REVIEW ARTICLE

A REVIEW OF LOCAL ANÆSTHETICS

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THE investigation of compounds possessing local anæsthetic activity has been in progress since 1884 when Köller[1] observed that a solution of cocaine when applied locally caused anæsthesia of the cornea. Cocaine was soon used to produce nerve block, infiltration and spinal anæsthesia. After it had been in use for 6 years, Folk[2] in 1890 reported 176 cases of acute intoxication, of which 10 were fatal. Einhorn[3] introduced the less toxic procaine (novocain) in 1904 and by so doing began the modern era. Procaine is still regarded as the safest and probably the most satisfactory all-round local anæsthetic. It is the purpose of this review (A) to discuss the mode of action of local anæsthetics and the molecular configurations responsible for their activity, (B) to consider their absorption and elimination, and other factors influencing their toxicity, and (C) briefly to describe some of the newer drugs which have been synthesized in an attempt to approach an apparently unattainable ideal.

(A) MODE OF ACTION OF LOCAL ANÆSTHETICS

Knowledge of the exact mode of action of drugs interfering with the transmission of impulses along nerve fibres has not progressed *pari passu* with the increase in understanding of the effects of drugs causing neuromuscular or ganglionic block. Certain facts, however, are known, and an attempt will be made to correlate the action of local anæsthetics on the nerve fibre with the action, in their respective regions, of neuromuscular and ganglionic blocking agents. A first step will be to examine the behaviour of solutions of local anæsthetics when injected into the tissues.

Behaviour of Solutions of Local Anæsthetics After Injection.

Chemically, local anæsthetics are bases. For them to be effective they must come in contact with nerve fibres as free base. Free local anæsthetic base, however, has a low water solubility and hence these agents are used in the form of soluble salts, which ionise only to a small degree according to the following equation:

$$\underset{\text{Anæsthetic salt}}{R \equiv NHCl} \rightleftharpoons \underset{\text{Cation}}{R \equiv NH^+} + \underset{\text{Anion}}{Cl^-}$$

These salts are combinations of a weak base with a strong acid, and the addition of alkali to the above equilibrium will therefore result in the liberation and precipitation of free base.

$$R \equiv NHCl + NaOH \rightleftharpoons \underset{\substack{\text{Anæsthetic}\\\text{base}}}{R \equiv N\downarrow} + NaCl + H_2O$$

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The extent of this liberation of free base, and therefore the anæsthetic activity of the solution under clinical conditions, depends upon the alkalinity of the medium into which the local anæsthetic is introduced.

The hydrogen ion concentration at which precipitation occurs varies with each drug and with the concentration of its solution; free base is precipitated more readily from a strong than from a weak solution[4].

Three important practical points follow:—

(i) The addition of excess of alkali to solutions of a local anæsthetic may result in precipitation of anæsthetic base and therefore in loss of potency of the solution[5]. This fact is appreciated by both manufacturers and clinicians. Alkali-free glass must be used for ampoules and bottles which contain anæsthetic solutions, and during processing no alkali must be permitted to come into contact with the anæsthetic salt. Clinicians are well acquainted with the inactivation of local anæsthetic solutions that may follow upon the sterilisation of syringes or dishes in water which contains alkali and, prior to the advent of dry sterilisation, a trace of acid was frequently added to water in sterilisers, used for these purposes.

(ii) Body tissues have a considerable buffering capacity, and injected solutions, provided they are not too acid, rapidly assume their slightly alkaline hydrogen ion concentration (*p*H 7·4). Active base is therefore liberated from solutions of local anæsthetics on injection into the tissues. It follows that acidifying local anæsthetic solutions more than is required to ensure stability tends to prevent or to slow down liberation of free base, and a practical point is that such solutions, besides being less effective, may cause pain on injection. Severe necrosis has resulted from procaine[6] at *p*H 1·0 to 2·9. On the other hand, alkalisation short of the critical point for precipitation might be expected to speed the onset of anæsthesia, but the general opinion is that, within the likely range of *p*H of the solution injected, the tissues are effective buffers and no advantage is to be gained by the addition of alkali[7].

(iii) Local anæsthetics are less effective when injected into inflamed tissue. This is probably attributable to more rapid general absorption resulting from an increased vascularity, but the acidity of pus (*p*H 5 to 6) may be a factor[8].

Action of Local Anæsthetic Bases on Nerve Fibres.

To be comprehensive it is necessary to mention that local anæsthetics affect the metabolism of nerve fibres.

Procaine and cocaine inhibit the respiration of the sciatic nerve in the rabbit[9] and it has been demonstrated that these and other local anæsthetics interfere with the intracellular oxidation of glucose, succinate and ascorbate, but not with anærobic glycolysis by brain homogenates[10]. The degree of this effect varies greatly for a wide range of substances, cocaine, procaine and piperocaine (metycaine) having the least effect, whilst tetracaine (amethocaine) and butacaine are more and cinchocaine the most potent of the substances tried. There is a positive correlation between these *in vitro* experimental results and the *in vivo* potency of the drugs, and it is suggested that blockage of the enzymatic chains involved

in intracellular respiration by local anæsthetics occurs at the cytochrome-C-cytochrome oxidase level.

This inhibition of tissue respiration may have little to do with the actual block of conduction caused by these substances, because nerve block may be produced by concentrations of cocaine which do not, in fact, affect the uptake of oxygen[11].

Local anæsthetics, like the general anæsthetics, are more soluble in lipoids than in water. As nerve tissue is rich in lipoids the suggestion was made that lipoid solubility was related to anæsthetic properties and effects[12,13,14,15]. Certainly this solubility plays some part in the entrance of these agents into the lipoid-rich plasma membrane, and polar association between the amino group common to local anæsthetics and polarised lipoids in the membrane may be an essential aspect of their action[15]. For a clearer insight, however, into this difficult subject it is necessary to examine briefly the ionic hypothesis which to-day holds the field as an explanation of the conduction of impulses along nerves, across synapses and at myoneural junctions.

The Ionic Hypothesis of Impulse Conduction of Nerve Fibres.

A very fine exposition of this theory and its experimental basis has recently been given by Eccles[16].

Histology. A nerve fibre (axon or dendrite will not here be distinguished) is a cylinder of semi-fluid cytoplasm—axoplasm—bounded by a specialised membrane of lipoid and protein perhaps only two molecules thick. This plasma membrane is not identifiable histologically and must not be confused with the neurolemma; it separates the axoplasm from the surrounding extracellular interstitial fluid. The neurolemma is a histologically differentiated membrane which, in the case of myelinated nerves, is separated from the axon by a sheath consisting of concentric sheets of protein supported by radial layers of lipoid (myelin)[17]. The myelin sheath is absent at the nodes of Ranvier which occur approximately every millimetre along the nerve.

Polarisation.—In the resting state there is a difference of potential between the interior and the exterior of the plasma membrane (Fig. 1A). The interior is at a negative potential to the exterior. This "demarcation" potential is due to an asymmetrical distribution of ions on either side of the plasma membrane which, in turn, is accounted for by (*a*) the permeability characteristics of the membrane and (*b*) an active mechanism extruding sodium ions—the sodium pump.

The plasma membrane is permeable to potassium and chloride ions, and relatively impermeable to sodium, amino-acid and protein ions. Under such circumstances the ionic equilibrium for potassium and chloride will be established according to Donnan's law. So that:—

$$(K_i^+) \times (Cl_i^-) = (K_o^+) \times (Cl_o^-)$$

Hence

$$\frac{(K_i^+)}{(K_o^+)} = \frac{(Cl_o^-)}{(Cl_i^-)}$$

where (K_1), (K_o), (Cl_1) and (Cl_o) are concentrations of potassium and chloride ions respectively inside and outside the plasma membrane.

Sodium ions are being actively extruded from the interior, the energy necessary being liberated probably by the enzymatic breakdown of lactic

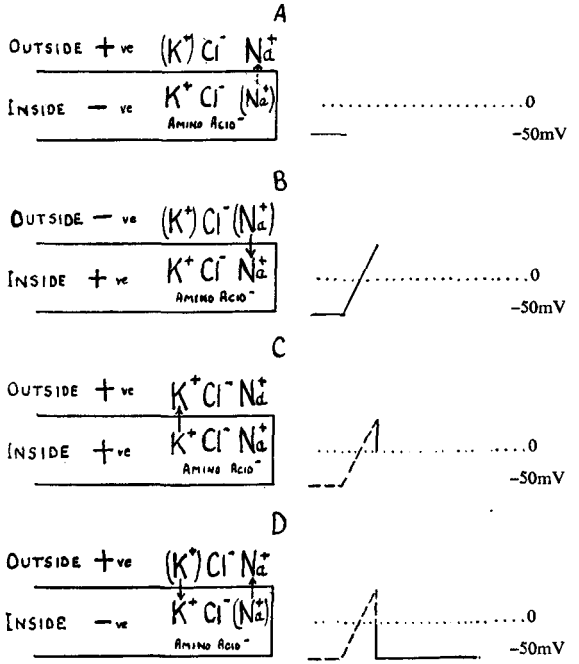


FIG. 1. Changes in distribution of cations between the interior and exterior of the nerve fibre during activity. The changes in anionic distribution for the sake of clarity have been ignored. The parentheses indicate a small concentration; the arrow shows the direction of ionic movement. A—at rest; B—activity, first stage; C—activity, second stage; D—return to rest. C and D represent the refractory period. On the right the potential changes are indicated graphically. *(Reproduced by permission of the Royal College of Surgeons).*

and pyruvic acid. As a result, the concentration of the potassium ions inside the cell is considerably higher than the concentration outside and at rest it has been established that the ratio

$$\frac{(K_1^+)}{(K_o^+)} = 20 \text{ to } 50.$$

With this relative concentration of potassium ions a potential difference will exist, and its predicted value of 75 to 100 mV. is in accord with the experimental findings[18].

