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Advances in the Chemistry of Anaesthetics (1961 - 1971)

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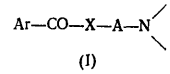
The most important studies on the chemistry of anaesthetics during the last decade are reviewed. Anaesthetics belonging to different classes of organic compounds (aminoalcohol esters, aminoamides, aminoacid amides, aminoketones, etc.) are considered mainly in terms of the relation between structure and physiological activity. Much attention has been devoted to the consideration of the available literature data on the mechanism of the action of anaesthetics.
The bibliography includes 411 references.

CONTENTS

I. Introduction	876
II. Anaesthetic activity of compounds containing amino- and carbonyl groups	877
III. Anaesthetic activity of compounds containing one functional group	881
IV. Some hypotheses about the mechanism of the action of anaesthetics	883

I. INTRODUCTION

During the ten years which have elapsed since the publication of our previous review[1], the total number of reports dealing with anaesthetics† has continued to increase. More than two hundred publications now appear on this subject every year, more than half of which deal with the problems of the mechanism of anaesthetic action, while the syntheses of new preparations are published in brief patent reports with increasing frequency. The result of electrophysiological, physicochemical, biochemical, and other studies discussed below make it possible to formulate fairly definite ideas about the mechanism of the action of anaesthetics with aminoester and amide structures at the cellular and subcellular levels. However, by no means all problems may be regarded as solved. In the first place this applies to the mechanism of the action of anaesthetics at the molecular level and to the determination of the relative role of factors responsible for the quantitative differences in the strength of anaesthetics. The latter problem is closely related to that of the specificity of their action. An enormous amount of experimental data have shown, on the one hand, a high specificity–small changes in structure lead to a sharp decrease in activity up to its complete disappearance[1-9], while at the same time drastic structural changes—for instance, transition from aminoesters to aminoketones or amines involving a complete change in all chemical characteristics—do not deprive the preparation of its capacity to interrupt the nerve pulse. Admittedly, the absence of experimental data makes it impossible to rule out the hypothesis that in such cases the mechanism of action at the cellular or molecular level is different and such substances cannot then be called anaesthetics, although the final physiological result is the same. So far we are forced to treat these substances together with "typical" anaesthetics having ester and amide structures in accordance with the terminology adopted by the authors who describe them. However, considerable difficulties then arise in the classification of published data. Therefore, in the present review the available results are described on the basis of ideas which may be regarded as a development of the old concept of the "anaesthesiophoric group" (I), although its limitation has already been noted[1]:



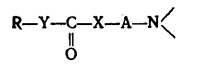
(I)

Statistical data have shown that, despite the wide variety of structures investigated, certain groups are nevertheless encountered most frequently in reactive compounds. These include the amino-group (about 98%) and the carbonyl group (about 80%). Most anaesthetics, including the most active preparations which have found applications, contain both these groups. This suggests that the above combination of functional groups is important for the formation of the steric structure and distribution of electron density in the molecule which is responsible for anaesthetic activity. The environment of these groups, particularly that of the carbonyl group, may be extremely varied and the "structure–activity" problem reduces mainly to the analysis of the nature and mechanism of the influence of substituents in various parts of the molecule on pharmacological activity. There are many views on this topic. Thus, according to Löfgren[10], the strength of anaesthetics is related to the electron density at the oxygen atom of the carbonyl group, which behaves as an electron donor. In many cases, this factor is undoubtedly important—in particular it can account for the increase in the strength of anaesthetic action following the introduction of electron-donating groups (NHR, OR) in the *para*-position of diethylaminoethyl benzoate and the opposite effect of electron-accepting groups such as NO_2. Similar observations have been made for aminoacid amides[11,12] and a number of other types of anaesthetic substances[13] and sometimes it was even possible to observe a quantitative correlation between anaesthetic activity and electron density at the C=O bond[14]. The increase of the activity of the compounds on replacing the ester group by the amide group can itself be related to the increase of electron density at the carbonyl oxygen atom[11].

On the other hand, many facts demonstrate the inadequacy of this hypothesis. Thus when the compounds

†A terminology somewhat different from that current abroad is used nowadays in the Soviet literature; instead of the terms "local anaesthetic" and the Russian equivalent "mestnyi anestetik" employed previously, the term "anaesthetic" is now used, while "narcotic" corresponds to the term "general anaesthetic". This terminology will be used in the present review.

under consideration are represented by the general formula (II)

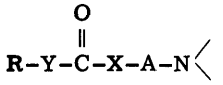


(II)

where X and Y can represent NH, NR, O, S, or C< and A is an alkyne chain or an aromatic residue, it is found that the anaesthetic activity is retained not only on replacement of O by NH but in many cases also on their replacement by the CH_2 group. These groups are isoelectronic and in most cases isosteric, whence one may conclude that geometrical (steric) effects play a considerable role. Numerous data concerning the high activity of compounds containing an *ortho*-disubstituted benzene ring—amino-esters [15-17], anilides [8,9,18,19], and many others—support this view.

Thus, although at present the mechanism of the action of anaesthetics can be regarded as established in broad outline, it is as yet impossible to determine unambiguously the general relation between the structure of the compounds and their anaesthetic activity—different factors are of primary importance in different cases. The "kind" of atoms and their relative positions are probably not the only important (and possibly not the most important) factors; other significant factors are physical parameters characteristic of the molecule as a whole: the relation between hydrophilic and lipophilic properties, the general distribution of the electron cloud, and other features which are related to molecular structure in a complex manner. Recognising this, in classifying anaesthetics we are nevertheless obliged to employ the structural principle as the only one possible at present. It is based on formula (II) and the classification has the form shown in Table 1.

Table 1. Classification of compounds of the type



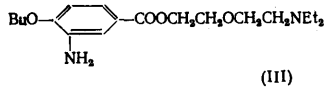
X	Y	Type of compound	X	Y	Type of compound
O	C<	Aminoalcohol esters	C<	NH	Aminoacid amides
NH	C<	Aminoamides	O NH	NH O	Carbamates
C<	O	Aminoacid esters	C<	C<	Aminoketones

II. ANAESTHETIC ACTIVITY OF COMPOUNDS CONTAINING AMINO- AND CARBONYL GROUPS

1. Aminoalcohol esters (X = O, Y = C<)

As before, most attention is devoted to varying the acid component of the molecule in esters of diethylaminoethanol $RCOOCH_2CH_2N(C_2H_5)_2$ and related aminoalcohols. Studies on the classical series of substituted benzoic acids—aminobenzoic [20-23], alkylbenzoic acid [15,24], alkoxybenzoic [16,25-31], and others [32,33]—are being continued. It has been found that the increase of activity in the series *ortho* < *meta*- < *para*-alkoxybenzoic acids [26] and on enlarging R from C_1 to C_4 as well as its decrease when R is branched take place in parallel with the change in the surface activity of these compounds and in many cases (for positional isomers) a parallel variation with partition coefficients is observed.

