REVIEW ARTICLE

THE MODE OF ACTION OF LOCAL ANAESTHETICS

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IT is exactly a century since Niemann first isolated the alkaloid cocaine and noticed its local anaesthetic properties. He reported that it "benumbs the nerves of the tongue, depriving it of feeling and taste." In 1884 Koller introduced cocaine as a local anaesthetic in ophthalmology, and its use spread later to general surgery.

Various attempts have been made to explain the mode of action of such drugs, but no clear cut case has yet been made out. Claude Bernard[1] in 1875 insisted that all agents which depress nerve cells, including heat and asphyxia, do so by producing the same modification in the cell, i.e. there is a single and universal mechanism of narcosis. Seventy-five years later, Butler[2] expressed dissatisfaction with this concept: he believed that when two different drugs produce the same apparent effect, it is not justifiable to assume, without further evidence, that the same mechanism is involved in both instances.

Between these two observations many investigations have been performed upon general anaesthetics, and various hypotheses have been advanced about their mode of action. It follows that, as both general and local anaesthesia relate to drug action on nervous tissue, theories about the former should be applied to local anaesthesia, and must merit study. It is also apparent that attention should be paid to the transmission of nerve impulses, as there may well be factors involved in it which affect the action of the drug in producing a local anaesthetic effect. In the present review both these aspects are considered, together with other factors which appear to be important in local anaesthesia. This is followed by an examination of various problems which arise.

TRANSMISSION OF THE NERVE IMPULSE

It is not the purpose of this study to discuss the various theories of transmission at length, but certain features are pertinent.

Current Theory

There is a potential difference across the membrane of resting nerve, the protoplasm being negative and the interstitial tissue fluid positive. Bernstein[3,4] observed that the concentration of potassium ions is much greater inside nerve fibres than outside: he considered that, if the membrane is impermeable to anions and sodium ions, the difference between the internal and the external concentrations of potassium would explain the resting potential. He suggested that, during activity, the selective permeability for potassium collapses, and the membrane potential subsequently approaches zero.

This concept forms the basis of the present commonly accepted theory of nerve conduction. Some doubts about the hypothesis arose from observations by Hodgkin and Huxley[5,6] and Curtis and Cole[7,8] that the membrane

potential of squid giant-axon does not merely drop to zero at the peak of the action spike, but is substantially reversed.

Resting nerve exhibits a continuous energy expenditure which is directed towards the uptake of potassium: opposing this is a high intracellular potassium concentration which tends to escape from the nerve fibre at a rate determined by the concentration gradient and by the permeability of the membrane. The surface concentration of potassium is low, but escape of it from within, such as occurs during the passage of a nerve impulse, activates a restoration mechanism at the surface.

In 1949 Hodgkin and Katz[9] suggested that action potential is due to the movement of sodium ions, thus the rising phase of the spike results from a specific increase in the sodium permeability of the membrane, whilst potassium permeability is more than normal during the falling phase. Measurements of ionic movements during nervous activity, both by indirect methods and by using radioactive tracers, confirm this: details are given in Hodgkin's review[10] and by Hodgkin and Keynes[11].

Most of the original work was performed on squid tissue but the general pattern of behaviour is seen in other tissues and species. On stimulation, activity is triggered by the spread of electrical current from a neighbouring region. It is accompanied by permeability changes in the membrane, which breaks down partially or completely. The process is marked by definite electrical changes: the initial positive deflection observed is probably due to sodium ion entry, as it is absent in sodium-free solutions, and the changes in current are subsequently continued by an outward movement of potassium ions. The sodium movements provide the current required to depolarise the resting membrane ahead of the active region. After the change the nerve fairly quickly returns to normal, and can conduct another impulse, the fibre having gained a small amount of sodium, and having lost a similar quantity of potassium. The ionic movements are the immediate energy source for impulse conduction, and are reversed later by a slow process requiring metabolic energy.

Calcium concentration has also been implicated in nerve processes. Low calcium values produce an increase in excitability, and Keynes and Lewis[12] have shown that the total internal concentration of this ion may be about 1/30th of that outside. This suggests that there may be some control of calcium values around the nerve. In his comprehensive review, Hodgkin[13] suggested that calcium ions are not directly involved in the conduction of impulses, but are important in influencing the permeability and excitability of the membrane. Regarding the former, he suggested that there are special channels for sodium and potassium: when the nerve conducts an impulse the channels open up, allowing first sodium, and then potassium ions to move down their concentration gradients. These movements generate the action potential.

Nerve has been represented as a cored conductor, the axis cylinder being surrounded by a more or less insulating layer of lipid (the membrane), beyond which there is an external longitudinal conductor (the interstitial tissue fluid), and functional models, such as the iron wire one of Lillie[14], have been constructed. Hirschfelder and Bieter[15] believed

that alterations in the surface layer of this model upon "stimulation" are analogous to the passage of the action current in a nerve fibre, where an increase occurs in the permeability of the lipid layer. They concluded that, in general, substances which increase the permeability of the lipid layer (in non-destructive concentrations) might increase nerve actions and sensations, whilst those which decrease the permeability to water and ions might act as anaesthetics.

Structural Factors

The differential effects of local anaesthetics raise the question of whether peripheral nerves differ anatomically or physiologically. The possession of myelin may create a major distinction, although it is usually claimed that its function is purely an acceleratory one.

Gasser and Erlanger[16] stated that the important variables are the threshold of excitation and the velocity of conduction, both of which depend upon fibre size. Hence the order in which fibres are blocked may be a linear function of their diameter. Experimental results suggest that there is much truth in this assertion.

Another important structural feature is the connective tissue sheath around nerve. Lorente de Nó[17] believed that it could be ignored in surface potential analysis, despite claims that it distorts the potential difference obtained. His view deserves comment, as it depends on the thesis that the tissue sheaths provide little or no electrical or diffusion resistance, and this is opposed by considerable evidence that the sheath *is* a diffusion barrier and has a high electrical resistance. Bishop, Erlanger and Gasser[18] in 1926 suggested that many 'nerve' properties might be features of this non-nervous structure. In 1949 Rashbass and Rushton[19] compared intact and desheathed frog nerves. They revealed a close conformity to exist between nerve and the simple cable theory of conduction, when the epineurium was removed. Later histological work by Krnjević[20] suggested that the perineurium, rather than the epineurium, is the barrier to diffusion, but he demonstrated that desheathing always removes the perineurium. They believed that much of the earlier work on nerve resistance, permeability, and polarisation needs re-interpretation in the light of the possible effects of a highly polarisable resistance being interposed between the nerve axon and the electrode. Despite this, Lorente de Nó clung to his contention, describing desheathed nerve as "abnormal". Krnjević[21] obviated this criticism by using perfused nerves, thus bringing drugs into intimate contact with nerve tissue, and simultaneously evading any effects produced by the sheath. His results clearly show, as did those of Rashbass and Rushton with a long electrode inserted below the sheath, that the latter is a very significant barrier.

Consequently, it is inevitable that the views of Lorente de Nó should be treated with reserve. He rejected the concept of a porous membrane whose permeability might be influenced, and he repeatedly[17,22] emphasised metabolic effects. It is true that metabolism must supply energy for nerve function and for the maintenance of the resting membrane potential, but it does not follow that it is the sole key to the production of block.

Indeed, Lorente de Nó himself reported that nerve cannot be stimulated unless the resting membrane potential is above a critical excitability level, and he admitted that lack of sodium ions, or anaesthetics of the cocaine type, may prevent the production of the action potential without lowering the resting membrane potential. The last is an important admission.

Acetylcholine and the Nerve Impulse

It has been suggested that acetylcholine may propagate the nerve impulse along the axon, and this idea has influenced certain researches on local anaesthetics.

The chief protagonist of the theory, Nachmansohn[23,24], claimed that acetylcholine is released from an unknown precursor and depolarises the membrane, thus establishing a local circuit which excites neighbouring regions. The acetylcholine is immediately destroyed by cholinesterase, and is re-synthesised into the inactive precursor during the recovery period, by the enzyme choline acetylase. Acetylcholine and the two enzymes do exist in nervous tissue, but the action outlined above is strongly contradicted by considerable experimental evidence, chief amongst which is that acetylcholine, even in massive concentration, does not depolarise nerve[25]. Nevertheless, Nachmansohn continued to assert the validity of his theory. Feldberg[26] has stated that Dale's words of 1948 are still true . . . "the ingenuity of its (the theory) supporters is sorely taxed to discover even plausible ways of escape from the facts which contradict it".

Saltation

Erlanger and Blair[27] suggested that the impulse is transmitted along the nerve in a jumping (saltatory) fashion, each segment between two nodes of Ranvier behaving as a unit. Restriction of excitability to the nodes has been confirmed, and Rashbass and Rushton[19] envisaged that impulses pass quickly along myelinated sections of nerve and receive a "boost" at the nodes. Huxley and Stämpfli[28] regarded myelin as a conductor which increases conduction velocity by making local circuits act at considerable distances ahead of the active region. They supposed that the action potential process is generated at the nodes. This view is favoured by the fact that agents producing stimulation or depression of conduction have a stronger action on the nodes than on the internodes. Blocking an internode stops the impulse, presumably due to the interruption of current flowing forward in the axis cylinder and back in the fluid of the myelin sheath. A similar arrangement seems to exist in unmyelinated fibres.

Impulse Initiation

Katz[29] studied the depolarisation of sensory terminals and the genesis of impulses in frog muscle spindles. Stretching depolarises the endings, and a local potential change can be recorded from the afferent axon at a point close to the spindle. The potential varies with the rate and amplitude of stretching, and generates repetitive impulses in the sensory nerve.

Depolarisation increases with velocity of stretching until it attains a maximal value. On analysing the stretch two phases were revealed. The first coincides with the period of initial lengthening, and is due, Katz suggested, to changes in membrane capacity. In the second, the depolarisation and rate of discharge are maintained at a lower level, which may be due to a change in membrane permeability. It is noteworthy that the membrane is implicated in both phases. In 1951 Albert[30] stated that the cellular membrane plays an essential rôle in the propagation of excitation, and is therefore a likely site for the action of hypnotics.