During activity the plasma membrane becomes freely permeable to sodium ions (Fig. 1B), due perhaps to activation of a carrier mechanism, or to the activity of some transmitter liberated in the nerve fibre, e.g., acetylcholine. The carrier mechanism, or the production of the transmitter substance, is triggered off by spread of electric current from the neighbouring active area.

Whatever may be the reason for the altered permeability, the entrance of sodium ions into the fibre is not at first accompanied by a corresponding *exitus* of potassium ions. Thus the interior of the fibre becomes electropositively charged relative to the exterior—a state of reverse polarisation. Potassium ions now migrate outwards and thus neutralise the potential difference, the interior and exterior of the fibre at this stage being in an equipotential state (Fig. 1C). During recovery, sodium ions are again extruded by the sodium pump, potassium ions re-enter the axon either because of the electro-chemical gradient or else, as suggested recently by Hodgkin and Keynes[19], impelled by a similar "pump" mechanism. The resting state of polarisation is thus restored (Fig. 1D). These changes in potential due to ionic migration are sufficient to fire off similar changes in the neighbouring area of axon, and the impulse is thus conducted without decrement.

Saltatory action. In myelinated nerves ionic migrations occur only at the nodes of Ranvier; the myelin sheath acts as an insulator with the result that the local circuit currents set up by the action potential at one node exert an effect some distance ahead, namely at the next node. In this way the myelin sheath permits an extremely efficient conduction of the impulse with the expenditure of considerably less energy than would otherwise be required[18,20]. In this respect it should be remembered that myelinated nerves are excitable only at their nodes[21], a fact which has considerable bearing on the action of local anæsthetics, which are effective only at the nodes.

Modification of the Mechanism of Nerve Conduction by Local Anæsthetics.

There is evidence[22,23,24] that local anæsthetics stabilise the plasma membrane in respect of ionic permeability and in some way not finally explained prevent the ionic migrations necessary for the conduction of the impulse. As would be expected, they are effective only at the nodes of Ranvier, without being active in the inter-nodal region[25,26]. This stabilisation of the plasma membrane with maintenance of the demarcation potential is in contrast to the action of potassium or calcium. These ions block the nerve impulse by depolarising the resting fibre[24], that is to say, by a removal of the normal demarcation potential, thus making impossible the changes in polarity necessary for conduction of the impulse.

Such a conception of the mechanism of action of local anæsthetics is in line with the action of drugs which produce block of conduction at myoneural junctions and ganglionic synapses. Curare and curare-like substances cause block at the end plate region of voluntary muscles and also, though to a lesser extent, in sympathetic ganglia, by preventing the changes of polarisation which characterise activity.[27] Other substances, such as decamethonium iodide at the end plate[28], or nicotine at the ganglionic synapse[29], cause block by producing a state of depolarisation similar to that produced in nerve fibre by excess of calcium and potassium.

Possible relation to transmitter substance. In myoneural and ganglionic transmission on arrival of an impulse at the synapse or end plate, acetylcholine is liberated and alters the permeability characteristics of the

plasma membrane, thus permitting the depolarisation which is responsible for transmission of the impulse[30].

It has been suggested that acetylcholine[31,32] or perhaps some other humoral transmitter plays a similar rôle in nerve conduction. If this is so, then local anæsthetics may have an action on nerves analogous to that of curare at the myoneural junction: that is, they may act by competing for the specific acetylcholine receptors. However, such a rôle, if any, of acetylcholine in nerve conduction is far from being finally determined. It has been shown that acetylcholine even in massive concentration does not, in fact, depolarise nerve fibre, as it does the end plate region or the ganglionic synapse[33]. *In vivo* acetylcholine may be liberated actually in the plasma membrane, whereas, in the *in vitro* experiments in which this failure to produce depolarisation has been demonstrated, it was only applied to the surface of the membrane. It is possible that this may account for the discrepancy.

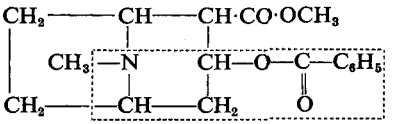
An alternative theory for the part played by acetylcholine has been suggested[34]. Liberated acetylcholine may, through the catalytic action of an enzyme, react with phosphocreatine and thus fire off the adenyl phosphate chain reaction, the energy thus liberated being the stimulus for the freeing of acetylcholine in the neighbouring area. It is suggested that local anæsthetics, owing to the structural similarities of their molecules to acetylcholine, may compete for the specific enzyme concerned in this chain reaction, and may thus interfere with the propagation of the impulse.

Attention has been drawn to the similarities which exist between the pharmacological actions of local anæsthetics and anticholinergic and antihistaminic drugs[35]. All 3 substances can be shown to exhibit (*a*) local anæsthetic activity, (*b*) blocking activity at the myoneural junction, (*c*) activity in prolonging the refractory period of smooth (including cardiac) muscle, and (*d*) parasympathetic depressant activity. The local anæsthetic activity of antihistaminic drugs is well known and has been demonstrated not only in animals[36,37], but also in humans, in whom they have been employed to obtain topical anæsthesia of the urethra[38] and the œsophagus.[39] As a corollary, procaine has been demonstrated to have antihistaminic activity of the order of one hundredth that of antazoline (antistin)[40]. A link between these various mutual activities may be seen in the facts that histamine can be demonstrated in nerve fibres[41,42] and that histamine can temporarily reverse procaine block[43]. This latter observation may, however, be fallacious in that the reversal might have been due to the acidity of the histamine solution preventing the liberation of free anæsthetic base[44]. Similarly, anticholinergic drugs exhibit local anæsthetic activity. Adiphenine (trasentine), atropine and quinidine[45] can block nerve conduction, and, furthermore, these and procaine can antagonise the action of acetylcholine on striated muscle[45].

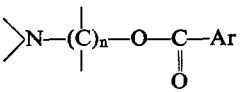
Burn[46] suggests that the basis of this common activity is the property these substances have of depressing the effects of the three humoral transmitters, acetylcholine, histamine and adrenaline, and the probability is that they act similarly by competitive inhibition[47].

Relation of Chemical Structure to Local Anæsthetic Properties.

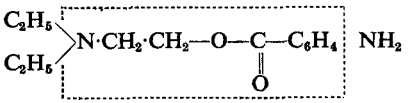
The discovery of the chemical structure of cocaine by Wilstätter[48] led to the search for similar molecules which might have local anæsthetic effects but less toxicity. A first step was the identification of the active part of the cocaine molecule. The structural formula of cocaine and the probable anæsthophoretic part of the molecule are shown below. A similar molecular formation is found in procaine and in the majority of local anæsthetic drugs[49]. Modification of the cocaine molecule has produced through the decades an unending stream of local anæsthetic substances, and recently Quevauviller[50] has traced this genealogy in a comprehensive review.



Cocaine



Anæsthophoretic grouping



Procaine

With few exceptions, e.g., acoin, diocaine and phenacaine (holocaine), local anæsthetics conform to the following general structure:

aromatic residue—intermediate chain—amino group[15].

However Büchi[51] considers there are too many exceptions for this to be a valid rule. He is of the opinion that such a generalisation may be misleading, and that the expectations based upon the existence of such general laws, which are supposed to govern the relation between constitution and local anæsthetic activity, have failed to materialise.

He instances the following objections:—

1. Substances with local anæsthetic activity have, in fact, widely differing chemical constitutions, and may belong to very varied chemical classes. A remarkably large number of molecular configurations appear to be qualified to produce a state of local anæsthesia.

2. Numerous compounds which from their general chemical structure might be expected to possess local anæsthetic properties are, in fact, inactive.

3. Experience has repeatedly shown that a relation between structure and function can be found only within closely defined narrow limits and then only in series of compounds which are practically homologous. As examples Büchi quotes the basic esters of benzoic and *p*-aminobenzoic

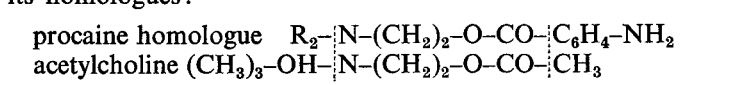
acids. The introduction of the amino group into the aromatic ring, as in the latter compounds, markedly increases the local anæsthetic activity. The position of the amino group matters, the *para*-position being more effective than the *meta*- or *ortho*-positions. Furthermore, alkylation of this amino group increases both potency and toxicity. While the methylamino compound is only slightly more potent than procaine, the potency increases through the ethyl and propyl homologues to the butyl (*p*-butylaminobenzoyldimethylaminoethanol is tetracaine). On the other hand, in regard to the aliphatic amino group of Lofgren's general formula, only a few primary esters have anæsthetic activity.

Despite these objections the attribution of local anæsthetic activity to certain groupings has produced results for the synthetic chemists, and Quevauviller[50] has traced the influence of various modifications of a basic local anæsthetic structure. He has summarised admirably the effects of unsaturation, isosterism and stereoisomerism as well as other factors on anæsthetic potency. His basic general formula consisted of:

1. A lipophilic portion consisting of cyclic and heterocyclic hydrocarbon formations, including a varying number of substituted isosteric groups. This portion of the molecule provides the lipoid solubility necessary for local anæsthetic activity.
2. An intermediate portion in the form of an ester or isosteric group which he considered as a pivot.
3. A hydrophilic group, usually an amino-alcohol or isosteric group, which provides the water solubility necessary.

