydrochlorides. For injection it is essential that solutions be made isotonic, otherwise tissue damage will result from the injection of a large volume of a hypotonic solution. When dissolved in solution two different constituents are present, namely: (1) the uncharged base B which has been shown to be responsible for the local anaesthetic activity of the solution; and (2) the correspondingly charged acid ion BH^+. At equilibrium there is thus $BH^+ \rightleftharpoons B + H$.

The balance between the concentration of base and the charged acid depends upon the hydrogen ion activity or pH of the solution and the ionization constant or pKa of the compound (Albert, 1952). The degree of dissociation can be calculated at different pH values. When the degree of dissociation is plotted against the pH, it can be observed that at a pH approaching the pKa of a compound this relationship is not linear but sigmoid in character. This means that around the pKa value the alteration in the degree of ionization is considerable for only a small change in pH.

Ehrenberg (1948) was able to demonstrate this effect of variation of pH on the minimal effective concentration of local anaesthetics in solution on a frog nerve muscle preparation. He was also able to calculate that the concentration of free base present at the different pH values which resulted in a nerve block was constant. This work confirmed the previous study by Trevan and Boock (1927) where similar observations were made following variation of pH of solutions of local anaesthetics applied to the cornea.

Unfortunately few investigators—using preparations of this type to test for local anaesthetic activity—have appreciated the significance of these findings, for many of the reports do not specify the pH of the solutions used. This objection does not apply when solutions are tested by injection into tissues which, by reason of their

strong buffering capacity, can correct the pH to that of the body, namely 7.4.

Comparison of local anaesthetic activity.

The author has reviewed some of the tests used to compare local anaesthetic activity (Geddes, 1955). These tests are often difficult to perform and details vary from laboratory to laboratory. There is also a failure to standardize methods of comparison and this makes correlation virtually impossible for investigating local anaesthetic drugs. Lofgren (1948) points out that "some authors investigate the minimal effective concentration, others the duration, and others again the latency time".

Further, there is no one accepted local anaesthetic which is used as a standard to compare with compounds of unknown activity. Some investigators use cocaine, others procaine; more recently lignocaine has been taken as the reference substance.

Cocaine.

The numbing effect of cocaine on the tongue has been known since it was brought to Europe by the early Spanish colonizers of South America. The alkaloid responsible for this property was isolated from the leaves of the cocaine plant "Erythroxylon coca" by the German scientist Albert Niemann in 1860. The clinical application of the local anaesthetic effect was not appreciated till 1884, when Koller, following animal experiments, introduced cocaine into ophthalmic surgery. It was not long before cocaine was being used for infiltration, nerve blocks and spinal anaesthesia. Under these circumstances cocaine is highly toxic and numerous fatalities were soon being reported. Other problems are the effects associated with cortical stimulation which produce addiction and the legal restriction of its use. These disadvantages have prompted a ceaseless search for a non-habit-forming, less toxic, and longer-lasting local anaesthetic.

The search for the active part of cocaine.

Following the extraction of the various alkaloids of cocaine the synthetic chemists established their chemical structure. Cocaine was found to be readily hydrolyzed to give rise to the base ecgonine, benzoic acid and methyl alcohol. The formula for cocaine is based on the alkaloid ecgonine, a tropane derivative which atropine and scopolamine have as a common parent compound. Cocaine is the benzyl derivative of the methyl ester of ecgonine (fig. 2).

A number of experiments were carried out to determine which parts of the molecule were essential for the local anaesthetic activity (fig. 2). These included: (1) hydrolysis of the carbomethoxy group (this gave loss of anaesthetic activity); (2) hydrolysis of the benzoate group (this gave loss of local anaesthetic activity); and (3) restoration of the benzoate group in a decarbomethoxylated compound results in the restoration of local anaesthetic activity giving tropacocaine (fig. 2).

The importance of the ring system.

To investigate the importance of the ring system (fig. 3) the six-membered ring of the tropane system piperidine was combined with para aminobenzoic acid, and one of the resulting active compounds which was used clinically was β Eucaine. It was thus established that the tropane ring was not essential for local anaesthetic activity.

