SOME RELATIONSHIPS BETWEEN CHEMICAL STRUCTURE AND PHARMACOLOGICAL ACTIVITIES

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Earlier reviews in this series dealt with some relationships of chemical structure with biological activities (1–3); the present assignment is restricted essentially to pharmacologically active compounds. As with the earlier reviews, the published literature is not covered exhaustively, but some new reports and observations are included which appeared from about September, 1964 [termination of coverage of last review (1)] to May, 1967. Where useful for purposes of relationship, selected older literature is cited.

Over the years attempts have been made to devise general hypotheses pertaining to structure-activity relationships (SAR) and drug mechanisms of action. Recent efforts include variations of receptor occupancy hypotheses (Ariens, Stephenson), rate or kinetic hypotheses (Paton), and more chemically descriptive concepts (Belleau and others). In reviewing publications of the past two years that could be considered pertinent to SAR, one is impressed by the gulf that exists between most synthesizers of new molecules and the developers of general hypotheses. For example, from 310 complete articles published in J. Med. Chem. (1965–66), only six made reference to these hypotheses either as stimuli for the project or as vehicles for correlating SAR. This might indicate that the hypotheses are sterile or inadequate for either predictive or correlative purposes or that there is little interest or inclination among most investigators in relating specific observations to general hypotheses. Most of these hypotheses have indeed offered little that is of substantive value from a chemical perspective of devising novel molecules of biological interest. However, the efforts are commendable and some of these hypotheses may evolve and develop into theories with useful correlative and predictive values. As hypotheses become more chemically descriptive, one can anticipate that there will be a greater consideration of such hypotheses by the designers of new, biologically interesting molecules.

Their more recent concepts have been summarized by Ariens (4) and Paton (5). Shortcomings of the Ariens and Stephenson receptor occupancy and the Paton rate hypotheses have been analyzed by Belleau (6) as background for discussion of his "conformational perturbation" hypothesis. Bloom & Goldman (7) further consider these and modify and extend some of Belleau's views in proposing a "dynamic receptor hypothesis" relevant to catecholamine-adenine mononucleotide interactions in adrenergic mechanisms. These reviews are recommended to the cautious reader; space does

not permit extensive discussion here. For biochemical perspective, one should also refer to observations by Koshland (8).

A potential source of unnecessary controversy could be the matter of identities or differences among "receptors," a term not applied with conceptual uniformity. In a functional sense, a receptor is a site with which a substance may interact to induce an observable biochemical, physiological, or pharmacological response. The chemist thinks of receptors in terms of chemical structural components, the biologist perhaps more in microanatomical terms. Since the measure of activities usually begins with biological test systems, it is logical that receptor distinctions are initiated from differences in biological responses and sites of action of reference test compounds. The pharmacologist speaks of "muscarinic" (or "cholinomimetic") and "nicotinic" sites, and although there are certain structural differences among related compounds preferentially active at each site, we have no compelling evidence that the interacting receptor biochemical functional groups are different. We have not adequately distinguished between the effect of a structural change on the relative ability of a molecule to reach the biochemical site as against the ability of the molecule to interact once there. The same could be said of so-called α- and β-adrenergic receptors. The further suggestion that there may be two kinds of β-receptors (9) is entirely based on quantitative pharmacological differences which may relate to gross differences in receptor accessibility as well as to differences in receptor chemical structure. If we attempt to describe a receptor in essentially chemical terms, how shall we draw its bounds? Can a biochemical receptor site be considered as that within range of bonding interaction of a test molecule? What of a site containing several chemical functional groups (such as a cholinesterase)? Is each considered a separate receptor or is the collection of groups a receptor? What of allosteric sites? We may not have enough information to strictly define a receptor, but some effort should be made to restrict its meaning.

Pharmacological and Biochemical Characteristics

Agents simulating or interfering with acetylcholine (ACh).—Interest in cholinergic systems and mechanisms continues at a high level. A symposium in May, 1966, on Cholinergic Mechanisms (10) reflected the diversity of current interest in the subject. Specific facets have served as subjects for numerous reports. Adding to the interest in cholinergic mechanisms is the possible joint involvement of ACh with norepinephrine in sympathetic synaptic events (11–13). Certain cholinergic fibers may be adrenergic in effect by having ACh discharge catecholamines from their stores. Both epinephrine and norepinephrine are reported released from the adrenal medulla following exposure to ACh with certain other agents providing more selective release (14). Neurotransmitter functions for ACh are generally accepted, although the supportive evidence ranges from relatively strong for neuromuscular and autonomic transmission to circumstantial or presumptive for components of the central nervous system. The possible existence and involvement of re-

lated ACh-like agents in the central nervous system continues to attract attention (15). Acetyl-1-carnityl CoA (16, 17) has been investigated as a source of ACh-like activity in brain homogenates. This CoA derivative appears to interact with choline to yield acetyl-1-carnitylcholine rather than ACh as an active agent (18).

Compounds influencing ACh actions may act at pre- or post-synaptic loci or both. For many years, interest was concentrated and events were interpreted in terms of postsynaptic or postjunctional receptor interactions of cholinergic and anticholinergic compounds. During the past decade, presynaptic processes have attracted increasing attention but are still poorly understood. Reports on the action of hemicholiniums (in particular HC-3) in interfering with ACh synthesis (among other effects) led to observations of additional compounds with such properties, including norphenylhemicholinium-3 (19), triethylcholine (20), tetraethylammonium, troxonium (triethyl-2-hydroxyethylammonium) (21, 22), and basic esters of trimethoxybenzoic acid (23). Their mechanism of interference with synthesis remains to be defined, although it has been suggested that these compounds may act by interfering with choline transport to the prejunctional synthesis site or by blocking ACh storage or binding sites. In general, the more potent hemicholinium-related quaternary ammonium salts bear polar, hydrophilic substituents. Long et al. (24) compared five separate pharmacological characteristics of a variety of HC-3 analogues with structural variations in the cationic head. The range of activities led to the suggestion that the various receptors involved may be structurally similar and activities are a reflection of what occurs after drug-receptor combination. A number of compounds have been reported to display still other presynaptic actions. Tetraethylammonium, for example, enhances ACh release from terminals of stimulated cholinergic nerves (25). Carbachol induces release of significant quantities of ACh from nerve endings (26). That exogenously administered cholinergic agents might contribute to postjunctional depolarization indirectly by displacing ACh from prejunctional storage sites may be a more common phenomenon than is generally accepted (27). ACh, itself, may induce antidromic discharges at a presynaptic locus of motor nerve terminals (28) and at sympathetic ganglia (29). Evidence has been offered by a number of investigators that blockers of neuromuscular and ganglionic transmission have distinct presynaptic actions. Hexamethonium has been reported to have a presynaptic action (29) along with nicotine, pempidine, and other drugs (30). Riker, Standaert, and colleagues in a series of papers (31, 32) have attributed prejunctional actions to *d*-tubocurarine, succinylcholine, and other agents active at the neuromuscular junction. In an early paper (31), the end-plate depolarizer, phenyltrimethylammonium, was shown to be relatively inactive, compared to its 3-hydroxy derivative, in serving as an antagonist to curare at the nerve terminal, suggesting prejunctional specificities. On the guinea pig ileum preparation, even uncharged alkanolacetate esters induce contractions attributed to release of ACh from nerve endings, the acetates also acting as inhibitors by