There seems to be a fine balance between these lipophilic and hydrophilic groups. If the latter predominate, the local anæsthetic characteristic is lost, for the base will not be precipitated on injection into the tissues. On the other hand, if the molecule is too lipophilic, it becomes insoluble in water and therefore clinically useless.

In conclusion, in order to bring these chemical characteristics into line with the theories of local anæsthetic action which have been discussed, Thimann[52] related the structure of local anæsthetic substances to acetylcholine. This relationship is easily appreciated in the case of procaine and its homologues:—



Such a structural similarity supports the theory that local anæsthetics act by competing for acetylcholine receptors.

(B) Absorption and Elimination of Local Anæsthetics

Solutions of local anæsthetics are not absorbed from the intact skin. Administered *per rectum* a blood level comparable with that obtainable during intravenous infusion can be obtained[53,54]. The usual route of introduction of these substances is either by application to mucous membranes—topical anæsthesia—or by injection into the tissues, either widely—infiltration—or in the immediate neighbourhood of nerves, as in regional and subarachnoid anæsthesia.

Following injection, the rate of absorption will depend on the vascularity of the part and will be speeded up by increased vascularity, as in inflammation, or slowed by the simultaneous injection of vasoconstrictor agents[55,56,57]. Too high a concentration of vasoconstrictors in local anæsthetic solutions is detrimental, not only because of the generalised reaction likely to follow injections of such substances as adrenaline, but also because the local ischæmia produced, if too intense or persistent, may delay healing or result in necrosis. Tissue sloughing has been described following the use of a local anæsthetic containing 1:20,000 adrenaline[58] and this has been without doubt a significant ætiological factor in the incidence of "dry sockets" following dental surgery[59]. Some newer vasoconstrictor agents, particularly *l*-noradrenaline, while more effective locally show promise of causing less general upset than adrenaline. A considerable amount of research has been carried out to determine the manner of elimination of local anæsthetics after injection.

Enzymatic Breakdown

Procaine in dogs and rabbits is rapidly broken down into *p*-aminobenzoic acid and diethylaminoethanol by an esterase[60]. The demonstrations that this procainesterase is present in human serum[61,62,63], that its activity is inhibited by the same agents as cholinesterase[64,65,66,67], and that the levels of both enzymes rise in toxic goitres[68,69,70] and fall in liver disease[68, 71,72,73], have led to the suspicion that procainesterase and serum cholinesterase may be identical[66]. A further indication that the two enzymes are related is afforded by the fact that substrate competition for pseudocholinesterase has been demonstrated *in vitro* between procaine and suxamethonium[74]. Kalow[75] showed that not only did local anæsthetics inhibit the action of esterase on acetylcholine, but also the converse applied, that is to say the hydrolysis of procaine by esterase was inhibited by acetylcholine. The action of anticholinesterases such as physostigmine is obviously of importance in this respect. All investigators are agreed that physostigmine inhibits the hydrolysis of procaine in *in vitro* experiments[64,65,67,70]. *In vivo*, however, there is some doubt about its ability to inhibit procainesterase[65,67,76]. On all the evidence it seems likely that the two enzymes are closely related and may prove to be identical.

Serum esterase hydrolyses many other local anæsthetics, and the extent of its action can be compared on a molar basis. 1 l. of human serum hydrolyses *in vivo* under optimum conditions about 6 to 7 mg. of procaine hydrochloride per minute. Tetracaine is hydrolysed 4 to 5 times more slowly, and piperocaine about 6 times faster. The affinity of esterase for tetracaine is of the same order as for physostigmine[75]. Apparently some non-enzymatic breakdown of procaine occurs, the amount varying from tissue to tissue up to 20 per cent. of the total in some tissues[67].

The fate of breakdown products from *p*-aminobenzoyl esters is of interest. It seems that following procaine breakdown 25 per cent. of the diethylaminoethanol is excreted in the urine, the remainder being metabolised[77]. It is possible that some degradation product has an affinity for hæmoglobin, for cyanosis has been observed in patients having

intravenous procaine despite adequate oxygenation[78]. Diethylaminoethanol injected into dogs modifies hæmoglobin and reduces its oxygen carrying power[78].

Excretion Unchanged.

While the *p*-aminobenzoic esters and similar local anæsthetics are thus broken down in the body, drugs with more complex molecular structure are at least partially eliminated unchanged through the kidneys. McIntyre[79] was able to recover 429 mg. of cocaine from the urine of a patient, who in error had received 800 mg. injected into the peritonsillar fossæ and who survived 12 hours. There is, however, considerable species difference, for, while dogs excrete cocaine in the urine, rabbits do not[80]. The latter species detoxicate cocaine, whilst guinea-pigs and cats are less efficient in this respect. The recently introduced and widely used lidocaine (lignocaine) is excreted, at least partially, in the urine[81].

Other Factors Influencing Toxicity of Local Anæsthetics.

Species difference is also evident from toxicity tests on different animals when the results are compared on a body weight basis. Tetracaine and cinchocaine are considerably more toxic for guinea-pigs than for mice, while the reverse is true of procaine[82].

Effect of Anticholinesterase Drugs. Because of the possible common identity of pseudocholinesterase and procainesterase the effect of the anticholinesterase drugs on the toxicity of intravenous procaine is of interest. In this respect physostigmine and neostigmine differ[76,83]. Physostigmine and, incidentally, di*iso*propyl phosphorofluoridate (DFP), when injected into mice provide considerable protection against the toxic effects of procaine. The LD50 of procaine was increased by 23 per cent. after physostigmine and 16 per cent. after di*iso*propyl phosphorofluoridate. Quite contrary to this finding neostigmine increased the susceptibility of mice to procaine by 35 per cent. In the latter animals, death was instantaneous and no convulsions were observed. A further fact is that in cats physostigmine, neostigmine, methylene blue, and di*iso*propyl phosphorofluoridate do not influence procaine plasma concentrations during intravenous infusion[65].

These results indicate that the protective effect of physostigmine and di*iso*propyl phosphorofluoridate against the toxic effects of procaine must be attributable to factors other than their anticholinesterase properties. Confusion reigns supreme when one finds Buff[84] using injections of neostigmine in the treatment of 20 cases of circulatory toxic reactions to procaine. The beneficial results of such an administration would appear to be due to control of the tachycardia by the cholinergic effect of neostigmine.

Effect of breakdown products of procaine. Following the intramuscular injection of procaine in guinea-pigs the incidence of convulsions was found to be substantially reduced by the prior administration of *p*-aminobenzoic acid and diethylaminoethanol[85]. It is suggested that, acting by substrate competition, they occupied receptors in the brain thus preventing

procaine from exerting its convulsive effect. However, here again there are diverse findings for mice premedicated with diethylaminoethanol are more sensitive to intravenous procaine[86].

Effect of barbiturates. Following upon the work of Tatum[87] in dogs, Leshure recommended the prophylactic administration of a barbiturate to prevent reactions to local anæsthetics in man. He used a fairly heavy dosage, 6 to 12 gr. of sodium barbitone[88]. Steinhaus and Tatum[89] found that in dogs a sedative dose, one sixth the anæsthetic dose, resulted in relatively little protection, but adequate prophylaxis against cocaine intoxication was afforded by one half the anæsthetic dose.

This observation has been extended to other local anæsthetics[90]. It would appear that the efficiency of a *sedative* dose of barbiturate pre-operatively has been over emphasised. However, once convulsions have appeared a barbiturate should be given as an anticonvulsant to control the patient and facilitate the administration of oxygen.

Pyrithyldione (presidon), a relatively short acting hypnotic, belonging neither to the barbiturate nor to the ureide series, has been used to protect guinea-pigs, rabbits and dogs from toxic reactions to procaine[91]. It was found to be effective in one third the hypnotic dose, whereas the protective action of pentobarbitone was of the order of one-half the hypnotic dose. Thus in these species pyrithyldione has a higher protective index than pentobarbitone. In mice the protective indices of the two compounds were similar. No application of these observations to man has been reported.

The addition of hyaluronidase to local anæsthetics. Hyaluronidase is the "spreading factor" described by Duran Reynals[92] and has been used to facilitate the spread of local anæsthetics and increase the area of resultant anæsthesia. By liquefying the viscous polysaccharide hyaluronic acid found in the interstitial spaces of tissues, hyaluronidase allows the rapid spread of fluids if there is adequate pressure to furnish the necessary mechanical impulse[93].

The purpose of combining hyaluronidase with local anæsthetic solutions is to facilitate spread of the solution in the hope of increasing the number of successful nerve blocks, and to hasten the onset of anæsthesia. If these two aims can be achieved without increasing the toxicity of the solution its addition is justified. It is disappointing to find that, in fact, its use does not always increase the number of successful regional nerve blocks[94]. This may be to some extent due to the fact that hyaluronidase does not facilitate penetration of fascial planes and periosteum[95]. The onset of anæsthesia is, however, hastened by hyaluronidase both in local infiltrations[95] and topical anæsthesia[96]. In a recent review[97] of the clinical uses of hyaluronidase, attention is drawn to its value in preventing deformation of the tissues following infiltration anæsthesia.

It is necessary to examine the influence of hyaluronidase on the absorption of local anæsthetic solutions from the point of view of the duration of anæsthesia and the incidence of toxic reactions. As might be expected, wider spread of the solution will facilitate absorption and shorten the duration of anæsthesia[95]. In man it has been reported that

the incidence of toxic reactions is higher when hyaluronidase is used[94,95]. Experiments in mice[98] to investigate the blood levels of procaine and tetracaine following subcutaneous injection showed that, when hyaluronidase was added, there was a more rapid increase in the concentration of local anæsthetic in the blood than in the control series, but the maximum blood concentration achieved in both groups was similar.