The synthetic chemists were therefore encouraged to synthezise simpler compounds. At the turn of the century attention was focused on derivatives of para amino benzoic acid (fig. 4). Benzocaine (ethyl para amino benzoic acid) is still in use as a topical anaesthetic in lozenge form, and even in 1954, Kohn, Rutter and Vitali incorporated benzocaine (2 per cent) in urethane (40 per cent) to produce a long-lasting anaesthetic for the treatment of amputation neuromas.

Einhorn and Oppenheimer (1900) stated that local anaesthetic activity could be expected from an ester of any aromatic acid containing, but not always, a basic group. Orthocaine (Orthoform) (fig. 4) was introduced by Einhorn and Oppenheimer (1900), and this was the methyl ester of hydroxy aminobenzoate. Following difficulties with the large-scale production of orthocaine, orthocaine new, a closely related compound was prepared (fig. 4) and used clinically.

Many allied compounds have been synthesized. In general, lengthening of the alkyl chain increases the local anaesthetic activity; however, due to their insolubility in water these local anaesthetics are mainly of value as surface anaesthetics.

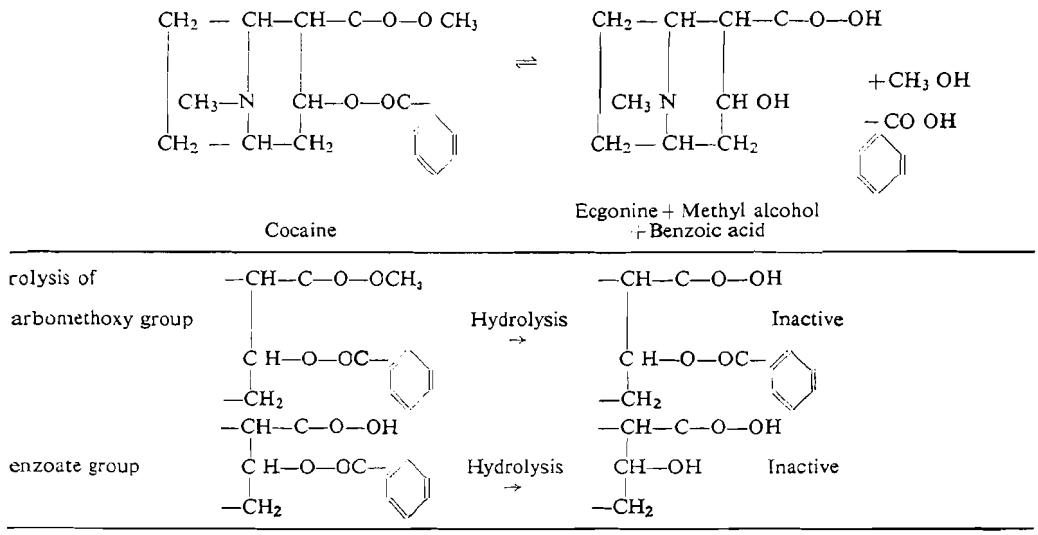


FIG. 2

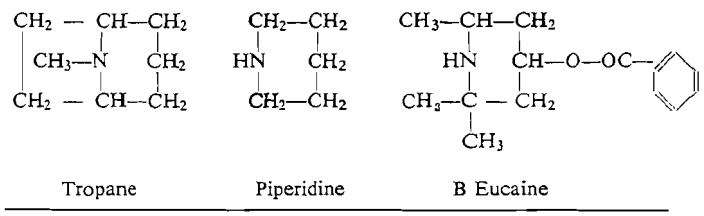


FIG. 3
Importance of ring system.

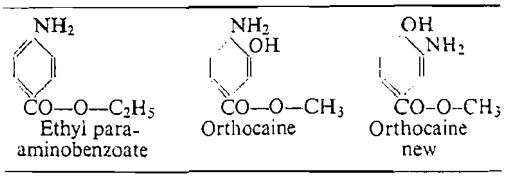


FIG. 4

Derivatives para-aminobenzoic acid.