combining with receptors on the muscle (33). Although the compounds reported to have such prejunctional activities have chemical structural features associated with alleged postjunctional interaction propensities, there is yet too little information to permit meaningful conjecture as to relationships of chemical structures with prejunctional actions. The experimental evidence for a number of these conclusions implicating prejunctional interactions seems as yet rather tenuous. An article by Hubbard on the origin and significance of antidromic activity may be of interest (34).

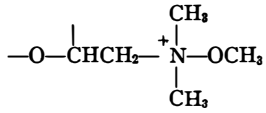
Postjunctional actions may involve ACh-like effects or blocking actions at a predominantly muscarinic or nicotinic responsive site, but frequently such responses are multi-faceted and dose-related. Ganglia may be depolarized by either pure muscarinic, nicotinic, or combined types of drug action (35). Cholinergic and depolarizing properties are evident among many compounds containing a compact quaternary ammonium group, such as trimethylammonium, separated by an unhindered linking moiety, such as methylene, to an appendage structure of limited size which determines the scope of pharmacological effects (36). Volle (37) and Bebbington & Brimblecombe (38) have provided recent summary reviews of agents stimulating muscarinic and nicotinic receptors.

Examples continue to appear in the literature of influences of variations in structure of appendage R groups in $(CH_3)_3N^+$-CH_2-R on cholinergic specificities (39–41). Efforts to increase lipid solubility of ACh-like agents by incorporation of long chain (such as C_{12}) aliphatic appendage groups yield inhibitors rather than simulants of ACh (42). ACh analogues with highly lipophilic substituents have been of interest for their anticipated facility for penetration of highly lipid barriers, such as the myelin sheath. The penetration of lipid rich barriers by a molecule may be influenced by a number of structural and physical chemical factors, and some lipophilic features might provide sufficient affinity for the lipid barrier to retard rather than facilitate penetration. The generalization that lipophilicity increases lipid membrane penetration probably has been overextended.

Sulfur and selenium analogues of ACh and choline have been further studied by Mautner and colleagues (43–45). In the eserinized electrɪplax preparation, depolarizing activity is progressively reduced as the ester-linking oxygen of ACh is replaced by sulfur and selenium. Although choline is relatively inactive, thiocholine and acetylthiocholine are of comparable activity. The corresponding sulfur and selenium analogues of cholinemethylether were more active than the oxyether. Axonal and junctional blocking properties have certain similarities in SAR among some O, S and Se analogues of dimethylaminoethylbenzoate (46). Although steric and dimensional characteristics for the O, S and Se analogues are not greatly different, the authors recognize that electron distribution characteristics would differ. The lower activity of choline may also result from a greater solvation of it than of the S and Se analogues, thereby reducing its ability to leave the aqueous phase for receptor interaction. That thiol ester analogues of ACh and its β-methyl

derivative have much weaker muscarinic but greater nicotinic activities was reported years ago by Hunt & Renshaw (47).

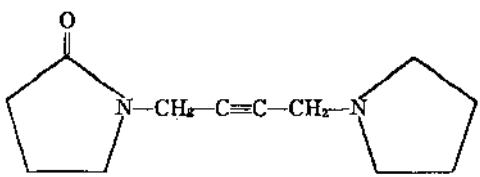
An interesting variation of the trimethylammonium moiety among ACh, methacholine, carbachol, and related compounds was reported by Darko et al. (48). One of the N-methyl groups was replaced by methoxy. The authors recognize that since replacement of one N-methyl by an ethyl in ACh



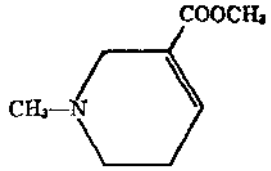
reduces muscarinic activity (49), steric considerations would lead one to expect similar trends here, and indeed this is the case. There is less difference in activity between ACh and its N-methoxy analogue than between members of the methacholine and carbachol pairs; however, without blocking cholinesterase in the test preparations, differential susceptibilities to this enzyme could have a quantitative influence on observed potency.

Although a large variety of trimethylammonium derivatives have ACh-like properties, other types of compounds with sterically unhindered cationic centers, including some amines, also are very active. Among quaternary ammonium derivatives, this includes ganglionic stimulants such as dimethylphenylpiperazinium (50), 4-methyl-5-β-chlorethylthiazole-N-methiodide (51), and N-benzyl-N-methyl-3-acetoxypyrrolidinium (52). Amines with some ACh-like properties such as nicotine, pilocarpine, arecoline, and oxotremorine presumably exert their pharmacological effects in the protonated onium form. This appears to be supported by recent observations of Hanin, Jenden & Cho (53) that the muscarinic activity of arecoline, pilocarpine, and oxotremorine decreases with increase in pH within the range of about six to eight, whereas the methiodides of oxotremorine and arecoline show a constant activity in this range. The quaternaries among this group appear to be less active than the corresponding amines. This also is reported by Gloge et al. (54) for arecaidine esters. Among these esters, arecaidine ethyl ester and arecoline (arecaidine methyl ester) were the most active agonists on the guinea pig ileum preparation; reduction of the ring double bond in the tertiary arecaidine esters reduced activity. Although the tertiary amine analogue of ACh, dimethylaminoethyl acetate, and even uncharged carbon analogues, such as 3,3-dimethylbutyl acetate (55) are reported to have ACh-like properties, the lower orders of magnitude of these activities makes structure-activity relationships of dubious significance. Citation (33) was made earlier of acetates of amyl, butyl, and propyl alcohols which displaced ACh from nerve endings to indirectly induce a muscarinic response prior to blockade. Among highly active nonquaternary amines, ionization, steric freedom of approach of the cationic center to receptors, lipophilic-hydrophilic balance and resultant influence on distribution would be dominant factors in influencing activity both qualitatively and quantitatively. Oxotremorine has served as

an interesting tertiary amine muscarinic agent for investigation of SAR.