There is little doubt that the use of hyaluronidase will hasten absorption and, if toxic amounts of anæsthetic solution are injected, there are more likely to be toxic reactions because of the more rapid achievement of a dangerous blood concentration. The addition of adrenaline to the solution will limit this effect, and will prolong the duration of anæsthesia. These effects of adrenaline are achieved without influencing the spreading action of hyaluronidase[95].

Dermatitis from local anæsthetics. Cases of localised or generalised dermatitis may occur as a result of sensitisation to local anæsthetic drugs. It is an occupational hazard for such people as dentists who are continually exposed to contact with them[99]. In sensitised persons a skin reaction to topically applied local anæsthetics usually develops after a delay of from 16 to 48 hours[100]. The possibility of sensitisation must be remembered when preparations containing local anæsthetics are used for the relief of pruritus. Lane and Luickhart[101] have reviewed 107 cases of skin sensitivity to local anæsthetics of which 73 per cent. had positive patch tests. Adler[102] has investigated the importance of specificity in these reactions by examining the precipitin reactions of sensitised rabbits to 25 different local anæsthetics using procaine-azo-protein as an antigen. A positive precipitin reaction occurred only to esterified derivatives of *p*-aminobenzoic acid in which the amino-group has no side chain. Strong group specificity was thus demonstrated. It follows that when allergy exists to one anæsthetic of the procaine series, local anæsthetics with a different chemical structure and not derived from *p*-aminobenzoic acid can be safely employed. Dermatitis attributed to the procaine fraction of procaine benzylpenicillin has been reported[103,104]. Angioneurotic œdema has followed the use of oral procaine amide hydrochloride (50 mg.) to control ventricular extrasystoles[105].

(C) The Ideal Local Anæsthetic

Before discussing briefly some of the recent drugs which have been investigated in an attempt to arrive at the ideal it will be well to be clear as to what is required of a local anæsthetic.

A local anæsthetic should have the following properties:—

1. A potency which gives a complete anæsthesia.
2. Reversible action.
3. Rapidity of onset. This is desirable no less in the operating theatre or pain clinic than in the dental surgery.
4. Penetrating properties enabling it to be used as a surface anæsthetic.
5. Produce no pain or harmful tissue reaction on injection.
6. Be stable in solution and capable of being sterilised by heat.

7. Have a large safety margin, that is to say, a high potency as a local anæsthetic in strengths and dosage safe from danger of toxic reactions. This may well be largely a matter of the rate of absorption as compared with the rate of elimination[57].

8. Be free from idiosyncratic reactions.

Despite this formidable list no mention has been made of duration of action. Clearly the ideal in this respect will vary with the occasion of use. A long acting drug is less desirable for bronchoscopy and for many dental and oral operations where a rapid return of sensation is required. On the other hand, something which will produce prolonged intercostal anæsthesia after abdominal or thoracic operations would be a boon. There will always be a place for drugs of different lengths of action.

The ideal local anæsthetic has not yet been found and the hundreds of drugs that have been subjected to pharmacological investigation and clinical trial are evidence of the search in progress. Of these hundreds only 4 have gained general approval, procaine, tetracaine, cinchocaine and lidocaine. Of the remaining compounds it is likely that few have come to stay. On their introduction to the profession many claims are made for their pharmacological superiority, and the literature is full of laudatory statements supporting these claims. The real crux of the matter is that there is no absolutely satisfactory method of comparing the potency of local anæsthetics.

TABLE I

METHODS OF TESTING LOCAL ANÆSTHETICS

SURFACE ANÆSTHESIA	Tongue	Human[106,107]
	Skin	Frog[108,109]
	Cornea	Rabbit[110,111,112,113,114,115,116]
		Guinea-pig[117,118]
CONDUCTION ANÆSTHESIA	Muscle Nerve Preparation	Frog[119,120,121,122,123,124,125]
		Rabbit[126,127,128]
		Guinea-pig (*in situ*)[129,130,131,132]
	Isolated Nerve	Frog[84,133]
	Spinal Anæsthesia	Frog[134,135,136]
		Rat[137]
		Rabbit[138,139]
INFILTRATION ANÆSTHESIA	Intradermal Wheal	Guinea-pig[82,114,121,140,141]
		Man[142,143,144]
	Tail	Rat[145,146]
IRRITATION	Cornea	Rabbit[139,147,148]
	Ear	Rabbit[139,149]

Space does not permit a full discussion of the various ingenious tests used by pharmacologists to compare the activity of local anæsthetics (Table I). Recent summaries of the more common methods are given by Munch[150], Hirschfelder and Bieter[8], Burns[151] and Carney[152]. There are almost as many different methods as investigators, and unfortunately minor variations in technique, or the physical state of the solutions used can materially alter the activity of the local anæsthetic under scrutiny. The commonly employed rabbit cornea test illustrates this, for variation of *p*H of the solution applied to the cornea can influence the duration of anæsthesia. The average duration for procaine 4 per cent. at *p*H 5·5

is 2·5 minutes, whereas at *p*H 7·4 it is 35·7 minutes[153]. This is due to the lack of buffering power of the cornea, and Ehrenberg[125] has shown this also applies to the nerve muscle preparation. Very little attention has so far been paid to this important factor in the literature when reporting the activity of local anæsthetics. In injection methods the tissue fluids are capable of buffering the anæsthetic solution to a *p*H of approximately 7·4, and, provided the solutions are not too acid, this emphasis on *p*H of the test solution is not so important.

There is no international standardisation of testing methods, and, as Lofgren[15] has pointed out "some authors investigate the minimal effective concentration, others the duration, and others again the latency time, thus the situation becomes confused." Until a standard method of evaluation is agreed upon, it will be impossible to correlate the vast accumulation of data from research laboratories throughout the world; as with toxicity tests, it is only possible to compare relative values[154]. Clinical evaluation of such tests as there are is rarely unbiased. An excellent example is provided by Bullock[155] who described a clinical trial of two local anæsthetic solutions in which experienced observers came to diametrically opposite conclusions. The cautious surgeon is not easily tempted to abandon drugs that have stood the test of time.

There seems little to be gained by discussing *in extenso* all the individual local anæsthetics, as has been done in reviews such as those of Hirschfelder and Bieter[8] and Büchi[51] and in pharmacological text books. It is considered that some purpose will be served by referring briefly to the four drugs which are the mainstay of clinicians and draw attention to recent attempts to improve upon them.

Procaine and its Derivatives

Procaine has been for almost 50 years the nearest approach to the ideal. Its intravenous administration to produce generalised analgesia, and to control cardiac irregularities by virtue of its quinidine-like effects, is a tribute to its safety[156]. Its pharmacology has been recently reviewed by Hazard[157]. It is, however, a weak local anæsthetic. In safe concentrations its potency when used to achieve nerve block often leaves much to be desired. Although its duration can be prolonged by the addition of adrenaline, repeated injections are often required in major surgery.

Oily Solutions.

In an attempt to prolong its effect, oily solutions were introduced for use after painful operations—as in proctological surgery. The aim was to achieve slow release of the active procaine base[158,159,160,161,162]. The claims for prolonged anæsthesia with such solutions have not been substantiated[163,164], and the oil only serves to increase the incidence in the tissues of inflammatory reactions, suppuration and necrosis. Meidinger[165] prolonged the effect of procaine by increasing the viscosity of the solution using 40 per cent. polyvinylpyrrolidone.

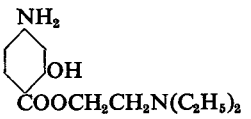
Efocaine is a non-oily solution of procaine base and 5 per cent. of butyl *p*-aminobenzoate dissolved in 2 per cent. polyethylene glycol (300) and

78 per cent. propylene glycol[166,167]. It is claimed that the insoluble base is immediately precipitated on contact with the tissues, and provides a depot for prolonged action. It is emphasised that only small quantities, 1 ml. per nerve, are required. Thus to ensure accurate location of the solution it is best injected at the time of operation under direct vision. This claim has been substantiated by Roualle[168]. 3 cases have recently been reported in America of serious neurological complications after the use of efocaine. In one patient transverse myelitis with hemiplegia developed following postoperative paravertebral injection of the recommended dose of efocaine. The remaining patients had symptoms of toxic neuritis and prolonged sympathetic block[169].

Related Compounds.

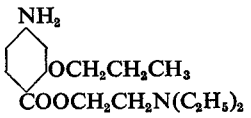
The success of procaine has resulted in a close scrutiny of related compounds in the hope of finding a superior local anæsthetic. Carney[152] has given a comprehensive survey of 1060 benzoic, *p*-aminobenzoic and *p*-oxybenzoic acid esters. This class of compound has been exhaustively surveyed and a large series of useful preparations has resulted. Among the most recent to be investigated are the 2-alkoxy analogues of procaine and tetracaine[132]. The results have shown that certain rather consistent relationships are apparent. 2-Alkoxy substitution in the 4-amino-benzoate structure results in progressively increasing activity and toxicity with increase in the length of the ether side chain. The increase in toxicity, however, in most cases, does not keep pace with the increase in activity.

Hydroxyprocaine (oxyprocain, the hydrochloride of diethylaminoethanol 4-aminosalicylate).



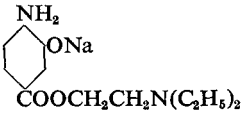
has been used clinically in Germany[170,171,172,173,174]. The onset of anæsthesia is claimed to be more rapid and the duration slightly exceeds that of procaine. For experimental animals its toxicity is slightly greater than procaine. Bacteriostatic properties have been claimed following *in vitro* experiments[175,176,177].