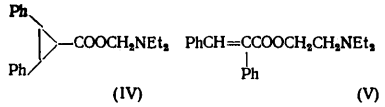
Promising preparations have been found among *p*-alkoxyethoxybenzoates [25] and 2,6-dimethylbenzoates [15]. The latter act over longer periods, possibly owing to steric hindrance to hydrolysis due to the *ortho*-methyl groups, which is characteristic also of other *ortho*-substituents [17]. Among alkoxybenzoic acid derivatives, it was possible to find a substance (III) combining high anaesthetic and vasoconstrictor activities [21]:



(III)

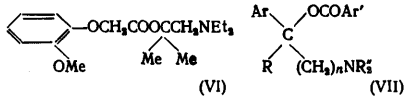
On the other hand, despite their high activity, the aminoesters of halogenobenzoic acids were found as a rule to be unsuitable owing to their considerable toxicity and side effects [29,32].

The esters of certain other aromatic [34-36] and heterocyclic acids [37-42] and also of cinnamic acid and its analogues [43,44] were found to exhibit anaesthetic activity. The derivatives of 2,3-diphenylcyclopropane-1-carboxylic acid [45] may be included among acids of this type. It is interesting to note that the (−)-isomer of (IV), which is a compound in this series, was found to be twice as active as the (+)-isomer. Shah and Ketcham [43] observed that the *trans*-form of compound (V) has a higher anaesthetic activity than the *cis*-isomer:



(IV) (V)

Finally, a high activity has been found in many aminoesters of diarylacetic and similar acids [16,46-51] and also in phenoxyacetates [52-54]. Thus compound (VI), the toxicity of which is smaller by a factor of 7, gives rise to an anaesthetic effect lasting twice as long as that of xylocaine [54]. This confirms the earlier conclusion [1] that the presence of a conjugated chain is not always necessary for anaesthetic activity and that the substituent R in compounds (II) need not necessarily be an aromatic group or its vinylogue:

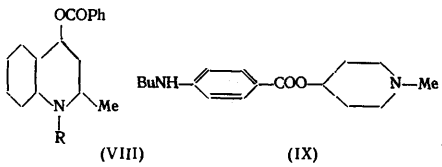


(VI) (VII)

Relatively less attention has been devoted in recent years to varying the alkyl and amino-components of the aminoester molecules. The esters of aliphatic-aromatic aminoalcohols [44,52,53,55-63], including derivatives of type (VII), [52,55-60] were studied in greater detail in this respect. As in many other series, it was found that the shape of the molecule and the dimensions of its constituent units play a significant role in the activity of these compounds [52]. Thus compounds with a trimethylene chain proved to be the most effective, while derivatives of aminoethanols and aminobutanols are relatively inactive [52,56,57]. The accumulation of alkyl substituents round the ester group promotes a high activity, which may be attributed to their electron-donating influence, leading to an increase of electron density at the C=O group and to steric effects,

for example in consequence of the resulting hindrance of hydrolysis. On the other hand, the introduction of various substituents in Ar or Ar′ does not have satisfactory results [52,55,59]. The activity decreases sharply when Ar or Ar′ are replaced by saturated residues [52,58,60,61].

The role of the geometrical structure may be followed by analysing data for the activities of the stereoisomeric esters of γ-piperidinols and γ-decahydroquinolinols [64-68]. It was found that, among benzoates of type (VIII), the esters with a *cis*-diaxial disposition of the CH_3 and C_6H_5COO groups and the *trans*-junction of the rings are much less toxic and more active in terminal [caudal!] and conduction anaesthesia than their epimers. In infiltration anaesthesia the behaviour is somewhat different—here the highest activities are shown by the *trans*-isomers with an equatorial C_6H_5COO group [65,68]. The change from the *trans*- to the *cis*-junction of the rings reduces both activity and toxicity in all cases.



(VIII) (IX)

Similar conclusions were reached by Nobuo [69] in a study of decahydroisoquinoline derivatives. Among piperidine derivatives, the axial isomers show the most effective properties [68,70]. All these data confirm the earlier hypothesis [52] of the importance of the geometrical structure of the molecule in view of the necessity for similarity (isomorphism) of the anaesthetic and a receptor surface for the activity of the preparation.

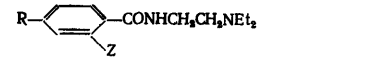
In conclusion we may note a few other aminoesters which exhibit a high anaesthetic activity—"paridocaine" (IX) [23] which has a more prolonged and intense action than novocaine, 2-piperidinoisopropyl diphenylacetate which is 40 times more effective than xylocaine in surface anaesthesia and 3 times more effective in infiltration anaesthesia [71], 2-diethylaminoethoxyethyl benzoate ("kallocaine") which is twice as effective as xylocaine on surface administration and four times as effective on administration by infiltration [72], and also certain other preparations containing ester oxygen in the alkyl chain [73,74].

Other ways of varying the alkyl and amino-components of the aminoester molecules, involving the doubling of the number of functional groups, the introduction of sulphur atoms or the hydroxyamino-group, and the use of various heterocyclic structures, were not appreciably successful [16,27,75-80].

2. Aminoamides (Y = C<, X = NH)

Among aminoamides (i.e. diamines in which one amino-group is acylated), the amides of the heterocyclic acids, which include the familiar anaesthetic sovcaine (cinchocaine, dibucaine, percaine), have been investigated in greater detail [3,35,81,82]. The activity of these compounds increases as a rule after the introduction of bulky alkyl and alkoxy-groups [81]. It is interesting that the amides of 3-alkoxycinchoninic acid do not exhibit anaesthetic activity, in contrast to the 2-alkoxy-derivatives [39].

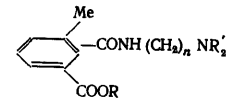
Alkyl and alkoxy-groups promote the appearance of pharmacological activity not only in the series of sovcaine analogues but also among the amides of substituted benzoic acids, which were previously frequently regarded as relatively unpromising [1]. Thus *o*-alkoxybenzamides, particularly the *o*-butoxy- [83,84], *o*-benzyloxy- [85], and *o*-allyloxy-derivatives [86], for example compound (X), proved to be effective, their anaesthetic activity being close to that of xylocaine; 2,4,6-trimethyl- [87,88] and 6-alkoxycarbonyl-2-methylbenzamides (XII) [89] are also active. The activity of the diamide (XI) [90]



(X, Z=OCH2CH=CH2)
(XI, Z=NHCOC6H17)

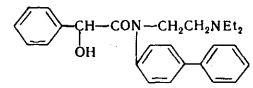
exceeds that of novocaine by a factor of 200.

Compounds containing substituents in the *para*-position are usually less active, but some of them, for example *p*-$ClC_6H_4OCH_2CONHCH_2CH_2NR_2$, are nevertheless used in view of their low toxicity [91].