OXOTREMORINE



ARECOLINE

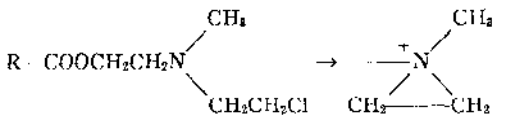
Bebbington & Brimblecombe (38) conclude that among oxotremorine analogues activity is favored by relatively small N-alkyl moieties, such as pyrrolidine and lower dialkylamines, the acetylenic linkage and the five atom ring lactam. The active nonquaternary agents, such as arecoline and oxotremorine, demonstrate central actions (56) as a result of their facility for penetration of the blood-brain barrier.

Specificity among blocking agents often is a quantitative function of dose rather than a purely qualitative characteristic. The pharmacological end result of a block alone does not pin-point the biochemical mechanism involved. Compounds of as diverse structure as hexamethonium, TEA, nicotine, tubocurarine, and bretylium (57) can block ganglionic transmission. Agents as varied as tubocurarine, TEA, decamethonium, guanethidine, and pempidine, which block ACh at the neuromuscular junction or at sympathetic ganglia, also appear capable of blocking release of norepinephrine from sympathetic post-ganglionic fibers (58).

Structural modifications continue to be made of prototype sympathetic ganglionic blockers. A number of bis-nitrobenzyldimethylammonium analogues of hexamethonium showed ganglionic blocking properties which varied inversely with neuromuscular blocking activities (59). Choline disulfides and diselenides were slightly more active than hexamethonium as antidepolarizing agents on the electroplax preparation (45). Some additional sterically hindered methylpiperidines have been evaluated as ganglionic blocking agents (60). Their quaternary ammonium derivatives were more potent but of shorter duration than the secondary and tertiary amines.

As a structural type, unsymmetric α, ω-bis-quaternary ammonium substituted alkanes were shown in the 1950's to include highly potent ACh blocking agents (36). Optimum ganglionic blocking activity of long duration was shown to be associated with a C_2 or C_3 alkane link separating a small from a large lipophilic substituted cationic head. Takeda et al. (61) recently described a series of such compounds in which the large head is a dibenzobicyclo (2.2.2) octadienopyrrolidinium group. Kido et al. (62) found that the compounds generally were ganglionic blockers, but at larger doses also showed muscle relaxant and anti-strychnine effects, the former attributed to muscle spindle depression. A comparison of one of these with other blockers such as chlorisondamine, hexamethonium, TEA, etc., showed these others not to demonstrate spindle blocking properties (63, 64).

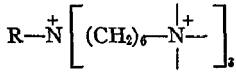
Parasympatholytic and antispasmodic characteristics have been investigated among a variety of classes of compounds. Musculotropic spasmolytic activities have been observed among dialkylaminoethyl ethers of phenolic propiophenones (65) and several diethylaminoethyl xanthene-and thioxanthene-9-malonates (66). Among alkyl mono-quaternary salts of 2-(β-dialkylaminoethyl) pyridine (67), changing methyl to ethyl resulted in reduced nicotinic effects and increased ganglionic blocking activity, particularly on parasympathetic ganglia. Among their bis-quaternaries (68), ethyl or cycloalkyl derivatives usually possessed greater sympathetic ganglionic blocking properties than did the methyl analogues. Active antispasmodics have been derived by di-esterification of N,N¹-di-(2-hydroxyethyl)-piperazine with 1-naphthylacetic acid; less active derivatives were obtained from 2-naphthylacetic or phenylacetic acids (69). Gill & Rang (70) investigated a benzilylcholine analogue in which a chlorethyl substituent on a tertiary nitrogen atom can cyclize to yield the ethylenimonium derivative.



The compound selectively inhibits parasympathetic effects of exogenous ACh but does not block ganglionic or neuromuscular transmission. The compound is of longer duration than benzilylcholine and rate constants show reaction with ACh receptors to be similar in association rate but much slower in dissociation of the chloralkyl analogue. The immonium on species seems to be the active form (as with dibenamine-like drugs) and presumably bonds by alkylation of a receptor group. Quaternary ammonium derivatives without small alkyl substituents, such as benzyl-tri-*n*-amylammonium (71), have been claimed to inhibit gastric secretion in rats without any evidence of effects on the autonomic nervous system or spasmolytic actions.

The neuromuscular junction continues to be utilized frequently as an ACh functional site in the pursuit of SAR. Among polymethylene α,ω-bis-(hydroxyethyl, dimethylammonium) homologues with a 3 to 10 methylene chain range, the decamethylene derivative, as expected, was the most potent member, although much weaker than decamethonium (72). An initial depolarizing block in experiments on cats was followed by a hemicholinium-like effect in inhibiting ACh synthesis. The tropeine moiety has been a favored cationic structure for introduction in ACh blocking agents (73). Szendey (74) compared properties of bis-quaternary tropeines of the polymethylene, phenylene-dimethylene, and biphenylene-dimethylene series. The tropine substituted analogue of decamethonium is relatively inactive, but esterification of the 3-OH group yields active compounds. The non-esterified moiety would be more hydrophilic and one could expect lower activity. The flexibility of the interquaternary chain influences selectivity of

action. For example, autonomic blocking tendencies are reduced among the rigid structures compared with the polymethylene chain derivatives. The continued use of and interest in succinylcholine appears to stimulate interest in other ester-linked analogues. Oxydiacetic-, thiodiacetic- and dithiodiacetic- dicholine esters are 10- to 20-fold less active than succinylcholine, but in doses 100- to 200-fold smaller than those blocking the neuromuscular junction, a ganglionic stimulation is evoked (75). Symmetric bis-quaternary substituted esters of isomeric truxillic acids showed differences in onset and duration of action as well as potency among α,γ and ϵ isomers (76). Maximal activity has been associated with α-derivatives, amide linked, with 3-carbon chains between onium and nucleus (77). Edwards, Lewis, & Marren (78) reported on a further series of polyonium blockers. These curare-like agents show considerable differences in species sensitivities. The most active compound among the present group of tetra-onium derivatives was the completely ethyl-substituted analogue,



McCarty & Chenoweth (79) reported that activity comparable with tubocurarine was evidenced among polybutylene glycols bearing terminal diethylenetriamine substituents. Both amine and quaternary ammonium forms of these polymers were active. The presence of multiple amine groups in a flexible polymer may provide a sufficient concentration of protonated units to permit firm electrostatic bonding with receptors comparable to that of quaternaries. Two studies of omega-aminoacylcholines have been reported. Although these are di-cationic, only one group is quaternary and completely ionized. With 5-,6- and 7-amino *n*-alkanoylcholines, Ono & Hashimoto (80) reported activities of one-fifth to one-tenth that of succinylcholine in dogs and cats. Foldes & Foldes (81) investigated the series in the aminobutyryl through aminooctanoyl range as well as some methylamino and dimethylamino analogues for their plasma cholinesterase catalyzed hydrolysis rates and inhibitory activities, and a few for neuromuscular effects. The potency and duration of blocking action in man of some of these varied inversely with their rate of enzymatic hydrolysis. Among other chemical categories of neuromuscular blockers may be included ortho-, pyro-, and hypo-phosphoramide esters (82). Some parallelism was evident between neuromuscular and anticholinesterase potencies of the pyro- and hypo-phosphoramides.