Ravocaine (pravocaine, 2-diethylaminoethyl 4-amino propoxybenzoate hydrochloride)



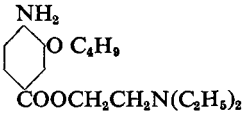
possesses an activity half-way between that of procaine and cocaine, a topical activity of one and a half times that of cocaine, with the same intravenous toxicity as tetracaine. On clinical use in 0·1 per cent. solution it resembled procaine[178]. This concentration was found to be inadequate and further clinical trial is proposed at a higher concentration.

Metahydroxyprocaine has been prepared and its sodium salt studied



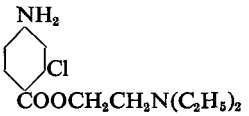
pharmacologically[179]. It was found to be slightly more potent and less toxic than procaine hydrochloride.

Butoxyprocaine is a further close relative to procaine that is claimed



to have superior properties, though its toxicity is greater than procaine[51].

2-*Chloroprocaine* has been used clinically for nerve blocks, dental

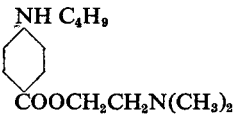


anæsthesia and spinal anæsthesia[180]. The toxicity in mice is half that of procaine, whilst the duration of local anæsthetic effects exceeded procaine. In *in vitro* studies, 2-chloroprocaine is hydrolysed by plasma procainesterase about 4 times as fast as procaine[181]. In cerebrospinal fluid 2-chloroprocaine is hydrolysed mainly by the alkalinity of the cerebrospinal fluid, but partly by enzymes. Rapid onset of anæsthesia and low systemic toxicity is claimed for this substance[182].

Procaine ascorbate. The addition of ascorbic acid to procaine hydrochloride markedly reduces the toxicity of procaine in vitamin C-depleted guinea-pigs[183]. When procaine and ascorbic acid are mixed it has been shown that they unite to form procaine ascorbate which has a toxicity to mice and rats less than half that of procaine hydrochloride. No report is available of its local anæsthetic potency or stability, but it has been suggested as a substance worthy of clinical trial[184].

TETRACAINE

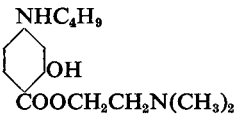
Tetracaine hydrochloride (amethocaine, anethaine, butethanol, decicaine, pontocaine, 2-dimethylaminoethanol 4-*n*-butylaminobenzoate hydro-



chloride). Bonica[185] has exhaustively reviewed the literature concerning the toxicity and pharmacology of this established local anæsthetic, and has described 3000 cases of its clinical use for regional anæsthesia, apart from topical and spinal use. Tetracaine is approximately 6 to 10 times

as toxic but also 10 to 15 times as potent as procaine, and is of great value for surface anæsthesia. The duration of anæsthesia in nerve block is 2 to 3 times that of procaine, but its onset can take up to half an hour. It is stressed that tetracaine should be used in dilute solutions, and the total dose should not exceed 1 mg./lb. body weight.

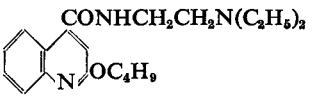
Hydroxytetracaine (hydroxamethocaine, rhenocain, *p*-butylaminosalicyldiethylaminoethanol hydrochloride) has been found to be one third



as toxic in experimental animals as tetracaine and has been used clinically in Germany for tracheobronchial anæsthesia[186,187].

CINCHOCAINE

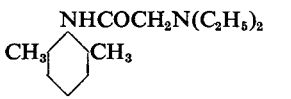
Cinchocaine (nupercaine, hydrochloride of the 2-diethylaminoethylamide of 2-butoxycinchonic acid)



The anæsthetic properties of cinchocaine were discovered by Meischer and reported by Uhlmann in 1929[188]. Cinchocaine is extremely potent and affords long lasting anæsthesia. It is the most toxic local anæsthetic in use, its toxicity being 25 times that of procaine, but, on the other hand, the minimal effective concentration is about 1/40th that of procaine[189]. The maximum dose is of the order of 1 mg./kg.[190]. Toxic reactions have been reported frequently[191,192]. Cinchocaine base is readily precipitated from solutions of the salt in the presence of alkali, with consequent loss of local anæsthetic properties. Further research by Büchi[51] into substances closely related to cinchocaine resulted only in the production of compounds either more toxic than cinchocaine, or with very poor local anæsthetic potency.

LIDOCAINE

Lidocaine (lignocaine, xylocaine, diethylaminoacet-2:6-xylidide)



was synthesised by Lofgren[15] in 1943. It is very stable, enduring, without decomposition, 8 hours boiling with 30 per cent. hydrogen chloride, or heating with strong ethanolic potassium hydroxide.

Many workers have reported on the pharmacology and toxicology of lidocaine, and found the toxicity varies with the concentration used, being equal to procaine at 0·5 per cent., but one and a half times as toxic at 2 per cent.[116,144,193,194]. It is compatible with adrenaline and is used clinically in 0·5 to 2 per cent. solutions for infiltration and nerve blocks. The onset

of anæsthesia is rapid and its effect lasts longer than procaine. Lidocaine is also employed as a surface anæsthetic in 2 or 4 per cent. solution. It has been used intravenously for analgesia in a dilution of 0·5 per cent. in saline solution[195], and complete anæsthesia of the skin occurred in 35 to 55 minutes. In 2 cases, however, where lidocaine was used for analgesia in childbirth, muscle twitching developed and persisted for 2 hours. Blood levels of lidocaine have been shown by McMahon and Woods[81] to decline slowly over a period of 6 hours and about 10 to 20 per cent. of the drug is recovered unchanged in the urine in 24 hours.

Local side reactions to lidocaine in the form of œdematous swellings were observed by certain dentists. This only occurred when adrenaline was added to the solution, and it has been shown[196] that these reactions were due to heavy metal ions, especially copper, which had been released from hypodermic syringes by the acid solution. A similar reaction can occur with procaine adrenaline solutions. Wiedling[197] showed that in the absence of adrenaline the metal ions were absorbed before a local toxic action had time to develop.

Lidocaine is the most satisfactory local anæsthetic at present available to clinicians and is already widely used, despite its comparatively recent introduction. A comprehensive survey of the clinical literature is given by Wiedling[198]. Southworth and Dabbs[199] have examined 25 publications in which 68,281 cases were reported, the total incidence of reactions being low (0·005 per cent.).

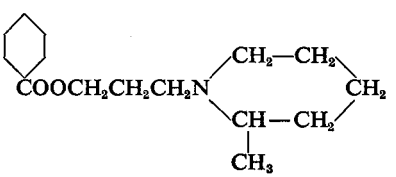
Other Compounds Recently Introduced

Butethamine (monocaine, *iso*butylaminoethyl *p*-aminobenzoate). The

hydrochloride is slightly more toxic than procaine on subcutaneous injection in white mice[200]. 2 per cent. butethamine with adrenaline 1 : 50,000 is less toxic than a similar concentration of procaine and adrenaline in mice[201].

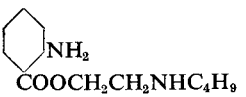
References to its clinical use have been summarised[202]. It is claimed in 1·5 per cent. solution to be of low toxicity, rapid in action, and more stable than procaine. The formate has been used to produce low spinal anæsthesia[203].

Piperocaine (neothesin, metycaine, 3-(2-methylpiperidino propyl benzoate hydrochloride).



Pharmacological observations showed that the subcutaneous toxicity of piperocaine is lower than that of cocaine and comparable with that of procaine in several species of animals[204]. In the dog, piperocaine is metabolised relatively rapidly after absorption[205]. Kalow found piperocaine to be hydrolysed faster than procaine in *in vitro* experiments[75]. The potency is about one third greater than procaine so that it is used in three quarters of the dose for injection anæsthesia[206]. Onset of anæsthesia is quicker and the duration exceeds that of procaine. Piperocaine may be employed for infiltration, spinal and surface anæsthesia.

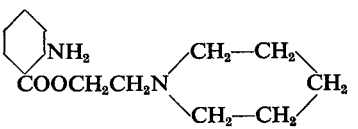
Unacaine (2-*iso*butylaminoethyl *m*-aminobenzoate) has, in mice,



approximately one third the subcutaneous toxicity of procaine. The anæsthetic activity is at least twice that of procaine[207].

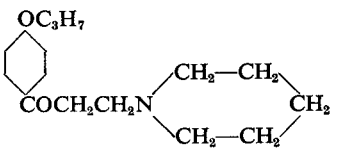
It has been employed clinically in dentistry and the anæsthesia is claimed to be of rapid onset with a low incidence of toxic symptoms[207]. A clinical impression has been reported that bleeding was increased following the use of unacaine in dental surgery[208]. It is suggested that unacaine is less likely to give rise to allergic reactions owing to the *meta*-position of the amino group on the benzene ring[207].

Lucaine (β(2-piperidyl)ethyl *o*-aminobenzoate hydrochloride) was



found to be the most promising of a series of new piperidine compounds. Its toxicity in several species of animals compared favourably with piperocaine and procaine and the minimal anæsthetic dose was smaller[209]. It has been used in spinal anæsthesia where selective sensory analgesia is produced with minimal effect on motor fibres[210,211,212].

Falicaine (piperidinoethyl 4-propoxyphenylketone). The toxicity of

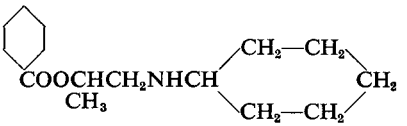


falicaine has been worked out in mice. Given intravenously it is 4 times, and subcutaneously 10 times as toxic as procaine[213]. Falicaine is not broken down in the body. It is claimed to be bacteriostatic and does not require sterilisation. If a solution of falicaine is boiled an increase in toxicity results apparently from some chemical change[214].