The question of impulse transmission is not entirely straightforward, and this is true when transmission is applied to sensation. Intensity of stimulation has to be expressed, and this can be done by frequency of impulses[31]. If all sensation were equally anaesthetised the problem would be simpler. This is not the case, hence the suggestion[32] that some lines are preferentially paralysed.

Such difficulties are bound to cloud any clear appreciation of local anaesthetic action, and are difficult to overcome completely.

Theories of General Anaesthesia and their Relevance to Local Anaesthesia

The Overton-Meyer Theory

The first essays in this field were made at the time of the clinical introduction of ether and chloroform. Their solvent properties produced the suggestion that narcosis is caused by dissolving some fatty constituents of the brain which are re-deposited in the liver. The concept fails to explain the reversible effect of the anaesthetics, unless there is a rapid re-synthesis of the constituents, or a re-transfer of the original ones from the liver back to the brain.

Overton coined the term "lipoid"[33] to describe the true fats, and the more elaborate fat-like substances, such as lecithin and cholesterol. In analytical research it proved impossible to employ brain tissue or even the extracted and denatured brain lipids: consequently a simple model substance was often employed, the original and commonest one being olive oil.

The basic concept was to relate anaesthetic activity of a drug to its partition coefficient, making use of this model. It is relevant to note here that both local and general anaesthetics are usually more soluble in fat than in water. The full theory, endorsed by Overton, was published in 1899 by Meyer[34], and propounded that drugs which are lipid soluble, and can become distributed in protoplasm, act as narcotics: the partition coefficient is important as it determines the relative distribution of the drug in the mixture of body constituents, including water and lipids.

The shortcomings of the theory were later defined[35]. It was suggested that inhibition mechanisms vary, that is to say different drugs may act at different points, and produce depression in a variety of ways, and the theory only applies to the "indifferent narcotics" (an ill-defined group of fat-soluble organic compounds which includes alcohol and chloroform). Such propositions necessarily limit the theory.

The theory has been criticised because the critical lipid phase of neurones is relatively unknown, and because many anaesthetics fail to conform to it. The latter was true when Löfgren tested local anaesthetics on a water and oleyl alcohol model[36] which has often been regarded as a better representation of the cellular lipids involved in narcosis. (A lecithin in gelatin one has been used with fair success for local anaesthetic studies). Löfgren concluded that local and general anaesthetics are not strictly comparable. In his opinion, a major drawback to the theory is that compounds with widely differing activities may have the same coefficients.

From the literature it seems that many workers have attempted to apply the concept too rigidly with a model which was chosen for convenience and simplicity. On the other hand, Collander[37] commented that lipid molecules are orientated in layers in membranes, whilst in bulk phases, as in models, they are randomly distributed, and may behave quite differently. He saw little theoretical advantage in studying coefficients with solvents that are chemically more closely related to the membrane than is olive oil. Failure to imitate cell membrane lipids, for example, cholesterol, may explain the anomalous drugs which have high partition coefficients but are not depressants[30]. Attempts to rectify this have only been limitedly successful.

Cell constitution is very important in the application of this theory. Cellular protoplasm is separated from the environment by the plasma membrane, and any substance entering the cell must pass the membrane. Work and Work[38] commented that the degree of correlation of lipid solubility and penetrant powers of a drug is noteworthy, but stressed that some lipid-insoluble substances may penetrate into cells. They suggested that the membrane might be a continuous lipoprotein skin, or a sieve-like structure. The second would allow the entry of lipid-insoluble substances without requiring the agency of an active transfer mechanism.

Burger[39] admitted that the true anaesthetic is preferentially absorbed by cells containing large amounts of lipid, but argued that the composition of nerve invalidates the theory, since only half of the solids are lipids, whilst up to 90 per cent of the nerve is water. This is ludicrous: nerve may contain a mere 5 per cent of lipid, but even if there was only a fraction of this amount present, there is no reason why it should not govern anaesthetic action, provided that it is situated at strategic positions for producing block.

In 1948 Löfgren[36] stated that many experiments supporting the theory had, in some way or other, been inadaequately performed. In his own work especial care was taken to maintain pH constancy. He found that various general narcotics may act as local anaesthetics, when they probably conform with the Overton-Meyer rule: with his own local anaesthetic compounds, including lignocaine, he concluded that their minimum effective concentrations cannot be a function of the distribution coefficient alone. However, he did not reject the rule completely, and he reported experiments to support the view that local anaesthetics behave ideally in the lipid phase. From this Butler[2] made the far-reaching suggestion

that physical properties might merely be a factor regulating the access of the drug to its site of action.

Barlow[40] conceived that drugs have to penetrate the neurilemma, hence fat solubility may be necessary for the entry of a drug into the axon, although Hansteen[41] maintained that lipid solubility and penetration are not related as it occurs in denatured lipids. Skou[42,43] carried the concept further. Using local anaesthetics and extracts of nerve lipids from desheathed frog sciatic nerve he concluded that a correlation exists between anaesthetic potency and penetration of a monolayer of nerve lipids. Like Löfgren, he was careful to use a constant pH in his experiments.

The strict interpretation of the theory immediately creates difficulties, since all fat-soluble substances are obviously not narcotics, and it also fails to explain why some drugs with normal[2], or "sub-depressant"[30], partition coefficients are convulsants: it is tempting to presume that inadequate lipid penetration, with consequent accumulation outside the tissue, is the cause.

Finally, careful note should be made of, (1) the admission[44] that the lipid content of brain cells must influence the surface tension theory, (2) the contention[41] that denatured lipid behaves like the normal substance, hence adsorption is the salient feature, and (3) the belief, expressed by Meyer himself[45], that the presence of the narcotic in the lipid changes the permeability of the cell wall.

Clearly, a link exists between this and other factors.

The Traube Hypothesis

The basis of this theory is that a change is caused in the surface tension of the cell. Traube[46] noted that substances which lower surface tension, including many narcotics, pass most rapidly into the cell, and concluded that this must be an important measure of their ability to pass the cell membrane.

The theory was formulated in two papers[47,48], and involved the measurement of capillary activity of the drug at an air: water interface. Commenting upon the hypothesis, Toman[49] suggested that it has not been subjected to a rigorous test. This seems to be a fair criticism. Moreover, Albert[30] has emphasised that air:water interface results are largely limited to members of homologous series of drugs, and merely signify the non-wettability of the substance, and do not imply any specific adsorbability on a cellular receptor.

As alkalisation increases the surface activity of alkaloids, Traube[50] attributed the increased potency of local anaesthetics in alkaline solution to this cause. Luduena and others[51] corroborated this.

Henderson[52] remarked that the importance of the theory lies in its connection with the adsorption one, and it is evident that they are closely related. It is clear, too, that it has important links with penetration and permeability.

Although some local anaesthetics may lower surface tension *in vitro*, many good narcotics do not lower the interfacial tension between oil and

water[53]. Results from water must be treated with caution in view of the contention[44] that the clinging intensities of narcotics to lipids and to water are often completely opposite. Correlations are obtainable, but the significant ones have always been derived from homologous series of drugs[17,30,51]. Moreover, some substances lower the interfacial tension between oil and water, for example, soaps and detergents, but have no narcotic properties[54].

Finally, the observation[36] that chloroform and lignocaine increased the surface tension of an ergosterol film completely contradicts the theory, but this may be due to the model chosen.

The Warburg Theory

Narcotics are readily adsorbed on surfaces *in vitro*, and a similar effect may occur at the cell surface. Warburg[55] showed that narcotics could displace amino acid from a charcoal surface, and claimed that narcosis is caused by adsorption, and this effect is independent of the chemical nature of the narcotic.

Henderson[52] commented that all the models used in examining the theory dealt with enzymatic effects, chiefly oxidation ones: this is important, as he was convinced that narcosis and depression of oxidation are not the same thing.

The Warburg and the Overton-Meyer theories have been linked by the work of King and others[56] using homologous drugs on a water and paraffin oil model, and Rider[57] claimed that the intact local anaesthetic salt is adsorbed by nerve cells, possibly by structures of a lipoid nature. Löfgren[36] suggested that, *in vivo*, the anaesthetic is strongly retarded at the node surface: consequently a highly concentrated layer of drug is formed, and when it has reached a critical value the disturbance of the film may reach the anaesthetic stage. Höber[58], however, pointed out that some narcotic substances are apparently not adsorbable upon any cell structure or constituent, and there are substances which are exactly the opposite.

Höber and others[59], later proposed that the adsorption layer protects the surface film of the nerve from the changes which are features of excitation, that is, it produces a form of membrane stabilisation.

In adjudging the Warburg theory it is likely that adsorption can potentially influence two processes. Firstly, it may decrease metabolism by "blanketing" oxidative processes, and secondly, it may affect permeability by decreasing porosity. Support and criticisms have been found for both views, but the decisive point is that both processes are covered by other theories. Adsorption, by itself, is unlikely to explain anaesthetic action.

The Permeability Theory

As normal nervous excitation involves changes in the membrane (including increased permeability to ions), a substance which can stabilise the membrane should prevent them, thus producing a conduction blocking effect.

The theory was formulated by Lillie[60], and he envisaged narcotic adsorption on, followed perhaps by dissolution in, the membrane, thus producing a change in its physical state.

Although the theory was advanced for the central nervous system, peripheral nerve fibres are more accessible for study of the effects of drugs on polarised membranes. In them the blocking of impulse depolarisation by a stabilising action has been demonstrated. Bishop[61] employed potassium chloride (KCl) and cocaine as blocking agents, and claimed that nerve block may occur without depolarisation. He decided that if depolarisation occurs it is a sign of the condition produced rather than the means of block.

Höber and others[59] concluded that narcotics are cytolytic, so normal selective cation permeability is lost, and all ions can pass through, with consequent depolarisation. Later, Höber[58] suggested that the interfacially-active narcotics produce a *decrease* in permeability by forming an adsorption layer upon the pore walls. This obstructs, or even completely blocks, the channels, so that even small molecules, such as water, may be excluded.