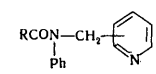


(XII)

A number of studies have been made on aminoamides with an arylated amide group [92,93]; according to the authors, compound (XIII) is a powerful anaesthetic:

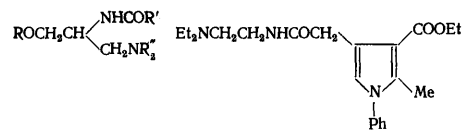


(XIII)



(XIV)

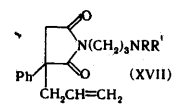
Among other active aminoamides, mention may be made of 4-alkoxyphthalimides [94], 3,3-diphenylacrylamides [95], and amides of type (XIV) [96] and (XV) [97]:



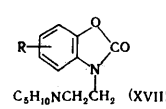
(XV) (XVI)

Compound (XIV), in which the structures of an aminoamide and aminoacid ester are combined, and which is said to induce rapid, stable, and prolonged anaesthesia [98] is interesting. Among dibasic acid imides, which attracted attention recently, compounds (XVII) [99], (XVIII) [100], and a number of others [101,102] proved to be active anaesthetics.

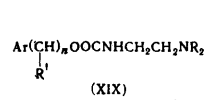
One can also mention the aminoamides of carbamic acids of type (II) (X = NH, Y = O), the infiltration activity of many of which is equal to that of xylocaine. As in other classes of compounds, in the series of substances of type (XIX) the maximum activity is attained with Ar = 2,4-$(CH_3)_2C_6H_3$ and 2,6-$(CH_3)_2C_6H_3$, while *p*-CH_3O, *p*-NH_2, and *p*-Cl substituents reduce it [103]:



(XVII)



(XVIII)



(XIX)

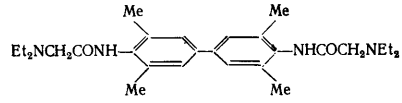
3. Aminoacid imides (X = C<, Y = NH)

Aminoacid amides are a class of compounds to which most attention has been devoted during the last decade. This is due to the abundance of very active preparations

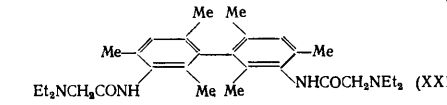
belonging to this class. It is sufficient to mention xylocaine, trimecaine (mesocaine), prilocaine (cytanest) and others. Starting with the structure of xylocaine, detailed studies were made on a wide variety of its analogues[8,9,104]. Studies involving the changes in amide moiety of the molecule, primarily by the introduction of various substituents into the anilide group, have been particularly numerous. As already mentioned, one of the most important factors here are the general lipophilic properties of the molecule, the enhancement of which by the introduction of additional methyl groups (for example in trimecaine[8,9,18]) or by replacing a methyl group by larger substituents[19] leads to an increase of activity; in the last case the fact that the structure of the amide group is sterically hindered may also play an important role.

Numerous compounds containing groups more polar than alkyl substituents in the benzene ring have been investigated. Alkoxy- and aryloxy-derivatives proved to be the most interesting[88,104-108] and, whereas the C_6H_5O group has the most marked effect in the *meta*-position, the $C_6H_5CH_2O$ and $C_6H_5CH_2CH_2O$ groups are most effective in the *para*-position[8,9]. Introduction of the more hydrophilic OH, $OCOCH_3$, and SH groups as well as halogen atoms or the NO_2 group in the benzene ring increases the activity sharply or completely abolishes it[12,88,107,109]. In contrast to other hydrophilic groups, the amino-group has a promoting effect on pharmacological properties, particularly in the 4-position[12,88].

Interesting data were obtained in the study of compounds which may be regarded as "dimeric" analogue of xylocaine (XX) or trimecaine (XXI)[8,9,45]. It was found that, when the distance between the nitrogen atoms in such a structure,



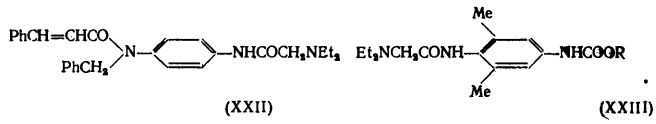
(XX)



(XXI) ,

is about 10.3 Å, the activity of the preparation is extremely high, when the distance is greater than this it is approximately equal to the activity of the monofunctional compound, and when it is less the activity falls sharply. These results partly indicate the possibility of many-centre addition of the anaesthetic to the receptor.

Certain other combinations of two amide groups in the molecule lead to highly effective anaesthetics, for example in compound (XXII)[110] or (XXIII)[111] whose toxicity is low, the activity of the latter exceeding that of xylocaine by a factor of 10, 20, and 60 respectively for R = C_4H_9, i-C_5H_{11}, and C_6H_{13}:

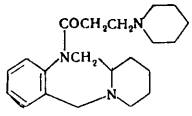


(XXII) (XXIII)

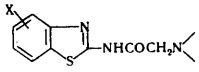
However, in most cases additional carbonyl-containing groups do not improve the properties of aminoacid amides[112-116].

Together with a substituted benzene ring as the aromatic residue, other aromatic and heterocyclic fragments have been frequently introduced into the aminoacid amide molecule. It was found that high activity and its long duration are characteristic of certain aminoacylamide derivatives of naphthalene[117,118] and phenothiazine[50,119-122]. However, the latter frequently exhibit an irritant action on the tissues and for this reason are unsuitable. Unexpectedly the results[120,121] show that, despite the generally held view, certain quaternary salts of 10-aminoacylphenothiazines are not inferior to tertiary amines in their anaesthetic activity or actually superior to them, The author claims that the activity of the preparations depends mainly on the dimensions of the group introduced on quaternisation. Bearing in mind the low activity of the preparations and their considerable irritant action, one might have doubted these claims, but recently a further report has been published[123] in which it is shown that xylocaine methochloride acts like xylocaine itself and the "dose–response" relation is approximately the same for both preparations. Possibly the mechanisms of the action of the base and the quaternary salt are nevertheless different, although so far there are no literature data on this question.

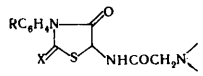
The interesting tricyclic amide (XXIV) has an anaesthetic activity equal to that of xylocaine and its toxicity is low (LD_{50} = 500–1250 mg kg^{-1}),[124]



(XXIV)

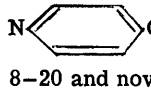


(XXV)

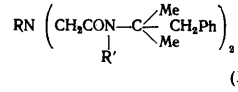


(XXVI) .