Introduction of procaine.

By combining the information derived from the degradation of cocaine and knowing the local anaesthetic properties of molecules such as those related to aminobenzoic acid, Einhorn in 1905 (Einhorn and Uhlfelder, 1909) introduced procaine. The presence of the structure of procaine within the active part of cocaine can be seen from the structural formula (fig. 5). Procaine has held pride of place in the local anaesthetic field for well over half a century and, though countless attempts have been made to introduce closely related esters, none has achieved the success of procaine. Some of the various derivatives of benzoic acid, para, meta and ortho aminobenzoic acid, hydroxy and alkoxy benzoic acids that have been investigated are given in figure 6. Carney (1951) has listed the local anaesthetic activity of 1,060 of such compounds and it can be presumed that this group has now been fully explored, and though compounds as effective or more active than procaine have been discovered often, an associated increase in the toxicity (both systemic and local) restrict their use.

Typical effects of alteration of substitution in a homologous series.

In a series of alkyl amino ethyl esters of meta amino alkoxybenzoates reported on by Epstein, Meyer and Ginsberg (1955), certain tendencies could be observed as longer chains were substituted. Figure 7 shows the chemical structure and details of the toxicity tests in mice, and the comparison of the local anaesthetic activity both in topical application and following nerve block. As the molecular weight increased there was an associated increase in the toxicity and also in the potency. It was also observed that the meta position of the amino group reduced toxicity when compared with similar substitution of the para amino compounds.

Out of this study came Primacaine which was tried clinically as a dental anaesthetic by Monheim (1955), who successfully used it for 3,000 dental injections.

From the point of view of structure and activity relationships, it is of interest to observe that included in the original animal tests was the meta butoxy amino analogue of Primacaine. This was found to be more toxic and also more active (fig. 7) as a local anaesthetic than Primacaine.

Halogen substitution.

The 2 chloro analogue of procaine 2 chloroprocaine (Nesacaine) (fig. 6) is claimed to be less toxic than procaine, due to a more rapid hydrolysis by the esterases responsible for the breakdown of this group of local anaesthetics in the body (Foldes, Davis and Plekss, 1956).

Halogen substitution in positions 3 and 5 of the benzene ring, however, results in greater stability with a decrease in the rate of hydrolysis by the esterases. The effects of halogen substitution may be due to an effect on polarity, which in the case of 2 chloroprocaine, is increased.

Amides.

Chance is often more important than logical deduction in medicinal chemistry. In 1932 Miescher was investigating the acetanilide series