Observing block without depolarisation, Bennett and Chinburg[62] were "forced" to the view that anaesthetics fix membrane conditions: the prevention of the calcium-induced shift in resting potential by pretreatment with procaine strongly supported this opinion. They also considered that the depolarisation by procaine and cocaine reported by Höber and others[59] was due to the use of excessive concentrations. (They were seven times stronger than those used by the authors to produce 90 per cent block in frog nerve: as many of Höber's results came from crab nerve, which is even more drug sensitive, the discrepancy may be greater still.)

Shanes has consistently supported the theory, and produced a comprehensive publication in 1958[63]. He based his work on the modified Bernstein theory, and recognised the importance of metabolism in ionic movement, designating it "active transport", but he did not believe that it contributes directly to membrane potential.

He did not regard permeability restriction as a surface obstruction effect. He visualised the membrane as a semi-rigid, semi-fluid, structure, with lipid molecules held together by intermolecular forces. He prescribed some flexibility in membrane molecule spacing, depending upon both physico-chemical factors and temperature.

He endorsed his earlier classification of two types of active substances, the stabilisers and the labilisers. The former, including calcium, procaine, and cocaine, reduce the electrical effectiveness of sodium, potassium, and other ions, whilst the latter, including low calcium and veratrine, accentuate the ionic effects on membrane potential. He defined stabilisers as agents blocking nerve or muscle impulses without any change in resting potential. Such agents "dissolve" by molecular displacement in the interpore regions, and thereby increase lateral pressure on the pores, thus decreasing channel size and permeability: the last prevents depolarisation on stimulation. About labilisers he was indefinite, suggesting that they

may reduce lateral pressure by adsorption on inter-channel regions rather than by being dissolved in them.

Certainly, Shanes' conception of stabilisation harmonises with observed results in the light of Hodgkin's description of nerve transmission[13].

Hardt and Fleckenstein[64] used various stabilisers to show that the prevention of depolarisation which they caused was accompanied by potassium retention: sodium was not investigated.

If a muscle is placed in Ringer solution where part of the sodium has been replaced by potassium, a swelling occurs, but treatment with cocaine reduces the causative entry of potassium chloride. Moreover, in a treated muscle, the normal depolarisation effect of KCl is reduced[65]. Shanes[66] extended the work to other local anaesthetics with similar results. Manipulations with sodium ions, using procaine and cocaine as stabilisers, yielded identical conclusions[67].

According to Shanes[63], the theory raises the factor of rate of action. It partly depends upon the speed of arrival at the site of action in the nerve, but could also be influenced if physiologically-active substances are emerging from the channels but cannot escape, and hence accumulate around the fibres. This may occur even in single fibres unless they are well irrigated. This feature might well be important in isolated tissues, although in the intact animal natural factors, such as the blood system, probably obviate it.

Calcium can act as an anaesthetic agent, whereas low calcium concentrations have a labilising effect which can be prevented by cocaine or procaine. Shanes rejected suggestions that modifications in the calcification of the nerve fibre surface can be produced, but he admitted that intracellular calcium might be important. He believed that calcium, and also low temperature, produce stabilisation, not by lateral pressure on the pores, but by increased rigidity of the inter-pore region: this reduces flexibility, and hence permeability, of the membrane.

Shanes finally considered that any weakness or lack of effect of stabilisers generally might be due to an inability of the channels in the membrane to be further compressed.

Lastly, it has been claimed[54] that narcotics variously affect permeability, the contention being that this factor might determine the entry of an agent into a cell without accounting for its action inside. This is not fully in accordance with the theory of membrane stabilisation, but is of interest, supposing as it does that permeability represents a phase, rather than the complete mechanism, of narcosis.

The Colloid and Protein Coagulation Theories

Bernard[1] showed that cell colloids may aggregate during anaesthesia, this process being reversible, and he conceived the view that narcosis consists of a reversible semi-coagulation of the substance of the nerve cell. This led to the formation of two related concepts of anaesthesia.

The basis of the first is that narcosis is a non-specific action, as also is simple surface adsorption, due to a change in the colloidal dispersion of protoplasmic components. This was alleged to be visible under the

ultramicroscope, to be reversible, and to involve proteins as well as lipids[68]. Barlow[40] rejected the theory on several counts. His criticisms arose from the observation that the narcotic concentrations of anaesthetic are much smaller than those needed to flocculate the colloids, and some narcotics apparently decrease the dispersion of the colloids.

Butler[2] regarded the theory as the product of over-simplification which showed a tendency to discount the complexity of living systems. This comment seems to be a justifiable one.

The protein theory was founded on the concept that narcotic concentrations of drugs produce a reversible coagulation of essential cell proteins, thus inhibiting normal function. Conflicting evidence was produced, but Henderson[52] presumed that the toxic effect of high concentrations of narcotics may be attributable to precipitation intracellularly, or at the cell surface. This seems to be drawing rather a thin line between this and the full precipitation events which occur, for example, in *rigor mortis*.

Several workers have demonstrated synergisms between various proteins and local anaesthetics, but serum proteins have been unsuccessful in this context. No conclusions about mode of action are forthcoming from them.

The two theories are so similar that joint criticism is justified. Neither has much supporting evidence, and neither appears to allow the speedy reversibility characteristic of local anaesthesia. Although colloid or protein coagulation may be produced by general or local anaesthetics there is no reason to suggest that these are in any way associated with the production of narcosis.

The Dehydration Theory

This states that anaesthesia is due to water loss from the cell or cells concerned. Kochmann[69] considered that anaesthetics reversibly dehydrate or stabilise the cell colloids, and thus reduce membrane permeability, which leads to metabolic inhibition and functional arrest. Winterstein[70] disputed this because dehydrated muscle can become very irritable.

The evidence for the theory is bald and unconvincing, and fails to substantiate the concept[15] that the action potential is accompanied by dehydration changes in certain areas of the nerve. As a theory of general anaesthesia, let alone local anaesthesia, it is quite unacceptable as it stands.

Acetylcholine Theories

The origin of these is difficult to trace. The concept of acetylcholine activity in nerve transmission is nowadays discredited, but its rôle in autonomic transmission is undisputed. Much evidence has been obtained from muscle preparations: this does not preclude it, but it must be treated with reserve.

Wilson and Wright[71] claimed that procaine inhibits acetylcholine release at the neuromuscular junction, whereas Thimann[72] concluded that procaine and similar local anaesthetics block the acetylcholine receptors

at sensory nerve endings. The tissue difference, motor versus sensory site, must be remarked. Conclusions about the relationship between procaine and the neuromuscular-blocking drugs have been very conflicting. Some of this may stem from species differences of the test animals.

Much the same difficulty arises in connection with anticholinesterase activity, as widely divergent results have been recorded. The involvement of esterases in local anaesthesia was propounded by Bieter[73] because di-isopropylfluorophosphonate (DFP) and eserine can abolish conduction without depolarisation or transient excitation. Toman, Woodbury and Woodbury[74] reported similar results with these drugs and procaine. They attributed the effect to an increase of the nerve conduction threshold above a critical value, although the Nachmansohn theory demands that anticholinesterases should produce an enduring nerve depolarisation. They suggested that the nerve block is due to side-effects which are independent of anticholinesterase activity: large doses of DFP are needed to produce block, whilst relatively low concentrations antagonise cholinesterase. Furthermore, all anticholinesterases do not act on nerve like these two: such discrepancies would not occur if acetylcholine accumulation is the basis of conduction block. Skou[75] studied local anaesthetics in the electric eel, and also concluded that cholinesterase inhibition is not related to peripheral nerve blockade. Any attempt to produce linear correlations was unsuccessful.

Although this work primarily referred to local anaesthesia, the results further confirm the rejection of the acetylcholine theory of nerve transmission.

Greig, Holland and Lindvig[76] introduced a novel concept by relating penetration to cholinesterase inhibition. They suggested that surface-active local anaesthetics, like butacaine, penetrate mucous membranes by inhibiting cholinesterase, while inactive ones, such as procaine, can produce anaesthesia here only if the enzyme is first blocked by eserine. They anticipated the obvious criticism by demonstrating that eserine alone was ineffective on the rabbit cornea tissue used. Their hypothesis, despite various assumptions they had to make, has not been seriously discredited, and should merit further investigation.

Many allusions have been made to the similarity between atropine and local anaesthetics[49], particularly procaine, and De Elió[77] has held that atropine has a local anaesthetic effect which is about 50 per cent that of procaine. Sinha[78], however, rejected these views. Moreover, in all his comprehensive studies he noted that procaine seems to play a lone rôle, and this observation may be important.

In the autonomic system little evidence is at present available from the synapse, though this field might be informative. With neuromuscular junctions results are obtainable that local anaesthetics are curariform, but there is no general agreement that the modes of attaining block are similar. That such effects may be side reactions is far from improbable, particularly when it is remembered that the *in vivo* use of local anaesthetics does not produce any obvious autonomic or neuromuscular actions, despite various means of administration.

The Histamine Theory

This hardly ranks as a theory, but a note of it is desirable. Many nerve fibres have been shown to contain histamine[79], and it has been proposed that it participates in nervous conduction. This view has failed to gain acceptance. Although many antihistamine drugs show local anaesthetic properties, Sinha[78] concluded that the two activities are not related. As, therefore, the relationship seems to be fortuitous, further consideration is unnecessary.

Metabolic Theories

Their basis is that narcotics interfere with cell oxidations, and that anaesthesia is essentially a type of asphyxia caused by a loose union between the drug and the oxygen-carrying groups in the cell. Much supporting evidence has been forthcoming, but reports have been made of no change in, or even increased oxygen consumption with some narcotics[70,80].

Warburg[81] showed that narcotics inhibit the oxidation of amino acids and similar substances. In much of his work charcoal was used as a model of the surface. The choice of both model and substrate cast some doubt on the cogency of his conclusions.