A number of very active preparations have been discovered by Indian investigators[125-129] and other workers[130-131] among aminoacyl derivatives of thiazoles, benzothiazoles, and thiazolidinones [(XXV)–(XXVI)] and also among the analogous bispiperazine derivatives. The absence of conjugation between the NH–CO group and the aromatic ring in compounds of type (XXVI) is striking. Such conjugation is probably not obligatory, which does not apply only to the above types of compounds—the number of active local anaesthetics discovered in the series of benzylamides[132-137] and compounds with an aromatic terminal group still more remote from the amide moiety has increased in recent years[138-141]. Some of these, for example the bisamides (XXVII), are extremely active[139,140,142]; in particular, the compound with R = $HOCH_2CH_2$ ("oxethazine) and also its analogues with R = $HOCH_2CHC_2H_5$, *p*-$NO_2C_6H_4COOCH_2CH_2$ and



$COOCH_2CH_2$ surpass sovcaine by a factor of 8–20 and novocaine and xylocaine by a factor of 2000 to 4000, while their toxicity is low (for oxethazine, LD_{50} = 400 mg kg^{-1}) and their irritant action is only slight. It is interesting that the activity disappears completely with R = $HO(CH_2)_3$.[140] Thus the position of the benzene ring in a molecule is not always of primary importance:

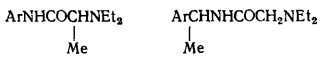


(XXVII) .

However, the norbornane and cyclohexane analogues of xylocaine exhibit only an extremely weak anaesthetic effect[143]. These data as well as a number of others described above suggest that the aromatic moieties in the molecule of the anaesthetic are not important solely because of their direct influence on the properties of the carbonyl group. Probably their role is largely to ensure that the compound is soluble in lipids and is capable of

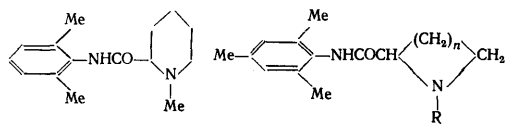
binding to the receptor via non-covalent bonds (hydrophobic binding, π-complex formation, etc.).[11]

Studies[144,145] on the pharmacological properties of *N*-aminoacylephedrines, which are interesting because all eight possible isomers of the amides formed by D- and L-*NN*-dimethylphenylalanines with D- and L-ephedrine and pseudo-ephedrine were investigated and it was shown that derivatives of L-*NN*-dimethylphenylalanine are the most active, merit consideration. On this basis, the authors put forward certain hypotheses concerning the structure of the receptor with which the above substances can interact. It was also shown for compounds (XXVIII) and (XXIX)[146] that the L-isomer has a much higher anaesthetic activity than the D-isomer. Recently this was observed for the anilides of *NN*-dimethylalanine[147]. On the other hand appreciable differences between the activities and toxicities of the D-, L-, and DL-isomers of prilocaine (see below) were not observed[148]:



(XXVIII) (XXIX) .

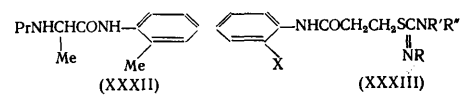
Together with studies on the amide component, much attention has been devoted in recent years to varying the aminoacyl component in aminoacid amides[108,132,135,149-180]. Thus many piperidinoacetamides, particularly those containing several methyl groups in the piperidine ring, proved to be highly active anaesthetics with low toxicity[132-135,149,150]. Together with carbocaine (mepivacaine), which has been known for a long time, its *N*-butyl analogue bupivacaine (marcaine) (XXX), which has a very prolonged anaesthetic action and low toxicity, has been actively investigated recently[151-153]:



(XXX) (XXXI) .

Studies on a series of mesidides of azacycloalkane-α-carboxylic acids (XXXI)[8,9,154-156] showed that, with increase of ring size (n = 2, 3, 4), the surface anaesthetic activity increases and the infiltration activity falls. The activity also increases with increase in the size of the group R, the optimal properties being obtained with R = C_4H_9, i-C_4H_9, and cyclo-C_6H_{11}. As a result of these investigations, two new highly active anaesthetics of type (XXXI) (n = 2)—pyrromecaine (R = C_4H_9) and cyclomecaine (R = cyclo-C_6H_{11})—have been proposed and introduced into clinical practice.

Compounds with other heterocyclic groups (pyrrole, nortropane, morpholine, and piperazine[133,149,157-161] and also with branched or polar aliphatic substituents at the nitrogen atom[162,163] are as a rule relatively inactive or toxic and behave as tissue irritants.



(XXXII) (XXXIII) .

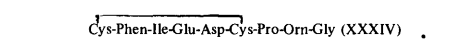
On the other hand, substances with a secondary amino-group, particularly so called prilocaine (propitocaine, cytanest, L 67) (XXXII), continue to attract interest[118,151,164-169]. According to a number of investigators, the activity of prilocaine is equal to that of xylocaine *in vivo*, while the duration of its action is longer and its toxicity lower, although in tests on an isolated neuromuscular preparation it was inferior to xylocaine[168]. The difference is attributed to the lower rate, compared with xylocaine, at which it is washed out by blood, although its *in vivo* decomposition is faster, which accounts for its lower toxicity[168]. Certain *N*-butyl derivatives, for example α-butylamino-3-chloropropionanilide, which according to Malatesta et al.[170] is 79 times more active than xylocaine, are not inferior to prilocaine. Compounds with an NH_2 group are as a rule inactive.

Compounds (XXXIII), which can be classified as aminoacid amides only by convention, have an unusual structure. Some of them [for example, compound (XXXIII) with X = R′ = R″ = H and R = cyclohexyl] are much more active than xylocaine on surface and subcutaneous administration[171,172].

The data on the role of alkylation of the amide nitrogen are contradictory. Thus, according to Kurihara et al.[173], the introduction of an alkyl group into the amide group of xylocaine analogues increases their activity, while the toxicity remains constant. Similar results have been obtained for *N*-benzyl derivatives[174]. On the other hand, according to other workers[132,175], *N*-cyclohexyl and *N*-ethyl derivatives of mesocaine are relatively inactive.

The branching of the aminoacid chain structure appears to have a mainly favourable effect, most probably as a result of an enhancement of lipophilic properties and a change in molecular geometry. This can be seen for the dimethyl analogue of priplocaine (LA - 012) which is superior to xylocaine and prilocaine both as regards activity and duration of action[176], as well as for certain other compounds[177,178]. Many derivatives of β-aminopropionic[179], γ-aminobutyric[106], and β-aminoisobutyric acids[180] are active, although the increase of their activity is frequently accompanied by an increase of their irritant properties and toxicity.

In conclusion mention should be made of the anaesthetic properties of the polypeptide (XXXIV)[181], which can be reasonably considered in this section, since it contains amide bonds:



Unfortunately quantitative data concerning its activity have not been quoted, although it has been stated that it also exhibits a vasoconstrictor activity and that its activity is potentiated by other anaesthetics.