A compound with both fascinating pharmacodynamics and opportunities for SAR studies is tetrodotoxin (83). The agent blocks nerve transmission by selective interference with the early transient conductance increase for sodium ions. A guanidino and hemiacetal group seem to be key structural requirements; additional features are being explored (84).

Just as we do not know much about the actions of endogenous ACh and related agents in the CNS, we know proportionately little of CNS effects of

the peripherally acting anticholinergics. The quaternary ammonium compounds in general pass the blood-brain barrier poorly, and the lack of CNS effects among these, to a large extent, may result from inaccessibility. A comparison of ratios of ED_{50} values of a variety of tertiary amines and quaternaries administered intravenously and intraventricularly showed a much higher ratio for the quaternaries (85). A number of muscarinic agents (oxotremorine, pilocarpine, arecoline, carbachol) induce excitatory CNS effects when administered via routes assuring access to CNS regions (86). Among a series of acetylenic amines related to oxotremorine, central tremorogenic and peripheral muscarinic activities showed a parallelism (87). A wide variety of quaternary ammonium salts including neuromuscular and ganglionic blockers, and cholinesterase inhibitors produced seizures in dogs on intracisternal administration (88). Central activity of both muscarinic (56) and blocking drugs (89) has been approximately correlated with heptane/water partition coefficients showing favorable lipid solubility and distribution.

It may be appropriate here also to consider compounds influencing cholinesterases. A survey of cholinesterases and anticholinesterase agents is available as a background source (90). A considerable amount of research continues with these esterases, and with acetylcholinesterase inhibitors, in particular, and with inferences one may draw as to structures of receptors based on SAR. Less published work appears on SAR among compounds subject to hydrolytic actions of the esterases and to agents protecting against or reversing the action of inhibitors. With reference to structural influences on rates of hydrolysis, it was reported for the previously cited ω-amino alkanoylcholines (81) that these were hydrolyzed more slowly than the analogous unsubstituted alkanoylcholines by human plasma cholinesterase, and that alkyl substitution on the ω-amino-group further reduced hydrolysis rate. Uncharged esters (carbon isosteres) can serve as substrates for acetylcholinesterase (91, 92) with evidence of structural specificity. From a comparison of muscarinic activity with enzyme-catalyzed hydrolysis rates of a group of acyl and benzoylcholines and thiocholines, Wurzel (93) supported the view that the rate-determining step, and perhaps the first step, in the biological action of choline esters is their hydrolysis by a cholinesterase. A two-stage action, only one of which is dependent on hydrolytic susceptibility, was proposed to account for activity of hydrolysis-resistant but active agents, such as carbamylcholine. The hypothesis suffers from complexities resulting from efforts to explain apparent exceptions. Acetylcholine, acetylthiocholine and acetylselenocholine are reported to be hydrolyzed at similar rates but have markedly different depolarizing activities (45). Structural features permitting esterase hydrolysis seem less critical than those for cholinergic site binding (94). X-ray crystallography indicates that acetylselenocholine has a *trans* (94), whereas ACh has a gauche (95) conformation about the C-C bond of choline. However, the radius of the hydrated ion also may have an influence here (96). The resistance of a quinuclidinium analogue of ACh to esterase hydrolysis was attributed to a lack of rotational flexibility of the N-

substituents (97); however, steric features about the ester moiety directly are more likely factors.

Studies with series of cholinesterase inhibitors frequently include attempts at correlation of activity with physical chemical, as well as structural characteristics. Hansch & Deutsch (98) concluded that hydrophobic bonding characteristics most closely correlate with biological effects of some phosphate esters and carbamates. The phosphate esters react irreversibly but the carbamates are less clear. Kellett & Hite (99) prepared N-alkylquinuclidinium salts to provide a rigid structure devoid of conformational variations and compared enzyme inhibitory activity with approximate ionic volumes. Symmetric tetraalkyl-and *n*-alkyltrimethyl-ammonium derivatives served as reference compounds. They concluded that activity was favored by ion volumes in the 110 to 150 $Å^3$ range, and the presence of one or more N-propyl groups; and affinity enhanced among compact, symmetric ions. From this, inferences were drawn as to size of a receptor cavity at the enzyme anionic site. Extension of the studies with consideration of other simple alkyl quaternaries later led (100) to a more cautious view that optimum ionic volume may vary with the particular homologous series and that no single molecular function serves to predict affinity for the anionic site. From the activities of some bis-(N,N-diethylnipecotamide)-alkanes, Beasley & Williford (101) suggest that stereochemistry and lipophilic characteristics are more influential than electronic and ionic volume factors. In these last several reports, activities were mediocre and differences not dramatic. Neely (102) attempts to correlate inhibitory activity of several carbamates and organophosphates with molecular orbital calculations. At present these correlations are limited to compounds with aromatic groups (π electrons). A study of the kinetics of inhibition of erythrocyte cholinesterase by some carbamates is consistent with the view that these are poor substrates of cholinesterases (103). There was no evidence of formation of a reversible complex with the enzyme. The results of this study are interpreted as at variance with the view that carbamates are competitive reversible inhibitors (104). Belleau, Tani & Lie (105) investigated binding characteristics of the *n*-alkyltrimethyammonium series from C_1 to C_{12} alkyl range. The influence of increase of alkyl chain length on esterase binding characteristics was compared with the transition of stimulant to antagonistic properties of this series in cholinergic test systems. The stimulant activity of C_1 to C_7 and antagonistic properties of C_9 to C_{12} homologues were ascribed to induction of "ordering" and "disordering" effects, respectively, at the receptor levels. These terms are not explicit in a chemical structural sense. Parmar et al. (106) investigated a series of quinazolones in which an N-alkyl pyridinium group was attached through the ring 2- or 4-position. Anti-acetylcholinesterase activity among the 4- linked series was related to length of the N-alkyl group, but this had no relation to inhibition in the 2- series. The proximity of the quinazolone nucleus to the pyridinium onium center in the 2- series was assumed to interfere with charge availability for bonding. Reactivators of phosphorylated inhibited cholinesterase also

show considerable structural specificity. Among a group of phenyl-1-methylpyridinium ketoximes, the *anti*-2 derivative was more active than the *syn*, the *anti*-4 less active than the *syn*, and the bis-4-quaternary derivatives much more active with both configurations (107). The ability of certain quaternary ammonium salts to protect acetylcholinesterase against prostigmine was found to be greater among bis- than mono-quaternaries (108). The inhibition of acetylcholinesterase by curare-like agents could be reversed by a polyanionic polysaccharide (109).