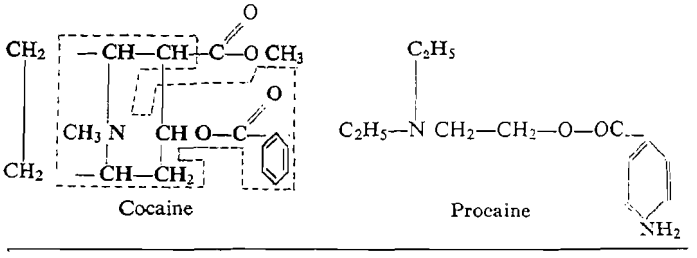


FIG. 5

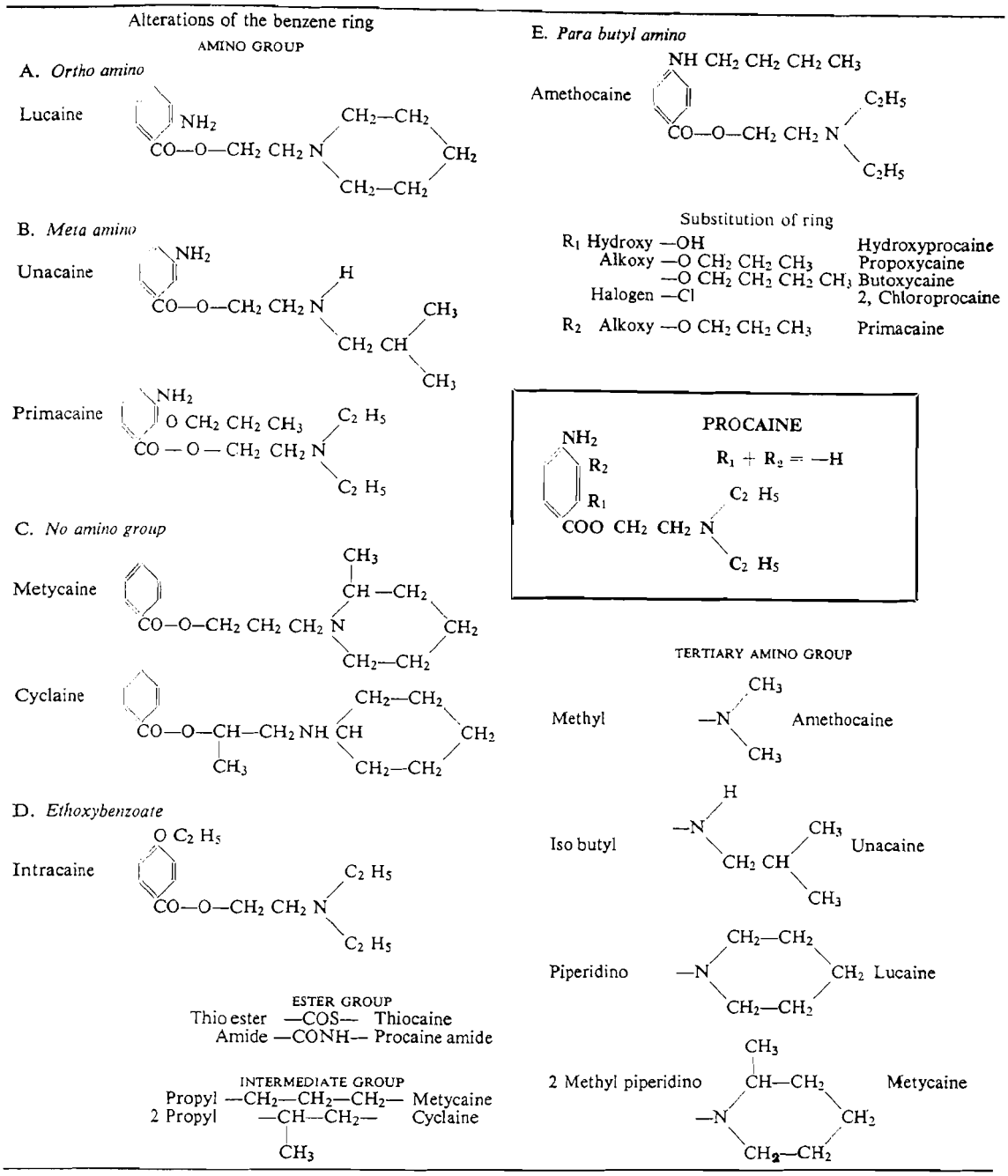
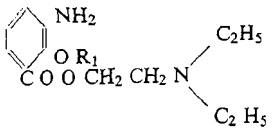
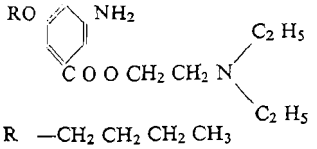


FIG. 6
Some variations in the structure of procaine.



		Relative toxicity (mice)	Relative anaesthetic activity Topical	Conduction
R_1	$-CH_2\ CH_2\ CH_3$	1·1	0·2	1·5
	$-CH_2\ CH_2\ CH_2\ CH_3$ (Primacaine)	2·5	0·5	2·0
	$-CH_2\ CH_2\ CH_2\ CH_2\ CH_3$	1·8	0·8	0·8
	$-CH_2\ CH_2\ CH_2\ CH_2\ CH_2\ CH_3$	16·0	2·0	2·0



R	$-CH_2\ CH_2\ CH_2\ CH_3$	3·2	0·3	3·0

FIG. 7
Meta-amino benzoates.