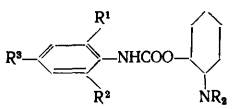
Aminoacid sulphonamides, some of which [for example, $ArNHSO_2CH_2CH_2(C_2H_5)_2$] have anaesthetic properties, can also be probably included in the class of compounds considered here[182].

4. Aminoacid esters (X = C<, Y = O)

In contrast to aminoacid amides, there has been a considerable decrease of interest in aminoacid esters without an amino-group in the alcoholic component. These compounds can be regarded as analogues of amino-alcohol esters with an "inverted" carboxy-group, such structural transformation being apparently unfavourable for pharmacological properties. Among the few substances that have been investigated[183-188], only preparations belonging to the group of aryl esters of *N*-morpholine- and *N*-methylpiperazine-α-carboxylic acids are of interest[183-185]. While their structures are similar to that of xylocaine, their activity is higher for the same toxicitv but they do cause appreciable tissue irritation. The other aminoacid esters investigated recently do not show an appreciable anaesthetic activity.

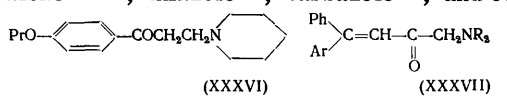
5. Carbamates (X = O, Y = NH)

The Czech school of investigators have been investigating compounds of this class most vigorously [186-193], concentrating attention mainly on 2,6-disubstituted carbanilates. As in many other instances discussed above, it was found that, together with physicochemical properties, the steric influence of *ortho*-constituents plays a significant role, since 2,6-dichloro-, 2,6-dimethyl-, 2-alkoxy-, and 2-aryloxy-derivatives have all been found to be active [103,186-180,194]. Some of them are 5–17 times more active than cocaine in surface anaesthesia and 7–20 times more active than novocaine in administration by infiltration, while having approximately equal toxicities [190]. 2-Butoxy-4,6-dimethylcarbanilate [195], 2-chloro-6-methylcarbanilate [194], and also the carbamates (XXXV) with a somewhat modified ester moiety are extremely active [192,196]. Among them, compound (XXXV) with R′ = CH_3, R^2 = Cl, R^3 = H and R_2N = NC_5H_{10} is 35 times more active than cocaine. Other carbamates with anaesthetic activity which may be mentioned are derivatives of *N*-pyridylcarbamic acids [197,198], phenothiazine-10-carboxylic acid [199], phenothiazine-10-dithiocarboxylic acid [200], and certain carbamoylazepines [201].


(XXXV)

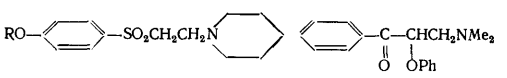
6. Aminoketones (X = C<, Y = C<)

A detailed review of aminoketones with anaesthetic activity was published quite recently [202]. Investigators concentrated attention mainly on the modification of the structure of falicain (XXXVI)—an active anaesthetic discovered at the beginning of the 1950's. It was found that, instead of the benzene ring, it was possible in principle to employ almost any aromatic residue—naphthalene [203,204], thiazole [205], carbazole [206], and others:


(XXXVI) (XXXVII)

The vinylogues of (XXXVII) are several times more active than xylocaine [207,208], in contrast to their hydrogenated analogues [207]. One should mention that, in contrast to falicain, the ketone (XXXVII) is an α-amino-derivative. Certain other α-aminoketones [209-211] and γ-aminoketones [212,213] were found recently to have anaesthetic activity. It was discovered that a sulpho-analogue of falicain—the aminosulphone (XXXVIII)—has a higher anaesthetic activity [214].

Among compounds produced by varying the amino-group, derivatives of hexamethyleneimine proved to be promising in this respect [202,215,216], particularly p-propoxy- and p-butoxy-β-*N*-hexamethyleneiminopropiophenones, the activity of which exceeds that of falicain and dicain, while their toxicity is lower and they do not give rise to side effects. The second preparation has been called "hexacaine"; the p-ethoxy-derivative ("ethamine") is somewhat less active [202].


(XXXVIII) (XXXIX)

A further increase in ring size is undesirable—derivatives of heptamethyleneimine are completely inactive [217]. The best results are obtained by the introduction of propyl [218] and butyl [219] substituents in the 4-position of the piperidine ring; substituents in the 2- and 3-positions are less effective [218]. Compounds with acyclic nitrogen are as a rule relatively inactive, although the activity increases sharply after the introduction of the phenyl [220] or phenoxy-group [16] in the α-position—for example, compound (XXXIX) is three times more active than cocaine in surface anaesthesia and five times more active than novocaine in infiltration anaesthesia [16].

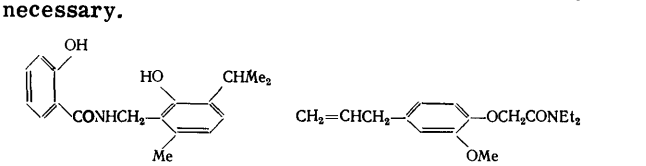
Compounds containing a carbonyl group attached directly to the heterocycle, which in this case combines the function of the amino-group and the carbon skeleton, may be classified as aminoketones with a structure somewhat different from that of falicain. Among these substances, 3-acylpiperidines [221] and 4-acyldecahydroisoquinolines [222] proved to be anaesthetics. Attempts to enhance the anaesthetic effect by doubling the aminoketone structure were unsuccessful—the aminoketones obtained by the Mannich reaction from diacetylbenzene are much less active than the corresponding monoaminoketones [223].

III. ANAESTHETIC ACTIVITY OF COMPOUNDS CONTAINING ONE FUNCTIONAL GROUP

Although the majority of active anaesthetics contain both amino- and carbonyl groups, nevertheless many studies dealing with compounds containing only one of these functional groups have been published.

1. Amides

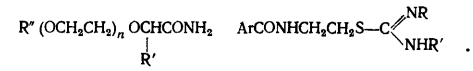
The amides of acids without a second amino-group have been known for a fairly long time as anaesthetics. Usually anaesthetic activity is observed either in acylated anilines [224,225] or in aromatic acid amides [226,227]. As in many other instances, the general lipophilic properties of the molecule and the steric environment of the amide group play a significant role here. Thus among amides of the type $CH_3(CH_2)nCONHAr$, compounds with n = 5–7 are the most active, while derivatives of lower acids are inactive [225]. Among aromatic acid amides, o-substituted derivatives are the most active, for example salicylamides of type (XL) [226]. However, the contiguity of the aromatic ring and of the amide group is not obligatory—many other derivatives show anaesthetic activity, including the amides of phenoxyacetic acid, among which an interesting preparation "detrovel" (XLI) has been discovered. It causes rapid anaesthesia, the intensity of which is equal to that induced by dicain but the duration of its action is much shorter [228], which is frequently necessary.