The chief advocate of metabolic theories has been Quastel. He demonstrated[82] that anaesthetic concentrations of narcotics reversibly inhibit the oxygen consumption of brain slices. This arrested the oxidation of several substances, but not succinate. Watts[83], however, was able to inhibit succinate oxidation in brain by using local anaesthetics: cinchocaine was the most effective compound, and cocaine and procaine the least effective ones. Earlier, Sherif[84] investigated several anaesthetics on isolated rabbit sciatic nerve: cocaine and procaine both reduced oxidation, and the effect increased with concentration. The most powerful agent for reducing metabolism was eucupinotoxin, but this has a negligible effect upon nerve conduction. 5 per cent urethane was roughly equivalent to 2 per cent procaine. Sherif considered that urethane affects nerve oxidations only in relatively high concentrations, though it has a marked effect on the oxidation processes of brain tissue. This is a notable idea, as it suggests a difference in reaction between the two types of nervous tissue: it keeps recurring.

Lorente de Nó[17] rated oxidative processes more highly than any ionic concentrations in maintaining membrane potential: he recognised the importance of sodium and potassium ions only as far as they directly or indirectly participate in enzymatic reactions. Nevertheless, from his work on cocaine he admitted that a drug might restrict metabolism in such a way that the membrane potential is maintained with a reduced oxygen consumption. Gerard, also,[54] declared that functional anaesthesia is not always attended by depressed respiration. He felt that narcotics probably act along oxidation-inhibition lines, but commented that the most convincing evidence of interference with cell metabolism is usually obtained from complicated systems rather than simple ones. Consequently much information has accrued about suspected locations

of block, while more fundamental considerations may have been omitted. Many sites have been proposed for blocking activity, but as Gerard rightly stressed, the limitation on all the work is that locations were determined by exclusion rather than by positive proof. He suggested that narcotics might inhibit complete metabolic systems by some relatively non-specific physico-chemical action, rather than by blocking a postulated link.

Gerard's views were not shared by others. Burger[39] favoured the idea of the high susceptibility of nervous tissue to oxygen lack, and named an enzyme link in the oxidation chain as a possible site of action. Barlow[40] also believed in enzyme inhibition, and drew attention to speed of onset, emphasising that an enzyme would probably be affected instantaneously. Much work on enzymes has utilised models, or simple mixtures of enzyme and narcotic. The drawback to this, and related approaches, is that it is certain that even the complete tissue *in vitro* may behave very differently from the same material *in vivo*. Barlow cited narcotics which, *in vitro*, lower creatine phosphate levels, whilst *in vivo* they have exactly the opposite effect. Presumably the basic physiological difference between nervous tissue *in vivo* and *in vitro* is that the former is still actively working. McIlwain[85] devised a method of electrical stimulation of cerebral cortex slices *in vitro*, and found that the levels of metabolic activity were then the same as in similar tissue *in vivo*. This technique may prove useful in future research, but could well be more applicable to the brain than to peripheral nerve. Potassium stimulation has also been used to overcome the difference, and it is claimed[86] that local anaesthetics can depress respiration in cerebral cortex slices thus treated.

Butler[2] has most relevantly indicated that neither inhibition of enzyme nor of brain tissue oxygen consumption are effects peculiar to anaesthetics. Indeed, some inhibitors are convulsants, like picrotoxin and leptazol, and he regarded the inability of the theory to distinguish between anaesthetics and convulsants as a serious deficiency. He also discounted the idea[87], derived from work with cocaine, that, although the total brain oxidation might show little change, small areas may suffer from oxygen shortage. Such a concept would be very difficult to prove satisfactorily, but it will require further substantiation if it is to be accepted.

Undoubtedly, inhibition of oxidation often accompanies anaesthesia. In the intact brain this might be due to a reduction in the number of neuronal discharges which occur continuously, and which, naturally, consume oxygen in their recovery phases.

Experiments with other nerve tissues have been most revealing. Larrabee, Posternak and Bronk[88] used narcotics in concentrations sufficient to block sympathetic-synaptic transmission. Sodium pentobarbitone and alcohol reduced resting metabolism, even in sub-blocking concentrations. The concentration of the former had to be raised 5 to 10 times to block B and C fibres. Cocaine, on the other hand, could be given in concentrations of five times the blocking dose, and yet it failed to depress resting metabolism. This is important as it provides clear evidence of a divergence of metabolic effects when general and local anaesthetics are employed.

Because of Quastel, much of the work on metabolism has dealt with oxygen utilisation, but inhibition of other mechanisms is a distinct possibility. Butler[2] noted that most of the quasi "narcotic" drugs can inhibit the breakdown of adenosine triphosphate (ATP), even in disrupted or dead cells, and he emphasised how little is known of the effects of anaesthetics upon phosphate metabolism. Recently it has been claimed that clear evidence exists suggesting that ATP is the energy source for sodium ion extrusion[13]. Caldwell and Keynes[89] made the relationship quantitative by claiming that four phosphate bonds are broken for each sodium ion ejected. Whittam[90] used human red blood cells, and concluded that ATP may be linked with active cation transport. This trend is both new and important. It is possible that hesitation had been felt previously about applying results which hold for muscle energy relationships to nerve.

In considering the influence of metabolism it must be appreciated that it is linked with the maintenance of the ionic states inside and outside the nerve. Interference with it must ultimately influence ion relationships, and hence conductivity. Conversely, if conditions in the nerve are altered it is likely that metabolism will be affected also.

One of the leading questions is whether the work done against the steady ionic leak from nerve is aerobic or not. Brain is very susceptible to oxygen lack, but it is conjectural if peripheral nerve is similarly affected[91]. Lorente de Nó[17] reported that anoxia alone does not totally depolarise, hence metabolism only depends indirectly upon respiration. His concept of a reserve of oxidised material seems reasonable, especially as there is an equivalent in muscle: it seems to be more typical of peripheral nerve than elsewhere, and it might create the impression of partial respiratory independence.

Ionic Influences

These have never been raised to the status of a theory, but the current views on nerve transmission indicate that ions are potentially important. The stimulation by small doses, and blocking by large doses, of potassium chloride have already been described. Sinha[78] claimed that the inhibition of KCl stimulation by means of local anaesthetics is a fairly accurate guide to their relative anaesthetic activities.

A sign of the complexity of the situation is the potassium loss reported in mammalian heart during vagal stimulation, as this ion effect must be linked with acetylcholine release[63].

Potassium studies probably evolved from local anaesthetic synergisms: the empirical surgical use of potassium sulphate with cocaine and procaine has long been practised. Hoffman and Kochmann[92] demonstrated a species difference effect using equivalent strength mixtures of local anaesthetics and potassium sulphate which were injected intravenously into guinea pigs and intradermally into man: the toxic effects were less in the guinea pigs.

Adriani has emphasised[93] that pain and oedema after injection may limit the usefulness of potassium potentiation. Other synergisms have

been reported, involving, amongst others, agents which have proved permeability-increasing or metabolic effects, which suggest links with other mechanisms in order to achieve the blocking effect.

Rider[57] investigated synergisms, especially that of butacaine with other local anaesthetics. That one local anaesthetic may behave like an inorganic substance towards kindred drugs seems quite anomalous, and yet butacaine can, like the others, be synergised by potassium sulphate. This sign of individuality should not be allowed to go unremarked.

Rider also showed that butacaine hydrochloride is more active than the sulphate, and concluded that this indicates potentiation by the chloride ion. This idea is surprising, because Rider himself furnished an alternative explanation. The hydrochloride is less soluble than the sulphate: he visualised that when two drugs are in contact with nerve cells, the less soluble one will tend to escape from water to any structure capable of receiving it. Furthermore, the presence of abundant body chloride may hinder sulphate as it may have to be adsorbed first, and may lose activity in so doing. This rôle of body chloride is important, because it creates the possibility that a drug may have completely different modes of action *in vitro* and *in vivo*. This leads to the whole field of pH effects, whether due to body constituents or to external manipulations. It is feasible that solubility effects such as Rider outlined may, in some way, explain the striking success of potassium sulphate as a synergistic agent.

Bein[94] claimed that optimal cell functioning depends on ionic ratios, especially of potassium and calcium, rather than on absolute amounts of them but that, in local anaesthesia, the situation may be sometimes completely reversed. Both potassium and calcium alone produced variable or indeterminate effects, but when combinations of one or other of them with procaine were made, the two ions appeared to be antagonistic. This illustrates how easily an effect can be modified, the difference here being between the ion effects in normal cells and in cells influenced by procaine.

Lorente de Nó[17] reported that excess of calcium ions caused irreversible deterioration of nerve fibres and, peculiarly, damaged the rapidly conducting A fibres more than the C ones. He ascribed this to penetration and accumulation of calcium ions in the myelin which causes a swelling due to an osmotic effect. This leads to myelin disintegration and consequent destruction of the conduction faculties. He alleged that excess of potassium has similar effects.

Gasser[95] suggested that after-potentials are signs of recovery processes following impulse conduction, and the modified Bernstein theory supports this. Lorente de Nó claimed to have found them in areas which have not been activated, and this could seriously upset the present views on the recovery period. However, Shanes has interpreted these potentials as signifying inadequacies of the metabolic recovery processes: if this is correct they need not be confined to nerve that has recently been activated.

McDowall and Soliman[96] suggested that many drugs produce sodium accumulation at specific receptors. In the light of present knowledge about transmission this effect might be expected if the action of the drug

is to facilitate membrane stabilisation: this affects membrane permeability, and hence the movement of sodium ions inwards at excitation.

Electrical Theories

Burge (see 92) reported a change of electrical polarity in fish brain cells from negative to positive under the influence of narcotic drugs, and attributed this physical change directly to the drugs. However, since sodium, potassium, and chloride ions carry the electrical charge in nerves[13,17], changes in ion distribution will produce electrical effects, and thus Burge may have seen the results, rather than the cause, of block.

A different approach is the production of narcosis by electrical currents. It is not, however, a practical means of producing local anaesthesia, nor has the work upon it been at all explicit.

Indeed, it is questionable how far the entire electrical approach can be taken. Bishop[61] has asserted that nerve block is not primarily due to altered potentials but to changed irritability. This appears to be true, hence the observation of electrical conditions, for example, membrane potential and action potential, can furnish important information about the events caused by local anaesthetics, but should not be regarded as a means of explaining modes of action.