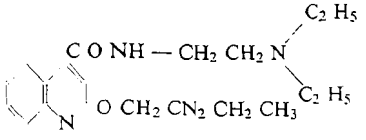
for antipyretics. One of the compounds he synthesized was devoid of antipyretic properties but instead it was found to have a long-lasting though rather toxic anaesthetic action. Cinchocaine (fig. 8) thus discovered, was found to be active in a concentration of 1:120,000 with anaesthesia lasting for a minimum of 2 hours. This is to be compared with a dilution of 1:1,000 for cocaine and 1:200 for procaine. Originally called Percaine in Europe, the name was so similar to the much less toxic procaine that on many occasions fatalities occurred due to dispensing errors and, as a result, the compound was renamed cinchocaine, and the trade name altered to Nupercaine. In the United States of America it is known as dibucaine. Despite its high toxicity the high anaesthetic potency has assured cinchocaine a place in clinical usage.

Buchi (1952) investigated further analogues of cinchocaine but was unable to discover a compound with superior properties.

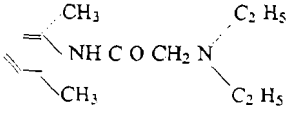
Lignocaine.

The next amide of note to be introduced into anaesthesia in man was also discovered indirectly. Lofgren (1948) in Sweden was investigating the substance responsible for causing a haemorrhagic disease in animals fed during the long northern winters with spoilt hay. Following the synthesis of some suspected compounds Lofgren observed that, when tasted, a numbing action on the tongue followed. After considerable work the successful local anaesthetic lignocaine (fig. 8) was synthesized. A full report of its local anaesthetic activity and that of other closely related compounds was given by Lofgren (1948). It is of interest to note that Einhorn and Oppenheimer (1900)—prior to the discovery of procaine—studied Nirvanine, also an amide and a close relative of lignocaine (fig. 8). Nirvanine was effective as a local anaesthetic and had a low toxicity; however, it was very irritating on injection. Irritation was also present in many of the other compounds of this type investigated by Lofgren. The principal indication for the introduction of lignocaine was because it proved to be the least irritating on injection.

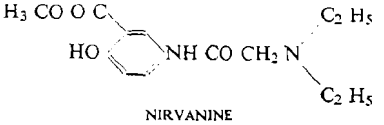
The local anaesthetic activity of lignocaine does not stand out as a prominent feature on pharmacological testing. The success of lignocaine is dependent upon the presence of adrenaline which prolongs its local effect especially in nerve blocks when used for dentistry. An important fact is that, since lignocaine is an amide and not an ester, it is not detoxified in the tissues at the site of injection by esterases, as are the local anaesthetics belonging to the ester group. It has been demonstrated by the use of C^{14} labelled lignocaine, that



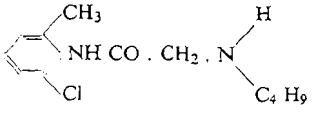
Diethyl aminoethylamide 2 butyl oxycinchonic acid
CINCHOCAINE



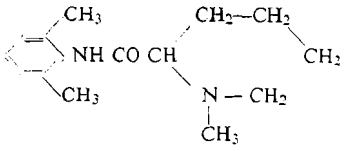
Diethyl amino 2,6 xylidide
LIGNOCAINE



NIRVANINE



Butyl amino 2, methyl 6, chloro xylidide
HOSTACAINE



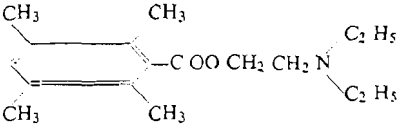
α1. N methyl pipecolic acid 2,6 dimethyl xylidide
CARBOCAINE

FIG. 8
Amides.

the liver is able to rupture the amide link and thus deal with what is otherwise an extremely stable molecule (Geddes, 1958).

Chemical stability of lignocaine.