(XL) (XLI)

In subsequent investigations it was shown that the anaesthetic activity disappears when the acetamide moiety is eliminated from compound (XLI) or when an ethylene

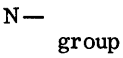
group is introduced. The degree of anaesthesia diminishes sharply also after various modifications of the acetamide moiety, after the displacement of methoxy- and allyl groups to other positions in the aromatic ring, or after replacing the allyl group by the ethoxycarbonyl group [229,230].

Among other amides, anaesthetic activity has been found in *N*-acylated derivatives of heterocycles [231,232] and in certain derivatives containing a ring carbonyl group [233-235]. Readily water soluble polyglycol ethers of type (XLII) containing an amide group have also been patented as anaesthetics [236]:



(XLII) (XLIII)

2. Amidines and Derivatives of Guanidine, Isothiuronium, etc.

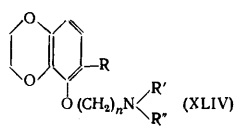
Earlier, it was noted [1] that compounds containing amidine, guanidine, and similar groups possess anaesthetic activity. Active amidines [88,237] and guanidines [238,239] have also been synthesised in recent years. Isothiuronium derivatives, anilides [171,172], and benzamides (XLIII) [240,241] are likewise powerful anaesthetics. Certain isothiuronium derivatives have an activity exceeding that of xylocaine by a factor of 4-20 in surface administration and by a factor of 2-6 in administration by infiltration. Regan et al. [241], who compared this structure with 2-aminothiazoles which also exhibit anaesthetic activity, assert that the  group can be regarded as a new anaesthesiophoric structure.

Finally, there exists yet another group, resembling the carbonyl group and related to it genetically, namely the aldoxime group, which also gives rise in many cases to anaesthetic activity in compounds containing it [242,243]. It has been noted [242] that, together with the aldoximes $ArCH{=}NOCH_2CH_2NR_2$, the isomeric *N*-oxides are active.

3. Amines

Despite the fact that anaesthetics employed in midical practice have not been found as yet among simple amines, these substances are apparently of interest by virtue of a number of advantages—relative simplicity of synthesis and resistance to hydrolysis-which are in many instances combined with high anaesthetic activity.

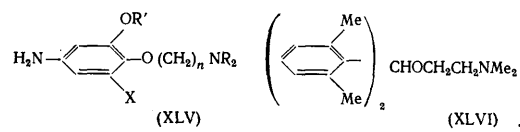
Compounds containing an ether oxygen atom (or several such atoms) together with the amino-group are most widely used. Thus Daukshas and coworkers made a detailed study of benzodioxan derivatives (XLIV) [244-246]:



(XLIV)

They showed that, in order to exhibit anaesthetic activity, compounds of this type must contain hydrocarbon substituents with a specified "bulk". The introduction of additional polar groups (OH, NR'_2) destroys their activity, apparently as a result of the enhancement of the hydrophilic properties, since the activity may be restored by the removal of the polar dioxan ring. The preparation with $n = 2$, $R = CH_2CH{=}CH_2$, $R' = H$, and $R'' = CH_3$ ("benzodiocaine") the activity of which exceeds that of dicain by a factor of 2.2 in terminal [caudal?] anaesthesia, while its toxicity is smaller by a factor of 2, proved to be the most active.

Anaesthetic properties have also been found in a series of phenyl [247-258], benzyl [259], and diphenylmethyl ethers [260-263], particularly those with *ortho*-substituents. It may be that the oxygen atom in these compounds simulates in some way the carbonyl group, which gives rise to similar structural characteristics. Thus it has been found that the activity, toxicity, and irritant properties of the series of compounds (XLV) become more marked with increase in the size of the group R', while substitution of a hydrogen atom in amino-group by an acyl group lowers both their activity and toxicity [250,251]. Basic ethers with a polyoxyethylene chain, $R(OCH_2CH_2)nNR'_2$, where R = 2-guaiacyl or 2-thyminyl residue ($n = 2-4$) [254], the analogous diphenylmethyl ethers [260], and also the diphenylmethyl ether (XLVI), which is 10 times more active than novocaine but causes irreversible tissue changes [261], were found to be active. Phenyl ethers substituted in the *meta*- and para-positions exhibit anaesthetic properties much more rarely [255,256].

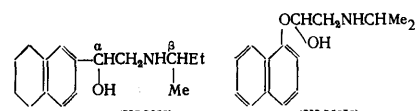


(XLV) (XLVI)

It is important to note that amines, aminoethers, and analogous compounds, which do not have an "anaesthesiophoric" structure, as a rule exhibit another kind of pharmacological activity (spasmolytic, antihistamine, cholinolytic, etc. [257,262,264-282]), as well as anaesthetic activity, which may be regarded as evidence in support of the non-specific mode of their action. Some of the most active (according to the data of the investigators who described them) amines, are listed in Table 2. Judging from the wide variety of structures of these preparations, the position of the oxygen atom in the molecule is not too significant and its role probably reduces to imparting to the substance the required physicochemical properties.

The mechanism of the anaesthetic activity of aminoalcohols is still obscure. Presumably the hydroxy-group of these compounds influences mainly their lipophilic properties. However, one cannot rule out the possibility that certain aminoalcohols do not act directly in the organism but are initially rapidly oxidised to the corresponding aminoketones, which then exhibit anaesthetic properties. Evidence in support of this hypothesis is provided by the finding that anaesthetic activity is as a rule shown by secondary aminoalcohols containing the group ArCHOH, which can be readily oxidised to ArC=O; for example, the tetrahydronaphthalene derivative (XLVII) has an anaesthetic effect comparable to that of xylocaine and novocaine [283,284].

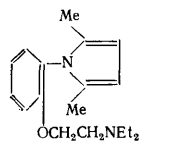
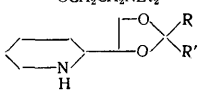
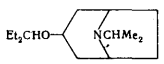
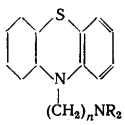
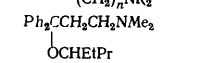
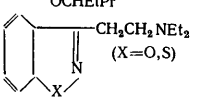
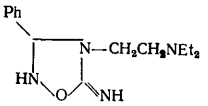
It is interesting that among the four stereoisomers (XLVII), which have been called "butydrine", the $\alpha S\beta S$-isomer shows the highest anaesthetic activity, while the $\alpha R\beta R$- and $\alpha R\beta S$-isomers exhibit a β-blocking activity [284]:



(XLVII) (XLVIII)

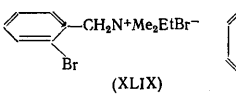
Certain other aminoalcohols of this type are also active as anaesthetics[207,285-288]; on the other hand, active preparations with a hydroxyl remote from the aromatic rings are fairly common[288-295], in particular propranolol (XLVIII) the activity of which is close to that of xylocaine[294,295].

Table 2. Physiological activity of certain oxygen-containing amines.