Thermodynamic Activity

This is an estimate of the molecular work needed to transfer the narcotic from the pure liquid phase to the unknown one of locus of action in the narcotised cell. It is derived from vapour pressure determinations. The theory was advanced by Ferguson in 1939[97], and was based upon the supposition that narcosis depends on a physical mechanism: any major deviation from the thermodynamic activity range would denote a chemical rather than a physical action.

Brink and Posternak[98] clearly recognised that thermodynamic methods of analysis will not reveal molecular mechanisms of narcosis. They proposed their use to measure narcotic effectiveness, but had to admit that ether often fails to conform to the theory, despite its clinical effectiveness. Butler[2] commented that no anaesthetics show regular relationships between potency and any physical property. He considered that physical measurement not only fails to predict anaesthetic doses quantitatively, but even fails to predict reliably the qualitative nature of the pharmacological action.

Evidently, classing this as a theory of anaesthetic action, even for general anaesthesia, as has often been done, is a misnomer. Like electrical activity, thermodynamic studies may be useful for predictions and observations of behaviour and effect, but they do not clarify the means of local anaesthetic action at all.

Other Factors in Local Anaesthesia

Several topics are closely related to the present problem and deserve further consideration.

Effects of pH

Investigations of pH have often provided information about the active form of local anaesthetics, whilst the study of the latter has frequently been governed by the pH. It is not thought desirable to divorce such information here, as the two are so clearly inter-related.

Bignon in 1892[99] showed that alkalisation increases the activity of cocaine solutions, and introduced an alkalised suspension of cocaine ("cocaine milk") into clinical practice: its activity was, in fact, very little greater than normal cocaine hydrochloride. Gros, however, confirmed the observation on other local anaesthetics and suggested[100] that the greater potency in alkaline solutions is caused by the free base being the only active constituent: alkalisation potentiates anaesthesia due to the increased amount of base liberated. Trevan and Boock[101] repeated this work and corroborated this theory, as did other authors[15,57,102]. Gros suggested that the free bases of all anaesthetics have much the same activity, but Löfgren[36] has strongly criticised this.

Sollman[103,104] showed that sodium bicarbonate increases the efficiency of cocaine and procaine about 8-fold on motor fibres, and 2 to 4 times on sensory fibres, of isolated nerve. He suggested that the alkali helps the liberated anaesthetic base to penetrate into the nerve trunks.

Régnier and David have consistently claimed that all the aqueous forms of cocaine and procaine, ions, base, and salt, are active, and that the alkali acts directly on the tissues concerned, because the addition of alkali to a saturated aqueous solution of cocaine base increased its anaesthetic action[105]. Although Trevan and Boock[101] explained this as a buffering effect by the alkali, allowing more of the poorly-buffered cocaine to be effective, Régnier and David remained adamant in their refusal to accept this, saying that release of the free base plays a minor part only in the phenomenon compared with the direct effect of the alkali[106,107].

In 1931 Gerlough[108] noted that the presence of acid seems to inhibit local anaesthesia, for example 0·25 per cent butacaine poorly anaesthetises rabbit cornea at pH 5·5, whereas at 7·4 the same concentration gives a considerable duration of anaesthesia. He suggested that this might explain why local anaesthetics often fail to act in acutely infected areas, as in abcesses. Bieter[73] attributed the acidity effect to decreased hydrolysis of the anaesthetic.

Hirschfelder and Bieter[15] considered that the free bases of alkaloids are usually more active than the salts because the latter are more soluble in water, whilst the former are more soluble in fat, lipids, and organic solvents. They felt that local anaesthetic potency should be a function of the degree to which the anaesthetic is hydrolysed, provided that as the free base it is sufficiently soluble to remain in solution or in a finely divided suspension. (Furthermore, anaesthetic effectiveness must also be a linear function of the pH of the tissue, hence a basic local anaesthetic is more effective in alkaline than in acid media.) Consequently, the weaker the base, the more free base is released, and the greater should be the anaesthetic potency. This is best achieved, at least in homologous

series, if the soluble anaesthetic salt is made from the base and a weak acid instead of hydrochloric or sulphuric acids. The findings of the authors held for the conjunctiva and for intradermal injection, but not in infiltration anaesthesia, or in the urethra. They believe that modifying factors may arise here: in deep tissues, or in the presence of urine, the anaesthetic salt reacts with sodium chloride which tends to decrease the hydrolysis and, by ionic interchange, to return much of the anaesthetic to the form of the hydrochloride, regardless of the acid used to form the salt. That is to say a buffering action occurs.

Krahl, Keltch and Clowes[109] used simple cells (*Arbacia punctulata* eggs and larvae) to investigate the form in which local anaesthetics penetrate the cell, and the probable form in which, once inside, they enter into chemical reactions giving anaesthesia. The total local anaesthetic concentration required to produce a 50 per cent reduction in cell division at pH 7·0 was 100 times greater than that needed at 9·1. They also reported an extraordinary tendency for the cations to escape from solution in the intracellular aqueous phase to adsorb on, or combine with, cellular constituents. They concluded that the anaesthetics penetrate only in the form of undissociated molecules, and considered that, unlike many other anaesthetic substances, it is the intracellular concentration of cation, and not the undissociated molecule, which causes the physiological effect. They further suggested that basic anaesthetics are local ones because cells at the site of application require so much anaesthetic to satisfy the laws of membrane penetration that relatively little is left to produce general anaesthesia.

Dawes carried this trend further. His work on the heart[110] supported the contention that local anaesthetic and quinidine-like properties characterise the free base. Not only are the most powerful local anaesthetics most active upon the auricle, but conversion into the quaternary salts, which stabilises the cation, of some of the "cardiac" compounds could abolish their activity, just as a similar conversion of local anaesthetics abolished their effects. The importance of this cannot be ignored. He decided that the free base can readily penetrate nerve and muscle, and once inside the cell it equilibrates with its cation again according to this equation.

$$\underset{\text{cation}}{R_3NH^+} + OH^+ \rightleftharpoons \underset{\text{base}}{R_3N} + H_2O$$

In this way cations of these substances could get inside the cells: previously it was thought that the free base of local anaesthetics, and quinidine substitutes, is the active constituent because of its penetrant powers. However, Dawes' concept makes it feasible that the function of the free base is merely to facilitate the entrance of the active cation. This conception is a most notable one.

Löfgren[36] maintained that much early work on minimum effective concentration is useless because of the use of unbuffered biological material, and lack of control of pH. Some authors appreciated this and took steps to obviate it[42,43,61,111]. A striking feature was the repetition

by Mongar[112] of work on guinea pig wheals[77] using buffered instead of unbuffered solutions: cinchocaine was 34 times as powerful as procaine, as against the earlier estimate of only 10 times.

In surgery, the natural body buffering probably conceals any variations in efficiency due to pH, but pH changes are obviously most important in surface anaesthesia. Mucous membranes have poor buffering capacities, so the usual surface anaesthetics owe their efficiency to a high activity: such drugs are often so toxic that they cannot be injected. Consequently Löfgren dismissed the idea that these substances have a special affinity for mucous membranes. Procaine is reputedly inactive on surfaces, but this is incorrect: since procaine solutions, compared with lignocaine, are not stable for long at pH values beyond 5, the surgical solution has a pH of less than 5, and *this* solution does not anaesthetise mucous surfaces. If, however, the pH is increased to 7 or more, the solution has such an increased effect on the surface that it even surpasses that of an equal concentration of cocaine.

Gray and Geddes[113] stressed two important features. The pH requirement varies with each drug and its concentration, since better precipitation of a free base occurs with a strong solution than a weak one. With inflamed tissue, the increased vascularity of the area as well as pH may lessen the effect.

Since the body represents one of the best systems of buffers than can be obtained, the effect of pH upon the mechanism of local anaesthesia and its influence upon the availability of the active form of the drug deserves serious consideration.

Differential Effects

That local anaesthetics elicit effects in various tissues has already been stated, but further examination of this is desirable.

Nervous tissue. It is well known that local anaesthetics can produce sensory anaesthesia without motor paralysis. Gasser and Erlanger[16] suggested that thresholds vary amongst sensory fibres, so the time for blocking depends on the functions mediated. They claimed that small fibres are usually blocked before large ones, but blocking is not effected with any precision. As small fibres have a relatively greater surface area than large ones, the smaller the fibre the greater should be the accessibility. On this basis washing should allow the smaller fibres to recover first: this is not so, and recovery proceeds in the reverse order to blocking. They justified their theory, however, by saying that in small fibres protoplasmic chemical combination with the anaesthetic goes far beyond the point of block into stages of disorganisation: on washing re-organisation is necessary before recovery can begin. Such a mechanism should cause fibre block on a systematic size basis: as this does not occur their explanation can only be a partial one.

Heinbecker, Bishop and O'Leary[114] demonstrated that local anaesthetics first block action potentials in unmyelinated fibres, and then the smallest myelinated ones, progressing up to the largest myelinated ones. Obviously

some structural modification tends to delay blocking in the second two types, provided that it is accepted that local anaesthetic efficiency is fundamentally the same for all nervous tissue[15]. Myelin is immediately suspect, and will be considered later. Hirschfelder and Bieter listed fibre activity loss as, vasoconstriction, temperature, pain, touch, joint and pressure sense. With intraspinal injection the curious fact emerged that motor activity disappeared before joint and pressure sense. This may be because, intraspinally, motor nerves are more bare and hence more vulnerable.[73] This concept is questionable: a more likely factor is that of accessibility to the, unmyelinated, motor nerve cells. Frumin and others[115], demonstrated that dorsal root blockade can be achieved with procaine doses which are too small to affect radically the passage of impulses in the root. They ascribed this to the lack of myelin on the ganglion cells which they therefore assumed to be more sensitive than either the dorsal root fibres or the spinal cord. In clinical doses motor paralysis frequently occurs, suggesting involvement of the ventral root as well.