The molecule of lignocaine is extremely stable to hydrolysis by acids and alkali (Bullock and Grundy, 1955). That this is so is not entirely due to the amide group; it is associated with the presence of the two methyl groups on the ring situated close to the amide group. Bullock and Grundy (1955) give data from the literature to support this statement. The effect of hydrolysis on a series of methyl substituted 2 acetamido benzenes closely related to lignocaine is shown to be dependent on the position of the methyl groups on the ring (fig. 9). This action of the methyl groups can be regarded as similar to a splinting effect which shields the amide linkage and protects it against hydrolysis. This effect of the methyl group is not only restricted to the amide linkage, for Rabjohn, Fronabarger and Linstromberg (1955) have shown that a similar effect occurs in ester compounds such as diethyl amino ethyl 2,3,5,6, tetramethyl benzoate, an active local anaesthetic, where the duration of anaesthesia is increased due to the increased stability associated with the methyl groups adjacent to the ester linkage:



Other amides used clinically.

Hostacaine (fig. 9) has a substituted halogen for one of the methyl groups and as such is not as stable as lignocaine and is more readily hydrolyzed by the liver (Ther and Harnisch, 1953). This anaesthetic has been used in Germany in dentistry, where it has been found to have a high incidence of side effects and to cause local irritation. As a result, one authority (Bjorn, 1956) considers that the clinical use of this preparation should be contra-indicated.

Carbocaine (Mepivacaine) (fig. 9) is to date the only serious competitor to lignocaine. Though not yet available commercially in Britain its use has been extensive in the New World. The structure of Carbocaine is of interest for it com-

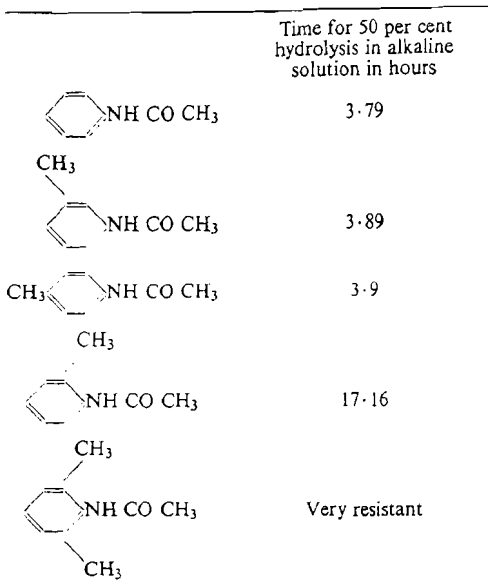


FIG. 9
Effect of methyl substitution.

bines the advantages associated with the amide group and the 2,6, dimethyl groups—as observed in lignocaine—with certain structural similarities to the active part of cocaine where, as we have seen, there is a piperidine ring. Cocaine is unique in that it has vasoconstrictor properties. The synthetic local anaesthetics are vasodilators and their efficacy is in no small part due to the addition of a vasoconstrictor. Initial clinical trials with Carbocaine suggest that if used in a concentration of 2 to 3 per cent without adrenaline it would be effective in the dental clinic and in general surgery to produce nerve blocks, epidural and caudal anaesthesia. Goulding, Ozdil and Powell (1961), have reported that with 2 per cent Carbocaine without adrenaline the average duration of anaesthesia was 2 hours; on occasions blocks lasting 3 hours were seen. They recommended the addition of adrenaline 1:200,000 if surgery was expected to last longer than 2 hours. In view of the recent studies by Nordqvist and Dhüner (1961), on the generalized effects of the addition of adrenaline to local anaesthetic solutions (which included a rise in oxygen consumption and also a significant elevation in levels of circulating blood sugar), it would appear that the next step in the development of a desirable property in a local anaesthetic would be to find one which is active (without a vasoconstrictor drug) and permits prolonged surgery without the necessity for further injections. It is felt that in Carbocaine the initial step towards this realization has been taken.

Aminoalkyl ethers.

Following the realization that replacement of the unstable ester group in local anaesthetics by the more stable amide linkage resulted in compounds of longer duration of activity, the even stronger ether linkage —O—(CH$_2$)$_2$—N< was found to give compounds suitable for use as topical anaesthetics, but these are not suitable for injection. Among these are others which have achieved clinical approval.