The activity on the rabbit cornea is 10 times that of cocaine, and on intradermal injection 10 times that of procaine. It has been used in minor and major surgery[215]. Falicaine is suitable for surface anæsthesia in a concentration of 0·5 to 1 per cent. Higher concentrations cause irritation

or even necrosis. A 0·1 per cent. solution is used for infiltration and, for nerve blocks, falicaine 0·25 per cent. without adrenaline has been employed[214]. The marked prolongation of anæsthesia eliminated the necessity for post-operative opiates in some cases. Falicaine has also been given intravenously where 5 to 10 ml. of 0·1 per cent. solution was effective in peripheral circulatory disturbances[215].

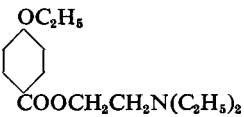
Hexylcaine (cyclaine, 1-*cyclo*hexylamino 2-propylbenzoate hydrochloride). In animals the toxicity of hexylcaine exceeds that of procaine



but it is less than piperocaine[216]. In conscious dogs, when compared with procaine, intravenous hexylcaine has similar effects on the cardiovascular system, but convulsions result with one third the dose of procaine[217]. The corneal activity exceeds that of cocaine, whilst on injection the duration of anæsthesia approaches that of tetracaine. Hexylcaine is hydrolysed more slowly than procaine by plasma[218]. This may in part account for the longer action of hexylcaine.

Clinically, hexylcaine has been used for spinal anæsthesia[219,220], regional nerve block[220] and topical anæsthesia for bronchoscopy[221]. It is claimed to be superior to procaine, but minor toxic reactions[221] and complaints of pain on injection with residual soreness[220] have been reported.

Diethoxin (intracaine, maxicaine, diethylaminoethyl 4-ethoxybenzoate hydrochloride)

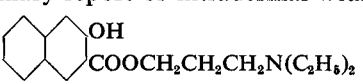


is more toxic to mice compared with procaine, but it is effective in about one-half the concentration and anæsthesia is appreciably longer[222]. This increased potency is believed to depend upon the lack of peripheral vasodilatation, and it is claimed to be effective without adrenaline[223]. It causes little irritation to tissues and has been found satisfactory for infiltration and nerve block anæsthesia[224]. Its topical use in approximately 4000 cases in the urological clinic has been reported[225].

Diethoxin has been used as a spinal anæsthetic and found to be useful as a mild anæsthetic for lower abdominal operations[226]. A 5 per cent. solution in oil has been recommended for prolonged caudal anæsthesia in rectal surgery[227].

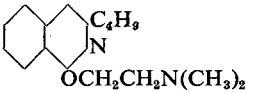
The accidental injection of 30 ml. of a 1 per cent. solution caused convulsions which responded to the administration of a barbiturate[224].

Bonacaine-G bitartrate (γ-diethylaminopropyl 2-hydroxy-3-naphthoate bitartrate). A preliminary report of intradermal weal tests in man with



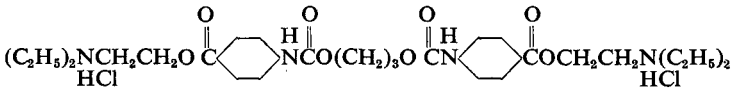
bonacaine-G bitartrate indicates that the anæsthesia following injection of this substance will be more extreme and of longer duration than that afforded by procaine. The results of toxicity tests in animals are not reported and its toxicity is claimed to be low[225]. Clinical trials have not been reported.

Quotane (1-(β-dimethylaminoethoxy) 3-*n*-butyl *iso*quinoline hydrochloride)



is an extremely potent corneal anæsthetic, being 10 times as potent as cinchocaine. On intraperitoneal injection in rats it was half as toxic as cinchocaine[229,230]. No clinical reports are available.

Tridiurecaine. The relative toxicity and local anæsthetic potency



is similar for procaine and tridiurecaine. Toxic doses of the latter, however, cause sedation instead of excitation, and death in dogs is from respiratory paralysis[231]. No report of its clinical use is yet available.

Conclusions

Much research remains to be carried out before knowledge of the mode of action of local anæsthetics reaches a level comparable to that of the mechanisms of block in other regions in the nervous system. It is the authors' considered opinion that potency and toxicity tests used to compare local anæsthetic agents in animals not infrequently give results which cannot be applied to the likely value of these substances in humans. Perfection seems far off in this respect. Experience during the years has shown that the only true criterion of a local anæsthetic is general acceptance. By this standard, lidocaine is so far, the only rival to procaine.

Appendix

Identification of Local Anæsthetics.

Ting, Coon and Conway[232] reviewed the literature on methods for quantitative estimation of procaine and described a simple spectrophotometric method for the determination of procaine and *p*-aminobenzoic acid in the blood in the presence of one another. It is based on the diazotizing reaction of Bratton and Marshall[233] originally devised for the determination of sulphonamides. The *in vitro* hydrolysis of the procaine is prevented by the addition of sodium arsenite to the blood. The sensitivity of the method is considerably enhanced by forming the azo dye in a small volume, and assaying its concentration by microspectrophotometry. This permits the estimation of plasma procaine concentrations as low as 100 μg./l.[234]. Colorimetric methods using reineckates have been described for procaine, tetracaine, cinchocaine[235] and lidocaine[236].

Kalow[75] gives the ultra-violet absorption spectra of 5 common local anæsthetics and Biggs[237] discusses the use of this method of identifying and estimating aqueous solutions of procaine.

Hucknall and Turfitt[238] described a scheme for the characterisation and identification of 11 local anæsthetic drugs of the benzoic ester group. A method of obtaining the hydrochlorides in a high degree of purity from biological materials or medicinal preparations is also given.

A simple scheme for the chemical identification of procaine, tetracaine, cinchocaine and lidocaine has recently been published[239] and a systematic micromethod for the recognition of 16 local anæsthetics which can be used on 1 to 2 ml. of solution at 1 in 2000 to 1 in 20,000 dilution has been described[240].

Wickstrøm[241] has discussed the optical crystallographic properties of 7 commonly used local anæsthetics.

Büchi[242] has recently reported on the use of Eder's method of vacuum sublimation[243] and its value in the identification of local anæsthetics. Summaries of important experimental conditions of pressure and temperature are given. Similar crystals result from different chemicals and their identity could not be determined simply by examining the crystalline character of the sublimates. Definite identification depends upon crystalline optical properties and micro melting points[242]. The strengths of solutions of salts of local anæsthetics can be determined by the separation of base by means of the anion exchange resin Amberlite IRA 400 and titration with acid[244]. The separation of local anæsthetics by paper chromatography has been reported[245,246]

REFERENCES

1. Köller, *Lancet*, 1884, **127**, 990.
2. Folk, *Therap. Monatch.*, 1890, **4**, 511.
3. Einhorn, quoted by Keys, *The History of Surgical Anesthesia*, Schumans, New York, 1945.
4. Bryce Smith, *Brit. J. Anæsth.*, 1950, **22**, 34.
5. Harris, *Mode of Action of Local Anæsthetics*, Livingstone, London, 1951.
6. Kendall, *J. Amer. med. Ass.*, 1948, **138**, 599.
7. Tainter, *Anesthesiology*, 1941, **2**, 481.
8. Hirschfelder and Bieter, *Physiol. Rev.*, 1932, **12**, 190.
9. Sherif, *J. Pharmacol.*, 1930, **38**, 11.
10. Watts, *ibid.*, 1949, **96**, 325.
11. Larrabee, Ramos and Bulbring, *Fed. Proc.*, 1950, **9**, 75.
12. Meyer, *Arch. exp. Path. Pharmak.*, 1899, **42**, 109.
13. Overton, *Studien über die Narkose, zugleich ein Beitrag zur allgemeinen Pharmakologie*, Fischer, Jena, 1901.
14. Tammelin and Lofgren, *Acta chem. scand.*, 1947, **1**, 871.
15. Lofgren, *Studies on Local Anæsthetics—Xylocaine*, Haeggströms, Stockholm, 1948.
16. Eccles, *The Neurophysiological Basis of Mind*, Clarendon Press, Oxford, 1953.
17. Wright, *Applied Physiology*, Oxford University Press, London, 1952.
18. Hodgkin, *Biol. Rev.*, 1951, **26**, 339.
19. Hodgkin and Keynes, *J. Physiol.*, 1953, **120**, 46P.
20. Hodgkin, *Biol. Rev.*, 1951, **26**, 409.
21. Lussier and Rushton, *J. Physiol.*, 1952, **117**, 87.
22. Shanes, *J. gen. Physiol.*, 1939, **33**, 57.
23. Shanes, *ibid.*, 1939, **33**, 75.
24. Bennett and Chinburg, *J. Pharmacol.*, 1946, **88**, 72.
25. Kato, *Cold Spr. Harb. Symp. quant. Biol.*, 1936, **4**, 202.