More appears to be known about structural features of cholinesterase receptor sites than for other ACh binding systems, although still little is known for any of these. Characteristics of the anionic center of esterases have been pursued further by Zupancic with investigation of the equilibrium constant for interaction of tubocurarine with plasma cholinesterase (110), which resulted in support of the view that these esterase anionic groups might function as cholinergic receptors (111). From a study of dissociation constants of some benzoquinonium and ambenonium analogues and the ACh receptor (electroplax), compared with those obtained with acetylcholinesterase (*Electrophorus*), Webb supports the view that these receptor sites are different in chemical structure (112). Belleau & Tani (113) studied a series of N,N-dimethyl-2-chloro-2-phenethylamines which act via the aziridinium ion to irreversibly inhibit acetylcholinesterase. Stereospecificity of the enzyme for the *levo* isomer was observed. Ring substituents reduce activity presumably not by preventing aziridinium formation, but by interfering with fit of the molecule near the receptor anionic site. Krupka (114) discusses the active center of acetylcholinesterase in terms of ionization characteristics of three sites in relation to an anionic site presumed to be a carboxyl group. On the basis of acetylcholinesterase hydrolysis rates of isomeric 3-trimethylammonium-2-acetoxy-*trans*-decalins and isomeric α,β-dimethylacetylcholines, Smissman et al. (115) concluded that the receptor degradation site is best fit by a completely staggered conformation. Muscarinic activity was also favored by the staggered form. These conclusions may be correct, but the significance of the data is questionable because of the low ranges of activities of these compounds. Changeux (116) reports results of an interesting study in which curare-like inhibitors of acetylcholinesterase are antagonized by depolarizing blockers, both types having a high affinity for the enzyme. From kinetic evidence, it is proposed that the bulky curare-like agents bind one receptor active site and one peripheral anionic center.

In comparison with the cholinesterase systems, we know relatively little of inhibitory phenomena of ACh synthesizing systems. The hemicholinium type compounds were cited earlier. These do not have any significant direct inhibitory action on cholineacetylase (choline acetyltransferase). Recently, some C_8 and C_6 polymethylene α, ω-substituted, unsymmetric bis-quaternaries have been reported to be very potent inhibitors (117). These had been of interest initially as highly active, short-chain bis-quaternary neuromuscular blocking agents (118). The acetylase inhibitory properties are asso-

ciated with the presence of a relatively large, conjugated, co-planar system (naphthylvinyl-pyridine). Additional structural and physical chemical parameters are being elucidated. It is quite evident from available data that these acetylase inhibitors will have SAR features unrelated to those of compounds acting at other ACh interacting sites.

Among many of the articles cited under this general section, speculations were included as to structural features of ACh-binding receptors. From studies with neuromuscular blocking agents, preference is expressed for two-point or multiple-point bonding interaction of bis- or poly-quaternaries with postjunctional receptor anionic groups (74, 78). The flexibility of the inter-quaternary chain is emphasized as a factor in permitting advantageous receptor interaction (74). Khromov-Borisov and Michelson (119) review some structural and physical chemical aspects of blockers of skeletal muscle receptors. Canepa (120) further considers physical chemical factors possibly involved in postjunctional receptor interactions, including charge localization, coulombic, hydrophobic and hydrogen bonding. A limitation of some suggested multiple-point bonding dimensional relationships between chemical groups of receptor and blocker is that they are designed to explain properties of curare and C_{10} type compounds, but are not adequate for some of the newer short-chain prototype blockers (118). On evidence of complex formation between blockers and mucopolysaccharides in essentially ***in vitro*** conditions, Chagas et al. (121, 122) and Ehrenpreis (123) had initially proposed that mucopolysaccharides might serve as receptor structures. This is probably a non-specific ion-exchange complexing. Binding of curare to protein fractions also seems to occur as a non-specific phenomenon (124). A case has been argued for phosphate moieties as receptor anionic sites (125). Ehrenpreis has investigated interactions between a variety of isolated macromolecules and compounds acting at cholinergic receptors, and recently reviewed the subject (126).

A number of articles particularly stressed stereospecific effects among compounds acting at ACh binding sites. Friess et al. (127, 128) reported different directions of stereospecific influences among aryl-and cyclohexyl-acetate esters of tropine and pseudo-tropine on interaction with postsynaptic nerve-muscle and acetylcholinesterase receptors. No consistent influence of stereospecificity seems evident from responses of receptor interactions of (+) and (−) nicotine (129) or (+) and (−) acetyl-α-methylcholine (130). Results vary considerably among test systems. Differences of opinion continue to be expressed relative to similarities and differences between cholinesterase and other ACh receptor structures. Evidence supporting differences include: dissimilarity between depolarizing activities and susceptibility to esterase hydrolysis among esters (45); suggested need of a gauche conformation for cholinergic receptor binding (acetylselenocholine) but not for cholinesterase hydrolysis (131); differences in affinity (dissociation constants) of benzoquinonium and ambenonium derivatives for electroplax ACh receptor and for acetylcholinesterase (112). Belleau & Lacasse (132) discuss at length

stereospecificity and bonding interaction possibilities between ACh-like molecules and ACh receptors on the basis of relative influences of some quaternary dioxolane derivatives on anticholinesterase and muscarinic properties.

From a study of hydrolysis rates of pyridyl- and pyridinium-carbinol acetates, Augustinsson (133) supports the view that butyryl- and acetylcholinesterase differ primarily in that the former contains a second nonesteratic site which bonds dominantly by van der Waals forces. Zupancic (110, 111), on the basis of equilibrium constant measurements utilizing tubocurarine and ACh, emphasizes similarities between the anionic centers of cholinesterases and ACh receptors. It may well be that there are close similarities with a minimal common anionic receptor component and differences become greater as one moves farther from this center (114, 134). Watkins (135) draws analogies between the potential interaction of ACh, γ-aminobutyric acid and glutamic acid with membrane phospholipid-protein complexes to induce dissociation of these complexes with resultant changes in membrane permeability.

In making generalizations about ACh-interacting receptors based on studies with stimulants and blockers, one might summarize by observing that the more restricted the group of reference compounds studied, the more detailed and complex a picture one may provide without fear of conflict, but as one attempts to account for a wider range of reported observations, more limited and simple generalizations become necessary. ACh receptor(s) might safely be considered to comprise at least a readily accessible anionic group of unproven nature.