Compound	Anaesthetic activity	Other types of activity	Refs.
	3 times and 20 times higher than the activities of cocaine and novocaine respectively	Antagonist of pilocarpine, morphine, and $BaCl_2$; 30 times more effective than papaverine	257
	50-80 times higher than the activity of novocaine	Spasmolytic	265
	100 time higher than the activity of cocaine	Antihistamine and atropinemimetic	266
	2-10 times higher than the activity of cocaine	Spasmolytic, sedative, antihistamine, analgesic, etc.	268-270
	Lower by a factor of 1.5 than the activity of dicaine	Cough suppressant midriatic	271
	Exceeds the activity of xylocaine	Spasmolytic, antihistamine	272
	3 times and 5 times higher than the activities of cocaine and novocaine respectively	Vasodilator, analgesic	273,274

The activity of certain phenolic compounds[296,297] and also of aminoalcohols of the diphenylmethanol series[298], which are altogether incapable of being converted into carbonyl compounds, have likewise been mentioned. Therefore the role of the OH group as well as that of the C–O–C bond in the anaesthetic activity of amines remains obscure, particularly since amines without other functional groups have shown such activity in fairly numerous instances.

Thus 2-naphthylalkylamines, which exhibit pronounced surface-anaesthetic properties, for example $Ar(CH_2)_nN(CH_3)C_5H_{11}$ (Ar = β-naphthyl), are more active than novocaine by a factor of 16.[299] The relations discovered between the physiological properties of these compounds and their structures are approximately the same in surface and conduction anaesthesia and are close to those observed in other series of compounds. β-(4-Methyl piperidinoethyl)naphthalene is 13 times as active as cocaine (in 0.5% solution)[300]. Anaesthetic properties have been found also in cyclohexylphenylamines[301], in bretilium (ornid) (XLIX)[302], although this compound does not in fact contain a quaternary nitrogen atom, in the diamine (L) which is 20 times as active as xylocaine and 4 times as active as dicain[303], in α-amino-4-dimethylaminodiphenylmethane, which gives rise to prolonged and intense anaesthesia[304], in many aromatic[305-310] and heterocyclic amines[311-322], and also in certain saturated amines[323,324]. However, all these compounds are as a rule non-specific and exhibit several types of physiological activity.



(XLIX) (L)

4. Compounds without Nitrogen Atoms

The anaesthetic activity of alcohols, particularly that of benzyl alcohol, has been known for a long time. The activities of more complex alcohols[325] and their derivatives, in particular of polyethers of the type $C_nH_{2n+1}(OCH_2CH_2)_mOH$ (Zipf and Dittmann[326]), and many others[327] have been mentioned in a number of studies. It was found that the anaesthetic activity of these compounds increases in parallel with chain length and with enhancement of their lipophilic properties and increase of the partition coefficient. It was discovered that the anaesthetic activity of the ether $(C_6H_{13}OCH_2OCH_2CH_2)_2O$ ("efiran") is close to that of cocaine, but the compound is less toxic and does not have an irritant action[328]. The alkyl esters of *p*-hydroxybenzoic[329] and gallic[330] acids were found to be active, the anaesthetic effect increasing with the size of the alkyl group; for example, the activity of dodecyl *p*-hydroxybenzoate is 6 times as great as that of novocaine[329]. However, the available data are too fragmentary to reach any conclusions concerning the mechanism of the action of compounds of this type.

IV. SOME HYPOTHESES ABOUT THE MECHANISM OF THE ACTION OF ANAESTHETICS

Until recently ideas about the mechanism of the action of anaesthetics were extremely speculative and indefinite and were based exclusively on empirical relations between structure and activity and therefore could hardly be regarded as of general validity. Direct electrophysiological investigation of the action of anaesthetics as substances acting on the generation and transmission of nerve excitation became possible only as a result of advances in the study of the generation and transmission of the nerve pulse in the last decades. Furthermore, detailed physicochemical and biochemical studies on anaesthetics were made in recent years.

As shown above, substances with a wide variety of structures and consequently differing in reactivity exhibit anaesthetic properties. All these findings suggested that the physicochemical processes determined by the physicochemical properties of the anaesthetics play an important role in the mechanism of anaesthetic action. For blocking action to take place, the anaesthetic must initially penetrate to the reaction site and must then interact with the receptor. At least three factors are therefore important for anaesthetic activity: (1) the capacity of anaesthetics to pass through various biological membranes (not linked directly to the nerve tissue) to the nerve fibres and to be adsorbed on their surface; (2) the capacity of anaesthetics to penetrate the membrane of the nerve fibre and their behaviour in the excited membrane; (3) the interaction

of anaesthetics with specific (in the chemical sense) receptor structures. The mechanism of the action of anaesthetics can be usefully considered on these lines.

Almost all anaesthetics are organic bases and therefore their capacity for ionisation is important for their activity. It was believed for a long time that the unionised base is in fact responsible for the anaesthetic effect. This conclusion was readily confirmed by well known data according to which the minimal effective blocking concentration of anaesthetics decreases with increase of the pH of the medium [331-334]. However, it was shown comparatively recently that there is no direct relation between basicity and anaesthetic activity [8,335] and, since with the majority of active preparations in the region of physiological pH values the concentration of the cation is more constant than that of the base, it was concluded that the cation is the active form of the anaesthetic [335-340]. On the other hand, it is evident that anaesthetics penetrate the myelin sheath of the nerve fibre [336-338] or the axon membrane [341] in the uncharged form. In a study of the effect of two lidocaine derivatives (pK_a = 6.3 and 9.8) on the membrane of the squid axon at different pH it was shown that the anaesthetics penetrate the membrane in the uncharged form but block the action potential only in the form of the cation [341]. The majority of anaesthetics employed in practice have pK_a = 7.0 to 9.0. [8,335,340] This limitation also suggests that both forms of the anaesthetic are important for its action: the unionised base is responsible for the migration of the anaesthetic to the reaction site and its cationic form is responsible for the direct interaction between the anaesthetic and the receptor [337,339,341-343].

For the anaesthetic substance to be able to reach the site of its activity (the axon membrane) it must have a definite solubility in water and lipids. The earlier attempt to relate the anaesthetic activity of substances to their partition coefficients between aqueous and lipid phases were unsuccessful [10,11]. However, recently it was possible to observe such a relation [8,344]. On the other hand, it has been discovered that the anaesthetic and surface-active properties of anaesthetics vary in parallel [345-347]. The surface and interfacial activities of compounds, their capacity to penetrate liquid monolayers and at the same time their anaesthetic activity increase when the pH of the medium is raised from 3.5 to 7.35. [335,348] It has been shown that anaesthetics are not only adsorbed by phospholipid layers but are also capable of interacting with certain phospholipids in cell membranes via ion–ion and ion–dipole mechanisms forming a 1 : 2 complex like Ca^{2+} ions [349]. They are probably bound to the phosphate groups of the lipids which interact with Ca^{2+} ions [349,350].