26. Tasaki, *Amer. J. Physiol.*, 1939, **125**, 367.
27. Eccles, Katz and Kuffler, *J. Neurophysiol.*, 1941, **4**, 362.
28. Burns and Paton, *J. Physiol.*, 1951, **115**, 41.
29. Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, Macmillan, New York, 1946.
30. Feldburg, *Brit. med. J.*, 1951, **1**, 4713.
31. Nachmansohn, *Ann. N.Y. Acad. Sci.*, 1946, **47**, 395.
32. Nachmansohn, *Johns Hopk. Hosp. Bull.*, 1948, **83**, 463.
33. Lorent de Nó, *J. cell. comp. Physiol.*, 1944, **24**, 85.
34. Rapp, *Oral Surg.*, 1948, **1**, 327.
35. Dawes, *Brit. J. Pharmacol.*, 1946, **1**, 90.
36. Dews and Graham, *ibid.*, 1946, **1**, 278.
37. Dutta, *ibid.*, 1949, **4**, 281.
38. Fitzpatrick, Orr and Stubbart, *J. Amer. med. Ass.*, 1952, **150**, 1092.
39. Reynolds, Kahn and Levy, *Gastroenterology*, 1950, **14**, 535.
40. Dutta, *Brit. J. Pharmacol.*, 1949, **4**, 197.
41. Kwiatowski, *J. Physiol.*, 1943, **102**, 32.
42. Von Euler, *ibid.*, 1948, **107**, 10.
43. Bárány and Nordqvist, *Nature, Lond.*, 1949, **164**, 701.
44. Cabrera and Thompson, *ibid.*, 1950, **165**, 681.
45. Elio, *Brit. J. Pharmacol.*, 1948, **3**, 108.
46. Burn, *Brit. med. J.*, 1950, **2**, 691.
47. Peczenik and West, *J. Pharm. Pharmacol.*, 1951, **3**, 36.
48. Wilstätter, *see* Büchi No. 51.
49. Charronat, *Prod. pharm.*, 1952, **7**, 307.
50. Quevauviller, *ibid.*, 1952, **7**, 533, 585.
51. Büchi, *Arzneim. forsch.*, 2, 1, 65, 114.
52. Thimann, *Arch. Biochem.*, 1943, **2**, 87.
53. Mushin and Rendell-Baker, *Lancet*, 1949, **256**, 619.
54. Swerdlow, *Curr. Res. Anesth.*, 1950, **29**, 169.
55. Braun, *Arch. klin. Chir.*, 1903, **69**, 541.
56. Sollmann, *J. Amer. med. Ass.*, 1918, **70**, 216.
57. Eggleston and Hatcher, *J. Pharmacol.*, 1919, **13**, 433.
58. Serafin, *J. Amer. med. Ass.*, 1928, **91**, 43.
59. Doubleday, *Dent. Rec.*, 1950, **70**, 196.
60. Dunlop, *J. Pharmacol.*, 1935, **55**, 464.
61. Legge and Durie, *Med. J. Aust.*, 1942, **29**, 561.
62. Kisch, Koster and Strauss, *Exp. Med. Surg.*, 1943, **1**, 51.
63. Hazard and Ravasse, *C.R. Soc. Biol., Paris*, 1945, **139**, 13.
64. Kisch, *Exp. Med. Surg.*, 1943, **1**, 84.
65. Burgen and Keele, *Brit. J. Pharmacol.*, 1948, **3**, 128.
66. Hazard, Pignard and Cornec, *C.R. Soc. Biol., Paris*, 1949, **143**, 1425.
67. Ting and Coon, *Curr. Res. Anesth.*, 1950, **29**, 263.
68. Antopol, Tuchman and Schifrin, *Proc. Soc. exp. Biol., N.Y.*, 1937, **36**, 46.
69. Vorhaus, Scudamore and Kark, *Gastrœnterology*, 1950, **15**, 304.
70. Hazard, Bonamy and Corned, *Pr. méd.*, 1949, **57**, 1133.
71. Kisch, *Exp. Med. Surg.*, 1945, **3**, 357.
72. Fiessinger, Hazard, Ravasse and Charles, *Bull. Acad. Méd., Paris*, 1945, **129**, 558.
73. Wilson, Calvert and Geoghegan, *J. clin. Invest.*, 1952, **31**, 815.
74. Foldes, McNall, Davis, Ellis and Wnuck, *Science*, 1953, **117**, 383.
75. Kalow, *J. Pharmacol.*, 1952, **104**, 122.
76. Conway, Ting and Coon, *ibid.*, 1949, **96**, 472.
77. Rosenberg, Kayden, Lief, Mark, Steele and Brodie, *ibid.*, 1949, **95**, 18.
78. Bonnycastle, White and Hellijas, *Fed. Proc.*, 1950, **9**, 259.
79. McIntyre, *J. Pharmacol.*, 1936, **57**, 133.
80. Tatum and Seevers, *ibid.*, 1929, **36**, 401.
81. McMahon and Woods, *Fed. Proc.*, 1951, **10**, 321.
82. Somers and Edge, *Quart. J. Pharm. Pharmacol.*, 1947, **20**, 380.
83. Conway, Ting and Coon, *Fed. Proc.*, 1948, **7**, 212.
84. Buff, *Amer. Practit. Digest. Treat.*, 1950, **1**, 347.
85. Richards and Kueter, *J. Pharmacol.*, 1946, **87**, 42.
86. Ting and Coon, *Proc. Soc. exp. Biol., N.Y.*, 1951, **76**, 543.
87. Tatum, Atkinson and Collins, *J. Amer. med. Ass.*, 1925, **84**, 1177.
88. Leshure, *ibid.*, 1927, **88**, 168.
89. Steinhaus and Tatum, *J. Pharmacol.*, 1950, **100**, 351.

90. Steinhaus, *Anesthesiology*, 1952, **13**, 577.
91. Migliarese, Bauer and Randall, *Proc. Soc. exp. Biol., N.Y.*, 1950, **73**, 53.
92. Reynals, *Bact. Rev.*, 1942, **6**, 197.
93. Kirby, Eckenhoff and Looby, *Surgery*, 1949, **25**, 101.
94. Eckenhoff and Kirby, *Anesthesiology*, 1951, **12**, 27.
95. Moore, *ibid.*, 1951, **12**, 611.
96. Howland and Papper, *ibid.*, 1951, **12**, 688.
97. Britton and Habif, *Surgery*, 1953, **33**, 917.
98. Sekijima and Fink, *Proc. Soc. exp. Biol., N.Y.*, 1952, **80**, 158.
99. Laden and Wallace, *J. invest. Derm.*, 1949, **12**, 299.
100. Sulzberger and Wise, *Arch. Derm. Syph., Wien*, 1933, **28**, 461.
101. Lane and Luickhart, *J. Amer. med. Ass.*, 1951, **141**, 1717.
102. Adler, *J. dent. Res.*, 1950, **29**, 713.
103. Peck and Fieldman, *J. invest. Derm.*, 1949, **13**, 109.
104. Hitschmann, Leider and Baer, *ibid.*, 1950, **15**, 165.
105. Koffler, *J. Amer. med. Ass.*, 1953, **152**, 28.
106. Wöhler, *Ann. Chem. Pharm.*, 1860, **114**, 213.
107. Sollman, *J. Pharmacol.*, 1919, **13**, 429.
108. Sollman, *ibid.*, 1918, **11**, 9.
109. Munch, Pratt and de Ponce, *J. Amer. pharm. Ass.*, 1933, **22**, 1078.
110. Sollmann, *J. Pharmacol.*, 1918, **11**, 17.
111. Schmitz and Loevenhart, *ibid.*, 1924, **24**, 159.
112. Gerlough, *ibid.*, 1931, **41**, 307.
113. Sinha, *ibid.*, 1936, **57**, 199.
114. Rose, *Curr. Res. Anesth.*, 1931, **10**, 159.
115. Leser, *J. Pharmacol.*, 1940, **63**, 389.
116. Goldberg, *Acta physiol. scand.*, 1949, **18**, 1.
117. McIntosh and Work, *Quart. J. Pharm. Pharmacol.*, 1941, **14**, 16.
118. Chance and Lobstein, *J. Pharmacol.*, 1944, **82**, 203.
119. Sollmann, *ibid.*, 1917, **10**, 379.
120. Sollmann, *ibid.*, 1918, **11**, 1.
121. Régnier, *Méthodes de mesure de l'activité des Anesthésiques Locaux*, Brulliard, Saint-Dizier, 1929.
122. Rider, *J. Pharmacol.*, 1930, **39**, 329.
123. Bülbring and Wajda, *ibid.*, 1945, **85**, 78.
124. Quevauviller, *Anesth. Analg., Paris*, 1951, **8**, 587.
125. Ehrenberg, *Acta chem. scand.*, 1948, **2**, 63.
126. Copeland, *Brit. med. J.*, 1924, **2**, 41.
127. Schmitz and Loevenhart, *J. Pharmacol.*, 1924, **24**, 167.
128. Hirschfelde-and Ridges, *Proc. Soc. exp. Biol., N.Y.*, 1933, **30**, 958.
129. Shackell, *Curr. Res. Anesth.*, 1935, **14**, 20.
130. Loomis and Spielmeyer, *Yale J. Biol. Med.*, 1946, **18**, 165.
131. Seevers and McIntyre, *J. Pharmacol.*, 1938, **62**, 252.
132. Luduena and Hoppe, *ibid.*, 1952, **104**, 40.
133. Bennett, Wagner and McIntyre, *ibid.*, 1942, **75**, 125.
134. Sollmann and Hanzlik, *Experimental Pharmacology*, Saunders, Philadelphia, 1928.
135. Essex and Lundy, *Proc. Mayo Clinic*, 1931, **6**, 227.
136. Bieter, Harvey and Burgess, *J. Pharmacol.*, 1932, **45**, 291.
137. Shackell, *Curr. Res. Anesth.*, 1937, **16**, 136.
138. Bieter, McNearney, Cunningham and Lenz, *J. Pharmacol.*, 1936, **57**, 221.
139. Luduena and Hoppe, *J. Amer. pharm. Ass. Sci. Ed.*, 1951, **40**, 132.
140. Rose, *J. Lab. clin. Med.*, 1929, **15**, 1218.
141. McIntyre and Seevers, *J. Pharmacol.*, 1937, **61**, 107.
142. Armstrong, Dry, Keele and Markham, *J. Physiol.*, 1953, **120**, 326.
143. Sollmann, *J. Pharmacol.*, 1918, **11**, 69.
144. Gordh., *Anæsthesia*, 1949, **4**, 4.
145. Mack and Nelon, *J. Amer. pharm. Ass., Sci. Ed.*, 1953, **42**, 101.
146. Herr, Nyiri and Pataky, *Arch. exp. Path. Pharmak.*, 1953, **217**, 207.
147. Coles and Rose, *J. Lab. clin. Med.*, 1929, **15**, 239.
148. Draize, Woodard and Calvery, *J. Pharmacol.*, 1944, **82**, 377.
149. Hoppe, Alexander and Miller, *J. Amer. pharm. Ass., Sci. Ed.*, 1950, **39**, 147.
150. Munch, *Bioassay*, Williams and Wilkins, Baltimore, 1931.
151. Burns, *Brit. med. Bull.*, 1946, **4**, 82.
152. Carney, *Medicinal Chemistry*, Wiley, New York, 1951.
153. Geddes, Investigations to be published.