Agents simulating or interfering with catecholamines.—This area will be treated briefly since there has been a plethora of recent reviews on the subject. Particularly useful background collections of reviews are the Ciba Foundation Symposium on Adrenergic Mechanisms (136), the more recent Second Symposium on Catecholamines (137) and the New York Academy of Science Annal on New Adrenergic Blocking Drugs (138). Receptor concepts and interactions at the molecular level are discussed by Belleau in the latter two references and by Bloom & Goldman (7). Recent reviews also have dealt with: adrenergic neurone blocking agents (139), β-adrenergic blockers (140), inhibition of norepinephrine uptake by drugs (141), agents influencing DOPAmine-β-hydroxylase (142), catecholamine-like compounds acting at adrenergic receptors (143), and 2-halogenoethylamine adrenergic blockers (144). The related subject of dihydroxyphenylalanine analogues also has been thoroughly covered (145). Discussions of SAR among compounds of this section will be limited to material in some very recent reports.

Among sympathomimetics, it has been generalized that differences in action on α and β receptors are essentially quantitative in contrast to the relatively selective α or β action of adrenergic blocking agents. The influence of steric effects has continued to be of interest among sympathomimetics. In a series of papers, Patil et al. (146–149) attempted to correlate stereospecificity

of pharmacological effects among D and L isomers of several adrenergic drugs. Studies were directed to assess the Easson-Stedman hypothesis (150) that dextro isomers, L(+), act like desoxy derivatives of sympathomimetic amines. The hypothesis was supported for directly acting L(+) isomers (norepinephrine and epinephrine) and their desoxy analogues (DOPAmine and epinine) but not for indirectly acting analogues (147). It was further shown (148) that the Easson-Stedman hypothesis held for a range of substances in catecholamine depleted preparations but not in untreated ones. Optical isomers of several β-adrenergic blocking drugs were studied for inotropic and chronotropic effects on isolated rabbit atria, but there seemed to be no simple relationships between these effects, chemical structure or beta blocking activity (151). Almirante & Murmann (152) found marked stereospecificity between optical isomers of 1-(4-nitrophenyl)-2-isopropylaminoethanol; the D(−) isomer was a potent β-receptor blocker, the L(+) was inactive.

Finger & Feller (153) investigated certain SAR among phenethylamines interacting with the adrenergic-adipose tissue receptor system. Significant mobilization of free fatty acids from rat epididymal fat tissues was induced by ring mono-hydroxylated analogues of the catecholamines. It was concluded that the OH on the β carbon of the side chain influenced affinity for the receptor system and that large N-alkyl groups (aralkyl, and others) enhanced activity. Compounds acting indirectly (by release of endogenous catecholamines) are not active in this system. Although both α and β stimulants are mobilizers, the β stimulants are more active. In a study of false neurotransmitter properties of sympathomimetic amines, Fischer, et al. (154) suggested that a β-hydroxyl group appears to favor such properties.

A wide variety of drugs acting on the sympathetic and central nervous systems have been evaluated for their abilities to release or inhibit release of norepinephrine from mouse hearts (155). Such properties extend across a diversity of chemical classes of drugs.

Among anti-adrenergic agents, Clark & Hughes (156) investigated the effects of alkyl substituents larger than methyl on the onium nitrogen of xylocholine. Only xylocholine had appreciable adrenergic neurone blocking properties; the presence of larger onium alkyl groups was concluded to provide local anesthetic activity.

Relative adrenergic neurone blocking and adrenolytic activities were evaluated among several series of 2-substituted 1,4-benzodioxanes. Among guanidinoalkyl derivatives (157) maximum adrenergic neurone blocking activity was shown by 2-guanidino-methyl and -ethyl derivatives substituted with methyl in the 7 or 8 benzo positions; 7-position substitution abolishes adrenolytic properties of the parent compound. Fenton et al. (158) report adrenolytic and adrenergic blocking properties among 2-aralkylaminomethyl derivatives with maximum activity in ortho methoxy substituted benzoxyethylaminomethyl members.

Guanidine derivatives have been evaluated both as adrenergic neurone

blockers and as antagonists of blockade. Among a series of N-aralkylguanidines, ring-substituted N-(1-phenethyl) guanidines were most active blockers (159). (+)-N-(1-phenethyl) guanidine was much weaker than its (−) isomer but could antagonize the blocking action of the latter on nictitating membranes. Within this series, induction of ptosis correlated with relaxation of nictitating membranes, but not with heart norepinephrine depletion (160). All inhibited MAO but not in relation to other properties. The compounds showed various degrees of activity in antagonizing adrenergic neurone blocking drugs (161). This reversal was not evident for blockers of sympathetic ganglia or α-adrenergic receptors. Among a series of aminoethylguanidine derivatives Ozawa & Sato (162) found that [2-(hexahydro-1-azepinyl) ethyl] guanidine was the most potent blocker and equal to guanethidine.

Graham & Al Katib (163) describe an interesting reversal of haloalkylamine block of alpha receptors by action of trypsin. The order in which trypsin reversed *in vitro* block by dibenamine and two other compounds was the same as for spontaneous recovery *in vivo*. From this and earlier data, they concluded that the anionic site is carboxyl rather than phosphate and that the receptor is part of an amino acid side chain containing arginine, lysine or both. The trypsin de-blocking is attributed to recovery of α receptors by action at an ester linkage. Belleau (137, 164) has argued strongly for a phosphate anionic site. Bloom & Goldman (7) go further in suggesting that the cationic heads of norepinephrine and epinephrine activate α-receptors by catalyzing an ATPase type effect.

Structural characteristics of α- and β-receptor interactions have been summarized essentially as follows by Belleau (137): for active α-receptor complexing, a small cationic head is required in a catecholamine; a substituent bulkier than methyl, such as isopropyl, hinders ion-pair formation with an α-anionic group but favors β-receptor activation. The catechol system contributes significantly to β-receptor activation. Biel & Lum (140) elaborate on structural requirements for both stimulants and blockers of β-adrenergic systems. Lands et al. (9) have proposed that at least two types of β receptors exist, one associated with lipolysis and cardiac stimulation phenomena, the other with bronchodilator and vasodepressor actions. There is no clear evidence as to whether differences between α and β receptors are related to basic structural features, to flexible conformational variants or to relative accessibility of receptors.

A few brief comments might be directed in this section to monoamine oxidase (MAO) inhibitors. These may increase endogenous catecholamines and 5-hydroxytryptamine or enhance exogenous amines. There is a waning of interest in these probably related in part to lack of correlation between MAO enzyme inhibitory activities and pharmacological or clinical manifestations. Enzyme inhibitory properties frequently show structural specificities within a family of compounds. Correlations between structural features and MAO inhibitory activities may vary considerably with the particular test system

used in measuring activity. For example, *cis*-2-phenoxycyclopropylamines, which had been reported to be appreciably more active than the *trans* (165), were later indicated to show no consistent differences among other tests (166).