Pramoxine (Tronothane) (fig. 10). This has been used as a surface anaesthetic with the advantage that there are few risks of sensitization (Schmidt, Blockus and Richards, 1953). Its use incorporated as a 1 per cent mixture in a heavy jelly has been recommended for application directly as a dressing to the operative site in both proctology and episiotomy wounds and lacerations (Peal and Karp, 1954).

Dimethisoquin (Quotane) (fig. 10). This is an extremely potent topical anaesthetic with the advantage that it has a very low index of sensitivity and thus has a place in the treatment of

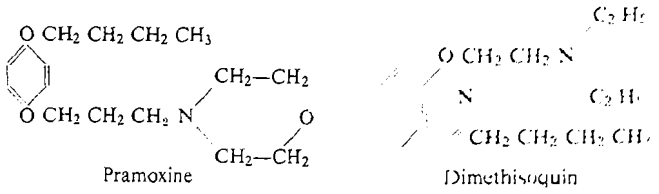


FIG. 10
Amino alkyl ethers.

pruritis and dermatological conditions (Fellows and Macko, 1951).

To date there has not been an amino alkyl ether subjected to extensive clinical trial which possesses the properties suitable for infiltration and nerve block.

Amidines.

These are compounds which possess the grouping

—C—NH
||
NH (see fig. 11).

Although many amidines have been tested as local anaesthetics the only useful example is phenacaine (Holocaine) which has been applied topically for anaesthesia of the cornea and conjunctiva in man. Its high toxicity renders it unsuitable for injection.

Guanidines.

These are compounds possessing the grouping similar to that in the amides except that there is an additional NH group present.

—NH—C—NH—
||
NH (fig. 11).

Acoin has been used as an infiltration anaesthetic.

Urethans.

These compounds combine an amide and an ester linkage.

—NH—C—O—
||
O (fig. 11).

Diothane with two such groups has been used for topical application but is not suitable for infiltration, for Maykut and Ryan (1953) have demonstrated that this results in ulceration and a fibrotic reaction.

Amino ketones.

The amino ketones with the grouping —CO.(CH_2)n N< (fig. 12), being extremely stable are not broken down in the body. Falicaine has been used for injection especially in dentistry but a local irritating effect is a disadvantage