There have been reports of block in A and B fibres before C fibres with KCl, anoxia, and the nerve narcotic phlorizin[17] as well as with cocaine[49]. There is no reason to doubt the accuracy of these observations, and it is apparent that there is more than one way of producing block, and even differential block.

Löfgren[36] pointedly remarked that local anaesthetic action is readily compared on isolated motor nerves, but that conditions for practical anaesthesia, sensory block in a complicated biological milieu, are difficult to survey in detail.

Toman[49] reasoned that different fibres might act by various chemical mechanisms, so long as the general explosive system occurs, and this would naturally allow different types of block to exist. The flaw in this view is the apparent lack of specificity, for types of nerve, of blocking agents, and the general conformity of nerve to the current transmission theory.

Barlow[40] considered that there might be different enzyme systems in sensory and motor fibres. He implied that the susceptibility of the particular enzyme system determines the rate of production of nerve block. He saw no reason why transport at mucous membranes and nerve surfaces should be identical, hence a local anaesthetic may be feeble on the eye, but quite active elsewhere. This may well be due to strictly local factors such as pH or cholinesterases.

Muscle tissues. In myasthenia gravis, procaine may sometimes accentuate the general muscular weakness, an observation which led to the idea that it either affects neuromuscular transmission or the muscle directly.

MacGregor[116] used both procaine and cocaine in skeletal muscles *in vivo*, and remarked a reduction in tension with both, cocaine having the more powerful effect. As pre-curarisation potentiated the effects it was considered that local anaesthetic and curariform actions are similar. MacGregor suggested that local anaesthetics may directly reduce excitability or contractility of muscle fibres, and considered that the action is

partially upon the motor nerve endings, and partially directly upon muscle fibres.

Sollman and Estable[117] investigated the action of procaine on the excitability of frog muscle and nerve tissues. They claimed that the depression is reversible only within rather narrow limits, and also that it depresses the excitability of skeletal muscle nearly as much as that of motor nerve fibres (given effective penetration, which depends on prolonged exposure to the drug). They concluded from this that nerve depression by local anaesthetics is not a distinct phenomenon but a manifestation of general "protoplasmic" depression, which is useful in practice because of the favourable ratio of anaesthetic action to local irritation and systemic toxicity. They felt that clinical practice contributes to the specialisation effect by ensuring that drug and nerve are in close contact. Procaine hydrochloride in relatively high concentrations, over quite long periods, induced irreversible paralysis in excised muscle and nerve: clinically this is not attained, because lower doses are used and the drug is removed by the circulation. Attempts to induce irreversibility in animals have failed indicating the wide margin of practical safety with procaine. The danger of comparing *in vivo* and *in vitro* results too closely is again apparent.

It has been claimed[118] that afferent proprioceptive fibres from muscle spindles are highly procaine-susceptible. However, Matthews and Rushworth[119] showed that procaine paralyses the large afferent and efferent fibres of the soleus muscle simultaneously, but the γ-efferent fibres, to the intrafusal fibres[120], much earlier. In a single afferent fibre from a frog muscle spindle, Matthews and Rushworth[121] claimed that there is a two-stage response when cocaine is applied to the nerve supplying the muscle. First, the frequency of spindle discharge falls suddenly to a new level similar to the one after ventral root section, apparently due to γ-fibre paralysis, and, second, the spindle afferent itself is affected, and before its complete paralysis will not transmit high frequency impulses. This appears to accord with the findings of Katz[29]. Procaine and cocaine therefore produce a reversible γ-de-efferentation of the intrafusal muscle fibres. Such evidence opposes the concept of direct muscular excitability depression, and emphasises that the situation is not as simple as was once thought.

Other factors. Action sites may be significant, because in excised nerve the anaesthetic soaks inwards from all points of the circumference, whilst in man, as probably in all *in vivo* experiments, a concentration gradient may exist across the width of the nerve. The situation of the nerve, and the site of drug application may well be the cause of this. Allied to the latter, Henderson[52] has suggested that the various differentials between tissue affinities for anaesthetics might be largely attributable to blood flow differences. This is certainly a possibility, and one that is known to be important for general anaesthesia.

Onset and duration of activity have been related to adsorption equations[52], but it is likely that they are related to concentration of the drug, time of contact, and the surface area of the exposed region. Kato[122] considered that the minimal effective concentration (C_m) of local anaesthetic

for a single fibre differs little from that of a nerve trunk, and this would be unlikely if adsorption were the basic cause. If a fibre is exposed to an anaesthetic slightly above its C_m value, block sets in almost immediately. From this Löfgren[36] decided that diffusion into the nerve is critical in onset of block. Good local anaesthetics should possess high activity coupled with a high diffusion coefficient: the criteria of usefulness are latency, duration, activity, and toxicity.

Anaesthetic Structure and Properties

A general recapitulation of evidence which has already been quoted is not proposed, but rather a consideration of any especial features which seem to relate to the present problem.

Löfgren[36] stressed that the common clinical local anaesthetics have a typical composition. They are pronounced basic esters or amides of aromatic carbonic acids. Their general formulation runs,

amino group—intermediate chain—aromatic residue.

The amino group, usually secondary or tertiary, is of great importance for specificity, and he claimed that virtually no usable anaesthetics omit this group. He explained some exceptions as a replacement of the hydrophilic amino group by another hydrophilic group, like hydroxyl, as in benzyl alcohol. Substitution of the aromatic residue by an aliphatic one results in a considerably inferior effect. Löfgren envisaged the hydrophilic group of the anaesthetic to make contact with a suitable polar hydrophilic group in the membrane (polar or "head" association), while the lipophilic part probably helps to form the complex (the "tail" acts on the membrane film by van der Waal forces) so that penetration can occur. Because of this Löfgren was not surprised that local anaesthetics do not follow the Overton-Meyer rule, since the distribution coefficients are important, but not dominantly so. Although many narcotics have local anaesthetic properties, the typical aromatic amine type of local anaesthetic cannot be used for narcosis. They are purely local, even on central nervous organs[39]: moreover, dosage increase does not give general anaesthesia, but only systemic poisoning as a toxic level is reached. In doses of a quarter to one half of the lethal one, local anaesthetics usually produce (cerebral) convulsions: there is a rough parallel between anaesthetic activity and convulsive power[123]. Benzyl alcohol produces an even narcosis, without convulsive activity, and Löfgren believed that this is attributable to the hydrophilic hydroxyl group.

Surface tension effects have been implicated in both local anaesthetic activity and irritancy. Luduena and others[51] investigated all three aspects with several local anaesthetics, and finally concluded that, although local anaesthesia may be independent of surface-tension lowering activity, the irritancy which can be caused by these drugs is caused by this, or a related, mechanism. Irritancy is a difficult thing to estimate, especially as that related to pH effects may be modified by the buffering action of the tissue fluids. The whole question must await further investigation. The same authors envisaged that local anaesthetic activity may result from a very

high affinity for some specific structure in the nerve fibre. Some characteristics may increase the activity of the molecule without modifying the physico-chemical affinity, for example the presence of a long carbon chain increases the lipid solubility of the molecule, provided that it does not interfere with the attachment of the polar group, or groups, in the drug, to the receptors (that is, the hydrophilic end).

Butler[2], however, declared that no specific chemical structure is necessary for general anaesthetic activity: he claimed that in the aliphatic alcohol series anaesthetic activity is almost equally correlated with vapour pressure, oil: water distribution coefficient, surface activity, and water solubility. Höber[58], too, had similar views, claiming that narcotics are chemically "indifferent", and that they do not react chemically with cell components.

The over-riding impression about structure-property relationships is that, super-imposed on the basic "local anaesthetic structure" of the molecule there is a series of structural modifications which may influence, directly or indirectly, the local anaesthetic effect.

Structural Features of Nerve

The modifying effects of the connective tissue sheath have been examined in an earlier section, but an observation by Lorente de Nó[17] requires comment. He claimed that the penetration of connective tissue sheath and nerve by veratrine-like substances is exceedingly rapid, and regarded this as evidence in favour of lack of sheath resistance. But Shanes[63] has described veratrine as a labiliser, that is to say, it destroys the permeability of the membrane, hence speed of penetration here is a characteristic of veratrine and not the sheath.

Another structural feature is myelin. Its insulating properties have been known for some time, and comprehensive work by Kato[122] has clearly endorsed the concept of saltation. Furthermore, studies on single fibres revealed a striking phenomenon, namely that nerve conduction can be blocked instantly by a drop of relatively dilute narcotising drug, or of isotonic sugar solutions, or even of distilled water, when applied to a region where nodes of Ranvier are exposed. If the sheath alone was exposed to cocaine or urethane in Ringer, conduction was often retained for well over an hour, but if a node was similarly exposed conductivity disappeared within one second. Kato concluded that narcotics diffuse into the axis cylinder only through the nodes, and spread in both directions along the fibres. Sub-threshold concentrations produced a sudden change in threshold, reducing excitability, and recovery on removal was similarly abrupt.

Lorente de Nó[17], however, categorically denied that myelin is an obstacle, and rejected the idea of substances acting on the nodes. He felt that such an assumption would be justified if test substances acted first upon myelinated fibres, and quoted some that act first on myelinated ones, none of which, it should be added, were local anaesthetics.

In his comprehensive treatise Löfgren[36] recapitulated Kato's views fairly fully, and the fact that he had no criticisms to make cannot be ignored. Lussier and Rushton[124] confirmed Kato's work, and produced

evidence that nerve threshold is about 30 per cent higher at the mid-internode than elsewhere. From this it is plain that myelin must not be mistaken for a perfect insulator, although its influence is great.

The fact that many nerves are not uniformly susceptible, owing to structural features, is something which may well influence local anaesthesia, if the word "local" is interpreted in its strictest sense.

Problems which arise

Inevitably, the primary question relates to the validity of applying theories of general anaesthesia to local anaesthesia. The answer is relatively simple: there is little choice, as all attempts have aimed at translating these theories into local anaesthetic terms, rather than formulating special theories *per se*. This is not altogether unreasonable, since the basic material in both instances, brain and peripheral nerve, is nervous, although in different locations.