Miscellaneous drug categories.—In this section, subjects will be treated without organization by any systematic mechanistic precepts.

Meaningful SAR among compounds in the amorphous category of psychotherapeutic agents are difficult to identify as yet. It would be repetitious to reiterate here recent material already ably summarized by Biel, Cain & Childress in individual reviews in the new series, *Annual Reports in Medicinal Chemistry* (167). Several structural patterns of compounds have been investigated extensively, such as the phenothiazines and their extensions to other fused tricyclic systems, the benzodiazepines, the carbamates, etc. Comparisons of activities become difficult outside of narrow structural categories and even narrower biological parameters. Laboratory animal test models are presumptive at best and tend to proliferate as feed-backs from clinical observations. Simple, rapid screens, such as subjective observations of effects of compounds on rodents, permit testing of large numbers of samples. The responses usually are compared with those of known drugs and such tests may detect new compounds with similar properties rather than novel psychotherapeutic agents. Screening in dogs with abnormal behavior characteristics has shown structural specificities among some cyclopropylpyridine derivatives (168, 169), and activity also seems evident in man (170, 171). Unfortunately, such tests have very limited capacity for screening numbers of compounds. Considerable effort has been expended on seeking measurable biochemical bases for identifying possible drug actions. Here, too, correlations between clinical or pharmacological properties and biochemical effects such as MAO inhibition, depletion of catecholamines, or cholinergic system interactions, have been unimpressive. Chauchard & Mazoue (172) examined many of the common drugs in rats and found no similarity between neuroleptic and tranquillizing drugs, as groups, against the effects of ACh, epinephrine, and serotonin. Possibly with more precise identification of site of action, such correlations may improve. Relatively little attention has been given to correlation of physical-chemical properties with activities of psychotherapeutic agents. Green (173) found no extensive correlation between depressant activities of phenothiazines and related drugs with ionization constants or water solubilities, although there was a trend for association of activity with low pKa and low solubility.

In the field of analgesics several recent reviews are available, including those by Mellett & Woods (174), de Stevens (175), Archer & Harris (176), Beckett & Casey (177), and the more recent period of reviews by Harris (167). These deal with correlations of biological properties among various structural categories of drugs used to relieve pain. Most of the so-called strong analgesics can be either historically or retrospectively related structurally to morphine, depending in some instances on one's imagination and

willingness to accept predominance of a particular conformation. The narcotic antagonists bear structural similarities to the morphine analgesics. The stereospecific features of the strong analgesics have promoted a number of proposals as to structural characteristics of receptor moieties with which interaction may be favored. Detailed discussions are available in the cited reviews. Additional considerations are summarized by Portoghese (178), who suggests that induced fit and differing modes of analgesic-receptor association may contribute to overall lack of consistency in SAR. Portoghese (179) had attempted to assess molecular bonding modes among analgesic series in which identical variations were made in the N-substituents. Comparison of isomeric members of a substituted decahydroquinoline derivative, rigid other than for the conformation of a 4-phenyl substituent, showed no definite conformational requirement for this group (180). Recent reports of analgesic and anti-inflammatory properties have appeared for a variety of chemical categories of compounds. Among aniline and anilide derivatives prepared (181–193) were some analogues of methadone, among which stereospecificity requirements did not conform to those for methadone compounds (183). *p*-Butoxyphenylacetamide was reported to be more potent than phenacetin and aminopyrine, but less than morphine (184). Among the series of aryl substituted acetic acids (185), nitriles (186), and amides (187, 188), analgesic and anti-inflammatory activities usually were greater among naphthyl than phenyl derivatives. Analgesic, anti-inflammatory, or both activities were observed among new series of phenetidines (189), alkylpiperizine esters (190), N-antipyryloxamides (191), arylacethydroxamic acids (192), 2,3-bis-(*p*-methoxyphenyl) indoles (193), some aminoguanidine sympathetic blockers (194), and imidazoles (195), and pyridobenzimidazoles (196). Additional variations of pethidine have been studied which range from less than 0.1 to 28 times its potency (197). Some δ-aminoketones appeared to have greater analgesic activity than the parent β-amino-cyclobutanes from which they were derived (198). A new steroid analgesic was reported to permit surgery following doses of 3 to 5 mg per kg in animals (199). A group of 1,4-benzodiazepines showed no analgesic activity by a rat tail-flick test, but some of the compounds were antagonists of meperidine analgesia (200). Related types of compounds with primarily antipyretic activity include 4-glutarimido-pyrazolones (201), 3-pyridyl-4-phenyl-5-pyrazolones (202), and some miscellaneous pyrazoles (203). Among some diphenyldioxopyrazolidine derivatives, a parallelism was reported between their anti-inflammatory and fibrinolysis-inducing capacities (204).

In the past, amides and urea derivatives have been extensively investigated for sedative, hypnotic, and anticonvulsant properties. Some new series of such compounds have been described, but without unusual characteristics. Sedative properties have been observed among imidazole and thioimidazole derivatives (205). Thioureas and corresponding urea and thiosemicarbazide analogues displayed either or both convulsant and anticonvulsant effects among structural variants (206). In mice, benzhydrylpiperazine derivatives

were appreciably more active than their piperidine analogues in protecting against electroshock (207). A large number of pregnanes and other steroids showed some hypnotic properties in mice on intravenous administration (208). Synthetic amino steroids with anticonvulsant and interneuronal blocking properties have been described (209). The marketing of methaqualone has spurred continued investigation of 2,3-disubstituted quinazolones, not only as mild sedatives (210), but for moderate antitussive activity (211).

During the early part of this decade, research with antitussives appeared to be a popular activity, particularly in Europe. Interest has waned, in part related to difficulties in quantitating efficacy in man. Among recent reports are observations of antitussive properties among a variety of 1,4-disubstituted piperazines (212, 213), alkoxydiphenylacetates (214) and a thioxanthine with little CNS depressant effect (215).

Diuretic and saluretic properties continue to be observed among a variety of structural prototypes. Considerable structural specificity was evident among substituted s-triazoles (216). Diuretic activity was evident among 7-substituted aminopteridinecarboxamides, but not the 7-hydroxy-analogues (217). Anti-DOCA diuretic activity was reported for some pyrimidine derivatives, particularly with 2-primary amino, 4–azido, 6-phenyl substitution (218).

Compounds of increasing pharmacological interest are the prostaglandins. The subject has been reviewed elsewhere (219). Among the pharmacological and biochemical properties observed on appropriate administration are: hypotension, positive inotropic effects, CNS depression, smooth muscle contraction, antagonism of ADP-induced platelet adhesiveness, and block of catecholamine-sensitive lipase. The alcohol group at C-15 of prostoglandin E_1 seems to be a structural requirement for smooth muscle and blood pressure activity; oxidation to the ketone markedly reduces activity while saturation of the double bond has little effect (220). One may anticipate much new research among synthetic variants of these novel fatty acids.