154. Perry, *Spec. Rep. Ser. med. Res. Coun. Lond.*, No. 270, 1950.
155. Bullock, *Quart. J. Pharm. Pharmacol.*, 1947, **20**, 449.
156. Graubard and Paterson, *Clinical Uses of Intravenous Procaine*, Blackwell, Oxford, 1951.
157. Hazard, *Actualitiés Pharmacologiques*, Masson et Cie, Paris, 1949.
158. Yeomans, Gorsch and Mathsheimer, *Med. Rec., N.Y.*, 1928, **127**, 19.
159. Gabriel, *Brit. med. J.*, 1929, **1**, 1071.
160. Gabriel, *ibid.*, 1930, **2**, 311.
161. Gabriel, *Practitioner*, 1934, **133**, 489.
162. Morgan, *Brit. med. J.*, 1935, **2**, 938.
163. Smith, *Sth. med. J. Bgham, Ala*, 1943, **36**, 650.
164. Kelly, *Lancet*, 1947, **252**, 710.
165. Meidinger, *C.R. Soc. Biol., Paris*, 1945, **139**, 907.
166. Gross and Shaftel, *N.Y. St. J. Med.*, 1952, **52**, 1413.
167. Ansbro, Iason, Shaftel, Halpern. Latteri and Bodell, *Anesthesiology*, 1952, **13**, 306.
168. Roualle, *Brit. med. J.*, 1952, **2**, 1293.
169. Shapiro and Norman, *J. Amer. med. Ass.*, 1953, **152**, 608.
170. Keil and Rademacher, *Arzneim. forsch.*, 1951, **1**, 154.
171. Keil and Brautigam, *ibid.*, 1951, **1**, 270.
172. Schoog, *Med. Welt.*, 1951, **20**, 1622.
173. Holler, *Zahnärztl Welt.*, 1952, **7**, 247.
174. Keil, Brautigam and Holler, *Arzneim forsch.*, 1952, **2**, 112.
175. Hirsch and Holler, *ibid.*, 1952, **2**, 313.
176. Keil and Holler, *Arztliche Praxis*, 1952, 16.
177. Müller, *Schweiz. Mschr. Zahnheilk.*, 1953, **63**, 374.
178. Crawford, *Anesthesiology*, 1953, **14**, 278.
179. Krantz, Carr, Vitcha and Musser, *ibid.*, 1951, **12**, 57.
180. Foldes and McNall, *ibid.*, 1952, **13**, 287.
181. Aven and Foldes, *Science*, 1951, **114**, 206.
182. Foldes, *J. Pharmacol.*, 1952, **105**, 253.
183. Richards, *Curr. Res. Anesth.*, 1947, **26**, 22.
184. Slaughter and Hazel, *Fed. Proc.*, 1951, **10**, 335.
185. Bonica, *Curr. Res. Anesth.*, 1951, **30**, 76.
186. Worth and Heinz, *Fortschr. Röntgenstr.*, 1952, **76**, 617.
187. Dietmann, *Dtsch. med. Wschr.*, 1952, **77**, 1123.
188. Uhlmann, *Narkose und Anæsthesie*, 1929, **6**, 168.
189. Israels and MacDonald, *Brit. med. J.*, 1931, **2**, 986.
190. Pitkin, *Conduction Anesthesia*, Lippincott, Philadelphia, 1946.
191. Hewer, *Recent Advances in Anæsthesia and Analgesia*, 7th Ed., Churchill, London, 1953.
192. *Brit. med. J.*, 1952, **2**, 672.
193. Goldberg, *Svensk. Tandlärk. Tidskr.*, 1947, **40**, 819.
194. Wiedling, *Acta pharm. tox., Kbh.*, 1952, **8**, 117.
195. Gilbert, Hanson, Brown and Hingson, *Curr. Res. Anesth.*, 1951, **30**, 301.
196. Lundqvist, Lofgren, Persson and Sjogren, *Acta chir. scand.*, 1948, **97**, 239.
197. Wiedling, *Acta pharm. tox., Kbh.*, 1948, **4**, 351.
198. Wiedling, *Der Anæsthetist*, 1952, **1**, 119.
199. Southworth and Dabbs, *Curr. Res. Anesth.*, 1953, **32**, 159.
200. Epstein and Silver, *ibid.*, 1945, **24**, 38.
201. Strean, *ibid.*, 1952, **31**, 141.
202. Burdich, *ibid.*, 1947, **26**, 82.
203. Nesbit and Butler, *Anesthesiology*, 1948, **9**, 430.
204. Coles and Thompson, *J. Lab. clin. Med.*, 1930, **15**, 731.
205. Coles and Rose, *Curr. Res. Anesth.*, 1931, **10**, 103.
206. Lundy, *J. Amer. med. Ass.*, 1938, **110**, 434.
207. Nevin, Epstein and Nevin, *Oral Surg.*, 1952, **5**, 1228.
208. MacDonald, *Dent. Items*, 1951, **73**, 1074.
209. Hunt and Fosbinder, *Anesthesiology*, 1940, **1**, 305.
210. Finer and Rovenstine, *ibid.*, 1947, **8**, 619.
211. Cull and Shotz, *ibid.*, 1950, **11**, 353.
212. de Vivo, *J. med. Soc., N.J.*, 1952, **49**, 58.
213. Hannig, *Arch. exp. Path. Pharmak.*, 1952, **216**, 166.
214. Drebinger, *Dtsch. Gesundh. Wes.*, 1951, **6**, 1505.
215. Eggero, *ibid.*, 1951, **6**, 1507.
216. Beyer, Latven, Freysburger and Parker, *J. Pharmacol.*, 1948, **93**, 388.

217. Beyer and Latven, *ibid.*, 1952, **106**, 37.
218. Wiebelhous, *see* Orkin and Rovenstine, reference 221.
219. Ruben and Anderson, *Amer. J. Surg.*, 1949, **78**, 843.
220. Anderson and Ruben, *Anesthesiology*, 1952, **13**, 429.
221. Orkin and Rovenstine, *ibid.*, 1952, **13**, 465.
222. McIntyre and Seevers, *J. Pharmacol.*, 1937, **61**, 107.
223. Archer, *A Manual of Dental Anesthesia*, Saunders, Philadelphia, 1952.
224. Rovenstine and Cullen, *Curr. Res. Anesth.*, 1939, **18**, 86.
225. Baurys and Morton, *Bull. Guthrie Clin.*, 1952, **21**, 109.
226. Sappenfield and Rovenstine, *Curr. Res. Anesth.*, 1940, **19**, 48.
227. Green, Barcham and Berkowtiz, *ibid.*, 1952, **31**, 87.
228. Graubard, Breidenbach, Alpin and Soroff, *N.Y. St. med. J.*, 1952, **52**, 1909.
229. Fellows and Macko, *Fed. Proc.*, 1949, **8**, 291.
230. Fellows and Macko, *J. Pharmacol.*, 1951, **103**, 306.
231. Rau and Westfall, *ibid.*, 1950, **99**, 421.
232. Ting, Coon and Conway, *J. lab. clin. Med.*, 1949, **34**, 822.
233. Bratton and Marshall, *J. biol. Chem.*, 1939, **128**, 537.
234. Brodie, Lief and Poet, *J. Pharmacol.*, 1948, **94**, 359.
235. Steiger and Hippenmeyer, *Pharm. Acta Helvet.*, 1949, **24**, 443.
236. Ortenblad and Jonsson, *Acta chem. scand.*, 1951, **5**, 510.
237. Biggs, *J. Pharm. Pharmacol.*, 1952, **4**, 479.
238. Hucknall and Turfitt, *ibid.*, 1949, **1**, 462.
239. Cooper, *Pharm. J.*, 1953, **171**, 68.
240. Guagnini and Vonesch, *An. Ass. quim. argent.*, 1952, **40**, 118.
241. Wickstrøm, *J. Pharm. Pharmacol.*, 1953, **5**, 158.
242. Büchi, Perlia and Strebel., *Pharm. Acta Helvet.*, 1952, **27**, 334.
243. Eder, *Uber die Mikrosublimation von Alkaloiden in luftverdünnten Raum*, Diss ETH, Zurich, 1912.
244. Jindra and Rentz, *J. Pharm. Pharmacol.*, 1952, **4**, 645.
245. Vitte and Boussemart, *Bull. Soc. Pharm., Bordeaux*, 1951, **88**, 181.
246. Jaminet, *J. Pharm., Belg.*, 1951, **6**, 81.