Thus, by virtue of their lipophilic properties and surface activity, anaesthetics penetrate the neural membrane and alter its physicochemical properties: hydrophobic properties [351], electrical resistance [352] and pH, while at high concentrations they coagulate aqueous phospholipid dispersions. The change in physicochemical properties alters the functions of the membrane, which is reflected in physiological processes. The parallel variation of the physicochemical properties (lipophilic properties, partition coefficient in the nerve, capacity for adsorption in the nerve, surface and interfacial activities, and capacity for adsorption) and of anaesthetic activity mentioned above is related to these factors, which has made it possible to explain certain empirical relations between the structure of the compounds and their pharmacological activity and even to predict the activity of many new preparations [8,335].

Clearly no serious investigation is now conceivable without taking into account the influence of the physicochemical factors discussed above. The action of anaesthetics is nowadays treated mainly on the basis of the generally accepted theory of the generation and propagation of electric potentials in neuromuscular tissue [353,354].

Experimental studies have shown that anaesthetics interfere with the transmission of the nerve pulse, mainly by their capacity to inhibit the increase of permeability to sodium in the region of the Ranvier node in the axon membrane [355-364].

There are divergent opinions in the literature concerning the specific action of anaesthetics on the sodium system of the membrane. The majority of investigators believe that anaesthetics reduce the "maximum permeability to sodium", i.e. block the sodium channels in the membrane [355,357,360,365-369]. On the other hand, there are data [370,371] showing that anaesthetics can activate the systems governing the permeability of the membrane to sodium. This is supported by the known ability of anaesthetics to "interfere" with the motion not only of Na^+ but also of other ions: potassium [359,360,372,373], calcium [360-362,371,374-378], lithium [363,379], nickel, cobalt, cadmium [380], and magnesium [381]. In this respect the study of the effect of Ca^{2+} ions, to which much importance is attached in the mechanism of the change in the ionic permeability of the membrane on excitation [354,381-383], is of particular interest.

The most common view held at present is that Ca^{2+} ions and anaesthetics act at the same sites in the membrane and therefore compete for the sodium "pores" or "transferring agents" in the conducting system of the membranes [351,361,270,383-386]. Such sites are probably the phosphate groups of lipids [349] acting as agents transferring Na^+ and K^+ ions across the membrane.

The charged molecules of anaesthetics can strongly inhibit this process by combining with the anionic centres of phospholipids [349,375]. However, the hypothesis of a direct competitive interaction of anaesthetics and Ca^{2+} is not free from contradictions [349,371,385].

There are numerous data indicating the capacity of anaesthetics to react not only with phospholipids, the role of which in the mechanism of the action of anaesthetics has been proved, but also with other natural substances—thiamine [387], RNA [388], adenine, and ATP. [389] It has been shown that anaesthetics are antagonistic to various amino-acids and alkaloids [390,391], nucleotides [389,392,393], and proteins [386,394,395], which has led to the hypothesis that such interactions are in fact responsible for anaesthetic activity [6,396]. One of the most thoroughly developed hypotheses of this kind is that of the competitive antagonism of anaesthetics and acetylcholine in their interaction with a specific receptor [397-400]. Such antagonism has indeed been demonstrated in a number of experiments [401-403]. However, despite a number of attempts, the result of numerous investigations on different lines contradict the acetylcholine theory of the generation and transmission of the nerve pulse in the peripheral nerve [396,404,405].

Theories which explain the action of anaesthetics by their influence on cell metabolism should also probably be treated with much caution. This explanation is unlikely primarily because even the fastest of the enzymatic processes involving the decomposition or synthesis of lipids known at present take place at a rate the order of magnitude of which is much lower than that of the blocking of ion transport, which constitutes the basis of the generation and transmission of the nerve pulse. Next it was shown that neural conduction and its blocking by

anaesthetics can be achieved equally in the presence of natural axoplasm and after its replacement by an artificial salt solution[406]. Hence one may conclude that a specific effect of anaesthetics develops in the membrane and does not depend significantly on intracellular oxidation-reduction processes. Therefore, despite the numerous data showing the influence of anaesthetics on cell respiration[407-409] and its coupling with phosphorylation[410], there are no grounds for the belief that these processes are responsible for specific anaesthetic action, since many anaesthetics are central nervous system depressants and their effect on the oxidation-reduction processes in the nerve tissue can be in no way fully related to the observations made on the axon membrane. So far it is difficult to assess the role of enzymes in the effect of anaesthetics on the Na^+ and K^+ transport systems, since hitherto it has not been established exactly what types of enzymes may be included in the operation of the sodium-potassium pump in the membrane[411]. Moreover, so far there have been no quantitative estimations of the reactivity of anaesthetics in their interaction with the structures of the excited membrane (receptor), of the kind that have been made, for example, for cholinesterases, MAO [monoaminooxidase] inhibitors, cycloserine derivatives, and other substances. It appears that due consideration has yet to be given to this important problem.

Summarising the above findings, the action of anaesthetics can be represented as follows. By virtue of their surface-active and lipophilic properties, anaesthetics pass through various media to the axon, are adsorbed on the cell surface in concentrations sufficient for their activity, and penetrate the excited axon membrane in the region of the Ranvier node, altering at the same time the orientation of the molecules in the membrane. The permeability to anaesthetics is greatly influenced by the degree of their ionisation and their capacity to exist in the region of physiological pH as an equilibrium mixture of two forms—the cation and unionised base—is important for their anaesthetic action, since their activity depends on both these species. In the axon membrane anaesthetics are held by virtue of the interaction of the cation with the polar group of phospholipids and phosphoproteins and as a result of the hydrophobic interaction of the unionised base. In the course of binding to the axon membrane, anaesthetics most probably enter into a competitive interaction with Ca^{2+} ions, which play an important role in the mechanism of ion transport. The displacement of Ca^{2+} from the structure of the membrane is one of the main causes of the marked inactivation of the sodium transport system with a simultaneous retention or even some increase of the rest potential. As a result of these effects, in the presence of anaesthetics and the normal transmembrane potential difference and the normal content of bivalent ions in the medium are no longer sufficient to maintain the membrane in a state of readiness for response to stimulation. Therefore, in order to restore this capacity, it is necessary to either increase considerably the above potential difference by a hyperpolarising current or to increase the concentration of Ca^{2+} (or Ni^{2+}) in solution. Only at very high concentrations of the anaesthetic are the hyperpolarising current and Ca^{2+} or Ni^{2+} ions no longer capable of restoring fully the damaged structure of the membrane. Thus anaesthetics inactivate the mechanism of the change in permeability to sodium on depolarisation. In consequence of all the phenomena enumerated above, electrical activity ceases without depolarisation. This probably constitutes the essential feature of the action of anaesthetics.

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