The looseness of the terms used is, however, unfortunate, for example, "narcotics" may include hypnotics, general, and local anaesthetics, hence caution has to be exercised in much of the interpretation.

The thesis presented here is that local anaesthesia is not explicable in terms of any one theory, not from any particular inadequacy of these, but because it is considered that anaesthesia can be produced in different ways.

Conduction failure may arise from increased threshold, fall in spike amplitude, or sub-critical resting potential. The last implies that the normal ionic balance is lost: this depends on metabolic processes as well as ion concentrations, diffusion gradients, and membrane penetrability. Interference with any of these factors is potentially capable of producing block.

Toman[49] has rightly remarked that the mechanism of nerve conduction does not fit into any of the schemes devised for ganglia and neuro-effector systems. This again underlines that results and theories must not be too readily transposed from one part of the nervous system to another.

The present discussion is divided into two sections. In the first, features which have limited either results or theories will be examined: in the second, an attempt will be made to resolve various topics which appear to be significant in this field.

Limiting Factors

The effect of pH. The practice of potentiating local anaesthetics with alkali indicated that the two are related, provided that the drug is a basic one; the neutral compound, benzyl alcohol, is not influenced by hydrogen ion concentration. The contention by Sollman[103,104], that alkalisation increases the effect on sensory fibres less than on motor ones is curious: it may well be that the drugs were more effective on the former in the first place, and this could easily limit further improvement.

The buffering by the body is obviously important, and it is impossible to emulate such conditions in isolated tissues. The lack of adequate pH

control may have influenced the results of many experiments found in the literature, although workers like Löfgren and Skou have stressed the need to minimise variations in such tissues by keeping the pH constant. Löfgren suggested that in some of the common local anaesthetic test methods, an alteration of one pH unit may change the minimum effective concentration value tenfold. The link between pH and procaine stability, instanced by the same author is interesting. Earlier, Bullock and Cannell[125] showed that at pH 4·3 about 2·5 per cent of the drug is available, whereas at 7·5 about 75 per cent is available.

Finally, Höber's statement[58] that the paralytic effect increases with rising pH in local anaesthetics, is independent of pH in the alcohols, and decreases with increasing pH in general anaesthetics of the barbiturate type, is most notable in view of the close parallels sometimes sought between the three classes.

Species differences. That these exist is undisputed, for example the observation[92] that equivalent local anaesthetic mixtures are more toxic to man than to guinea pig. The gap is especially wide in places, stretching as it does across the division between invertebrates and vertebrates. The surprising thing is that invertebrate results, such as those of Lillie[126], which formed the basis of the permeability theory, have been successfully applied to many other animals. On the other hand, Krnjević has somewhat disturbingly suggested that actions in frog preparations may vary in animals obtained in the autumn from those found in frogs taken in the spring[21]. Quite evidently the application of observations from one animal to another is accompanied by considerable uncertainty.

Tissue differences. Much the same limitation occurs here, too, despite the claim by Lorente de Nó[17] that the electrical phenomena, at least, in muscle and nerve are identical. Shanes[63] believed that vertebrate muscle is more like invertebrate nerve, especially crab, than vertebrate nerve. The claim that anaesthetic action on skeletal muscle and motor nerves, given effective penetration[117], is comparable, is not too serious: the authors admitted that muscle has to be well soaked, and formulation of such conditions must damage the comparison. Moreover, penetration is probably of less importance in sensory nerves and, in particular, the unmyelinated pain fibres. The difficulties are well illustrated by the anti-acetylcholine activity displayed by local anaesthetics in rabbit intestine and ear vessels, whereas extremely variable results, ranging from antagonism to synergism, were forthcoming from cardiac muscle of the same animal[77].

The effect of drugs like procaine on muscle γ-efferent nerves[121,127] may lead to further confusion, as this nervous effect could be misinterpreted as a muscle reaction.

Tissue distortion. This is an important factor, and much of the evidence about the connective tissue sheath and the barrier effect of myelin has already been described. Lorente de Nó's claims, based on the effects of veratrine[17] must inevitably cast doubts about the validity of his arguments in this sphere, and, particularly, his view that myelin is not a barrier to penetration.

Recently the proofs of distortion of results by nerve connective tissues have been listed by Shanes[63]: the presence of such factors must surely affect drug action, in particular its onset and reversibility of action.

The experimental phase used. Differences between local anaesthetics *in vivo* and *in vitro* were tentatively suggested in 1930[57]. The evidence[117], quoted earlier, that procaine can cause irreversible paralysis in excised muscle and nerve, whereas, *in vivo*, the safety margin is unlimited, powerfully supports this.

Watts[83] has claimed that the results of oxidation inhibition by various local anaesthetics on a brain homogenate show a correlation between *in vivo* and *in vitro* results. However, the discrepancies in creatine phosphate levels with central narcotics, quoted by Barlow[40], were only remedied by electrical stimulation of the isolated material. It is hard to see why local anaesthetics apparently worked better on brain oxidations than central narcotics: practical usage does not reflect these results. It could be that, unlike peripheral nerve, brain is unconcerned with phosphate metabolism.

Welch and Bueding[128] have claimed that the only enzyme action seen *in vitro*, which has been confirmed *in vivo*, is that of eserine. This is an assertive remark, but the gulf between the intact animal and isolated tissue has frequently been confirmed. Nevertheless, to preclude results on these grounds would eliminate most of the information there is, hence they must be utilised, but with reserve.

Homologous series. The convenience of using related compounds is undoubted, especially to minimise errors from factors such as differences in diffusion and detoxication rates[129], and they have often been employed. This is perfectly acceptable, and it is not surprising that such series have shown some regular features which allow predictions to be made (for example concerning the Overton-Meyer theory[39]), or which show certain correlations (thus, between surface activity and local anaesthetic potency[30]), but their use must stop there. It is wrong to carry conclusions from them to unrelated substances. Luduena and others[51] admitted that the surface tension relationship, cited above, exists in homologous series, but they emphasised its absence when comparing compounds with radically different structures. This must be true of the wide variety of substances embraced by the term "local anaesthetic".

Use of models. Models have been used frequently, the most famous one being Lillie's iron wire. The Overton-Meyer theory was derived from a simple one which has been criticised. The difficulty of constructing models of nerve has been emphasised[17], not merely in creating the concentric layers of axon, sheath, and external medium which are involved, but in giving it a resting membrane potential: it has to be dynamic.

Notwithstanding, models have been, and must be, an important, and sometimes the only bridge between a theory and the complete tissue or system.

Temperature. Löfgren[36] felt that the effect of temperature should be considered, although rating it of less consequence than pH. It is certainly important in the contemporary topic of freezing anaesthesia. Little

work has been done on the mode of action of low-temperature anaesthesia, though Lorente de Nó has claimed[17] that hypothermia, oxygen lack, and depolarising agents all act identically on action potential. No conclusions can be drawn from this electrical reaction alone, and the possibility exists that refrigeration produces its effect in a similar fashion to the widely quoted means of obtaining local anaesthesia (often accidentally produced) of anaemia. The latter presumably arises from metabolic effects, although not necessarily direct ones upon aerobic mechanisms: van Harrevald and Christensen[130] have suggested that a slow depolarisation is produced, owing to a reduced metabolism which cannot maintain the membrane potential. Alternatively, the effect may be related to van't Hoff's Law, producing a physico-chemical activity depression to subfunctional proportions. However, Shanes[63] has prescribed an increase in membrane rigidity, and this seems to be a more likely approach. It must not be overlooked that the effect of temperature, *per se*, is potentially important, apart from variations in it produced deliberately.

Anaesthetic ratings. Potency ratios are often used in these studies. These are based on several test methods, some involving minimum effective concentration, others effective duration, and yet others, latent period. Such lack of uniformity has been criticised[36,131] and must surely influence quantitative results.

Qualitative ratings, too, are important, as few drugs have a single effect. Atropine, procaine, quinidine, pethidine, and papaverine have been listed[30] as having the following common properties, local anaesthetic, spasmolytic, analgesic, cardiac retardation, and anti-acetylcholine effects, in a number of tissues. Each drug has one property highly developed at the expense of the others but, even so, such multiplicity may lead to confusion. These remarks certainly apply to other drugs as well, and the view that benzyl alcohol is a general, rather than a local, anaesthetic[123] illustrates this point clearly.

Procaine. Despite its wide use experimentally, there are grounds for doubting whether procaine can be regarded as a standard local anaesthetic. For example, it can be injected intravenously, a property shared only by lignocaine, although, from the literature available (including [36,132,133]) it seems that lignocaine acts in a "normal" local anaesthetic fashion in other respects.

Other experiments have been described[78,134,135] pointing to different behaviour by procaine compared with other local anaesthetics. Toman has especially underlined[49] its activity on muscle tissues which seems to be more highly developed than is usual in local anaesthetic drugs. Examples of this have been instanced above, as also its anti-acetylcholine activity. Toman remarked that death from overdosage is usually caused by cardiac arrest.

Evidently, many limitations restrict the results of local anaesthetic researches. It is problematic how much weight attaches to each aspect, but it is clear that, if taken to their logical conclusions, virtually every result would be invalidated on one score or another: that local anaesthetic

theory does show some relation to practical activity of the drug indicates that this must not happen. Rather, the results must be taken and used cautiously in lieu of further proof, which, it is to be hoped, will be forthcoming.

Features for Resolution

It remains to be seen if any points can be resolved, within the limits of available information, which bear upon local anaesthesia. An attempt will be made to answer certain definite questions.

Is Local Anaesthesia a Surface Activity?

Lillie's nerve model showed characteristic surface changes during "activity", and the membrane has been named as a key site in transmission[13,30,36,63]. Consequently, it is a likely situation for drugs to act. The attempt[16] to relate differential blocking effect to fibre size is an expression of a belief that surface area, at least, is important. Several of the theories of anaesthetic action are linked with surface phenomena and the important work by Bennett and Chinburg[62] cited the cell membrane as the probable site of action of local anaesthetics.