A variety of sulfamylurea derivatives have been evaluated as hypoglycemic agents, among which some 4,4-disubstituted piperidine derivatives were comparable in potency to chlorpropamide (221). The series was admirably evaluated by the investigators with efforts made to correlate physical with biological properties. Among factors influencing activity were particle surface area which controlled rates of solution and, thus, oral absorption, and increase in acidity which increases resistance to metabolism and thus duration of action (222, 223). Since the compounds have a high lipid: water partition ratio, small changes in lipophilicity had no significant effect on activity. Hypoglycemic activity has been observed among a number of 4-(1-naphthyl)-butylamine derivatives (224, 225).

Structural specificity among hypotensive agents varies considerably in different chemical classes of compounds. Optimum and critical structural requirements in quaternary ammonium ganglionic blocking agents, cited in an earlier section, have not been materially changed for about ten years.

Among amines (with a probable ganglionic site of action), Easton et al. (226) found that cyclic hindered amines, including tri-, tetra- and penta-methyl pyrrolidines and piperidines, were more potent hypotensives than closely related open-chain amine series. Hypotensive polymethylated cyclobutanolamines may be primary, secondary, or tertiary as long as the alkyl groups are close to the N atom; the properties of one of these ganglionic blocking members has been described in more detail (227). Structural specificity was demonstrated by cinnamylguanidine in which the *cis* was more active than the *trans* isomer (228). Among hypertensive patients, the L-isomer of α-methyl-DOPA was more effective than the DL-form in lowering blood pressure (229). A novel prototype is the mesoionic pseudo-oxatriazole, of which several alkyl derivatives were reported to have a modest hypotensive activity (230). Polypeptides with hypotensive properties were the subject of an international symposium in 1965; the complete papers have been published (231) as well as the abstracts (232). The SAR features of some eledoisin and physalaemin analogues have been further described (233).

Coronary dilator activity was correlated with structural features among a large number of diphenyl-alkylamine derivatives (234). Activity was evident among members containing two aromatic rings separated by a propyl chain from a secondary amine.

The influences on activity of structural variations in posterior pituitary hormones have been pursued further. Replacement of the half-cystine residue at position 1 in oxytocin by penicillamine yields an inhibitor of oxytocin (235). Replacement of H by methyl at the β-carbon of the β-mercaptopropionic acid residue in the 1-position of potent deamino-oxytocin results in decrease in activity (236). Activities of 8-alanine-oxytocin and -oxypressin and their deamino analogues have been reported (237). Surprising activity was evident in deamino-oxytocin not containing a disulfide bond (238). A variety of vasopressin analogues have been studied (239). Lysine-vasopressin analogues modified at position 9 have been found to be of low activity (240).

Among other miscellaneous activities for which structural correlations have been noted may be cited porphyria-inducing characteristics of certain dihydropyridines (241, 242), platelet-aggregation inhibition by antihistamines and adenosine derivatives (243), weaker lipolysis inhibitory activities of 3-pyridyltetrazoles compared with nicotinic acid (244), and the structural and stereospecific features of the selective rat toxicant, norbromide (245).

The greater application of broad screening of new compounds, particularly in industry, has resulted in more publications which describe a variety of pharmacological characteristics in terms of semi-quantitative statements of activity for selected members. These articles usually are of little value as a basis for structure-activity correlations.

Chemists periodically have structural fashions which appear among experimental medicinals. A few years ago it was fashionable to introduce fluorine in place of certain hydrogen atoms. The trifluoromethyl group then became extensively investigated as a replacement for methyl. In the past

two years, the adamantyl group has appeared in some unusual places. The use of isosteric structural variants, of course, has been assessed in the past among many groups of compounds. Silicon as an isostere for carbon has been sporadically investigated and apparently can provide active isologues (246), but no particular advantages in its use have developed. In earlier sections S and Se choline derivatives also were cited.

Some Physical-Chemical Considerations

In publications describing new compounds of potential bio-medical interests, few investigators attempt to interpret structural variations in terms of associated changes in physical chemical characteristics. Perhaps a reason such efforts have not been more productive resides in individual interdisciplinary limitations of the synthesizing chemist, physical chemist, and pharmacologist to appreciate that which is significant in the other's discipline. Nevertheless, some encouraging efforts are evident.

One of the earliest and most general parameters of interest has been the ionization characteristics of biologically active molecules. Charge distribution is increasingly being considered. Among some local anesthetics, not only pKa values but infra-red absorption characteristics and charge distribution, as well as other properties have been assessed (247, 248). As anticipated, correlations are limited to narrow ranges of structural variations. Measuring the influence of pH on activity in a suitable biological test system is another approach to assessing the influence of ionization (53). Perkow (249) speaks of a "biologically active center" with a decreased density of electrons as a prerequisite of a correlation between a variety of classes of drugs and receptors. Burgen has correlated charge characteristics and steric and bulk features of certain molecules interacting with ACh receptors (55).

Hansch and coworkers have reported a number of studies in which linear free energies and partition characteristics have been associated with biological activities. From so-called substituent constants, effects of groups were factored into electronic, steric, and hydrophobic components (98). Related studies have been reported and recently reviewed (250–252). Kopecky & Bocek (253) correlate linear free energy expressions of Hansch (254), Zahradnik (255), and Boyce & Milborrow (256) in SAR. Neely (102) makes an interesting case for consideration of molecular orbital calculations in SAR utilizing some cholinesterase inhibitor models. Whether through this or other techniques, it is likely that more attention will be paid to the behavior of π electrons in biochemical phenomena and SAR. Much more background information would be needed before these approaches could have predictive values.

Canepa (120) has interpreted the effect of temperature on neuromuscular junction activity of some quaternary ammonium compounds in terms of their physical chemical properties such as ionic characteristics and charge distribution, hydrophobic character and steric features. The physical chemical considerations are elegantly developed but the pharmacological differences are more tenuously related to these.

Lipid solubility has been assumed to account for the penetration of a variety of classes of drugs through membrane barriers. The central nervous system and blood brain barrier has been a favorite target for consideration. Recent studies include partition coefficient determinations for cholinomimetic (56) and cholinolytic (89) drugs, with centrally active members favoring lipophilic distribution. Ionization constants and partition coefficients of some 2-benzylbenzimidazole related analgesics were interpreted as possibly influencing transport characteristics and thereby activity, but these factors alone could not account for the properties of all members in that structural specificities also seemed involved (257). The ability of a number of psychoactive drugs to interact with anionic (phospho) lipid films has been interpreted as evidence that these agents penetrate such films (258). Evidence of reaction specificities and relation to pharmacological properties would appear to be needed.

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