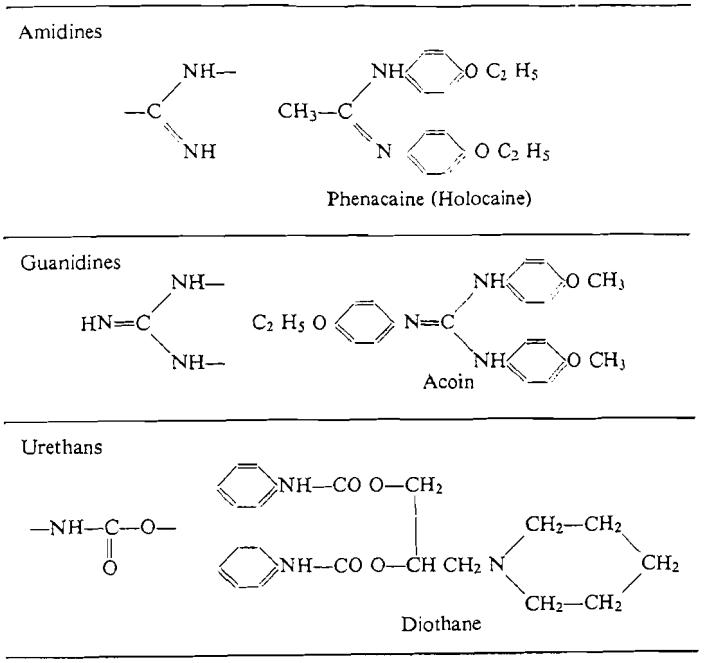


FIG. 11

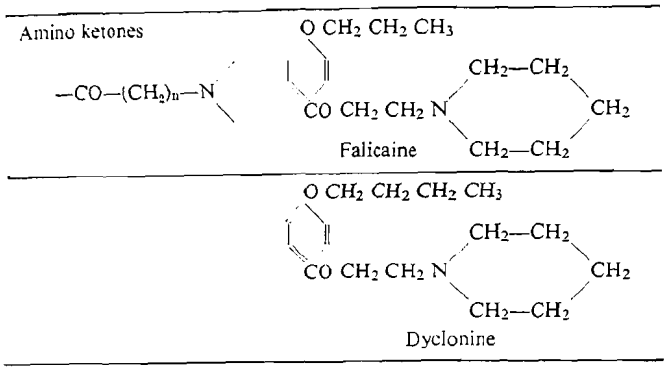


FIG. 12

(Hannig, 1952). The homologous butoxy derivative Dyclonine has, however, proved to be a safe and effective topical anaesthetic and has been used as a 1 per cent solution on the eye, and to anaesthetize the mucous membrane of the oropharynx and trachea. Intravenous injection of 200 to 500 mg has been given to adult humans with no adverse symptoms. Irritation was, however, present on infiltration (Harris, Parry and Greifenstein, 1956).

CONCLUSION

There are thus many chemical groups that can possess local anaesthetic properties. A search for a common link has resulted in a simple formula given by Lofgren (1948) which fits most, but not all, compounds.

AROMATIC or HETEROCYCLIC GROUPS — INTERMEDIATE CHAIN — AMINO GROUP

This can be further classified into

LIPOID RESIDUE—HYDROPHILIC GROUP.

The specific property apparently essential for local anaesthetic activity is a lipophilic group separated by an intermediate chain some 6 Å units in length which terminates in a hydrophilic group. Buchi (1959) suggests that these groups may be at a critical distance apart to allow them to fit into receptors (fig. 13). This combination may occur in compounds in use for other pharmacological properties.

Antihistaminic drugs have marked local anaesthetic properties (Keating and Code, 1948).

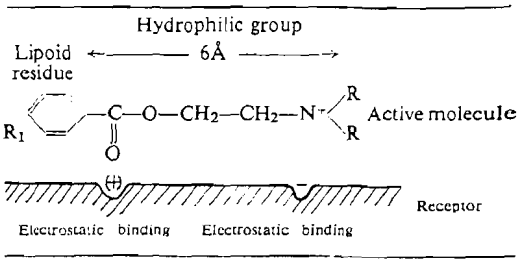


FIG. 13
Active receptor structure.

Tripelennamine hydrochloride (Pyribenzamine hydrochloride) (fig. 14) has been recommended as a topical anaesthetic and used clinically (Yonkmann et al., 1949).

Mephenesin (Myanesin) (fig. 14) was discovered by Berger and Bradley (1946) when investigating the local anaesthetic properties of the glycerol ethers. Mephenesin is not only a muscle relaxant but also has local anaesthetic properties. This is important when it is administered orally, for the protective laryngeal reflex may be obtunded and inhalation of fluids has followed failure to appreciate its topical effect on the larynx.

Much requires to be discovered before we can state more than that local anaesthetics act by stabilizing plasma membranes of nerves. They prevent ionic exchange and impair conductive efficiency and cause a block in transmission of the nerve impulse. It is, however, possible to say that this is in some way intimately bound up with the possession of a lipophilic-hydrophilic grouping

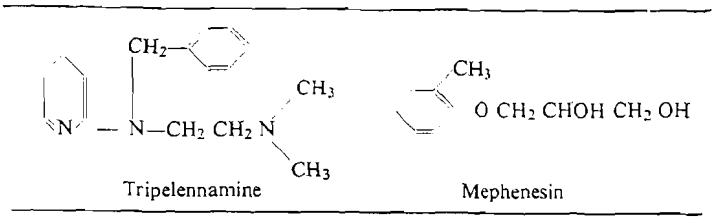


FIG. 14

which is responsible for the orientation of local anaesthetics at interfaces. This causes, by some mechanism as yet unknown, a block of conduction. It is by such reasoning that a unifying link can be found to explain how so many different groupings can give rise to local anaesthetic activities.

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Remember, wherever you go.....there you are.

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