Velocity of reaction, too, suggests an effect at the surface, and this has aroused comment with both local anaesthetics[18] and with calcium ions[136]. Finally, with many local anaesthetics, the permeability theory of nerve transmission is worthy of very close attention, and its relation to activity at the surface is undisputed.

On balance, therefore, it is probable that many local anaesthetic drugs act at, or around, the surface of the cell.

What is Known About the Membrane?

It has been conjectured that the membrane need not be anatomically distinct, but could be a fluid entity[17]. However, as early as 1932 it was envisaged as a continuous layer of fat, and alternative suggestions of an emulsion containing fat and protein[15], and a strongly organised lipoprotein film combined with metal ions[36], have been put forward. Furthermore, von Muralt[137] claimed to have photomicrographed the membrane in ultra-violet and polarised light.

Shanes[63] has recently emphasised that myelin sheaths, Schwann cells, and connective tissue sheaths are relatively rigid, and must not be mistaken structurally for the membrane which is found only at the nodes. Notwithstanding he cited evidence that myelin and the physiological membrane have similar dimensions, comparable electrical characteristics, are depolarised by KCl, and, significantly, both react similarly to local anaesthetics[138,139]. Skou[43] used local anaesthetics to demonstrate that stabilisation is associated with a tendency of the lipid phase of the membrane to expand: myelin and nodal membrane behaved like each other. Shanes quoted studies with X-rays and polarised light indicating that the lamellar structure of the membrane is essentially the same as the physiological membrane, that is a double layer of lipid molecules, perhaps

bounded at each aqueous interface by a layer of protein[140]. The active membrane is relatively thick, probably being up to about 100 Å.

Barlow's[40] comment that neurilemma contains fat provides a timely reminder that myelinated CNS fibres have no neurilemma, in contrast with similar peripheral fibres. It is probable that most work on peripheral nerve employed medullated fibres, and it is consequently an unavoidable inference that the possession of a neurilemma must be regarded as a factor, distinguishing central from peripheral nervous tissue, which could influence drug actions, no matter whether they are general or local anaesthetics.

What is the Rôle of Myelin?

That myelinated fibres are most excitable through the nodes has been clearly demonstrated. The threshold of stimulation is up to 30 per cent higher in the mid-internode region, and it is thus clear that myelin exercises some form of protective function, apart from any acceleratory one with which it invests nerves. It is therefore to be expected that unmyelinated nerves should be more susceptible to drug action than myelinated ones.

What Causes Differential Effects?

Evidence for differential block has been advanced, and this is important in view of the present concept[31,32,120] that receptors can signal stimulus intensity by means of impulse frequencies. The block of high frequency impulses would surely lead to differential effects, and Bennett and Chinburg[62] attempted an explanation of how this block occurs. Moreover, Granit[120] has claimed that the sensations of touch and pressure are merely distinguished by the numbers of stimuli involved, and he also asserted that warmth and cold are identified by patterns of impulses. The scope for "selective" effects thus appears to be quite wide.

The work by Katz[29] is of interest because he reported that the action of procaine upon the receptors showed the normal blocking effect without any depolarisation. It raises the possibility that the sensory arc may be more sensitive to local anaesthetic in the vicinity of the receptor than in its nerve. Certainly it should be borne in mind that many local anaesthetic injections are made into regions, particularly subcutaneous ones, which are rich in receptors. Even with medullated nerve there is bound to be a gap between the myelin sheath and the receptor itself: it is quite possible that at this gap, and perhaps the receptor itself, are points of hyper-susceptibility to anaesthetics.

The cases of preferential blocking of A and B fibres[17] may have two explanations. These faster conducting fibres may be more susceptible to metabolic upset, for example to oxygen lack, than C ones, or Toman's theory[49] of different conduction mechanisms may be substantially correct. However unacceptable the latter appears it must be admitted that central and peripheral neurohumours vary, just as nerve conduction and end-plate transmission probably differ. The fact that synapses are more

susceptible to drug action than nerve cells, and neuromuscular junctions less than either[39] lends some support to this.

In all the results, it should be remembered that it is easier to obtain normal reactions from motor than sensory nerves, and this must inevitably colour the conclusions.

Finally, the results of Forbes and others,[141] deserve mention: they claimed that, in general anaesthesia, electrical representation of sensory stimuli reaches the cortex with undiminished, or even augmented, intensity, but due to the depression they are not recognised. Clearly the drugs involved were in no way local anaesthetic, and if this is substantiated it must raise doubts about the activity which is thought to be common to both local and general anaesthetics, although action sites are obviously implicated.

What is the Influence of the Structure of the Drug?

The importance of structure was appreciated early[142]. Various features are associated with drug action phases.

The union of the drug and the receptive surface. Löfgren[36] has clearly shown that the possession of a hydrophilic grouping in the molecule is of great importance, although excessive hydrophilic properties may produce interaction with the membrane and different anaesthetic activities as a result[39].

Lipid solubility characteristics of the molecular have been remarked[51], but they are clearly secondary to hydrophilic properties.

Its fate there. Some sort of blanketing effect has been suggested as many drugs act in the form of undissociated molecules[94]. The largest body of opinion favours the concept of hydrolysis of the drug.

Its destiny thereafter. Assuming that changes of a hydrolytic nature occur, the free base commands attention. Increased anaesthetic activity with alkalisation supports this[100], and the relationship has been recognised, to some degree, at least, in muscle and nerve[15,51,101,116]. On balance it seems quite clear that the importance of the free base lies in its penetrant powers into the nerve. A different view, based on procaine, is that the cation is involved[67]. It is likely that this conclusion was based on an anomalous observation, but it serves as an introduction to the concept[109] that the efficacy of local anaesthetics depends on cations acting intracellularly. The loss of potency accompanying stabilisation of the cation[110] strongly supports this view.

How Important is Penetration?

It was early suggested that rates of action and diffusability might be as important to local anaesthetics as to other drugs[143]. If local anaesthetics act by film penetration they might display some haemolytic activity. Gessner, Walter and Reinhardt[144], investigated about fifteen of them: all produced haemolysis, and a fair correlation was obtained between local anaesthetic potency and haemolytic power. Since then penetration has been cited frequently, and significantly, in connection with various effects including surface tension[46], adsorption[145], anticholinesterase[76],

potassium synergism[15], and permeability[63], the last author stating that the high lipid solubility of many compounds used in narcosis is consistent with this view. Skou[111] has claimed that the anaesthetic content of nerve lipid is directly proportional to the free base, but that the cation may have a part to play. The view, expressed in 1955[146] that, once through the membrane, the free base dissociates and acts on axoplasm seems to accentuate the importance of penetration, and to link this section with the preceding one.

Conclusions

Various theories have been said to be valid for local anaesthesia. Most authors appear to have recognised the shortcomings of such a policy: the danger lies, not in applying a theory to local anaesthesia, but in taking results from general anaesthesia of the central nervous system and applying these indiscriminately to peripheral nerve. It has rightly been said . . . "most axonology seems considerably removed from problems of central nervous function, except by broad analogy"[49]. This statement is not upset by the observation that, just as general anaesthesia is inexplicable by one theory alone (and the use of such diverse agents as progesterone[147] and xenon[148] amply confirms this), the same is applicable to local anaesthesia. Many substances can stabilise the membrane or inhibit metabolism, but are not local anaesthetics. On the other hand, many local anaesthetics seem to act in ways explicable in terms drawn wholly, or partially, from several theories: that the same theories are not named each time strengthens the belief that various mechanisms are involved, and block by such dissimilar agencies as refrigeration and oxygen under high pressure[149] confirms this.

The fact that a model, or isolated tissue, is no substitute for the living cell or tissue in its natural surroundings is inescapable: that models, at times, provide information which would be entirely lacking otherwise is true, but, as with general anaesthetics, they must not be used as a basis for generalisations about local anaesthesia.

Finally, it is possible to compile a list of salient features, most of which have been fairly clearly proved.

1. The scientific investigation of local anaesthesia and its practical application are often unrelated. A striking example of this is the effect of hydrogen ion concentration upon the action of procaine at mucous surfaces.

2. The current views on nerve impulse transmission give added prestige to concepts of nerve block being caused by changes in permeability. It is worthy of note that many local anaesthetics stabilise membrane conditions.

3. That some agents block by depolarisation is undeniable, but as the nerve impulse is accompanied by a wave of depolarisation, it is clear that, if "conventional local anaesthetics" behaved in this way, their action would be preceded by a stimulatory effect. This is not borne out in clinical practice.

4. From studies of conduction it is to be expected that inhibition of metabolism may ultimately cause block, but it is a fairly slow process, owing to such factors as the anoxic reserve.

5. Permeability or metabolic effects occur at, or in, the surface, and this must be partially governed by lipid solubility (Overton-Meyer theory), and also by adsorption (Warburg theory).

Sooner or later the drug penetrates the cell, and in most local anaesthetics, of the basic type, the free base is the agent which achieves this. Owing to this action of the free base, the pH of the anaesthetic solution, and the modifying effect of the surrounding medium, are important in the efficacy of the drug.

There is a growing body of evidence that, after securing penetration into the cell, the free base is converted into the cation, which is the true "nucleus" of anaesthetic activity.

6. Considerable variation in drug activity is caused by impedance from connective tissues around the nerve fibres. This, coupled with site of injection, and pH, may explain many of the delays in onset of drug action. Myelination constitutes a further barrier to drug action, as the drug has to effect an entry first at the nodes of Ranvier. It effectively ensures that, under normal conditions the unmyelinated fibres, including the pain ones, block first. Furthermore, although it is not vital to the present study, the peculiar susceptibility of the nodes of Ranvier to drug action lends support to the saltatory theory of nerve conduction.

7. Further differentiation is provided by partial blocking, which disrupts some impulse frequencies in nerves, whilst leaving others unchanged. By virtue of this, certain intensities, and perhaps patterns, of sensation may be selectively eliminated before other ones.

There is some evidence for preferential local anaesthetic effects in the vicinity of the sensory nerve ending, that is, at the receptor, or immediately adjacent to it. This could well allow a further differentiation of effect if some endings are more susceptible than others.

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